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Measures

PRINCIPAL INVESTIGATOR: Satu M. Somani, Ph.D.

CONTRACTING ORGANIZATION: Indian Pharmacological Society  
Springfield, Illinois 62794-9629

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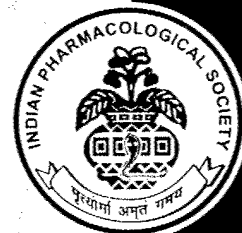
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# XXXV ANNUAL CONFERENCE OF INDIAN PHARMACOLOGICAL SOCIETY

26-29 November, 2002



# Scientific Programme Abstracts

Drug Development Research in India.

Defence Research and Development Establishment  
Ministry of Defence, Government of India  
Gwalior - 474002, India.

**IPS**  
2002

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# PROGRAMME

35<sup>th</sup> Annual Conference of Indian Pharmacological Society  
(November 26-29, 2002)

**Defence Research and Development Establishment,**  
Defence R&D Organisation, Min. of Defence, Govt. of India  
GWALIOR

26-11-2002 TUESDAY

## INAUGURATION

<u>Time (Hrs.)</u>	<u>Programme</u>	<u>Venue</u>
1500 Onwards	Registration	L.N.I.P.E. Auditorium
1630 - 1830	Inaugural Ceremony	L.N.I.P.E. Auditorium
1830 - 1900	TEA	L.N.I.P.E. Auditorium
1900 - 2030	Cultural Programme	L.N.I.P.E. Auditorium
2030 - 2230	Dinner	L.N.I.P.E. Lawn

27-11-2002

WEDNESDAY

**PLENARY LECTURES**

---

Time	Hall	Presenter	Title
0900-0945	A	<b>Dr. W. Selvamurthy</b>	Herbal Medicine for Armed Forces Chairpersons: Prof. P.K. Das and Dr. K. Jagdeesan
	B	<b>Prof. R.R. Choudhury</b>	Accelerating..Drug Development at the Toxicology- Clinical Trial phase Chairpersons: Dr. Ashwani Kumar and Dr. P.B. Deshmukh
	C	<b>Prof. M.K. Ticku</b>	Differential Regulation of GABA <sub>A</sub> and NMDA receptor Gene Regulation by Alcohol Chairpersons: Dr. D.K. Jaiswal and Dr. A. Sankaranaryanan

---

**Dr. G. ACHARI ORATION**

1000-1045 A **Prof. S.K. Gupta**  
Chairpersons: Dr. R.K. Srivastava and Prof. R.N. Sharma

**Dr. B.N. GHOSH ORATION -**

1000-1045 B **Dr. P.R. Dua**  
Chairpersons: Prof. O.D. Gulati and Prof. R.K. Goyal

**Dr. R.N. CHOPRA ORATION -**

1000-1045 C **Prof. S.K. Kulkarni**  
Chairpersons: Prof. J.M. Patel and Prof. S. Chattopadhyay

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1045- 1100 TEA BREAK

27-11-2002

WEDNESDAY

Time	Hall	Presenter	Title	A. Code
<b>SYMPOSIUM I - Chemical Warfare: Current awareness I</b> Chairpersons: K. Sekhar and Com. J Romano				
1100-1300	A	R.K. Gordon	Detection...sponges	IL-1
		B. Lukey	Current...review	IL-2
		R. Vijayaraghavan	Prophylactic...routes	IL-3
		M. Adler	Toxicodynamic of toxin.	IL-4
		Ashima Saxena	Human...agents	IL-5
		B.P. Doctor	In search...toxicity	IL-6

**SYMPOSIUM II - Herbal Medicine (Sponsored by Dabur Research Foundation, Ghaziabad)**  
Chairpersons: Dr. W. Selvamurthy and Dr. Rama Mukherjee

1100-1300	B	Rama Mukerjee	Challenges ..... industry	IL-7
		P.V. Diwan	A serendipity...research	IL-8
		G.P. Meshram	Cancer...herbs	IL-9
		S.K. Tandon	Prevention...garlic	IL-10
		R. Mathur	Herbal...distracters	IL-11
		A. Biswas	Effect of...rats	OP-1
		A. Chakraborty	Preliminary...models	OP-2
		S. Das	Studies...N. arbortristis	OP-3
		C.V. Rao	Antiulcer...extract	OP-4
S. Samanta	Antiulcer.....drug	OP-5		

**SYMPOSIUM III - Rational Use of Drugs (Sponsored by Delhi Society for Promotion of Rational use of Drugs, New Delhi)**

Chairpersons: Prof. Ranjit Roy Choudhuary and Prof. Usha Gupta

1100-1300	C	Usha Gupta	A survey....status	IL-12
		Y.K. Gupta	Rational...Antibiotics	IL-13
		O.P. Asthana	Rational....Antimalarial	IL-14
		S. Sharma	Rational....Anti HIV	IL-15
		Vaishali Dadkar	Drug prescription .... pattern	IL-16

1300-1400 **LUNCH BREAK**

1400-1545 **D Presentation of left over speakers from Hall A, B and C**

PL	-	Plenary Lectures	PZA	-	Prof.G.Achhari Prize
IL	-	Invited Lectures	PZU	-	Prof.U.K.Sheth Prize
OP	-	Oral Presentation	PZG	-	Gufic Prize
PP	-	Poster Presentation	PPZ	-	Prof.P.C.Dandiya Prize



27-11-2002

WEDNESDAY

Time	Hall	Presenter	Title	A. Code
<b>SYMPOSIUM IV - Chemical Warfare: Current awareness - II</b>				
Chairpersons: Dr. B. Lukey and Dr. R. Vijayaraghavan				
1400-1545	A	B.K. Bhattacharya	Retrospective ... samples	IL-17
		J. Romano	Chemical...outcomes	IL-18
		S. Baskin	New approach.... toxicity	IL-19
		R. Bhattacharya	$\alpha$ -KG ... poisoning	IL-20
		J.R. Dave	Subacute ... leukocytes	IL-21
		V.K. Rastogi	Bacterial enzymes....	IL-22

**Scientific Session I - Indigenous Drugs I**

Chairpersons: Dr. K.P.Mohanakumar and Prof. R. Mathur

1400-1545	B	B. Singh	Adaptogenic... <i>T. Gaerten</i>	OP-20
		A.G. Hannan	<i>Tinospora</i> ...study	OP-21
		A.K. Ram	Evaluation...diseases	OP-22
		S. Bose	Effect...pain	OP-23
		S.Z. Rahman	A case...Drug	OP-24
		A.O. Prakash	Perspectives...contraceptive	OP-25
		V.L. Kumar	Wormicidal... <i>C. procera</i>	OP-26
		V. Gowda	Evaluation ... rats	OP-27

**Scientific Session II - Cardiovascular Pharmacology and Anti-inflammatory agents.**

Chairpersons: Prof. M.K. Ticku and Dr. D. Parmar

1400-1545	C	K. Husain	Physical...hypertension	IL-56
		R.K. Goyal	Role of...diabetes mellitus	IL-57
		A.K. Das	Comparative...hypertension	OP-28
		G.J. Rao	The effect...rats	OP-29
		J. Seshadri	Comparison...rats	OP-30
		R.S. Bargaje	Prediction...factors	OP-31
		N. Khanna	Antioxidant...model	OP-32
		K.V Tamhankar	Effects of ...animals	OP-33
		M.B. Girish	Evalaution...rats	OP-34
		A.B. Sharma	A simple...oedema	OP-35
		A.V. Turankar	Antiinflammatory...rats	OP-36

1545-1600 TEA BREAK

1600-1800 D Presentation of left over speakers from Hall A, B and C

27-11-2002

WEDNESDAY

Time	Hall	Presenter	Title	A. Code
<b>Scientific Session III - Rational Use of Drugs</b>				
1600-1800	A	Chairperson: Prof. Vaishali Dadkar and Prof. N.S Parmar		
		P.R. Shankar	A study...Nepal	OP-37
		C. Sarkar	Medication...Nepal	OP-38
		B. Das	A study...Nepal	OP-39
		R.M. Barve	Study...dispensing	OP-40
		V.A. Badar	Surveillance...Nagpur	OP-41
		S. Pradhan	Intensive...Centre	OP-42
		P. Goyal	Prescribing..rationality	OP-43
		G. Dakhale	Prescribing...Nagpur	OP-44
		V.J. Shah	Study...hospital	OP-45
		M.A. Khan	Antimicrobial...hospital	OP-46
N.J. Patel	Prescription...Gujarat	OP-47		
<b>Scientific Session IV - Indigenous Drugs II</b>				
1600-1800	B	Chairpersons: Dr. Ram Raghuvir and Dr. J.R. Behari		
		P.M. Gokhale	Comparison...rats	OP-48
		P.K. Shankar	Evaluation...rats	OP-49
		D. Das	Assessment...volunteers	OP-50
		K.C. Singhal	Potential...sources	OP-51
		D.T. Selvam	Evaluation...activity	OP-52
		D.M. Usham	Preliminary...robustum	OP-53
		C.C. Barua	Ethnopharmacological...	OP-54
		R. Rukmani	Investigation...extract	OP-55
		R. Balaraman	Antiulcer...formulation	OP-56
		Anil Kumar	Nootropic...fruit	OP-57
M.G.M. Rao	Hepatoprotective....rats	OP-58		
<b>Scientific Session V- Biochemical Pharmacology</b>				
1600-1800	C	Chairpersons: Prof. Anna B Fischer and Dr. Louis Premkumar		
		L. Premkumar	Modalities...mechanisms	IL-58
		Anil Balapure	Primary...choice	IL-59
		S.K. Mishra	Structure...channels	IL-60
		V.Ramkumar	Modulation....adenosine	IL-61
		Shyamal Pal	Fermentor...development	OP-59
		S.S. Devi	EGFR/MAPK...rats	OP-60
		V. Gota	Genetic...therapy	OP-61
		S.N. Sarkar	Effects...rat	OP-62
		N. Gopalan	Kinetically... <i>quinquefasciatus</i>	OP-63
		U.N. Harle	Potential...rats	OP-64
		V.P. Singh	Effect...rats	OP-65
		R. Sharma	Pharmacological...agents	OP-66
		K. Sumitra	Kinetic...therapy	OP-67
S.C. Pingie	Adenosine.....cytotoxicity	OP-67A		
1630-1800	Poster Session I (Co-ordinator - Dr. Dinesh B. Kumar)			
1900 - onwards	BANQUET (HOTEL LANDMARK LAWN)			

28-11-2002

THURSDAY

Prize Session

Time	Hall	Presenter	Title	A. Code
<b>ACHARI PRIZE</b>				
Chairpersons: Prof. Y.K. Gupta and Prof. R. Raveendran				
0900-1045	A	P.S. Naidu	Effect...action	PZA-1
		N.S. Mittal	Anticonvulsant.pregnanolone	PZA-2
		L. Datta	Evaluation... <i>spreng</i>	PZA-3
		A. Mehta	Lead...rats	PZA-4
		K.N. Mehta	Effect of...study	PZA-5
		N. Dhananjay	Fenoldopam...rats	PZA-6
		M. Agarwal	Effects of...rats	PZA-7
<b>U.K. SETH PRIZE</b>				
Chairpersons: Prof. V.N. Puri and Prof. Hardayal Singh				
0900-1045	B	G.K. Randhawa	Prescribing...life	PZU-1
		R.R. Goyal	Surgical...hospital	PZU-2
		S.S. Dhanure	Evaluation...hyperplasia	PZU-3
		Sunita Sharma	Pharmacokinetic...extract	PZU-4
		R.C. Gupta	Clinical...centchroman	PZU-5
		M. Geetha	Dose...reaction	PZU-6
		N.R. Biswas	Multiple...trials	PZU-7
<b>SYMPOSIUM V - Ocular Pharmacology (Sponsored by BACFO Pharmaceuticals India Ltd.)</b>				
Chairpersons: Prof. S.K. Gupta and Prof. S. Ghose				
0900-1045	C	N.R. Biswas	Recent...therapeutics	IL-23
		N. Nayak	Laboratory...keratitis	IL-24
		S.K.Gupta	Recent.....cataract	IL-25
		S. Joshi	Galactosemic...pyruvate	IL-26
		S. Srivastava	<i>Ocimum</i> ...agent	IL-27
		D. Trivedi	Lycopene..... development	IL-28
1045-1100	<b>TEA BREAK</b>			

Time	Hall	Presenter	Title	A. Code
<b>Scientific Session VI - Chemotherapy of Cancer and Microbial Infections</b>				
Chairpersons: Maj Gen T. Ravindranath and Dr. K. Husain				
1100-1300	A	S.P.S. Monga	Therapeutic...growth	IL-62
		T. Ravindranath	Development...cancer	IL-63
		B.S. Dwarakanath	Improving...deoxy-D-glucose	IL-64
		G.B.K.S. Prasad	Potential.....therapies	IL-65
		P. Senthilnathan	Effect of...carcinoma	OP-68
		V. Magesh	Rehabilitating...metabolism	OP-69
		P.N. Venkatesan	Apigenin...ATPases	OP-70
		J.P.V. Singh	Protection...markers	OP-71
		K. Selvendiran	Protective...mice	OP-72
		A.T. Shafiq	Leucovorin...leukemia (ALL)	OP-73
		A.A. Raje	Effect of... <i>F. gigantica</i>	OP-74
<b>SYMPOSIUM VI - Toxins and Biological Warfare Agents</b>				
Chairpersons: Prof. Nancy Khardori and Brig. J.K. Bansal				
1100-1300	B	Nancy Khardori	Anthrax: Pharmacology	IL-29
		Brig. J.K. Bansal	An overview...weapons	IL-30
		H.V. Batra	Biology...agent	IL-31
		SB Deshpande	Brevetoxin.....transmission	IL-32
		P.V.L. Rao	Cyanobacterial...measures	IL-33
		A.S.B. Bhaskar	Cyanobacterial...carbon	OP-6
		B.D. Parashar	Biological... <i>deniconius</i>	OP-7
<b>Scientific Session VII - Neurodegenerative disorder and Neuropharmacology - I</b>				
Chairpersons: Prof. K.D. Gill and Dr. S.P.S. Monga				
1100-1300	C	S.K. Kulkarni	An insight...dyskinesia	IL-66
		O.N. Tripathi	New insights...blockers	IL-67
		Anuradha K.	Hypoglycemic...transmission	OP-75
		M. Thiyagarajan	Neuroprotective...ischemia	OP-76
		S. Kumar	Reversal...rats	OP-77
		A.K. Agrawal	Olfactory...cells (VMC)	OP-78
		A.G. Vij	Substance P...deficits	OP-79
		B. Prakash Babu	Effect...mice	OP-80
		T. Ghosh	Spastin...paraplegia	OP-81
1300 -1400		<b>LUNCH (DRDE LAWN)</b>		
1400-1535	D	Presentation of left over speakers from Hall A, B and C		

Time	Hall	Presenter	Title	A. Code
<b>Scientific Session VIII- Toxicology and Safety Evaluation</b>				
Chairpersons: Dr. Steven Baskin and Dr. P. Balakrishna Murthy				
1400-1545	A	Anna B. Fischer	Toxicological...capsaicin	IL-68
		P.Balakrishna Murthy	Issues of GLP..studies	IL-69
		P.B. Deshmukh	Toxicology...compliance	IL-70
		Pravin Kumar	Sensory...analogues	IL-71
		D. Parmar	Toxicological...chemicals	IL-72
		S. Das Gupta	An overview...treatment	IL-73
		M.P. Kaushik	A new...irritant	OP-82
		T.S. Mohan Kumar	Incidence...poisoning	OP-83
		T.K. Mondal	Short-term...rats	OP-84
		K. Gulati	Studies...mice	OP-85
		R.P. Prabhu	A study...venom	OP-86
		K. Ganesan	Comparative...repellents	OP-87
<b>Scientific Session IX - Clinical Pharmacology I</b>				
Chairpersons: Dr. B.S. Dwarkanath and Dr. Anil Balapure				
1400-1545	B	A Sankaranarayana	New.....diabetes	IL-74
		D.D. Rajgor	Efficacy...India	OP-88
		M. Nasiruddin	A study...disease	OP-89
		R.A. Patil	A double...fracture	OP-90
		V.R. Ambavane	Pattern...unit	OP-91
		R.M. Joshi	Erectile...treatment	OP-92
		V. Roy	Cough...a survey	OP-93
		S. Purushothaman	Efficacy.... planus.	OP-94
<b>SYMPOSIUM VII- Oxidative Stress in health and Disease</b>				
(Sponsored by Aventis CropScience, Mumbai)				
Chairpersons: Prof. SK Kulkarni and Prof. YK Gupta				
1400-1545	C	K.D. Gill	Calcium..... neurotoxicity	IL-34
		Neeta Singh	Oxidative stress...cancer	IL-35
		Y.K. Gupta	Oxidative stress...disorders	IL-36
		S.K. Gupta	Oxidative.....cataractogenesis	IL-37
		Arunabha Ray	Free Radical and Immuno..	IL-38
		K.P.Mohanakumar	Neuroprotective ..... disease	IL-39
		M. Khan	Evaluation... <i>vitro</i>	OP-8
		S.K. Raza	Analysis...spectrometry	OP-9
		L. Pari	Antioxidant...Toxicity	OP-10
		S.C. Pant	Sulphur...mice	OP-11
		Ramesh Chander	Tata tea...lipids	OP-12
1545-1600	<b>TEA BREAK</b>			
1600-1800	D	Presentation of left over speakers from Hall A, B and C		

28-11-2002

THURSDAY

Time	Hall	Presenter	Title	A. Code
<b>GUFIC PRIZE</b>				
1600-1830	A	Chairpersons: Prof. S.B. Deshpande and Prof. B. Gitanjali		
		M.L. Pardeshi	Screening...JC-Q2	PZG-1
		R.S. Hiray	Screening...JC-01	PZG-2
		K. Datta	Evaluation...models	PZG-3
		R.K. Gupta	Antinociceptive...extract	PZG-4
		Manish Rachchh	Anti-ulcer...rats	PZG-5
		G. Mehta	Safety...rats	PZG-6
		Amanpreet Singh	<i>Withania</i> ...rats	PZG-7
		S.L. Vishwakarma	Effect of...rats	PZG-8
		D.P. Bhagwat	The ...laminaceae	PZG-9
		Sanjay Kumar	Analgesic...rats	PZG-10
		Upendra B. Ayar	Effect...rabbits	PZG-11
		B. Andallu	Metabolic...laves	PZG-12
		D. Langade	A comparative ....in-Ano	PZG-13
		S. Ghose	Acute...potential	PZG-14
		Dinesh Kumar	Modern...agents	PZG-15
		V. Jagadeesan	Hepatoprotective...	PZG-16
		D. Rai	Adaptogenic...(Brahmi)	PZG-17
		U.R. Pingali	Randomised...subjects	PZG-18
		P.S. Rawat	DARL-2..... Eczema	PZG-19
<b>SYMPOSIUM VIII - Environmental pollutants and arsenicosis</b>				
(Sponsored by Labindia Instruments Pvt. Ltd., New Delhi)				
1600-1800	B	Chairpersons: Dr. S.K. Tandon and Prof. T. Venkatesh		
		S. Chattopadhyay	Apoptosis...exposure	IL-40
		J.R. Behari	Arsenic...aspects	IL-41
		S.J.S. Flora	Chronic arsenic...treatment	IL-42
		T. Venkatesh	Lead...policies	IL-43
		Manju Gupta	Hazardous...exposures	IL-44
		S.N. Dube	Pharmacology...arsenide	IL-45
		A.K. Jain	AAS - Latest developments	IL-46
		S. Shrivastava	Influence...rats	OP-13
		Sonia Johiri	Duration...exposure	OP-14
		Pragya Dixit	Effect...rats	OP-15
		Tripti Sharma	Lanthanum...regulation	OP-16
		U. Arora	Effect...ruminants	OP-17
		V. Shrivastava	Blood.....women	OP-18
<b>Scientific Session X - Neurodegenerative disorder and Neuropharmacology - II</b>				
1600-1800	C	Chairpersons: Dr. B.P. Doctor and Prof. N.A. Adibatti		
		Ram Raghubir	Cerebral... expression	IL-75
		S.K. Agrawal	Calcium... injury	IL-76
		Archana Jha	Anoxia .... mechanism	OP-95
		J.N. Singh	<i>Ptychodiscus</i>	OP-96
		M. Chattopadhyay	Adaptation...receptors	OP-97
		S. Anjali	Antidepressant...mice	OP-98
		D. Joshi	Reversal... quercetin	OP-99
		G. Kumar	Role of... epilepsy	OP-100
		C. Nath	A study... rats	OP-101
		Y.R.Khan	Clobazam.....phenytoin	OP-102
0900-1300		Poster Prize Session (P.C. Dandiya), Co-ordinator - Dr. S. Das Gupta		
1400-1730		Poster Session-II, Co-ordinator - Dr Manju Gupta		
1830-2000		<b>GENERAL BODY MEETING</b>		
2000-2200		DINNER (DRDE LAWN)		

Time	Hall	Presenter	Title	A. Code
<b>Dr. S.B. PANDEY ORATION</b>				
0900-0945	A	<b>Dr.O.N.Tripathi</b>		
Chairpersons: Dr. R.K. Gordon and Dr. S.K. Mishra				
<b>Scientific Session XI - Teaching Methods and Psychopharmacology</b>				
Chairpersons: Dr. O.N. Tripathi and Prof. Sushma Mengi				
0900-1045	B	G. Palit	Stress...body	IL-77
		R. Raveendran	Manuscript...review	IL-78
		B. Gitanjali	Plagiarism..... Plague	IL-79
		Meena Shrivastava	Paper...pharmacology	IL-80
		V.N. Puri	Pharmacology...planning	IL-81
		S. Patnaik	Surveillance.....Uttaranchal	OP-103
		T. Sharma	A study...Uttaranchal	OP-104
		R. Bhardwaj	A study...Uttaranchal	OP-105
		P.V. Dixit	Oxidative...field (EMF)	OP-106
		S. Malini	Reversal...rats	OP-107
		R.P. Jagtap	Validity...analysis	OP-108
		S.B. Nayak	Blunder...students	OP-109
<b>SYMPOSIUM IX - Pharmacology of Nitric Oxide (Sponsored by Lupin Laboratories, Mumbai)</b>				
Chairpersons: Prof. A. Ray and Dr. Madhu Dikshit				
0900-1045	C	Arunabha Ray	Nitrix oxide & stress	IL-47
		Madhu Dikshit	Regulation.. conditions	IL-48
		J. Bhaduri	NO.....potential	IL-49
		J.M. Patel	Dyanamic...calreticulin	IL-50
		K.P.Mohanakumar	Nitric oxide..... fallacy	IL-51
		P. Khurana	Significance...polyphenols	OP-19
<b>Dr. N.S. DHALLA ORATION</b>				
1000-1045	A	- Awaited -		
Chairpersons: Dr. Michael Adler and Dr. G. Palit				
1045-1100		<b>TEA BREAK</b>		
1100-1300	A	<b>Panel Discussion</b>		
<b>PHARMACEUTICAL INDUSTRY AND ACADEMECIA INTERACTION</b>				
(Sponsored by Panecea Biotec Ltd, Lalru, Punjab)				
Co-ordinator - Dr Amarjit Singh				
Panellist - Prof. S.K. Gupta				
Prof. Y.K. Gupta				
Prof. S.K. Kulkarni				
Prof. A. Ray				
Dr. Rama Mukherjee				
Dr. A. Sankaranaryanan				
Dr. J. Bhaduri				

29-11-2002

Friday

Time	Hall	Presenter	Title	A. Code
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**Scientific Session XII- PHARMACOKINETICS AND DRUG DELIVERY**  
1100-1300 B

Chairpersons: Prof. M.U.R. Naidu and Prof. N.R. Biswas

M.U.R. Naidu		Fast...development	IL-82
P.K. Sharma		Pharmacokinetics...infants	OP-110
A. Kondal		Influence...rabbits	OP-111
S. Malhotra		A study...volunteers	OP-112
J.C. Shobha		Bioavailability...volunteers	OP-113
S. Pant		Intravenous...chickens	OP-114
S. Ramesh		Effect...goats	OP-115
P.A. Thakur		Pharmacokinetics...Mumbai	OP-116
S. Babu		Disposition...administration	OP-117

**Scientific Session XIII - CLINICAL PHARMACOLOGY - II**  
1100-1300 C

Chairpersons: Prof. Meena Srivastava and Prof. K.L. Bairy

D.Sakthisekaran		Rehabilitating...cytotoxicity	IL-83
M. Gupta		Patterns...hospital	OP-118
R. Ahmad		Cisplatin...pilot study	OP-119
S. Sheetal		Sublingual...study	OP-120
S. Vasu		Genetic...population	OP-121
A.T. Naveen		Genetic...population	OP-122
R.B. Mhatre		Plasma...experience	OP-123
B.G. Kirodian		Biodistribution...rifampicin	OP-124
SS Dudhgaonkar		Oral.....volunteer	OP-125
K.D. Kamtekar		A prospective...malaria	OP-126
A.R.S Patil		Comparative.....study	OP-127
RB Sangha		Effects..... seizures	OP-128
HN Gopala Krishna		Screening.....rats	OP-129

**SYMPOSIUM X - Pharmacology in India: Future perspective**

1100-1300 D

(Sponsored by Pfizer India Ltd., Mumbai)  
Chairpersons - Dr. Shoibal Mukherjee and Dr PV Diwan

S. Mukherjee		Emerging ..... an overview	IL-52
A Sankaranarayanan		Drug discovery .... future	IL-53
N. Mahalaxmibala		Growth ..... in India	IL-54
Sadhna Joglekar		Pharmacoeconomics .... Need	IL-55

1300-1400

1400-1500

1500-onwards

**VALEDICTORY FUNCTION**  
**LUNCH**  
**LOCAL SIGHT-SEEING**

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## PLENARY LECTURES

**Dr. W. Selvamurthy** : Herbal Medicine For Armed Forces

**Date** : 27-11-2002

**Time** : 0900 - 0945

**Venue** : Hall - A

**Chairpersons** : Prof. P.K. Das, Dr. K. Jagadeesan

**Prof. R. R. Choudhary** : Accelerating Drug Development At The  
Toxicology-Clinical Trial Phase

**Date** : 27-11-2002

**Time** : 0900 - 0945

**Venue** : Hall - B

**Chairpersons** : Dr. Ashwini Kumar , Dr. P.B. Deshmukh

**Prof. M. K. Ticku** : Differential regulation of GABA<sub>A</sub> an  
NMDA receptor gene regulation by  
alcohol

**Date** : 27-11-2002

**Time** : 0900 - 0945

**Venue** : Hall - C

**Chairpersons** : Prof. J.M. Patel, Prof. S. Chattopadhyay



**PL - 1**

**HERBAL MEDICINE FOR ARMED FORCES.**

**Selvamurthy W.**

Advisor, Biomedical Sciences, DRDO, Delhi.

**PL - 2**

**ACCELERATING DRUG DEVELOPMENT AT THE TOXICOLOGY -  
CLINICAL TRIAL PHASE.**

**Ranjit Roy Choudhury**

National Institute of Immunology, New Delhi.

It has often been felt that approval of toxicology studies leading to clinical evaluation of new products is a constraint towards speedy drug development. Even after the toxicology clearance approval of the clinical trial protocol is perceived to be another factor for delay. These delays can be reduced if there is proper documentation of toxicology studies carried out within a scientific framework for such studies and when well planned ethical clinical protocols are submitted for approval. A greater attempt towards partnership between the pharmaceutical house and the regulator having more regular dialogue would result in speedy clearances and approval of clinical trials. This acceleration in drug development in a competitive world would be of beneficial to scientists and to the country.

PL - 3

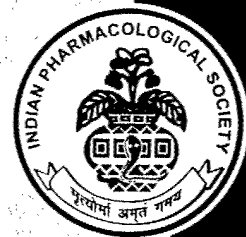
**DIFFERENTIAL REGULATION OF GABA<sub>A</sub> AND NMDA RECEPTOR GENE EXPRESSION BY ALCOHOL**

**Maharaj K Ticku.**

Department of Pharmacology, UTHSCSA, San Antonio, TX, USA.

Alcohol has different effects on GABA<sub>A</sub> (inhibitory) and NMDA (excitatory) receptors in the brain. Acute alcohol treatment increases GABA<sub>A</sub> but decreases NMDA receptor mediated functional responses. Chronic use of alcohol produces adaptive changes in the brain, which can result in altered physiological responses. Chronic alcohol treatment while not altering the binding of various radio ligands to the GABA<sub>A</sub> receptor, increased the diazepam-insensitive Ro 15-4513 (a partial inverse agonist) in cerebral cortex and cerebellum. Chronic alcohol treatment produced down regulation of the mRNA and polypeptide levels of the  $\alpha$ 1-subunits, and up regulation of  $\beta$ <sub>2,3</sub>,  $\alpha$ -4 and  $\alpha$ -6-subunits. In contrast, same chronic alcohol treatment produced an up regulation of NMDA receptor binding, function, gene and protein expression. The changes in NMDA receptor gene and protein expression were brain region specific. Chronic ethanol increased the NMDAR1 and NMDAR2B mRNA levels in cortex and hippocampus, but not in cerebellum. The molecular basis of these actions included stabilization of the NMDAR 1 mRNA levels and an increase in the transcription of the NMDAR2b mRNA levels. Thus, chronic alcohol treatment altered NMDAR's at both transcription and post-translational levels. In summary, these results have implication in alcohol induced tolerance and physical dependence.

Supported by NIH-NIDA grants M 04090 and M 10552



# ***Orations of The IPS***

**XXXV ANNUAL CONFERENCE OF  
INDIAN PHARMACOLOGICAL SOCIETY**

**IPS  
2002**



## ORATIONS OF THE IPS

### Dr. G. ACHARAI ORATION

Orator : Prof . S.K. Gupta  
Title : Awaited  
Date : 27.11.2002  
Time : 1000-1045  
Venue : Hall A  
Chairpersons : Dr. R.K. Srivastava and  
Dr. R.K. Sharma

### Dr.B.N. GHOSH ORATION

Orator : Dr. P.R. Dua  
Title : Awaited  
Date : 27.11.2002  
Time : 1000-1045  
Venue : Hall B  
Chairpersons : Prof. O.D. Gulati and Prof. R.K. Goyal

### Dr.R.N. CHOPRA ORATION

Orator : Prof . S.K. Kulkarni  
Title : Awaited  
Date : 27.11.2002  
Time : 1000-1045  
Venue : Hall C  
Chairpersons : Prof. J.M. Patel and  
Prof. S. Chattopadhyay

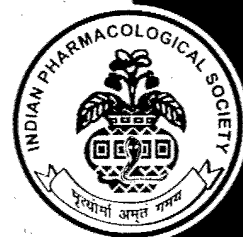


**Dr.B.S.PANDEY ORATION**

**Orator** : **Dr.O.N.Tripathi**  
**Title** : **Awaited**  
**Date** : **29.11.2002**  
**Time** : **0900-0945**  
**Venue** : **Hall A**  
**Chairpersons** : **Dr.R.K.Gordon and Dr.S.K.Mishra**

**Dr.N.S.DHALLA ORATION**

**Title** : **Awaited**  
**Date** : **29.11.2002**  
**Time** : **1000-1045**  
**Venue** : **Hall A**  
**Chairpersons** : **Dr.Michael Alder and Dr.G.Palit**



# **Symposia Sessions**

**XXXV ANNUAL CONFERENCE OF  
INDIAN PHARMACOLOGICAL SOCIETY**

**IPS  
2002**



# ***Symposium I***

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## **Chemical warfare - Current awareness I**

**Date** : 27-11-2002  
**Time** : 1100-1300  
**Venue** : Hall - A

**Invited Lectures** : Dr. R K Gordon  
Dr. B J Lukey  
Dr. R Vijayaraghavan  
Dr. M Adler  
Dr. Ashima Saxena  
Dr. B P Doctor

**Chairpersons** : Mr. K Sekhar  
Com. J Romano



**IL - 1****DETECTION, DECONTAMINATION, AND DETOXIFICATION OF CHEMICAL WARFARE AGENTS USING POLYURETHANE ENZYME SPONGES.**

Gordon RK<sup>1</sup>, Gunduz AT<sup>1</sup>, Askins, LY<sup>1</sup>, Strating SJ<sup>1</sup>, Doctor BP<sup>1</sup>, Clarkson, ED<sup>2</sup>, Skvorak JP<sup>3</sup>, Maxwell DM<sup>2</sup>, Lukey B<sup>2</sup>, Ross M<sup>3</sup>.

<sup>1</sup>Walter Reed Army Institute of Research, Division of Biochemistry, 503 Robert Grant Ave, Silver Spring, MD 20910-7500, USA.

<sup>2</sup>United States Army Medical Research Institute of Chemical Defense Drug Assessment Division, Basic Assessment Branch, and Division of Pharmacology, Aberdeen Proving Ground, Edgewood, MD 21010, USA.

<sup>3</sup>United States Army Medical Research Medical Command, Ft. Detrick, MD 21702, USA.

During combat, personnel have been exposed to organophosphates (OPs). Other exposures to chemical toxins include pesticides or terrorist acts in subways or sports events. Thus, we are developing enzyme-immobilized polyurethanes configured as (1) biosensors for OPs or (2) as sponges to soak up and inactivate the OPs. Enzyme sensors have the advantage of selectivity, sensitivity and, most important, specificity, ease and portability, and markedly simplified instrumentation. Our immobilized enzymes will not leach from the polyurethane support so that the product - an OP badge - can now be used to sample anything from soil, water, to air. In the second configuration, 18 polyurethane sponges are synthesized with enzymes and agents for external treatment of OP contaminated skin and other sensitive and exposed surfaces. To detoxify OPs, the cholinesterase is combined with oximes so catalytic activity of OP inhibited enzyme is continuously restored. As a biosensor for OPs, the polyurethane matrix is composed of cholinesterase or other OP hydrolyzing enzymes to both indicate the presence of the OP agents, and to differentially indicate the type of OP present in the field. Resulting sponges for decontamination provided protective ratios of about 15 and 100 fold for soman and VX, respectively, when tested in a guinea pig model, and reduces methylene blue uptake in mustard exposed animals. In conclusion, these immobilized enzyme biosensors and sponges by virtue of their high capacity for enzymes, stability, specificity, sensitivity, and resistance to harsh environmental conditions, can be used under diverse conditions encountered by troops and civilian first responders.

**IL - 2****CURRENT AND POTENTIAL SKIN DECONTAMINANTS FOR CHEMICAL WARFARE AGENT EXPOSURE - A LITERATURE REVIEW.**

Brian J. Lukey<sup>1</sup>, Charles G. Hurst<sup>1</sup>, Richard K Gordon<sup>2</sup>, Bhupendra P Doctor<sup>2</sup>, Edward Clarkson<sup>1</sup>.

<sup>1</sup>United States Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, MD 21010-5400, <sup>2</sup>Walter Reed Army Institute of Research, Washington, DC 20307-5100.

The objective of this study is to identify the US military's guiding principles in developing skin decontaminants for chemical warfare agent exposure and to discuss potential products. The US Army Medical Research and Materiel Command established a research effort to develop skin decontaminants for chemical warfare agent exposure. Because the war fighter will not likely know the specific agent that was delivered, a desirable skin decontaminant should be universally effective for all chemical warfare threat agents. However, highly-reactive decontaminants that work well on equipment may damage the war fighter's skin and actually worsen the chemical warfare agent effects. Also, the skin has absorptive properties that make it much more difficult to decontaminate than a flat, impervious surface. Consequently, the optimal skin decontaminant should not cause harm to the skin or react negatively with one's body either by itself or with the reactive products it produces yet it should remove or destroy agents quickly. It should be easy to use, readily available and relatively inexpensive. Current US military fielded skin decontaminants are the M291 resin kit and 0.5% hypochlorite. Other potentially effective skin decontaminants are the Reactive Skin Decontamination Lotion, Diphoterine, Sandia Laboratory's Foam Decontaminant, and Reactive Sponge. This presentation will describe, as a literature review, the research efforts being conducted on the potential decontaminants and will stress the importance of quick physical removal as the best means to decontaminate skin.

IL - 3

**PROPHYLACTIC EFFICACY OF AMIFOSTINE AND DRDE-07 AGAINST SULPHUR MUSTARD ADMINISTERED THROUGH VARIOUS ROUTES.**

**Vijayaraghavan R<sup>1</sup>**, Kulkarni A, Pravin Kumar, Lakshmana Rao PV, Pathak U, Raza SK and Jaiswal DK.

Defence Research and Development Establishment, Jhansi Road, Gwalior - 474002.

**Objective:** After the successful implication of the Chemical Weapons Convention a prophylactic agent will be very useful for personnel engaged in the destruction of sulphur mustard (SM). Due to the simple method of preparation, SM can also be used clandestinely during war or by terrorist groups, and a prophylactic agent will be necessary. Amifostine and one of its analogues DRDE-07, were found to be good prophylactic agents when given orally against percutaneously administered SM. We studied the efficacy of amifostine and DRDE-07 against SM administered through various routes.

**Methods:** Amifostine and DRDE-07 were given 30 min prior to the administration of SM through percutaneous, oral, subcutaneous and inhalation routes in mice. Various doses of SM was used and a protective index was determined as a ratio of LD<sub>50</sub> with prophylactic agent to LD<sub>50</sub> of SM alone. LD<sub>50</sub> of SM was also determined by various routes in mice and rats. The protective efficacy of amifostine and DRDE-07 on the decrease in GSH and increase in DNA fragmentation induced by percutaneously administered SM was also evaluated in mice.

**Results:** Oral administration of amifostine and DRDE-07 (0.2 LD<sub>50</sub> dose), gave a protection index of 9.5 and 27.0 respectively, when SM was administered through percutaneous route. Amifostine and DRDE-07 significantly protected the decrease in GSH and the increase in DNA fragmentation induced by SM. DRDE-07 was better than amifostine. But, amifostine and DRDE-07 did not give a significant protection index against SM, when the latter was administered through oral, subcutaneous or inhalation routes. Interestingly, percutaneously administered SM was more toxic than the other routes. The LD<sub>50</sub> (14 day observation period) of SM was 5.1, 8.1 and 23.0 mg/kg respectively for percutaneous, oral and subcutaneous routes in mice, and 2.0, 2.4 and 3.4 mg/kg respectively for percutaneous, oral and subcutaneous routes in rats.

**Conclusion:** Amifostine and DRDE-07 are good prophylactic agents when SM is administered through percutaneous route. Decrease in GSH and increase in DNA fragmentation induced by percutaneously administered SM was prevented by amifostine and DRDE-07, and DRDE-07 was better than amifostine. Percutaneously administered SM was more toxic than oral and subcutaneous administrations, showing bizarre nature of SM.

IL - 4

**TOXICODYNAMICS OF TOXINS.**

**Adler M.**

United States Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, MD 21010-5400

**IL - 5****HUMAN BUTYRYLCHOLINESTERASE: A FUTURE GENERATION ANTIDOTE FOR PROTECTION AGAINST ORGANOPHOSPHATE AGENTS.****Saxena A, Luo C, Bansal R, Sun W, Clark MG, Ashani Y<sup>#</sup>, Doctor BP.****\*Division of Biochemistry, Walter Reed Army Institute of Research, Silver Spring, MD 20910-7500; <sup>#</sup>Israel Institute for Biological Research, P.O. Box 19, Ness-Ziona, Israel.**

Human butyryl cholinesterase (Hu BChE) is the most suitable candidate that may be used as a pretreatment against nerve agent poisoning. A dose of 200 mg of Hu BChE is envisioned as a prophylactic treatment in humans that can protect from exposure of up to  $2 \times LD_{50}$  of soman. We recently developed a procedure for the large-scale purification of Hu BChE from Cohn Fraction IV, using affinity gel for batch extraction followed by anion-exchange chromatography, which yielded ~6 g of purified enzyme from 120 Kg of Cohn fraction IV-4. The enzyme activity was stable when stored in liquid form at 4°C and 25°C and in lyophilized form at 4°C, 25°C or 37°C to date (3 months). The enzyme did not exhibit any toxicity in mice even at doses of up to 30 mg/Kg as measured by general observation, serum chemistry, complete blood count, and gross and histologic tissue changes. Mice exposed to a dose of 90 mg/Kg of Hu BChE did not exhibit toxic neurobehavioral effects even at a dose 30-fold higher than that necessary for protection against  $2LD_{50}$  of soman in humans. Work is currently underway to transition this procedure to isolate tens of gram quantities and eventually Kg amounts of Hu BChE from Cohn fraction IV under GMP conditions, evaluate its use as a bioscavenger for safety and efficacy in humans, examine it for lack of an auto immune response, and establish its pharmacokinetic and pharmacodynamic properties in rodent and non-human primate animal models. Hu BChE will be the first successful pretreatment/treatment that can afford protection against not only mortality, but also against the adverse physiological and behavioral effects of nerve agent exposure.

**IL - 6****IN SEARCH OF AN IDEAL BIOSCAVENGER FOR ORGANOPHOSPHATE CHEMICAL WARFARE AGENT TOXICITY.****Doctor BP, Saxena A.****Walter Reed Army Institute of Research, Silver Spring, MD 20910-7500; USA.**

Among the enzymes being considered and evaluated as bioscavengers of highly toxic organophosphorus (OP) nerve agents, are: OP hydrolase, OP anhydrase, paraoxonase, parathion hydrolase, PON1, and A & B esterases including, carboxylesterases and cholinesterases (ChEs). Almost all OP hydrolases have a relatively narrow specificity, which is mainly directed to OP pesticides. They are essentially ineffective in hydrolyzing OP chemical warfare agents at a rate needed to be effective bioscavengers. Therefore, the use of catalytic bioscavengers at present is in the exploration phase. On the other hand, plasma-derived ChEs such as acetylcholinesterase (AChE) from fetal bovine serum (PBS) and butyrylcholinesterase (BChE) from equine and human (Hu) serum have been successfully used as safe and efficacious prophylactic treatments to prevent poisoning by OP compounds, in both rodent and non-human primate models. In order to avoid any adverse immune reaction, only native or recombinant ChEs from human sources are suitable for human use. At the present time, Hu BChE is a better bioscavenger for OP poisoning than Hu AChE for the following reasons: (1) To date, only plasma derived ChEs have been shown to be effective bioscavengers due to their long mean residence time in circulation and only BChE is present in human serum; (2) glycosylation contributes to the circulatory stability of ChEs, and BChE has 9 glycosylation sites versus 4 in AChE; (3) in case of use of recombinant enzyme, its stability will have to be improved by PEGylation, and BChE has 31 lysine residues on the surface versus 8 for AChE.





# ***Symposium II***

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## **Herbal medicine**

- Date** : 27-11-2002  
**Time** : 1100 - 1300  
**Venue** : Hall - B
- Invited Lectures** : Dr. Rama Mukerjee  
Dr. PV Diwan  
Dr. GP Meshram  
Dr. SK Tandon  
Dr. R Mathur
- Oral Presentation** : OP 1 - OP 5
- Chairpersons** : Dr. W. Selvamurthy  
Dr. Rama Mukherjee
- Sponsor** : **Dabur India Ltd.**



IL - 7

## CHALLENGES OF TRANSITING FROM GENERIC DRIVEN TO INNOVATIVE R & D DRIVEN BUSINESS FOR INDIAN PHARMACEUTICAL INDUSTRY.

Rama Mukherjee.

Director R & D, Dabur Research Foundation, Sahibabad , UP.

The challenges of finding newer generations of cost-effective therapeutic molecules for treating and diagnosing human diseases require discovery and development of newer, more potent and specific drugs and therapeutics. India's participation in this business has to be considerably stepped up to make a significant global impact. The model currently employed by some of the Indian Industries of licensing their R & D molecule in pre-clinical stage or after phase I clinical development is more out of compulsion than that of choice. Generic pharma business in India has been good and has provided drugs at affordable price to the working and the rural population. Generic business however should have been complemented with R & D driven business decades ago. Loss of knowledge, skill and technology can not be quantitated in financial terms alone, it has had untold negative economic and social impact. Lack of understanding of need of development of infrastructure, expertise, and culture of innovation has deprived the opportunities to Entrepreneurs to innovate and develop R & D based Pharmaceutical industries.

We still have the possibilities of making up at this juncture of genomic and proteomic era to initiate a very high level R & D capable of generating a new generation of world class block buster drugs for the treatment of diseases of global significance. This would have significant effect in India's capability to generate the revenues in global terms and contribute to the global knowledge. The industrial R & D should be encouraged to value continuous basic research to produce technological advances under take long-term drug development projects and the adoption and integration of new cutting edge science and technologies for delivering improved drugs.

Technological advances are most needed for the pre clinical and clinical development of new and novel molecules in line with the rest of the global R & D. Market research and market development has to receive equally important focus. Given the large scientific force and the will to do so in the country it should be possible to take these challenges.

IL-8

### A SERENDIPITY IN HERBAL RESEARCH.

Diwan PV.

Scientist, Pharmacology Division, Indian Institute of Chemical Technology, Hyderabad - 500007.

The herbal medicines have become integral part of the health care system and will be more so after 2005. The rich heritage of Indian herbal wealth is unexplored, which does not enjoy the status of western medicine which is based on the scientific platform. Several reasons can be attributed but the fact remains that herbs are unearthed wealth for the human suffering. A failure of allopathic medicine turns an eye towards the alternative medicines. Hence the herbal medicine still enjoys wide popularity in our country and abroad. India was pioneer in herbal medicine and today we are nowhere in world map. Mainly because not protecting the wealth and utility. It is alarming that only 2% of the plants have been explored and still 98% are awaiting to be explored for its medicinal value. The scientific validity is an order of the day for its therapeutic utility. The meticulous research will answer for the deadly disease. Now the people are opting for the ayurvedic medicine because the allopathic medicines have high cost, toxicity, environmental pollution, and no cure. The key issues to make it perfect are authenticity, quality and safety for the herbal drugs, which is a serious concern in pharmaceutical industry. The research on medicinal plants has taken the fast track and every multinational company is putting its efforts to bring out a new drug with great therapeutic value. Pharmacological screening of herbal extracts is a "Herculean Task" as there are lapses in animal model on test. The ayurvedic medicine of proven value in human does not faithfully predict in animals. This needs a careful understanding to establish the efficacy. A deeper scientific understanding of herbal therapy is still a hidden treasure. The scientific outlook needs a sea change. The herbal preparations are active only when they are given as a whole, but the chemists try to isolate and characterize the active ingredient which fails in therapy. However now the concepts are different and scientists are willing to follow the ayurvedic way of preparation of drugs formulation. The herbal research is not free from constrains, hence the excellent drugs may not reach the market i.e. Privor an anti-diarrhoeal and "arogyapacha" (good health). The meticulously planned attempts are needed to bring the drug to the stage of its use for the various diseases from plants. These drugs are needed for deadly diseases like, irritable bowl syndrome, aids, leprosy, skin diseases etc. The herbal medicine does have answer, if used appropriately, as mentioned in ayurveda. Today modern scientific community is fascinated by herbal preparations. But the herbal medicines have failed because of many problems such as authenticity, quality and good manufacturing practice, no clear theoretical basis, lack of transparency accomplished by some rituals etc. At present the plant research is standstill and require an insight to understand its potential for pharmacotherapy. The boom of advertisement attracts persons to opt for the herbal medicine. But advertized drugs do more harm than a good. The adulteration plays an important role which hinders the research output. The magic herbs and plants are around and waiting to be discovered and commercialized. Because they are now definitely recognized and accepted as a perennial storehouses of infinite, limitless benefits to man. Therefore a link between plant research and modern medicine will cater to the need of health care in the new millennium.

IL-9

## CANCER CHEMOPREVENTING HERBS.

Meshram GP.

Defence Research and Development Establishment, Jhansi Road, Gwalior - 474002.

For thousands of years, the Earth's many civilizations have used herbs for their healing properties. Through "trial and error" our ancestors discovered the different healing properties- possessed by various plants, and as time went on, a variety of "herbal cultures" evolved. Today, in modern medicine, we are still learning, discovering, and implementing the healing properties of different herbs (medicinal plants). Despite the terrific advances and progress technology has presented to healthcare, herbal remedies are continually being explored. Continued understanding about the complexity of cancer process right from causative agents to ultimate metastasis, we are compelled in believing the notion that the prevention of disease is better than cure. It is probably as old as the concept of restoration of human health by medical intervention. Many human cancers are preventable because their possible causes have been identified in the human environment. The finding that regular consumption of certain constituents of herbs, spices, fruits and vegetables might protect us from increasing risk of cancer. Herbal medicine is continuously evolving and playing an influential role in reducing the risk of cancer as well as in modern health care, worldwide. In modern society the practice of herbal medicine has changed dramatically and there is now a growing trend towards what are called phytomedicine or complementary or alternative medicine.

One of the most popular ancient remedies, which have tested well in today's modern laboratories, is Green Tea Extract (GTE). Experimental and epidemiological studies have proved to have cancer preventing potentials in GTE by inhibiting the mutagenesis induced by various chemical carcinogens. *Ginkgo biloba*, Turmeric, Garlic, Ginger are another herbs and spices which have been used in oriental medicine for ages and also have stellar effects in clinical testing. These herbs and their active phytochemicals established to possess cancer chemopreventing potentials, reducing the cancer risk from various environmental mutagens and carcinogens. Large number of herbs and their active phytochemicals to which man exposed, needs systematic evaluation for their possible role in protection of cancer. Few among many herbs are also found to possess noxious mutagenic and carcinogenic potentials, although extrapolation of their risk to human is not clear, which needs their simultaneous evaluation for risk and antirisk potential in respect to cancer. More than 70% of antimutagenic and anticarcinogenic research findings in published literature came by using an in vitro Ames Salmonella mutagenicity test. Our research work also revealed that Ginger (*Zinziber officinales*), red chillies (*Capsicum* sp.) and Ajowan (*Carum copticum*) found to have possible cancer chemopreventing potentials by inhibiting the induced mutation of different human and rodent carcinogens. However, more experimental in vitro and in vivo studies required to carry out to know their mechanism of action.

**IL-10****PREVENTION OF LEAD OR CADMIUM INTOXICATION BY GARLIC.****Tandon SK.**

Ex- Scientist-G, Industrial Toxicology Research Centre, Lucknow - 226001.

There has been an increasing public and scientific interest in herbal medicines. Garlic (*Allium sativum*) is widely cultivated and consumed worldwide and its beneficial effects have been known for centuries. Garlic is known to stimulate the body's immune system and protect against heart disease and strokes by lowering triglycerides, cholesterol and low-density lipoproteins concentrations in blood and the hypertension. Garlic has demonstrated anti-cancer effects owing to its potential to slow tumour growth, attributed to its chemical constituents mainly diallyl sulfide, diallyl disulfide and diallyl trisulfide. Garlic has also been shown to protect against damage from oxidation and free radicals. Garlic was investigated for its potential to prevent the accumulation of lead and cadmium, major environmental pollutants and to reduce their toxic effects in animals. The feeding of freshly minced garlic during intraperitoneal injection of lead acetate or cadmium chloride, daily for six weeks significantly decreased the accumulation of these toxic metals and prevented the metal sensitive biochemical parameters in blood, liver and kidney. The molecular mechanism of lead and cadmium toxicity has revealed the involvement of oxidative damage to the affected tissues. The ability of garlic to provide glutathione, biosynthesize metallothionein or similar protein and its antioxidant properties appear to protect against potential oxidative damage to tissues by lead or cadmium. The regular intake of garlic may be beneficial in reducing the toxic effects of these heavy metals in exposed population.

**IL-11****HERBAL MEDICINES: ATTRACTIONS AND DISTRACTERS.****Mathur R.**

School of Studies in Zoology, Jiwaji University, Gwalior - 474019.

Man's association with vegetation is as old as his origin. South-East Asian medicinal systems are replete with enormous information on plant preparations for treatment of variety of human and cattle disorders that are commonly used for similar treatment in different countries or have different uses at different places. The pioneer work by ancient practitioners has established a well-timed system of herbal treatment with profound base that enjoys the confidence of people till date. In India, China and Japan the herbal treatment has gained importance over last few years and their use is expanding in the western world as well. The present paper deals with the salient features which make herbal medicine a treatment of choice. Its centuries old testament, easy availability and commendable belief pursue the scientific community to verify the herbal potentialities. Modern formulations of these medicines are available as powders, granules, capsules, tablets and syrups. Office of the alternative medicines in United States is patenting many herbs used in medicinal preparations used for the treatment of a large variety of human disorders. WHO programme on antifertility has generated great interest in developing a contraceptive of plant origin throughout the world. General belief that herbal preparations are not toxic, need to be verified in context to the expanding use of such drugs. Presence of heavy metals like lead, cadmium, mercury and arsenic, misidentification of plant species, presence of bacteria and toxins make sufficient ground for taking great caution in use of herbal medicines by doctors not trained in their use.

OP- 1

### EFFECT OF AN INDIGENOUS PLANT PRODUCT X01 ON ALTERED REPRODUCTIVE FUNCTION OF MALE DIABETIC RATS.

<sup>1</sup>Biswas A, <sup>1</sup>Chatterjee M, <sup>1</sup>Dutta A, <sup>2</sup>Chatterjee U, <sup>1</sup>Hazra A, <sup>1</sup>Chattopadhyay S, Bhattacharya D, Tripathy PC, <sup>1</sup>Das J.

<sup>1</sup>Depts. of Pharmacology and <sup>2</sup>Pathology, University College of Medicine, Kolkata - 700020 and S.V.S.P Hospital, Kolkata - 700009.

**Objectives:** Reproductive dysfunction is a recognized consequence of diabetes mellitus. The objectives of the present study were to investigate whether 'X01', an established indigenous, hypoglycemic, insulinogenic medicinal plant derivative, can attenuate development of diabetes related complications in the male reproductive system of a rat model of diabetes.

**Methods:** A non-insulin dependent diabetes mellitus model was induced by intraperitoneal injection of Streptozotocin [STZ] 40 mg/kg body wt. Rats were divided into 6 groups of 6 animals each, namely, Group A [normal healthy controls], Group B [X01 treated], Group C [Glipizide treated], Group D [STZ treated], Group E [STZ + X01 treated] and Group F [STZ + Glipizide treated]. Following daily oral administration of X01 (150 mg/kg) or Glipizide (5 mg/kg) for 8 weeks, the animals were sacrificed.

**Results:** In diabetic rats, testicular weight was decreased as compared to normal rats. Morphologically, diabetic rats showed a thickening of the basement membrane that was accompanied by sperm maturation arrest. These rats had a 50% reduction in sperm count along with significant shortening of the sperm length. By treating with X01, all the above mentioned alterations were effectively reverted to near normal conditions.

**Conclusions:** Our data strongly suggests that altered reproductive functions observed in diabetic rats were markedly attenuated by X01. Since this product can effectively restrict hyperglycemia and the associated complications, it warrants further investigation.

OP - 2

### PRELIMINARY STUDIES ON ANTI-INFLAMMATORY AND ANALGESIC ACTIVITIES OF *SPILANTHES ACMELLA* IN EXPERIMENTAL ANIMAL MODELS.

Chakraborty A, Devi Bharati RK, Rita S, Singh IT.

Department of Pharmacology, Regional Institute of Medical Sciences (RIMS), Lamphelpat, Imphal, Manipur-795004.

**Objective:** *Spilanthus acmella* is an indigenous herb from the family Asteraceae. The whole plant is claimed to possess medicinal properties. Leaves and flowers are used to relieve toothache and sore throat. The present study was undertaken to evaluate the anti-inflammatory and analgesic activities of aqueous extract of *Spilanthus acmella* (SPA) in experimental animal models.

**Methods:** SPA was tested for anti-inflammatory action on carrageenan induced rat paw oedema by the method of Singh and Ghosh (1974). The analgesic property was evaluated by acetic acid induced writhing response in mice as described by Ghosh (1984).

**Results:** Anti inflammatory activity: Mean increase in paw volume in ml in standard drug aspirin (100 mg/kg, oral) was  $0.21 \pm 0.01$  ( $P < 0.001$ ); in SPA (400 mg/kg),  $0.25 \pm 0.33$  ( $P < 0.01$ ); (200 mg/kg),  $0.26 \pm 0.03$  ( $P < 0.01$ ); (100 mg/kg),  $0.27 \pm 0.06$  ( $P < 0.01$ ) and in control (N/S),  $0.57 \pm 0.14$  respectively. The percentage of inhibition of oedema for aspirin, SPA (400 mg/kg, 200 mg/kg, 100 mg/kg oral) were 63.1, 56.2, 54.4 and 47.3 respectively. Analgesic mean values of writhing response with aspirin (150 mg/kg SIC) was  $16 \pm 5.27$  ( $P < 0.001$ ); in SPA (400 mg/kg),  $27.66 \pm 3.48$  ( $P < 0.001$ ); (200 mg/kg SIC),  $39.33 \pm 6.46$  ( $P < 0.001$ ); (100 mg/kg SIC),  $42.67 \pm 4.18$  ( $P < 0.001$ ) and in control (D/W),  $80.33 \pm 0.95$  respectively. The percentage of protection with aspirin and SPA (400 mg/kg, 200 mg/kg, 100 mg/kg) were 80.09, 65.57, 51.04 and 46.88 respectively.

**Conclusion:** The present study indicates that SPA has significant anti-inflammatory and analgesic properties.



OP-3

**STUDIES ON CERTAIN PHARMACOLOGICAL ACTIVITIES OF THE FLOWERS AND SEEDS OF *NYCTANTHES ARBORTRISTIS* LINN.**

Das Sanjita\*, Sasmal D.\*\*

\*Department of Pharmacology, Seemanta Institute of Pharmaceutical Sciences, Jharpokharia, Orissa; \*\*Department of Pharmaceutical Sciences, B.I.T., Mesra, Ranchi, Bihar.

**Objective:** The medicinal importance of the plant *Nyctanthes arbortristis* Linn. is well documented. The work was carried out with the ethanolic extracts of the plant parts namely flowers and seeds, to study and confirm about certain Pharmacological activities like hypnotic, antispasmodic, antipyretic, anti-inflammatory activities.

**Methods:** The two dose levels of 300 mg/kg and 600 mg/kg body weight were selected after observing the LD<sub>50</sub> dose which was found to be more than 1.5 gm/kg body weight when the route of administration was intraperitoneal. After observing behavioural studies, the hypnotic activity was evaluated by observing the prolongation of sleeping time induced by pentobarbital sodium in mice. The antispasmodic activity was observed in isolated guinea pig ileum against acetylcholine. The antipyretic and anti-inflammatory activity were evaluated in male albino rats by inducing pyrexia with Brewer's yeast and inflammation with carrageenan respectively.

**Results:** It has been found out that they don't produce hypnotic activity themselves, rather potentiate the hypnosis induced by pentobarbital sodium. They antagonize the spasmogenic action of acetylcholine. They also showed antipyretic and anti-inflammatory activity which were found to be dose dependent.

**Conclusion:** The ethanolic extracts of the flowers and seeds of *Nyctanthes arbortristis* Linn. have CNS depressant activity, little antispasmodic activity and also have antipyretic and anti-inflammatory activities which were dose dependent.

OP-4

**ANTIULCER AND ANALGESIC ACTIVITY OF *TINOSPORA CORDIFOLIA* STEM EXTRACT.**

Rao CV, Ojha SK, Mehrotra S, Pushpangadan P.

Pharmacognosy and Ethno pharmacology Division, National Botanical Research Institute, Lucknow -226001.

**Objective:** *Tinospora cordifolia* Miers occurs throughout the plains of India. The present study has been planned to define the pattern of anti-ulcer and analgesic activity of the alcoholic extract of *T. cordifolia* stem (TCE).

**Methods:** Albino rats were prophylactically treated with TCE (100, 200 and 400 mg/kg, p.o.) for 5 days. On day 6 animals were subjected to Antiulcer (histamine, aspirin, cold restraint stress, ethanol and pylorus ligation) and analgesic (tail flick latency and acetic acid induced writhing) activity.

**Results:** TCE (200 and 400 mg/kg) were found to have a significant ( $P < 0.001$ ) antiulcer activity. The percentage of ulcer protection ranged from 32.42% to 81.10% respectively. TCE (400 mg/kg) increased tail flick latency ( $P < 0.01$ ) for more than 4 hrs and acetic acid-induced writhing ( $P < 0.01$ ) by 82%.

**Conclusion:** *T. cordifolia* exhibited as a potent Antiulcer and analgesic agent. However, further work needs to be done to establish the mechanism.

OP-5

**ANTIULCER ACTIVITY OF TRICYCLIC ANTIDEPRESSANT DRUGS.**

**Samanta S, Pal M, Sen T, Nag Chaudhuri AK.**

Division of Pharmacology, Department. of Pharmaceutical Technology, Jadavpur University, Kolkata 700032, West Bengal.

In present study, the Antiulcer activities of different tricyclic antidepressant were evaluated. The results indicated that amitriptyline and dothiepin significantly inhibited aspirin, alcohol and stress induced gastric ulceration in experimental animals. The studies also revealed significant antisecretory effect of the drugs in pylorus- ligated rats. The detailed results and their implications would be presented and discussed.



## ***Symposium III***

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### **Rational use of drugs**

**Date** : 27-11-2002  
**Time** : 1100-1300  
**Venue** : Hall - C

**Invited Lectures** : Dr. Usha Gupta  
Dr. YK Gupta  
Dr. OP Asthana  
Dr. S Sharma  
Dr. V Dadkar

**Chairpersons** : Prof. Ranjit Roy Choudhury  
Prof. Usha Gupta

**Sponsor** : **Delhi Society for  
Promotion of Rational  
Use of Drugs**



**IL-12**

**A SURVEY OF DRUG USE BEHAVIOUR IN COMMUNITIES FROM DIFFERENT SOCIO-ECONOMIC STATUS.**

**Gupta U.**

Dept of Pharmacology, Maulana Azad Medical College, New Delhi 110 002.

Socio-economic status is an important determinant of patients' awareness about health care strategies. Present survey has been undertaken to find out health seeking behaviour and drug use behaviour in the communities from slums, low middle level (L:ML), and middle level (ML) of socio-economic status. Trained pharmacists interviewed female/male respondents, from 226 households. Information about use of medicine was recorded in pre-designed proformas. Methodology and indicators described by WHO in manual "How to Investigate Drug Use in Communities" were used. Information on patient illness, source of consultation, possession of prescription, knowledge about dose and frequency of each drug prescribed, knowledge about use of ORS in diarrhea, knowledge about use of antibiotics and additional drugs stored in the household was recorded. Results showed that 50% of respondents from slums, 57% from LML, and 67% from ML had prescriptions. Only 19% patients from slum had the knowledge about the expiry date of the medicines. However, it was higher in both LML (69%) and ML (91%) communities. Only 50% respondents from slums, 86% from LML, and 77% from ML had the knowledge about use of ORS in diarrhea. None of the patients from slum had any knowledge about antibiotics and their use. On the other hand 30% respondents each from LML and ML knew about the use of antibiotics. The survey highlights the extent of lack of awareness about vital information on medicine used by public.

**IL-13**

**RATIONAL USE OF ANTIBIOTICS.**

**Gupta YK.**

Department of Pharmacology, All India Institute of Medical Sciences, New Delhi - 110029.

**IL-14**

**RATIONAL USE OF ANTIMALARIAL DRUGS.**  
Asthana OP.

**IL-15**

**RATIONAL USE OF ANTI HIV DRUGS.**  
Sharma S.

IL-16

## DRUG PRESCRIPTION - UTILIZATION PATTERN.

Vaishali Dadkar.

Dept. of Pharmacology, Pad. Dr.D.Y.Patil Medical College, Nerul, Navi Mumbai  
- 400706.

Prescription - Utilization pattern is no doubt a very important community based clinical issue. It deals with prescription and use of drugs in society with emphasis on resulting medical, social and economic consequences. Giving prescription does not necessarily mean proper utilisation particularly when therapy is unsupervised. Several physician related and patient related factors are responsible for wrongs in prescribing as well as utilisation. We need to develop strategies at modifying both. Studies involving estimates of drug use and prescribing patterns help in measuring and analysing trends in drug use, drug related ADRs and other public health issues. Drug Utilization Data involves cost as well as volume. Cost data helps in deciding economic impact of drug use whereas volume data represents amount of drug exposure in population. Another important aspect which needs to be looked into is appropriateness of drug use. Data on drug use needs to be related to reasons for drug use. Valuable data generated from various sources for this purpose, can help national scientific forums to take relevant decisions regarding therapeutic strategies and the regulatory authorities to take necessary actions. Today, lot of emphasis is put on drug safety and efficacy. We are also aware of financial implications of drug use and we are in computer era, with advanced technology at our disposal. Can these three elements ensure promising future for drug candidates?





# ***Symposium IV***

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## **Chemical warfare - Current awareness II**

**Date** : 27-11-2002

**Time** : 1400 -1545

**Venue** : Hall -A

**Invited Lectures** : Dr. B K Bhattacharya  
Com. J Romano  
Dr. S I Baskin  
Dr. R Bhattacharya  
Dr. J R Dave  
Dr. V K Rastogi

**Chairpersons** : Dr. B J Lukey  
Dr. R Vijayaraghavan



**IL-17****RETROSPECTIVE DETECTION OF NERVE AGENTS FROM BIOMEDICAL SAMPLES.****Bhattacharya BK, Suryanarayana MVS, Gupta AK, Kaveeshwar U, Waghmare CK.**

Defence Research and Development Establishment, Jhansi Road, Gwalior - 474002.

Detection of exposure of toxic nerve agents in biomedical samples is required to prove unequivocally the chemical nature of exposed toxicant as well as quantification of exposed agent in blood is useful for medical intervention. The nerve agents e.g., soman, sarin, tabun and VX are chemically organophosphorus esters and mimic pesticides in action. These are highly reactive and labile in biological fluids making these agents detectable for a limited period of time in their 'native' form. Hence it was attempted to detect soman and sarin from their protein bound forms. It was reported that a soman depot exists in rat diaphragm tissue. This depot was used for forensic detection of soman. Soman regenerated from its binding sites by the addition Na F was detected by the inhibition of externally added AChE. Inhibition of AChE was dependent on administered dose and a protein of diaphragm cytosol binds soman. Diaphragm specimen stored in liquid nitrogen for a month retained bound soman. A platelet soman depot was also identified and fluoride regenerated soman was quantified by AChE inhibition method. Soman can be detected till 24 hrs. post sub lethal dose treatment and platelets obtained from 4 ml blood yielded  $10^{-9}$  -  $10^{-12}$  M soman. Soman and sarin were also regenerated from blood plasma by Na F and quantified by  $IC_{50}$  determinations of AChE. Using this method 10  $\mu$ l plasma yields  $10^{-12}$  -  $10^{-14}$  moles soman and about 10 p moles sarin from 1 ml plasma. Soman or sarin regenerated by above methods can also be confirmed using SIM GC/MS by monitoring ions 99 and 126 for soman 99 and 125 for sarin. Serum albumin was found to bind these agents from where it can be regenerated. Soman or sarin leaves methyl phosphonic acid (MPA) bound to AChE as a process of aging. MPA was detected from erythrocyte membrane AChE after enzymatic digestion, by GC/MS after silylating it. MPA was detectable till 6 days post treatment of sublethal doses of these agents. It is concluded that both soman and sarin can be detected from victim's blood sample from their protein bound sites by converting into native agents by fluoride and subsequently can be analyzed by SIM GC/MS and quantitated by  $IC_{50}$  values for AChE. MPA detection is useful after aging.

**IL-18****CHEMICAL WARFARE AND CHEMICAL TERRORISM: PSYCHOLOGICAL AND PERFORMANCE OUTCOMES.****James A Romano Jr, James M King\*.**

US Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Maryland; \*Chemical and Biological Defense Information Analysis Center, Aberdeen Proving Ground, Maryland, USA.

The battlefields of the late 20th century have come to include a significant new health threat; the use of modern chemical weapons. The potential to cause large numbers of serious casualties among deployed and deploying military forces and among civilian populations provides a stark reminder to medical planners of the limits of military and civilian medicine. However, medical countermeasures to these chemical warfare agents (CWAs) have been, and continue to be, developed. These CWAs, their countermeasures, protective gear and decontamination practices, and their health care implications are described in this presentation. We suggest likely psychological, physiological, and neurological effects that will be encountered should these agents be employed against US forces on the integrated battlefield or against homeland facilities. Also suggested are countermeasures that US forces and medical teams may use to protect or treat our forces or citizens undergoing such CW A attacks. Knowledge of the behavioral effects of the CWAs and of their medical countermeasures is imperative to ensure that military and civilian medical and mental health organizations can deal with possible incidents involving weapons of mass destruction.

IL-19

## THE PHARMACOLOGY AND TOXICOLOGY OF CYANIDE AND ITS THERAPIES.

**Baskin SI, Kurche JS.**

United States Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, MD 21010-5400, USA.

Cyanide is a well-recognized poison and has been utilized as a chemical warfare agent. Cyanide is rapidly acting, inexpensive to produce, and has been reportedly used recently by terrorist organizations. Cyanide is used widely in industry but can also be found in nature. Numerous plants produce cyanogenic glycosides as byproducts of amino acid metabolism and many other organisms including humans maintain low levels of endogenous cyanide. Cyanide has been proposed to act principally by inhibiting cytochrome oxidase, thereby effectively blocking cellular aerobic respiration. However, cyanide has a high affinity for a number of cellular targets including other di- and trivalent metalloproteins and its toxicity may not be limited to its effect on cytochrome oxidase. Among pathways of cyanide metabolism there are two of particular interest to the toxicologist. Detoxification of cyanide occurs primarily through formation of thiocyanate, which is significantly less toxic than cyanide. The other pathway involves formation of 2-iminothiazolidine 4-carboxylic acid (2-ITCA), through a reaction between cyanide and cystine. 2-ITCA has been implicated to have its own intrinsic toxicity in neurological tissues. Formation of thiocyanate occurs through the transfer of a sulfane sulfur atom from a suitable substrate to cyanide by the mitochondrial enzyme rhodanese. Administration of sulfane sulfur donors -including sodium thiosulfate - to victims of cyanide poisoning has been shown to ameliorate toxicity. Antagonism of cyanide pathogenesis also includes administration of methemoglobin-forming drugs. Oxidized hemoproteins have a high affinity for cyanide and in some cases may bind cyanide more effectively than cytochrome oxidase. In all cases oxidized hemoproteins make effective scavengers for ambient cyanide. Improved sulfur donors and methemoglobin-formers are currently being developed to combat cyanide intoxication.

IL-20

**$\alpha$ -KETOGLUTARATE: A PROMISING ANTIDOTE TO CYANIDE POISONING.**  
**Bhattacharya R.**

Division of Pharmacology and Toxicology, Defence Research and Development Establishment, Jhansi Road, Gwalior-474002.

Cyanide is considered as a potent suicidal, homicidal, genocidal and chemical warfare agent. Occupational exposure and ingestion of cyanide-containing foods have also been associated with cyanide toxicity. Concomitant inhalation of hydrogen cyanide (HCN) and carbon monoxide (CO) are largely responsible for the toxicity of fire smoke. It is a cellular poison that can bind to many enzymes, having metallic component. The most notable enzyme to be inhibited by cyanide is cytochrome oxidase, resulting in histotoxic anoxia. Cyanide produces a rapid onset of toxicity which warrants immediate treatment to prevent morbidity and mortality. The currently approved treatment for cyanide poisoning is generally methemoglobin formers like amyl nitrite and/or sodium nitrite (SN) given in combination with sulfur-donors like sodium thiosulfate (STS). Additionally, many more therapeutic regimens have been proposed but all of them have some inherent problem limiting their use. Many carbonyl compounds have been shown to antagonize cyanide toxicity by rapid cyanohydrin formation.  $\alpha$ -ketoglutarate ( $\alpha$ -KG) is one such compound which has recently shown promising efficacy against experimental cyanide poisoning. The protective efficacy was not dictated by the route of administration of  $\alpha$ -KG or route of cyanide exposure. In order to develop  $\alpha$ -KG as an oral antidote to cyanide poisoning, various pharmacological and toxicological studies were carried out. Pre-treatment (10-60 min), simultaneous treatment (0 min) or post-treatment (up to 5 min) of  $\alpha$ -KG (2.0 g/kg) alone or in combination with STS were found to protect against various lethal doses of cyanide in rodents.  $\alpha$ -KG also showed dose (0.125-2.0 g/kg) dependent efficacy and adjunction of SN was found to augment the protection by >25 fold. Treatment of  $\alpha$ -KG was found to protect against many physiological and biochemical changes induced by cyanide.  $\alpha$ -KG is not considered harmful for human consumption because it is a biological entity and is sold as a nutritional supplement. Moreover, our studies did not reveal any acute toxicity of  $\alpha$ -KG at the recommended doses. This suggests that in circumstances where SN is contraindicated, oral treatment of  $\alpha$ -KG with STS can be more suitable alternative and in instances where SN and STS are indicated, an enhanced protection can be obtained with adjunction of  $\alpha$ -KG. However, clinical safety trials of  $\alpha$ -KG can only determine its prospects as cyanide antidote.

IL-21

**SUBACUTE LOW DOSE NERVE AGENT EXPOSURE CAUSES APOPTOSIS IN LEUKOCYTES.**

**Dave JR, Moffett JR, Anderson SM, Sipos ML, Moran AV, Tortella FC.**  
Departments: Div. Of Neuroscience, Walter Reed Army Inst. Res., Silver Spring, MD, USA 20910 and U.S. Army Res. Inst. of Chern. Defense, Drug Assessment Div./Advance Assessment Branch, Aberdeen Proving Ground, MD, USA 21010.

Exposure to low dose chemical warfare nerve agents (CWNA) is an ongoing threat to military personnel deployed overseas. Many pathological consequences of low dose CWNA exposure, including leukocyte apoptosis, have not been well characterized. The objective of present study was to determine levels of DNA fragmentation in blood leukocytes from guinea pigs by single cell gel electrophoresis (Comet Assay) after exposure to the CWNA, soman, at doses ranging from 0.1 LD<sub>50</sub> to 0.4 LD<sub>50</sub>, once per day for either 5 or 10 days. Post-exposure recovery periods ranged from 0 days to 17 days. Leukocytes were imaged from each animal, and then analyzed by computer (Comet Analysis System). Data obtained for exposure to soman demonstrated significant increases in DNA fragmentation in circulating leukocytes in CWNA treated guinea pigs as compared with saline injected control animals at all doses and time points examined. Notably, significantly increased DNA fragmentation was observed in leukocytes 17 days after cessation of soman exposure, perhaps indicating long-term damage to bone marrow stem cells. The mechanism of action whereby soman elicits apoptosis in blood leukocytes is not known, but it is clear that pathological responses to subacute, low dose CWNA exposure occur in the immune system. Leukocyte DNA fragmentation assays may provide a sensitive biomarker for low dose CWNA exposure.

IL-22

**BACTERIAL ENZYMES - POTENTIAL APPLICATIONS FOR PERSONNEL/  
CASUALTY DECONTAMINATION AGAINST G, V, AND HD CHEMICAL  
AGENTS.**

Tu-chen Cheng, Steve P Harvey, Joseph J DeFrank, James L Way and **Vipin K Rastogi.**

Biotechnology Team, US Army - ECBC, AMSSB-RRT-BT, APG, MD. 21010, USA.

Two classes of enzyme systems - A-esterases [human paraoxonases/arylesterase (PON), *Pseudomonas diminuta* and *Flavobacterium sp.* organophosphorus hydrolase (OPH), *Alteromonas* organophosphorus anhydrolase A (OPAA)]; and B-esterases [acetyl-/butyl-cholinesterases (AChE/BuChE), and carboxylesterases] - are known to interact with organophosphorus-based (OPs) chemical warfare agents (CWA) and agricultural insecticides/pesticides. In general, OPs inactivate B-esterases, i.e. AChE, by covalently reacting with serine in their active center, thus accounting for the toxicity to mammalian systems. The A-esterases are hydrolytic in nature and therefore detoxify a variety of OPs at varying rates. While OPH from bacterial systems mainly catalyzes detoxification of agricultural pesticides and is the best-characterized enzyme for V - type CW A, the other bacterial enzyme, OPAA exhibits higher rates of detoxification against GD. Both bacterial enzymes, OPH and OP AA, significantly catalyze hydrolysis of GF and GB. Recently, a bacterial enzyme was shown to catalytically hydrolyze sulfur mustard, HD (2,2'-dichlorodiethyl sulfide). This HD-degrading enzyme has been identified as hydrolytic dehalogenase.

We have been pursuing the development of enzymes-based broad-spectrum decontaminant by using the CWA-degrading enzymes in different materials for a variety of applications. In recent years, the construction of recombinant clones with high production of OPH and OPAA has been achieved. A high-expression clone of OPAA yields up to 0.6-1 gram of enzyme per liter of culture. In addition to the application of OPH and OPAA enzymes in large-area and building decontamination of CWA, other applications of these bacterial enzymes include detection and skin surface decontamination against CWA. The potential use of bacterial enzymes, OPH and OPAA, as modified antidotes against OP compounds has been also investigated. Both enzymes, OPH and OPAA, when introduced in conjunction with 2-PAM and/or atropine within liposomes afforded far superior protection to mice against toxic OP compounds (paraoxon and diisopropylfluorophosphate).





# ***Symposium V***

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## **Ocular pharmacology**

**Date** : 28-11-2002  
**Time** : 0900 -1045  
**Venue** : Hall - C

**Invited Lectures** : Dr. N R Biswas  
Dr. N Nayak  
Dr. S K Gupta  
Dr. S Joshi  
Dr. S Srivastava  
Dr. D Trivedi

**Chairpersons** : Prof. S K Gupta  
Prof. S Ghose

**Sponsor** : **Backo Pharmaceutical  
India Ltd.**



IL-23

### RECENT ADVANCES IN OCULAR THERAPEUTICS.

**Biswas NR.**

Additional Professor of Ocular Pharmacology, Dr. Rajendra Prasad Centre for Ophthalmic Sciences, AIIMS, New Delhi - 110029.

**Objective:** Corneal infection is one of the leading causes of blindness in patients of all age groups all over the world particularly in the developing countries. The objective of the lecture is to highlight the recent development in ocular therapeutics particularly combatting corneal infections and updated mode of drug delivery system in ophthalmology.

**Methods:** Bioavailability of newer fluoroquinolones like ofloxacin, pefloxacin, lomefloxacin and Sparfloxacin measured by HPLC and drug delivery through nano-particles and liposome in the eye will be discussed.

**Results and Conclusions:** It was found that ofloxacin aqueous concentration is better than lomefloxacin. Liposomated and Nanoparticulated drug delivery proved sustained release property of the system.

IL-24

### LABORATORY DIAGNOSIS OF INFECTIOUS KERATITIS.

**Nayak N.**

Associate Professor of Ocular Microbiology, Dr. Rajendra Prasad Centre for Ophthalmic Sciences, AIIMS, New Delhi - 110 029.

Corneal blindness is predominantly caused by infections. Breach in corneal epithelium, prior therapy with topical steroids, antibiotics, contact lens wear, trauma and sometimes ocular surgery are some of the risk factors leading to the development of corneal ulcers. Proper microbiological investigations are, therefore, necessary to initiate appropriate therapy and to know the etiological agent. In India, majority of infectious keratitis are of either bacterial or fungal origin. This is followed by infections due to Acanthamoeba and viruses. Nearly, 30-35% of all cases of culture positive cases are fungal in origin. Laboratory diagnosis basically depends upon proper collection and transport of clinical specimens (corneal scrapings). Specimens are best collected with the aid of slit lamp, after topical anaesthesia, with the help of sterile Kimura spatula. Several culture media are inoculated to allow for identification of wide range of microorganisms. The main drawback of the culture technique is that it requires a long incubation time ranging from 48 hours to 14 days depending on the type of organisms. Although, the specificity of the culture makes them indispensable for the confirmation of the diagnosis, yet culture techniques are not rapid. However, direct examination of the specimen is quick and is of immense help to the ophthalmologists, especially when techniques such as Gram stain, Giemsa stain, potassium hydroxide mount and fluorescent stains are used. Thus, with the rapid methods available for diagnosis, treatment of patients can be modified on the basis of their results as well as on the results of antibiotic sensitivity testing.

**IL-25****RECENT ADVANCES IN THE MEDICAL THERAPY OF CATARACT.****Gupta SK.**

Department of Pharmacology, All India Institute of Medical Sciences, New Delhi-110029, India.

Cataract is the leading cause of blindness worldwide. Though surgical extirpation of the cataractous lens is the standard treatment at present times, it has its own limitations. The problem of cataract remains consistent in the population despite surgical intervention because of continued aging and the consequent addition of new cases. Development of alternative means of attenuating cataract formation is, therefore, a desirable goal. Active research is going on all over the world since last three decades to identify an effective agent that can delay the onset as well as progression of cataract. Cataract is multi factorial in origin, but oxidative stress has been implicated as one of the major risk factor for the development of maturity onset cataract. Recently there has been much interest on the beneficial effects of nutrition, particularly those with antioxidant potential in prevention of cataract. Experimental studies indicate that vitamins A, C and E as well as carotenoids especially lycopene may have a protective role. Compounds receiving attention as potential anticataract agents include aldose reductase inhibitors, physiological antioxidants such as pyruvate, pantothine and non steroidal anti-inflammatory agents such as ibuprofen, naproxen, sulindac, etc. There is an upsurge of interest in the evaluation of medicinal plants for their potential anticataract activity. Since ancient times medicinal plant based formulations are being used to treat various ophthalmic disorders in the Ayurvedic system of medicine. The need of the hour is to scientifically validate and document their protective effect in disease prevention. Genetic approach to prevention of lens opacities is another area which is gaining momentum amongst lens researchers. The strategies currently being employed are the 'candidate gene' approach and 'sibling pair design'. A few of the above mentioned appear promising for the medical therapy of cataract prevention.

**IL-26****GALACTOSEMIC CHANGES IN HUMAN LENS EPITHELIAL CELLS AND MODULATION BY PYRUVATE.****Joshi S, Mohanty I, Trivedi D, Srivastava S, Tandon R, Gupta SK.**

Department of Pharmacology, All India Institute of Medical Sciences, New Delhi - 110029.

Cataract being a multifactorial disease, both osmotic as well as oxidative stress have been implicated in its etiology. Pyruvate - a physiological antioxidant has been demonstrated to prevent experimental cataracts by virtue of its action on various crucial sites in the process of cataractogenesis. These studies are primarily confined to the whole lens in experimental animals and the role of polyol pathway in the formation of diabetic cataract in humans is not clear. Since the anterior lens epithelium is the primary site exposed to any external stress and is responsible for the maintenance of lens homeostasis, in the present study, effect of pyruvate has been evaluated on galactose induced morphological and biochemical changes in human lens epithelial (HLE) cells in culture. Anterior capsule specimens obtained from infants were cultured in Dulbecco's modified Eagles Medium (DMEM) supplemented with 20% fetal calf serum. On confluency the cells were subcultured in DMEM containing either 30 mM D-galactose or 30 mM D-galactose + 5mM pyruvate for 72 h. The cells were observed under the phase contrast microscope for any morphological changes and then harvested for the estimation of reduced glutathione, protein, polyol, aldose reductase, Na<sup>+</sup>/K<sup>+</sup> ATPase, glutathione peroxidase, catalase, superoxide dismutase and glutathione-S-transferase. Our results show a significant increase in AR activity accompanied by the appearance of vacuoles and polyol accumulation in presence of galactose. Na<sup>+</sup>/K<sup>+</sup> ATPase and antioxidant parameters were found to be significantly altered. Inclusion of pyruvate prevented most of these biochemical changes significantly. Initial osmotic stress followed by membrane damage and weakened antioxidant defense mechanism action in concert may be responsible for early changes in human diabetic cataract. Pyruvate offers significant protection against these changes in HLE cells.

**IL-27****OCIMUM SANCTUM - A POTENTIAL ANTICATARACT AGENT.**

Srivastava S, Trivedi D, Joshi S, Halder N, Gupta SK.

Department of Pharmacology, All India Institute of Medical Sciences, New Delhi - 110029.

Oxidative stress is one of the major risk factors for age related cataract development. Several synthetic antioxidants have been found effective in preventing cataract development. The prophylactic treatment for cataract prevention would continue for a substantial time period. The limitation of the synthetic antioxidants is the associated toxicity on long term usage. Therefore, recently the focus has shifted towards the exploration of natural antioxidants of plant origin for their potential anticataract activity. In the present study *Ocimum sanctum* (Os) has been evaluated against galactose induced experimental cataract development. Wistar rats (60 - 80 g) were fed 30 % galactose in diet to induce cataract. They were equally divided into control and various test groups. The rats in the test groups were either instilled with 0.3 % or 0.1 % Os eye drops (1 drop/four times a day), or alternatively fed Os extract orally (50 mg/kg b.w./day). The incidence of cataract was observed at regular intervals. 100 % of the eyes developed cataract in the untreated group. In contrast only 25 % of the eyes in the rats treated with 0.3 % Os eye drops and those fed orally developed cataract. While in the rats treated with 0.1 % eye drops 42 % eyes developed cataract. *Ocimum sanctum* possesses anticataract activity and should be further exploited.

**IL-28****LYCOPENE ATTENUATES EXPERIMENTAL CATARACT DEVELOPMENT.**

Trivedi D, Srivastava S, Joshi S, Halder N, Gupta SK.

Department of Pharmacology, All India Institute of Medical Sciences, New Delhi - 110029.

Alternative strategies for the prevention of cataract are important to reduce both its incidence and prevalence. Recently there has been much interest in the impact of nutrition on the development of lens opacity. Among carotenoids, lycopene, a constituent of tomato, is one of the most potent singlet oxygen scavenger. Its anti cataract potential was evaluated in selenite and galactose induced cataract in rats, in vitro and in vivo. For in vitro studies, enucleated lenses were organ cultured with/without selenite (100  $\mu$ M) and in presence/absence of 10  $\mu$ M lycopene. Lenses were analysed for reduced glutathione, lipid peroxidation product and antioxidant enzymes. In vivo selenite cataract was induced in 9 day old rat pups by injecting 25  $\mu$ M sodium selenite s.c. A subgroup of the rats was injected 100  $\mu$ g/kg b.w. lycopene i.p. 30 % galactose was fed in the diet of rats to induce cataract. 200  $\mu$ g/kg/day lycopene was fed orally to a subgroup of these rats and cataract development was observed. Lycopene inhibited glutathione depletion and lipid peroxidation in the lenses. It restored the antioxidant enzyme levels. Administration of lycopene reduced selenite cataract incidence by 70 % as compared to untreated group. The incidence of galactose cataract was 35 % in the treated group and 100 % in the untreated group.



# ***Symposium VI***

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## **Toxins and biological warfare**

**Date** : 28-11-2002  
**Time** : 1100 -1300  
**Venue** : Hall - B

**Invited Lectures** : Dr. Nancy Khardori  
Brig. JK Bansal  
Dr. HV Batra  
Dr. SB Deshpande  
Dr. PVL Rao

**Oral Presentation** : OP6 - OP7

**Chairpersons** : Prof. Nancy Khardori  
Brig. JK Bansal





IL-29

**ANTHRAX: BACTERIOLOGY, CLINICAL PRESENTATIONS AND MANAGEMENT.**

**Nancy Khardori.**

Division of Infectious Diseases, Department of Internal Medicine, Southern Illinois University School of Medicine, Springfield, Illinois, USA.

IL-30

**AN OVERVIEW OF BIOLOGICAL WEAPONS.**

**Brig. Bansal JK.**

Institute of Nuclear Medicine and Allied Sciences, Timarpur, Delhi - 110001

World over it is widely agreed that preventing the spread of weapons of mass destruction is of central importance in building a lasting peace. While public concern has focussed on the dangers associated with proliferation of nuclear and chemical weapons, there has been little attention given to biological weapons (BW) of mass destruction. However, in general, it is simpler and cheaper to produce microbial B-weapons than other weapons. Green (1990) has argued that conventional forces are 2000 times, nuclear 800 times, and chemical 600 times more expensive than a comparable biological capability.

Although the cost of building, equipping, and staffing a recombinant DNA laboratory to develop and produce BW systems is not exactly known, Boyer et al. made in 1981 an estimation of the cost of establishing an international centre for genetic engineering and biotechnology. If these estimated costs are accurate, it seems possible for a nation to develop a respectable research and development capability and run it for five years for not much more than \$50 million. The estimated costs of developing nuclear weapons are in the range of billions of dollars, so, after comparing costs, a national decision maker may find the BW route to be the most attractive. With a concentrated effort, utilising both classical and recombinant DNA techniques, the potential power thus available could challenge the nuclear arsenals possessed by the superpowers. As the bio-techniques improve, they offer attractive possibilities to potential biological and toxin weapon manufacturers especially as a result of scale-up and automation. The successive steps required to develop BW can be summarised as: (1) cultivation of the B-agent, (2) collection, (3) storage, (4) dispersion and propagation. With access to gene technology, a further step may precede the cultivation: the modification of physical, biological and immunological characteristics of organisms to enhance their virulence, or even the introduction of toxin genes into non-toxic organisms. Knowledge acquired from civilian research and progress in many fields of microbiological technology can be transferred and misused for military purposes. Therefore, it becomes important to be aware about the different biological agents, likely to be used for biological warfare. It is also imperative to understand the potential agents and toxins which can be used as biological weapon. Their mode of transmission, incubation period and characteristic clinical features are to be clearly defined. Accordingly facilities for detection, diagnosis, production of prophylactic vaccine and effective treatment is to be developed and established for proper biodefence. Present talk will focus on all above aspects of Biological weapons.

**BIOLOGY OF YERSINIA PESTIS: A POTENTIAL BW AGENT.**

Batra HV.

Microbiology Division, Defence Research and Development Establishment,  
Gwalior - 474002.

"Plague"- the Black Death, has been successful enough to wipe out million of people from the face of the earth during the pre-antibiotic era. The causative agent named earlier as *Pasturella pestis* is known now as *Yersinia pestis*. Plague is a zoonotic disease, which is transmitted among humans by a flea vector. The genus *Yersinia* is a member of family enterobacteriaceae that consists of eleven species, 3 of which are human pathogens- *Y. pestis*, *Y. pseudotuberculosis*, and *Y. enterocolitica*. A genome size of ~4380 ± 135 kb with a G+C content of 46 - 47 percent has been estimated for *Y. pestis*.

*Y. pestis* is a non-motile, Gram negative coccobacillus, that shows bipolar staining with Wright, Giemsa or Wayson stain. *Y. pestis* is a lactose nonfermenter, urease and indole negative. It grows optimal at 28°C on blood agar or MacConkey agar, typically requiring 48 hrs for observable growth, but colonies are initially very small and may be overlooked. *Y. pestis* has a number of virulence factors that enable it to survive in humans by facilitating use of host nutrients, causing damage to host cells, and subverting phagocytosis and other host defence mechanisms. The virulence of *Y. pestis* is multifactorial, with genes responsible being present on the chromosome as well as on the three plasmids; 110 kb, 75 kb and 9.5 kb plasmids. The majority of the *Y. pestis* strains regardless of biotype or origin contain these three plasmids which have their own virulence determinants. The chromosomal virulence factors include fimbriae, siderophores, iron-regulated proteins (HMWP 1 and HMWP2), serum resistance protein, pH 6 antigen and catalase activity. The majority of virulence factors including the 12 *Yops*, 29 *Yop* secretion proteins (*Ysc*) and few specific *Yop* chaperone (*Syc*) are contributed by the 70 kb middle plasmid in addition to *f1* gene of 110 kb megaplasmid and *pia* gene of 9.5 kb small plasmid. To ascertain the virulence markers contributed by 70 kb LCR plasmid in the recently recovered Indian isolates of *Y. pestis*, 10 important *yops* of which 6 effectors (*YopE*, *YopH*, *YopJ*, *YopM*, *YopO*, *YopT*), 3 translocator (*YopB*, *YopD* and *YopK*) and 1 regulator (*IcrV*) were targeted for identification.

PCR was attempted for detection of these genes. For this, primers were designed, PCR conditions were standardized and test performed on all the 26 *Y. pestis* isolates. Sixteen out of 18 *Y. pestis* isolates from the outbreak regions exhibited PCR amplification for all the 10 *yop* genes tested and the products obtained were of expected sizes. Isolate no. 111 was negative for *yopE* gene and isolate no. 115 for *yopH* gene. Isolates recovered from *Tatera indica* rodents trapped during plague surveillance work from the region of Deccan plateau had lots of variations in the *yop* genes. The *yopD* gene appeared absent in all of these isolates, while *yopM* could be detected only in 1 isolate (IOR). Another isolate (9R) also had negative results in PCR for *yopB*. To ascertain the virulence markers contributed by the 102 kb chromosomal region in these recently recovered Indian isolates, 10 important genes of which 5 of pigmentation segment (*hmsH*, *hmsF*, *hmsR*, *hmsS* and *hmsT*), 5 of iron acquisition segment (*irp1*, *irp2*, *ybtA*, *yhtE* and *yhtT*) were targeted for identification. Identity of *pgm* locus was initially attempted by standardizing the PCR for all the mentioned genes using detection primers and evaluated on all the 26 *Y. pestis* isolates. Twenty five out of 26 *Y. pestis* isolates exhibited PCR amplification at expected size for almost all the genes tested except isolate number 111, 112 and 115 that were negative for *irp2* gene. In order to reconfirm the PCR results of different *yop* genes and *pgm* locus genes another experiment was planned, where the truncated PCR products of 3 *yop* genes, *yopM* (effector), *yopB* (translocator) *IcrV* (regulator) and *pgm* locus gene *hmsT* (hemin storage) were cloned to express recombinant proteins using pQE series of vector. The monoclonal antibodies generated against these 4 recombinant proteins (*Yops B*, *M*, *V* and *hms T*) were tested on Indian *Y. pestis* isolates. Reactions to recombinant proteins were observed at the expected sizes at 42 kDa for *YopM*, 41 kDa for *YopB*, 37 kDa for *LcrV* and 44 kDa for *hms T* of Standard *Y. pestis* AI 122 and isolates. The ELISA results with mononclonal antibodies were found correlating to the PCR results, thus reconfirming that the Indian *Y. pestis* strains are heterogenic in the *yop* genes of 70 kb plasmid but are homogenic for *pgm* locus genes.

**IL-32****BREVETOXINS ON SPINAL SYNAPTIC TRANSMISSION.****Deshpande SB.**

Department of Physiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005.

The *Ptychodiscus brevis* toxins (PbTx) are cyclic polyether compounds derived from the dinoflagellate algae, also known as brevetoxins. The respiratory arrest is a consistent feature of PbTx toxicity and was lethal. Artificial ventilation revived the respiratory depressive actions of PbTx but not the vasodepressive actions mediated by vagus (Koley et al., Eur.J. Pharmacol., 293: 483, 1995). However, the cause of toxicity leading to respiratory arrest is not known. Therefore, the experiments were conducted on isolated spinal cords from the neonatal rats to elicit the reflex transmission at 1a- $\alpha$  mononeuron synapse which is the final pathway. Stimulation of the dorsal root in an isolated hemisectioned spinal cord evoked monosynaptic (MSR) and polysynaptic reflexes (PSR) in the corresponding ventral root. The results indicate that the analogs PbTx possess structure activity relationship for depressing the reflexes. The analogs having an octyl and pentyl groups exhibited a greater potency. Further, the PbTx depressed the synaptic transmission involving NMDA and non-NMDA receptors. PSR was more sensitive to the actions of toxin than MSR. The results further demonstrate that NMDA/PbTx enhanced the GABA-induced depression and the PbTx-induced depression was blocked by bicuculline (GABA<sub>A</sub> antagonist). Strychnine, glycine antagonist, blocked only at the higher concentrations of the toxin. Further, PbTx also enhanced the frequency-dependent depression also. The brevetoxins thus depress the synaptic transmission via the NMDA receptor-dependent inhibitory interneuronal transmissions in the spinal cord (supported from the Grants from the DRDE, Gwalior).

**IL-33****CYANOBACTERIAL TOXINS- EFFECTS AND CONTROL MEASURES.****Lakshmana Rao PV.**

Division of Pharmacology and Toxicology, Defence Research and Development Establishment, Gwalior - 474002.

The growth of toxin-producing cyanobacteria in water bodies can decrease water quality and increase the risk of toxicity to animal and human health. The toxins are classified, according to the target of their toxic action, as hepatotoxins, neurotoxins and dermatotoxins. In fresh and brackish waters the most frequently found hepatotoxins are cyclic peptides, microcystins and nodularin. In addition an alkaloid cylindrospermopsin is common in tropical waters. Three types of neurotoxins are known: anatoxin-a, anatoxin-a(s) and paralytic shellfish poisons (PSPs). Cyanotoxins are responsible for or implicated in gastroenteritis, dermal contact irritation and primary liver cancer in humans. Several instances of human illness and recent death of 60 haemodialysis patients in Caruaru, Brazil, have been linked to microcystins in water. Microcystins are chemically very stable and are reported to withstand many hours of boiling and may persist for many years when stored at room temperatures. In response to growing concern about the lethal and non-lethal acute and chronic effects of microcystins, WHO has recently set a provisional guideline value for microcystin-LR of 1  $\mu$ g/litre in drinking water. The talk will address the issues concerning cyanotoxins and human health and also possible control measures.

OP - 6

### CYANOBACTERIAL TOXIN MICROCYSTIN-LR REMOVAL FROM POTABLE WATERS BY ACTIVE CARBON.

**Bhaskar ASB**, Jayaraj R, Dangj RS<sup>1</sup>, Prasad GK<sup>2</sup>, Beer Singh<sup>2</sup>, Rao PVL. Division of Pharmacology and Toxicology, <sup>1</sup>Process Technology Development Division, <sup>2</sup>Protective Devices Division, Defence Research and Development Establishment, Gwalior - 474002.

**Objective:** Cyanobacteria (blue-green algae) produce several types of toxins that can be harmful to humans. Most frequently encountered in freshwater are microcystins, a group of more than 60 cyclic heptapeptides. Microcystins released from cyanobacteria into water have been responsible for the death of humans and domestic animals. Microcystins are chemically very stable and many toxin removal processes have limited efficacy. Microcystin removal by active carbon has been one of the best methods available. The objective of this study was to evaluate three grades of active carbon for their efficacy of microcystin removal from water, confirm toxin quantitation by HPLC and mouse bioassay

**Methods:** 100 mg/25ml of 40, 60, and 80 CTC grade active carbon has been used. *Microcystis aeruginosa* PCC 7806 toxin extract at 4 mg/ml strength was used for spiking water sample. Sampling was done at the end of 0.5, 1, 2, 3, 6, 12, 24 and 48 h from different flasks each having 25 ml toxin in triple distilled water. Toxin extraction was done by solid phase extraction using RP-C<sub>18</sub> cartridges. Swiss albino female mice weighing 22±2 g were used for bioassay in the study.

**Results:** Mouse bioassay at different time points revealed that out of the 3 carbons, 80 CTC carbon gave maximum protection by removing microcystin in about 2 h, followed by 60 CTC carbon giving protection at 24 h and 40 CTC carbon at 48 h time. Quantitation by HPLC using standard MCLR as reference corroborated with the mouse bioassay results, showing decrease in the quantity of MCLR as time progressed for different grades of carbon.

**Conclusion:** Both mouse bioassay and HPLC quantitation confirms the removal of MCLR from water. Different grades of active carbon showed different levels of MCLR removal efficacy. 80 CTC active carbon removes MCLR from water in less than 2h time, which correlates with mouse bioassay.

OP - 7

**BIOLOGICAL EVALUATION OF PB-1 AND ITS ANALOGUES AGAINST FRESH WATER FISH *RASBORA DENICONIUS*.**

Gupta AK<sup>1</sup>, Dubey DK<sup>2</sup>, Parashar BD<sup>3</sup>, Gupta, GP<sup>3</sup> Kaushik MP<sup>1</sup>.

<sup>1</sup>Process Technology Development Division, <sup>2</sup>Vertex Laboratory, <sup>3</sup>Entomology Division, Defence Research and Development Establishment, Gwalior -474002.

A dense growth of blooms of dinoflagellates can occur under certain favourable conditions causing a phenomenon known as "red tide", that appears when pigment algae proliferate and form blooms or explosive growth. A catastrophic episode of red tide in Gulf of Mexico in 1946-1947 littered the beaches along the coast of Florida with tons of dead fish causing several millions of dollars loss in tourism and other recreation based business. Farmed fish are especially vulnerable because the caged animals cannot avoid the blooms. These bloom can wipe out entire fish form within hours. Thus algal blooms pose a large threat on fish farm and their insurance providers. More than 80 episodes of red tides have been recorded. Subsequently responsible organism was recognized as a new species of dinoflagellate and named *Gymnodinium breve*. About two decades ago, one of the phosphorus containing fish toxin was isolated and its structure was confirmed by X-ray diffraction. Its toxicity was reported 0.9 ppm against *Labestes reticulatus*. After a year, a second type of phosphorus containing fish toxin was also isolated from dinoflagellates. Its structure was established as O,O-Diphenyl N-cyclooctyl phosphoramidate (PB-1). The toxicity of PB-1 as reported against *Labestes reticulatus* and its LC<sub>100</sub> (1 hr) was 1 ppm. Because of the unexpected presence of simple phosphorus containing compound associated high degree of toxicity was not straight forward. Moreover a large number of phosphoramidates are known but very little information is available against fresh water fish toxicity. Additionally to it is not known how far this toxin PB-1 poses severe health hazard. It was of interest to synthesise several analogues of PB-1 by doing structural modification in its basic structure. After characterisation all these compounds were evaluated against fresh water fish (*Rasbora deniconius*). Out of them fourteen compounds including parent toxin showed very high degree of toxicity. The structure activity correlation data indicates that there is no significant change by increasing or decreasing the ring size alicyclic ring in parent toxin. However, cyclo octyl derivatives are generally very effective. The results of this study indicates that toxin PB-1 and its analogues are very effective fish toxin, as it provides easy method for capturing and collection of eatable fish. Provided they do not cause any adverse effect on biota present in fresh water ecosystem. However, this needs further studies.



# ***Symposium VII***

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## **Oxidative stress in health and disease**

- Date** : 28-11-2002  
**Time** : 1400 -1545  
**Venue** : Hall - C
- Invited Lectures** : Prof. K D Gill  
Dr. Neeta Singh  
Prof. Y K Gupta  
Prof. S K Gupta  
Dr. Arunabha Ray  
Dr. K P Mohanakumar
- Oral Presentation** : OP8-OP12
- Chairpersons** : Prof. S K Kulkarni  
Prof. Y K Gupta
- Sponsor** : **Aventis, Mumbai**





**IL-34****CALCIUM HOMEOSTASIS AND ORGANOPHOSPHATE INDUCED DELAYED NEUROTOXICITY.****Gill KD.**

Department of Biochemistry, Postgraduate Institute of Medical Education and Research, Chandigarh.

Apart from causing acute cholinergic effects, some organophosphates (OPs) are also capable of causing an irreversible, progressive delayed neurological deficit called organophosphate induced delayed neurotoxicity (OPIDN) in both humans and animals. It is characterized by the development of locomotor ataxia 2-3 weeks after a single exposure or following repeated low level exposure to an OP pesticide. Primary biochemical event known to be associated with the onset of OPIDN is inhibition of a neuronal enzyme, neuropathy target esterase (NTE). However, thus far it has not been possible to elucidate the exact sequence of events between NTE inhibition and the onset of OPIDN following exposure to OPs. It has been proposed that NTE inhibition by OPs is associated with an increase in  $[Ca^{2+}]_i$ , which in turn, may activate  $Ca^{2+}$ /Calmodulin dependent kinase leading to aberrant phosphorylation of cytoskeletal proteins. Increased  $[Ca^{2+}]_i$  may also lead to neuronal degeneration through the activation of calcium activate proteases like calpain which has been shown to be involved in the breakdown of cytoskeletal proteins in other neurodegenerative diseases. It needs to be seen if this also holds true for OPIDN. If so, then calcium channel blockers hold a promising future to be used as therapeutic agents against OPIDN.

**IL-35****OXIDATIVE STRESS AND CANCER.****Neeta Singh.**

Dept. of Biochemistry, AIIMS, New Delhi - 110029.

Oxidative stress arises from both exogenous and endogenous sources. Major exogenous causes of oxidative stress involved in carcinogenesis are tobacco smoke, UV light, fatty acids in food, alcohol, etc. Oxidative stress arises from overproduction of reactive oxygen species (ROS) or from deficiency of antioxidant defence or repair mechanism. Cell damage from ROS is ubiquitous. ROS related lesions that do not cause cell death can stimulate the development of cancer. Mutations through oxidative DNA damage are widely hypothesized to be a frequent event in the normal human cell. Evidence suggests important roles of ROS in the expansion of tumor clones and the acquisition of malignant properties. Thus ROS are an important class of carcinogens. In carcinogenesis, ROS appear to damage DNA by indirect action and modulate expression of genes affecting growth, differentiation and cell death. We and others have shown that Poly ADP-ribosylation of chromatin proteins in response to DNA damage represents another mechanism that modulates gene expression and is thought to be involved in tumor promotion. ROS have also been shown to be involved in apoptosis and cancer cells which overexpress the anti-apoptotic gene *Bcl-2* may escape elimination. We have also gathered insights into the gene regulatory and signal transduction mechanism(s) by which ROS act in tumor promotion and progression using bonafide tumor promoters PMA, Benzoyl peroxide, Xanthine/Xanthine oxidase in f6 mouse epidermal, tumor promoter responsive (pre-neoplastic and neoplastic) cells from the cell envelop to the nucleus on reactions that are likely to be on the pathway of growth and cell death i.e. intracellular calcium levels, translocation of protein kinase C, and modulation of expression of immediate early genes (c-myc, c-fos, c-jun), and transcription factors. We found higher constitutive levels of antioxidants in the promotable JB6 cells. We propose that a subtle balance between the dose of ROS and the cellular antioxidant defenses determine whether toxic or pathological effects predominate. We have also shown that ROS inactivate the cell death program but are not required for its execution. The involvement of oncogenes at all stages of ROS induced carcinogenesis evokes the possibility of gene therapy.

**OXIDATIVE STRESS IN NEUROLOGICAL DISORDERS.****Gupta YK.**Department of Pharmacology, All India Institute of Medical Sciences, New Delhi  
- 110029.

The central nervous system (CNS) is especially vulnerable to free radical damage as a result of (a) brain's high oxygen consumption (b) its abundant lipid content (c) the relative paucity of antioxidant enzymes as compared with other tissues. Free radicals e.g. superoxide anion, hydroxyl radical, hydrogen peroxide and peroxynitrite are normal products of cellular aerobic metabolism. The major sources of free radicals are mitochondrial oxidative metabolism, enzymatic reactions involving mixed function oxidases and auto oxidation. An array of cellular defense systems exists to counterbalance free radicals. These include enzymatic and non-enzymatic antioxidants that lower the concentration of free radicals species and repair oxidative cellular damage. A mismatch between free radicals and the ability of the cell to defend against them leads to a cytopathological consequence -oxidative stress.

Growing data from experimental models and human brain studies suggest that oxidative stress may play an important role in various neurological disorders such as Epilepsy, Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis. A net increase in free radicals can produce damage to lipids, proteins and DNA and can induce apoptosis and necrosis. In Alzheimer's disease (AD), free radicals are produced in the formation of amyloid plaques and neurofibrillary tangles. The defects in glucose energy metabolism in brains of AD patients, activated microglia and the amyloid plaque itself are also important contributing factors to oxidative stress. The role of antioxidants (melatonin, trans resveratrol, alpha lipoic acid) in experimental models of AD in rats is being presently investigated in our laboratory. In stroke elevated levels of both excitatory amino acids and free radicals are seen. We have established the middle cerebral artery occlusion model of cerebral ischemia in rats and have evaluated the effect of various antioxidants in this model by assessing neurological deficit, oxidative stress parameters, histology and magnetic resonance imaging (MRI). In experimental models of seizures (PTZ and FeCl<sub>3</sub> induced seizure, lithium pilocarpine induced status epilepticus), we have demonstrated the protective effect of adenosine and melatonin which possess antioxidant property. Role of antioxidants is also being investigated in the cognitive impairment subsequent to seizure/antiepileptic drug therapy. Understanding of the pathways important in the production and defense from free radicals may be important in devising new pharmacological strategies to slow or halt various neurological disorders.

**IL-37****OXIDATIVE STRESS AND CATARACTOGENESIS.****Gupta SK, Sujata Joshi.**

Department of Pharmacology, All India Institute of Medical Sciences, New Delhi.

Cataract is a multifactorial disease associated with several risk factors. In situ generation of free radicals and consequent oxidative stress constitute the major risk factor for cataract. It is generally accepted that opacification of the lens is the last step of a complex process in which oxidation is the predominant initiating event. Oxidative modifications of lens constituents such as protein, lipid and nucleic acid lead to clouding of the lens. Especially, oxidation of cysteine and methionine residues in protein, oxidation of glutathione, disulphide bond formation, protein unfolding with sulphahydril exposure, protein aggregation, protein insolubilisation and loss of membrane transport function are extensively investigated processes. Many of these alterations also occur with age, but at a slower rate. Oxidative modifications in the lens could be initiated by a variety of free radicals (eg. superoxide, hydroxyl as well as hydrogen peroxide). These oxidising agents can be generated in the eye either photochemically, enzymatically or by exposure to ionizing radiations. In the normal lens, these oxidants are probably reduced to harmless levels by a variety of protective enzymes (SOD, CAT, GPX, GST and GR). Besides, physiological antioxidants like ascorbate, tocopherol and pyruvate also contribute towards free radical defense. Failure of any one of these mechanisms could result in an increase of oxidative stress on the lens. For this

**IL-38****FREE RADICALS AND IMMUNOMODULATION.****Arunabha Ray.**

Department of Pharmacology, Vallabhshai Patel Chest Institute, University of Delhi, Delhi - 110007.

Free radicals play an important role in health and disease and oxidative injury has been implicated in a variety of pathophysiological states. Antioxidant defense systems are known to have protective influences in some cardiorespiratory and CNS disorders, and recent evidence has indicated that the immune system may also be susceptible to the effects of free radical generation. A wide variety of physiological and environmental factors are known to influence immune regulation and experimental evidence indicates that in such stressful situations pro-oxidant/anti-oxidant interactions may play a crucial role in immunomodulation. Emotional (behavioral) and environmental (xenobiotic) stressors induced suppression of both humoral and cell-mediated immune responses, and these effects were effectively neutralized by natural and synthetic adaptogens, as well as antioxidants. Both forms of stress-induced immune suppression were associated with lipid peroxidation (MDA elevations) and suppression of GGT levels, and these changes were attenuated by anti-stress agents. Further, emotional stress-induced immune suppression were associated with anxiety-like behavioral responses and elevations of brain MDA levels, which were predictably influenced by drug treatments. Such free radical mediated stress-immune interactions could have considerable applied significance.

IL- 39

## NEUROPROTECTIVE THERAPY IN PARKINSON'S DISEASE.

Mohanakumar KP.

Division of Neurosciences, Indian Institute of Chemical Biology, Calcutta-700 032.

Pathophysiology of Parkinson's disease (PD) is unknown. Nevertheless, a significant body of biochemical data from post-mortem human brain as well as those from reliable animal models point to an on-going process of metabolic compromise, oxidative stress and excitotoxicity in the substantia nigra which could initiate dopaminergic neurodegeneration in PD. Current therapies base pharmacological symptomatic treatments that undoubtedly render better quality of life and possibly prolongation of life for the patients. There is a dire need for better treatment procedures based on recently available evidences for retarding the progression of the underlying disease. Neuroprotective therapies are interventions that produce enduring benefits by favourably influencing underlying aetiology or pathogenesis of neurodegenerative disorders. Neuroprotection remains an unachieved goal of experimental therapeutics. This alone will pave the path to either halt, or at least retard the neurodegeneration or may restore or replenish the degenerating neurons. Several experimental animal models have been developed to study the molecular mechanisms underlying PD, by administering neurotoxins (MPTP, 6-OHDA), Fe-citrate, the mitochondrial toxin (rotenone), etc in primates and rodents. Investigations in our laboratory in the recent times on a number of animal models provide strong evidence for the active involvement of several factors (mitochondrial dysfunction, oxidative stress including dopamine autooxidation, excitotoxicity, calcium cytotoxicity, environmental factors, apoptosis, etc.) in the pathophysiology of PD. The neuroprotective efficacy of a number of experimental and clinically used drugs could be explained by identification of these mechanisms.

OP - 8

## EVALUATION OF ANTIOXIDANT ACTIVITY OF SPIRULINA EXTRACT IN VITRO.

Mahmood Khan, Shobha IC, Vijay Kumar K.

Dept of Clinical Pharmacology and Therapeutics, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad - 500082.

**Objective:** To evaluate the antioxidant activity of Spirulina extract in-vitro by applying ABTS decolorization assay and free radical-induced lipid peroxidation (MDA) by TBA method.

**Methods:** The antioxidant activity of Spirulina extract was measured by ABTS decolorization assay. The pre-formed radical monocation of 2,2'-azinobis-(3- ethylenzothiozoline-6-sulfonic acid) (ABTS), is generated by oxidation of ABTS with potassium persulfate and is reduced in the presence of hydrogen-donating antioxidants. Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid), a water soluble vitamin-E analogue was used as a standard antioxidant. The antioxidant activity of Spirulina extract was also measured by free radical induced lipid peroxidation *in vitro* and the lipid peroxides formed with or without Spirulina extract was estimated by TBA method. In vitro lipid peroxidation was induced in liver homogenate by Fe<sup>3+</sup>, ADP, ascorbic acid, hydrogen peroxide in HEPES buffer pH 7.4.

**Results:** Spirulina extract (50 mg/ml) significantly prevented the free radical induced lipid peroxidation *in vitro* by 54%. The antioxidant activity of Spirulina extract measured by ABTS decolorization assay showed dose dependent antioxidant activity with maximum effect was seen at 50 mg/ml (55%).

**Conclusion:** The results of the present study showed that Spirulina extract possess significant antioxidant activity.

OP - 9

### ANALYSIS OF MDA IN SM TREATED RAT LIVER BY GAS CHROMATOGRAPHY MASS SPECTROMETRY (GC/MS).

Kameswara Rao M, Sugendran K, Raza SK.

Defence Research and Development Establishment, Gwalior-474 002.

**Introduction:** The extent of lipid peroxidation has been measured by various methods, including the analysis of lipid hydroperoxides, conjugated dienes and w.active aldehydes. A widely used index of peroxidation is the measurement of the secondary product malondialdehyde (MDA). The MDA measurement is conventionally done by the TBA assay. However, due to the uncertainty in the structure of the derivative and the lack of specificity of the assay, the levels of MDA is usually expressed as thiobarbituric acid reactive substrates (TBARS). This assay is also hindered by the possibility of cross reactivities of other aldehydes with TBA and harsh conditions used in sample preparation. The problems have some times led to misinterpretation of the data. Recently methods using GC and GC/MS have been developed for the analysis of MDA using various derivatives.

**Methods:** Here we discuss the standardization of a methodology using NCI-GC/MS for the analysis of MDA in biological samples after derivatisation with pentafluorophenyl hydrazine (PFPH).

**Results:** The EI and CI spectra of the PFPH derivative of MDA were recorded. The molecular ion peak in both electron ionization (EI) and negative chemical ionization (NCI) spectra was observed at  $m/z$  234. The soft ionization mode obtained with NCI gives rise to a molecular ion peak with little or no fragmentation. This lack of fragmentation in part contributes to its enhanced sensitivity over EI, which we found to be over 100 fold for PFPH-MDA. In this study optimum sensitivity was found with the ion source temperature set at 150°C and the methane gas pressure at 4000 mtorr. The limit of detection for PFPH-MDA in biological sample was 1 nm with NCI operating in selected ion monitoring (SIM) mode. The calibration curves were drawn for the MDA-PFPH derivative in two different concentration ranges in order to quantify MDA in biological samples. The method has been successfully applied to the biological samples and MDA has been quantitated in control rat liver tissue.

**Conclusion:** A highly sensitive and specific method based on NCI-GC/MS has been standardised for the analysis of MDA in SM treated tissues after derivatisation with PFPH.

OP - 10

### ANTIOXIDANT AND BENEFICIAL ROLE OF ALPHA LIPOIC ACID IN CHLOROQUINE TOXICITY.

Pari L, Murugavel P.

Department of Biochemistry, Faculty of Science, Annamalai University, Annamalainagar - 608 002.

**Objective:** Alpha lipoic acid ( $\alpha$  LA), a naturally occurring free radical scavenger, and transition metal chelator has been implicated to play a major protective role in hepatitis, diabetes, atherosclerosis, urolithiasis and cataract. Chloroquine, an antimalarial drug, when taken at higher doses induces liver damage.  $\alpha$  - LA was investigated for its possible antioxidant and beneficial effect in Wistar rats against chloroquine-induced hepatotoxicity.

**Methods:** Rats were pretreated with  $\alpha$  - LA for 7 days at three different oral doses (10, 30 and 100 mg/kg body weight) and at the end of 7th day, chloroquine at 970 mg/kg body weight was given as a single dose (oral administration) and  $\alpha$  - LA treatment was continued for 3 more days. At the end of experimental period, the activities of serum enzymes (aspartate transaminase, alanine transaminase and alkaline phosphatase), bilirubin, tissue thiobarbituric acid reactive substances, cholesterol, triglycerides and free fatty acids were estimated.

**Results:** The administration of  $\alpha$  - LA significantly prevented the occurrence of chloroquine induced hepatic damage. The increased activities of serum enzymes (aspartate transaminase, alanine transaminase and alkaline phosphatase), bilirubin, tissue thiobarbituric acid reactive substances, cholesterol, triglycerides and free fatty acids observed in rats treated with chloroquine were significantly lowered in rats treated with  $\alpha$  - LA and chloroquine. The decreased level of tissue phospholipids and antioxidants (superoxide dismutase, catalase, glutathione peroxidase and reduced glutathione) observed in chloroquine treated rats were increased in rats treated with  $\alpha$  - LA and chloroquine.

**Conclusion:** The results of the study revealed that  $\alpha$  - Lipoic acid could afford a antioxidant effect against chloroquine induced hepatic damage.

**OP - 11****SULPHUR MUSTARD INDUCED OXIDATIVE STRESS AND ITS PREVENTION BY MELATONIN IN MICE.****Pant SC, Vijayaraghavan R, Rao PVL, Ganesan K.**

Division of Pharmacology and Toxicology, Defence Research and Development Establishment, Jhansi Road, Gwalior - 474002.

Sulphur mustard [bis (2-chloroethyl) sulphide] (SM), a bifunctional alkylating agent has been frequently used as a chemical warfare agent. Present study was designed to investigate the protective efficacy of melatonin on some biochemical and histological parameters in mice, treated with Sulphur mustard, 19.33 mg/kg, sc, and their protection by melatonin were examined over a period of fourteen days. Female albino mice were treated with either sulphur mustard, melatonin or melatonin plus sulphur mustard. Melatonin was given 100 mg/kg, ip, 30 min prior and 24 hr following SM treatment for four days. Animals were sacrificed on 7th and 14th day post treatment. Blood liver and lung tissues were prepared for biochemical analysis and visceral organs were processed for histopathological evaluation. Exposure of SM resulted in a significant loss of blood, hepatic and pulmonary glutathione (GSH) and an elevation of hepatic and pulmonary oxidized glutathione (GSSG). These biochemical changes were accompanied by number of histopathological alterations. The most prominent among them included congestion and degeneration in viscera and obliteration of chromatin material. Lung liver and renal parenchyma showed granulovacuolar degeneration and perinuclear clumping of the cytoplasm indicating decreased protein synthesis. Histopathological splenic lesions displayed a pattern of vascular congestion and accumulation of megakaryocytes. On 7th day these biochemical and histopathological changes were relatively less marked in animals pre-administered with melatonin and blocked their further progression on 14th day following by SM treatment indicating protective efficacy of the melatonin against SM induced oxidative injury in mice.

**OP - 12****TATA TEA INHIBITS THE PEROXIDATION OF LOW DENSITY LIPOPROTEIN LIPIDS.****Ramesh Chander, Khanna AK, Kanwal Raj, Rastogi AK.**

Biochemistry and Medicinal Chemistry Division, Central Drug Research Institute, Lucknow - 226001.

The leaf extract of tea (*Camellia* species) is used world wide as a refresher drink. It contains various pharmacotherapeutic properties. In an earlier report we have described the effect of TATA tea extract on platelet aggregation, CNS, hyperlipemia and also the inhibitory action on superoxide anion ( $\text{O}_2^-$ ) generation *in vitro*. Since chronic hyperlipemia causes hydroxyl free radical ( $\text{OH}$ ) mediated peroxidation of low density lipoprotein (LDL) lipids which play an important role in pathogenesis of atherosclerosis. In present study we describe the effect of CTC leaf as well as tea dust grade manufactured by TATA TEA Ltd. on lipid peroxidation of LDL and generation of  $\text{OH}$  *in vitro*. The reaction mixture containing human plasma LDL (1mg),  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  (10  $\mu\text{M}$ ) in absence or presence of tea extract from leaf and dust (15-300  $\mu\text{g}$ ) in  $\text{PO}_4$ -buffer saline was incubated at 37°C for 90 min and assayed for lipid peroxidation products by spectrophotometric methods. In another experiment  $\text{OH}$  was generated *in vitro* nonenzymically by  $\text{Fe}^{2+}$  sodium ascorbate,  $\text{H}_2\text{O}_2$  and deoxyribose in  $\text{KH}_2\text{PO}_4$  - KOH buffer. After reaction in absence or presence of both tea extracts (15-300  $\mu\text{g}$ ) the incubation mixture was assayed for lipid peroxide formed. It was observed that tea extracts prevented the formation of peroxide and hydroperoxide of LDL lipids and inhibited the generation of  $\text{OH}$  in concentration dependent manner and these effects were more than 50-80% at the maximum concentration of tea. In conclusion tea sample possessed potent antioxidant activity which may be due to its SOD like behaviour, inhibition of xanthine oxidase and metal ion chelation.

## ***Symposium VIII***

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### **Environmental pollutants and arsenicosis**

- Date** : 28-11-2002  
**Time** : 1600 -1800  
**Venue** : Hall -B
- Invited Lectures** : Dr. S Chattopadhyaya  
Dr. J R Behari  
Dr. S J S Flora  
Prof. T Venkatesh  
Dr. Manju Gupta  
Dr. S N Dube  
Dr. A K Jain
- Oral Presentation:** OP 13 -OP 18
- Chairpersons** : Dr. S K Tandon  
Prof. T Venkatesh
- Sponsor** : Labindia, New Delhi





**APOPTOSIS IN HUMAN FETAL BRAIN EXPLANTS EXPOSED TO ARSENIC AT LOW CELL PROLIFERATION RATE AND NECROSIS AT A LONGER PERIOD OF EXPOSURE.****Chattopadhyay S<sup>1</sup>**, Bhaumik S<sup>1</sup>, Purkayastha M<sup>1</sup>, Das Gupta S<sup>2</sup>.<sup>1</sup>Department of Life Science and Biotechnology, Jadavpur University, Kolkata 70003; <sup>2</sup>Centre for Applied Science and Technology, Kolkata.

**Objective:** In West Bengal, India, presence of arsenic in the drinking water at levels higher than the WHO (1992) recommendation of 0.05 mg/L was associated with classical symptoms of skin lesions. Examination of tissue samples from individuals exposed to arsenic contamination in drinking water showed presence of arsenic in the majority but not all of the samples indicating an expression of a defense mechanism. Investigation on arsenic toxicity showed oxidative stress induced increase in lipid peroxidation and membrane damage in brain. Apoptosis and the oxidative stress has been causally linked to degenerative diseases of brain.

**Methods:** The human fetal brain tissue collected from hysterotomy cases of 16 weeks gestation, were minced, washed, incubated for post shock adaptation and cultured in RPMI 1640 with 10% bovine fetal serum, phenol red indicator, penicillin 50 U/ml, streptomycin 50 µg/ml and HEPES buffer at pH 7.2. For low cell proliferation rate preparation arsenic, 0.3 mg/L, was added to the serum free medium for 24 hours, washed and maintained for 5 days in serum-replenished medium, and for long-term exposure arsenic was maintained in the medium for 18 days. The cell proliferation rates were determined by <sup>3</sup>H-Thymidine (9,800 mCi/mmole) and <sup>14</sup>C-Leucine (156 mCi/mmole) incorporation for 96 hours. The morphometric analyses were carried out by Zeiss Axiovert 10 inverted microscope attached with CCD and Frame Grabber Card to HCL-PC for image analyses. The degree of damage suffered by the membrane was determined by Trypan blue dye exclusion. The release of NO and ROS were quantitated by dispensing cells in fresh medium in 96 well plates, incubated, allowed to react with Greis and NBT reagents and the spent medium were assayed at 550 nm in Anthos 2001 microplate reader. Explants were stained for cytological reactions of NO and ROS release.

**Results:** The arsenic induced increase in production of NO, 20% and ROS, 25%, and decrease in synthesis of DNA, 62% and protein 64%. The morphological analysis showed growth of viable cells, neural networking vis-a-vis apoptosis on exposure to arsenic for 24 hours and necrosis and loss of ground matrix on arsenic exposure for 18 days. The generation and release of reactive oxygen-nitrogen intermediates were observed at an increased level in some cells. The occurrence of apoptosis in individual neuron and necrosis in cluster of cells were observed.

**Conclusion:** The occurrence of apoptosis along with cell proliferation and necrosis in cluster of neurons indicated a selective expression of arsenic toxicity in human fetal brain explants. The apoptosis may provide a defense mechanism at a low level of toxic insult due to arsenic.

**ARSENIC: ENVIRONMENTAL HEALTH AND ANALYTICAL ASPECTS.****Jai Raj Behari.**

Industrial Toxicology Research Centre, Lucknow.

Arsenic is the focus of public attention today from human health point of view since almost epidemic like problems are prevailing in West Bengal in India and Bangladesh besides a few other countries. This is mainly due to consumption of arsenic contaminated ground water for domestic as well as agricultural use in the affected rural areas. Arsenic along with mercury has been well known for its use both as homicidal and suicidal agent for long besides its medicinal use in Indian system of medicine. In the environment sixty percent of the anthropogenic arsenic emissions can be accounted for by coal combustion and copper smelting. Use as herbicide, in glass production, waste incineration and steel production are some of other sources of atmospheric arsenic fluxes.

Arsenic inhalation or oral exposure has relevance to human health. Arsenic accumulates mainly in hair, skin and nails and the normal intake for humans may range from 0.04 - 1.4 mg/day. Chronic arsenic exposure typically leads to hyperkeratosis on the palms of hands and soles of feet as well as skin pigmentation. Exposure to arsenic has further been implicated as a cause of cancers of lung, skin and bladder in humans. Attempts to find animal models however, for arsenic carcinogenesis have mostly failed. The increased cancer risk has been mainly attributed to the presence of trivalent arsenic. Recent studies have suggested that failure to find an animal model for arsenic carcinogenesis is because arsenite is not a carcinogen per se, but rather acts as a cocarcinogen with a genotoxic partner. In mammals including humans exposure to inorganic arsenic results in the formation and excretion of monomethyl and dimethyl arsenic as major metabolites which are excreted via urine and are considered less toxic species. The pathway of conversion of inorganic arsenic into methylated derivatives involves oxidative methylation and interconversions of arsenic from pentavalent to trivalent oxidation states. The toxicity of arsenic varies greatly with its oxidation state as  $As^{3+}$  is much more toxic and mobile than  $As^{5+}$ . Not only inorganic trivalent arsenic, recent studies have shown that trivalent methylated arsenic species are more potent cytotoxins compared to inorganic arsenic.

Ever since the reduction of permissible limit of arsenic in drinking water by WHO to 10 ppb level, the need of precise and accurate analysis of arsenic at ppb level is being realised for the purpose of field surveys. However, methods available so far are not so reliable and practical at the field level. Analysis of arsenic at ppb level is reliably performed in the laboratory using an atomic absorption spectrophotometer equipped with vapour generation assembly with minimum handling for water sample. Removal of arsenic from water has been an important area of research in the last decade. A variety of methods have been used for this purpose including coagulation/filtration, lime softening, ion exchange, reverse osmosis, or electro dialysis. For coagulation/filtration iron and aluminium salts have been used, the former with relatively high efficiency. The technology available so far are however not appropriate for most small systems and have high cost with a need of well trained operating personnel. The target of removal of arsenic from water to reduce arsenic to less than 2 ppb with simple adsorption process involving low capital and operating costs and minimum waste as well as media regeneration at rural community/domestic level is still to be achieved to help the affected masses.

IL-42

## CHRONIC ARSENIC POISONING: DO WE HAVE A TREATMENT?

Flora SJS.

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Symptomatic arsenic poisoning is rare, as occupational exposure to arsenic is not often seen. Chronic arsenic poisoning may result from deliberate long-term exposure or attempted homicide. Environmental arsenic pollution occurs due to its widespread toxic effects on human, animals, birds and animal life and plants through polluted ground water and food chains. Recently, accumulation of arsenic in ground water has posed serious threats to population of millions of human beings in India and Bangladesh. Skin pigmentation changes, palmar and plantar hyperkeratoses, gastrointestinal symptoms, anemia, and liver diseases are common. Noncirrhotic portal hypertension with bleeding esophageal varices, splenomegaly and hypersplenism may also occur. A metallic taste, gastrointestinal disturbances and Mee's may be seen. Bone depression is common. "Blackfoot disease" has been associated with the arsenic contaminated water. Total delirium and encephalopathy can be present.

Chelating agents used clinically in arsenic poisoning include dimercaprol (British Anti Lewisite; BAL), D-penicillamine (which is no longer recommended), meso 2,3-dimercapto succinic acid (DMSA; Succimer) and sodium 2,3-dimercaptopropane 1-sulfonate (DMPS, Dimaval). From the late 1940s, the common treatment for arsenic poisoning is the administration of BAL, a dithiol compound with a strong chelating affinity for arsenic. In the recent past two chemically related analogues of BAL, DMSA and DMPS were successfully tried against chronic experimental arsenic poisoning in animals. These chelating agents are water soluble, orally active and markedly less toxic than BAL. Recently, however, in a first randomized placebo-controlled trial it was reported that DMSA was ineffective in providing any clinical or biochemical benefits or histopathological improvements in patients with chronic arsenicosis. DMPS on the other hand was found to be temporarily associated with a dramatic improvement in peripheral neuropathy and in increasing urinary elimination of arsenic. DMPS however, is effective in improving the clinical features of chronic arsenic poisoning.

Recent investigations have shown that treatment with monoalkyl esters of DMSA would be superior to treatment with DMSA, in mobilizing toxic metals. We recently observed that MiADMSA could be a potential drug of choice for the treatment of chronic arsenic poisoning. The study also points to a beneficial role of MiADMSA in decreasing renal and hepatic oxidative stress and a significant effect in the reversal of altered haematopoietic system. In view of greater property of crossing cell membrane, leading to gaining access to metal bound to intracellular endogenous ligands, this compound should be explored further for treating chronic arsenic poisoning.

**LEAD POISONING AND CHILD'S HEALTH: INDIAN SCENARIO IN NUTRITIONAL MANAGEMENT AND ENVIRONMENTAL POLICIES.****Venkatesh T.**

Director, National Referral Center for Lead Poisoning In India, St. John's National Academy of Health Sciences, Bangalore 560034.

Amongst toxic heavy metals, the most useful and wonder metal "lead" is branded as number one environmental poison all over the world. Human health particularly that of young children is affected by environmental lead, which is 100 % preventable. In most parts of developed countries, in spite of their continuous efforts towards reducing the ill effects of lead through their national policies and their implementation the problem still exists. World has now realized that the cost benefit ratio of treatment of lead poison is too high when compared to the cost required towards preventive measures. Documented data in both developed and developing countries have indicated that the situation with regard to lead related health hazards is of more serious in nature when compared to many other health hazards.

Developing countries like India have other known associated problems such as poverty, mal-nutrition, over population and inadequate environmental policies to combat the ill effects of lead. With the increasing requirement of lead for various purposes, in our country we are unable to implement policies due to many reasons. Uncontrolled increase in the unorganized sector of smelters and recyclers of lead are continuously polluting our environment. Lack of facilities and the high cost involved in monitoring environmental and blood lead apart from priorities in our health care system are some of the known reasons of continuing problems associated with lead. All these have resulted in ineffective implementation of International or national policies. Lack of awareness about lead related health problems amongst general public has added to the existing problem especially in our country. The George Foundation (TGF) study recently concluded in India has revealed that over 50% of children below 12 years of age in seven major cities in India are having their blood lead levels above 10 mcg/dl which is known to reduce their learning abilities. It is also well documented that nutritional supplement of iron, calcium and zinc reduces the absorption of lead especially by a child.

The National Referral Center for Lead Poisoning in India established by The George Foundation and St. John's national Academy of Health Sciences at Bangalore has been successful in bringing about a change in this direction with in a short span of time of its establishment through various activities such as creating awareness, monitoring the blood lead levels, drafting national policies, dedicated website [www.leadpoison.net](http://www.leadpoison.net), apart from establishing nodal centers in the country. NRCLPI believes in the safe use of useful metal lead all over the world.

IL-44

## HAZARDOUS IMPACT OF NONESSENTIAL TRACE METALS ON HUMAN HEALTH DURING OCCUPATIONAL EXPOSURES.

**Manju Gupta.**

Institute of Nuclear Medicine and Allied Sciences, Timarpur, Delhi - 110001.

It is difficult to think about survival without considering immense role of metals in development of man kind. Metals start their role from essential to contaminant. Metals used in industries are generally hazardous to human health. Degree of risk depends on several factors; the amount of exposure, route, time frame and sensitivity of receptor to exposure; receptor sensitivity in turn depends on many variables such as individual's age, his/her general health, genetic or hereditary parameters, prior historical exposure to other elements which may come synergistic effects.

The most common toxic metals in industrial use are aluminium, arsenic, cadmium, lead and mercury. Aluminium - Absorbed aluminium is highly protein bound, making it difficult to remove from body tissues. Highest concentrations in blood and urine has been observed among welders and workers manufacturing aluminium flake powder. Patients developing acute neurological disorders such as dialysis dementia or dialysis encephalopathy have been shown to have high level of aluminium in their serum and brain tissue. IARC has concluded that there is sufficient evidence exposures occurring during aluminium production cause cancer of lung and bladder. Arsenic - Arsenic is one of the oldest poison used by man. In occupational settings, the respiratory tract provides the most common portal of entry for arsenic. Skin and gastrointestinal pathways are possible but less prevalent routes, unless by accident or medication. Trivalent form of arsenic compound is more toxic than any other form. 80% of ingested dose of dissolved inorganic trivalent arsenic is absorbed in gastrointestinal tract. Arsenic is known human carcinogen. Keratoses on the palm and soles are often related to skin cancer in arsenic exposed cases. Mercury - Due to vast uses in medicine and industries mercury is environmentally ubiquitous. It is protoplasmic poison and hazardous to all forms of life. Mercury is the responsible agent for infamous Minimata syndrome which is characterised by degenerative changes in central nervous system. Nephrotic changes and brain cortex degeneration have also been reported in workers exposed to the combination of both mercury vapour and dust. Cadmium - Cadmium appears mainly as a by product of mining and refining of ores. Smoking in a work place where cadmium is produced may also increase cadmium intake. Cadmium enjoys very long biological half life. Liver and kidney are main storage organs. The most dramatic example of detrimental health effects resulting from environmental exposure to cadmium is Itai-Itai disease, characterized by renal failure and bone degeneration. Lead - Lead is cumulative toxin that is absorbed by lungs and gastrointestinal tract. Biological monitoring for lead is mainly based on interference of lead with several stages of heme synthesis pathway.

Toxic metals especially their ions, once absorbed into the body bind tightly to structural or cellular components and this tendency complicates both the clinical picture and therapeutic approach to metal toxicity. Present talk will be focussed on toxic impact of metals on human health in general as well as author's own findings while conducting studies on occupational workers in occupation health laboratory, INMAS, Delhi will also be illustrated.

**IL-45****PHARMACOLOGY AND TOXICOLOGY OF GALLIUM ARSENIDE.****Dube SN.**

Department of Pharmacology and Toxicology, Defence R and D Establishment, Jhansi Road, Gwalior - 474002.

Gallium Arsenide (GaAs), a group III-VA intermetallic semiconductor, possesses superior electronic and optical properties and has a wide spread application in the electronic industry such as the integrated components of discrete microwaves devices, lasers, light-emitting diodes, photoelectric chemical cells, etc. Exposure to GaAs in the semi-conductor industry is a possible occupational risk, since cleaning and slicing of GaAs ingots to yield the desired wafer can generate GaAs particles. The toxic effect from the intermetallic semiconductors appears to occur from inhalation or oral exposure and may result in toxicity. Assessment of risk to workers engaged in GaAs production is difficult due to the lack of toxicity data for these compounds. Their toxicity is mainly estimated on the basis of inorganic arsenic because it is now well known that GaAs dissociates into their constituent moieties and exerts adverse effects on haematopoietic and immune system.

We recently reported that administration of a single dose of GaAs produced few alterations particularly at a higher dose level in the physiological variables viz. blood pressure, heart rate, respiration and twitch response as well as the biochemical variables of heme biosynthesis pathway. The peak adverse effects however were noticed at day 7 following single exposure compared to observation at two other time intervals (i.e., day 1 and day 15). Blood gallium concentration was not detectable in normal animals and rats exposed to 500 mg/kg GaAs. Blood arsenic concentration was, however, detectable even at the lower dose levels and increased in a dose dependent manner. As the toxicology of GaAs is still not very well understood and clearly defined, the treatment also remains to be doubtful. British Anti Lewisite (2,3-dimercaprol; BAL) which is known arsenic chelator has also been tried against GaAs. However, this compound suffers from many disadvantages like, low safety ratio, unpleasant side effects and difficulty in systemic administration. Two recent chelators meso 2,3-dimercaptosuccinic acid (DMSA) and sodium 2,3-dimercaptopropane I-sulfonate (DMPS) have shown some beneficial effects in reversing most of the immunosuppressive effects. Attempts are also being made in our laboratory to synthesise and evaluate mono and diesters of DMSA for treating chronic low level GaAs exposure. Preliminary results indicate beneficial role of monoisoamyl DMSA in treating GaAs exposure.

As evident from few above mentioned studies that these intermetallic semiconductor materials possess toxic biological properties and this may lead to potential occupational and environmental health consequences. Thus, in order to prevent such hazards associated with handling of this compound, detailed studies need to be conducted in several areas viz. target organ toxicity, mechanisms of action, specific biological indicators, preventive and therapeutic measures beside possible health monitoring of subjects handling these compounds.

**IL-46****AAS - LATEST DEVELOPMENTS.****Jain AK.**

**OP - 13**

### **INFLUENCE OF VANADYL SULPHATE ON LACTATING RATS.**

**Sadhana Shrivastava, Mathur R.**

School of Studies in Zoology, Jiwaji University Gwalior - 474011.

Vanadium is naturally occurring metal, number 23 on the periodic Table. It is a shiny silver soft metal mainly known for its corrosion resistance. It is essential in human nutrition (10 to 60 mg/day) because it has properties that are similar to zinc. It has significant insulin-mimetic properties in pharmacological doses. Its salts have been used as antiseptic and general tonic. It is used in steel industry, textile and ceramic industry. It causes damage to nervous system, liver and kidney. Vanadium exposure for 21 days at a dose of 7.5 mg/kg/day orally for 20 days, showed decrease in value of hemoglobin percentage and blood sugar. While serum transaminases and white blood corpuscles showed increased value. It induced elevation in glycogen and protein content of liver and kidney of mother and pups. There was increased enzymatic activity of acid phosphatase. On the contrary alkaline phosphatase and adenosine-tri-phosphatase showed inhibition. Lipid peroxidation showed enhanced values whereas glutathione showed inhibition in liver of mothers and pups. It also caused histopathological lesions in liver and kidney of mothers and pups. Therapy with Tiron and Tiron + Selenium for 5 days was effective in restoring the blood and tissue biochemistry. Histopathological changes were also recouped significantly.

**OP - 14**

### **DURATION DEPENDENT RESPONSE OF COMBINATION THERAPY OF ANTIOXIDANTS AN CHELATING AGENTS CONSEQUENT UPON BERYLLIUM EXPOSURE.**

**Sonia Johri, Sangeeta Shukla.**

Laboratory of Toxicology and Reproductive Biology, School of Studies in Zoology, Jiwaji University, Gwalior - 474011.

In the present study an effort has been made to minimize the toxic effect caused by the metal ion. Adult cyclic rats of Sprague Dawley strain were administered a bolus dose of 50 mg/kg beryllium as beryllium nitrate intramuscularly. The chelation therapy with GSH, DMPS + Se and DPA + Se was given for 3 days followed by a rest of 1,3 and 7 days respectively to 5 groups of 5 animals each. The results revealed a significant fall in the blood sugar level, serum alkaline phosphatase activity, serum proteins. A significant rise in the transaminase i.e. AST and ALT pattern is indicative of leakage of enzymes resulting in alterations in the cell permeability. A rise in the hepatic lipid peroxidation activity is a direct indication of oxidative damage resulting in free radical generation. Results of the distribution studies by atomic absorption spectrophotometry reveal an increased concentration of beryllium in liver and kidney followed by lung and uterus. The relative ability of 3 chelating agents to act as antagonists for acute beryllium poisoning have been examined in liver, kidney, lungs and uterus. The appreciable change in the beryllium concentration in various organs is duration-dependent during the entire period being highly significant after 7 days rest. From the biochemical assays, and distribution studies it can be assumed that DPA+Se was the most effective therapeutic agent followed by DMPS + Se and GSH. Thus it can be concluded that DPA + Se is a better therapeutic agent as compared to DMPS + Se and GSH.



OP - 15

### EFFECT OF CHELATING AGENTS ALONG WITH SUPPLEMENTATION OF VITAMIN E ON ALUMINIUM INDUCED TOXICITY IN RATS.

Pragya Dixit, Vohora SB.

Department of Medical Elementology and Toxicology, Jamia Hamdard, Hamdard University, New Delhi.

**Introduction:** Aluminum is one of the most abundant element in Earth's crust with several industrial and household uses (construction work, automobile, aircraft, electronic equipments, utensils, pharmaceuticals, dialysis dementia etc) specially during pregnancy there is evidence for developmental toxicity. The aim of the present study is to probe the therapeutic efficacy of chelating agents against aluminum toxicity when used alone and combination with Vitamin E.

**Methods:** Two chelating agents viz., Tiron and glutathione along with vitamin E, given for, 5 days were investigated in female rats following 28 days exposure with aluminum chloride (200 mg/kg po). Parameters for evaluation included serum proteins, AST, ALT, acid and alkaline phosphatase, gucose-6-phosphatase, ATPase, LDH, Lipid peroxidation, bilirubin, creatinine, urea and also aluminum content in serum, liver and kidney by AAS.

**Results:** Exposure to aluminum caused increase in serum AST, ALT, LDH, creatine and hepatic lipid peroxidation and decrease in serum protein, alkaline phosphatase, urea and tissue G-6-Pase and ATPase. Chelating agents normalized most of the parameters. The effects were enhanced when chelating agents were used in combination with vitamin E.

**Conclusion:** i) Of the two chelating agents studied, Tiron was found to be more effective followed by glutathione. ii) Synergistic action was observed on combined therapy with vitamin E.

OP -16

### LANTHANUM INDUCED REPRODUCTIVE TOXICITY AND ITS REGULATION.

Asha Mathur, Tripti Sharma.

Naveen Girls College, 17, New Saket Nagar, Gwalior, and Deptt. of Zoology, Govt. Science College, Gwalior.

With the rapid industrialization and fast mechanization of the present day life man is far more exposed to the ill effects of the various pollutants than in the past. Study of many occupational hazards has grown to a new specialty. The present study has been undertaken to report the toxic effects of lanthanum chloride on the reproductive organs of mice as lanthanum salts have gained much use in industry today and both male and female human beings are exposed to it. Detailed hematological study has been made to rmd out the changes in various blood parameters. A biochemical study of testes, seminal vesicles and prostate has been undertaken and glycogen, acid and alkaline phosphatases and cholesterol have been estimated. Histopathological study records through light and electron microscopy the lesions developed in reproductive organs. Bioassay and prophylactic study revealed the minimum dose and duration required to attain normal reproductive pattern.

OP - 17

### EFFECT OF COPPER ON SOME BIOCHEMICAL INDICES IN VITRO IN ERYTHROCYTES OF DOMESTIC RUMINANTS.

Arora U, Summer KH, Rao GS and Malik JK.

Division of Pharmacology and Toxicology, Indian Veterinary Research Institute, Izatnagar - 243122, India and Institute of Toxicology, GSF, Neuherberg, Germany.

**Objective:** The study was conducted to investigate the effects of copper on certain biochemical parameters in ruminant erythrocytes *in vitro*.

**Methods:** Blood was collected aseptically into heparinized tubes by jugular venipuncture from apparently healthy goats, sheep, buffaloes and cattle. Blood samples were incubated with 0.5 and 1.5 mM of Cu (CuSO<sub>4</sub>) at 37°C with gentle shaking. At 0, 4 and 8 h after addition of Cu, the blood samples were centrifuged and plasma and buffy coat were removed and the resulting erythrocyte pellet was washed thrice with PBS and kept as 50% suspension. Stock hemolysate (1:10) was prepared from the erythrocyte pellet for various biochemical assays including catalase, acetylcholinesterase (AChE), lipid peroxidation and reduced glutathione (GSH).

**Results:** Significant inhibition of AChE activity was observed after 8 h at 1.5 mM Cu concentration in buffalo erythrocytes only. Lipid peroxidation was induced in the erythrocytes of sheep and buffaloes after 8 h at both 0.5 and 1.5 mM Cu concentrations, whereas, such an effect was also noticed in buffalo erythrocytes after 4 h at the higher concentration of Cu (1.5 mM). In the erythrocytes of cattle, lipid peroxidation was induced after 8 h at 1.5 mM Cu concentration. Significantly reduced levels of GSH were seen in sheep erythrocytes after 8 h at 1.5 mM Cu concentration. GSH was significantly reduced in erythrocytes of buffaloes and cattle after 4 and 8 h at both 0.5 and 1.5 mM concentrations of Cu. Four and 8 h exposure of Cu at the two concentrations (0.5 and 1.5 mM) did not induce lipid peroxidation and produced no significant alterations in the levels of AChE and GSH in erythrocytes of goats. Cu also did not influence catalase enzyme in erythrocytes from any of the four ruminant species.

**Conclusion:** The results tend to suggest considerable interspecies variation with regard to biochemical effects of Cu in erythrocytes of domestic ruminant species.

OP -18

### BLOOD LEVELS OF ESSENTIAL METALS AND ANTIOXIDANT ENZYMES DURING MENOPAUSE IN WOMEN.

Shrivastava V, Singh N.

Department of Biochemistry, GR. Medical College, Gwalior.

Present study was carried out in 20 naturally terminated menopause women and 20 normal healthy women as control. The blood level estimation of estrogen, reduced glutathione and antioxidant enzymes (AOE) like glutathione peroxidase (GPx), catalase (CAT) and superoxide dismutase (SOD) was done. Since AOE are present as metallozymes, the estimation of metals (Cu, Fe, Zn) associated with them was done by atomic absorption spectrophotometer. The observation was, decrease in estrogen level ( $P \leq 0.01$ ) with simultaneous decrease in AOE level ( $P \leq 0.001$ ) and increase of the blood levels of essential metals ( $P \leq 0.001$ ) as compared to control subjects. The presence of these metals for longer time in free state in blood (due to un-availability of binding proteins) lead to toxicity. It is therefore concluded that during menopause if attention is paid towards the supplementation of proteins (as these are medium required to bind metal) rather than on essential metals, the complications during menopause can be avoided.



# ***Symposium IX***

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## **Pharmacology of nitric oxide**

- Date** : 29-11-2002  
**Time** : 0900 -1045  
**Venue** : Hall - C
- Invited Lectures** : Prof. Arunabha Ray  
Dr. Madhu Dikshit  
Dr. J Bhaduri  
Dr. J M Patel  
Dr. K P Mohanakumar
- Oral Presentation** : OP 19
- Chairpersons** : Prof. Arunabha Ray  
Dr. Madhu Dikshit
- Sponsor** : **Lupin Laboratories**



**IL-47****NITRIC OXIDE AND STRESS.****Arunabha Ray.**

Department of Pharmacology, Vallabhbai Patel Chest Institute, University of Delhi, Delhi - 110007.

Nitric oxide (NO) is a ubiquitous molecule with complex physiological and pharmacological effects, and its involvement in various pathophysiological states have been suggested. 'Stress' is defined as an aversive stimulus which disrupts the physiological homeostasis and the ability/inability to cope with such situations are crucial determinants of health and disease. A variety of stressful events can influence cardiovascular, CNS and immunological events, and recent experimental studies indicate that NO may play a crucial role in some of these stress related manifestations. Emotional stress induced anxiety-like behavioral responses which are attenuated by NO mimetics, and these were comparable to those of diazepam. On the other hand, the NO synthase inhibitors further aggravated these behavioral responses. Estimations of brain NO (nitrates/nitrites) indicated a correlation between the biochemical data and behavioral changes. Immunological studies showed that these stressors suppressed both humoral and cell-mediated immunity, and NO mimetics (and diazepam) attenuated, whereas, NO synthase inhibitors aggravated these stress effects. Further, studies also showed that there was a possible correlation between neurobehavioral and immunological effects during stress and NO could be involved in such CNS-immune interactions.

**IL-48****REGULATION OF NITRIC OXIDE AND REACTIVE OXYGEN SPECIES GENERATION IN THE POLYMORPHONUCLEAR LEUKOCYTES: IMPLICATIONS IN PHYSIOLOGICAL AND PATHOLOGICAL CONDITIONS.****Madhu Dikshit.**

Division of Pharmacology, Central Drug Research Institute, Lucknow - 226001.

Polymorphonuclear leukocytes (PMNs) constitute a major part of the circulating leukocyte population; these cells produce reactive oxygen (ROS) and nitrogen species (RNS). Studies conducted in our lab have demonstrated that resting PMNs spontaneously synthesize nitric oxide (NO), while in the activated PMNs ROS generation is preferred over NO synthesis. Lipopolysaccharide treatment leads to the induction of NO synthase as well as the uptake of L-arginine transport. NO released from the PMNs during hypoxia-reoxygenation, thrombosis and endotoxemia seem to modulate ROS generation from the PMNs. Calcium modulations also affect the ROS generation, which also influences NO release from the PMNs. Systematically conducted studies on the interaction of NO with superoxide radicals by using NO donors demonstrated modulation of PMNs ROS generation by NO in a biphasic manner. At higher concentrations it inhibits NADPH-oxidase activity and scavenges free radicals. In contrast, at lower concentrations it augments free radical generation via ADP-ribosylation and protein kinase C activation. Recent studies conducted in our lab demonstrate that high ascorbate content in the PMNs help in regulating the NOS activity by tetrahydrobiopterin stabilization, which modulates ROS generation. Our findings add new dimensions to the dual role of NO and ROS. Results obtained have clearly demonstrated the important physiological regulatory role of NO in addition to the conventionally described tissue damaging pathological effects.

**IL-49****NITRIC OXIDE: ITS THERAPEUTIC POTENTIAL.****Jaydip Bhaduri.**

Lupin Limited, Santa Cruz (East), Mumbai - 400098.

Nitric oxide (NO), a short half life free radical, is known to be highly reactive and ubiquitously present in the biological system. NO is involved in various biological processes such as homeostasis, neurotransmission, inflammation, regulation of immune responses, regulation of renal hemodynamics. NO is understood to play a critical role in physiopathological processes like vasodilation, alteration of vascular permeability, migratory behaviour of leucocytes, activation of leucocytes, to name a few. From the available data, though, it appears that NO is a double-edged sword with the beneficial or detrimental effects depending on the patho physiological context. A well after 15 years of identification of NO as a multi functional biological mediator and many years after nitrates have been introduced into therapeutics NO is an important target for development of newer agents in a variety of therapeutic areas. The introduction of Sildenafil has successfully established the biological importance of enhancement of NO levels in the tissue. While topical NO generating systems are being evaluated for serious dermal infections, the NO containing NSAID's (non-steroidal anti-inflammatory drugs) are considered to be potent anti-inflammatory agents with minimal gastrointestinal toxicity. The highly selective inducible variety of NO synthase (iNOS) is another novel target for development of newer and safer disease modifying anti-rheumatic drugs.

**IL-50****DYNAMIC REGULATION OF LUNG ENDOTHELIAL NITRIC OXIDE SYNTHASE : ROLE OF ANGIOTENSIN-IV AND CALRETICULIN.****Patel JM, Jianliang Zhang, Edward R Block**

Division of Pulmonary Medicine, University of Florida College of Medicine and VA, Medical Center, Gainesville, FL 32608-1197, USA.

Vascular endothelium plays a critical role in maintaining pulmonary vessel wall homeostasis and normal lung function. The endothelium-dependent regulation of vascular tone is mediated through generation and release of potent vasoregulatory agents such as nitric oxide (NO). Vascular endothelial cells generate NO from oxidative metabolism of L-arginine catalyzed by constitutively expressed NO synthase (NOS). Physiologic action of NO is mediated through a NO/cyclic guanosine monophosphate (cGMP) signalling mechanism that results in vascular smooth muscle relaxation. We recently reported that the hexapeptide angiotensin (Ang) IV, a metabolic product of Ang II, i) causes early and sustained activation of NOS by a post-transcriptional mechanism, ii) increases expression of calcium binding protein calreticulin, and iii) enhances NO and cGMP production, and NO/cGMP-mediated vasorelaxation of pulmonary artery. Because agonist-stimulated activation of NOS is mediated through intracellular calcium release and because physiologic stimuli including Ang-1V is known to increase synthesis of calreticulin, we sought to determine whether Ang-1V-mediated sustained activation of NOS is causally associated with increased expression of calreticulin as well as with protein:protein interaction between NOS and calreticulin in lung endothelial cells. Pretreatment of cells with the intracellular calcium chelator (BAPTA-AM) blocked Ang-IV-mediated NOS activation, calreticulin expression, and pulmonary artery vasodilation. Immunoprecipitation and confocal imaging studies revealed that NOS and calreticulin are co-localized in Ang-1V-stimulated lung endothelial cells. The studies monitoring the effect of calreticulin on the rate of electron transfer from reductase to oxygenase domain of NOS revealed that the calreticulin/NOS interaction promotes electron transfer and the catalytic activity of NOS. These results demonstrate that: i) Ang-1V-induced intracellular calcium mobilization is crucial for increased NOS activity and calreticulin express and ii) calreticulin/NOS protein:protein interaction enhances the rate of electron transfer, a critical event in the regulation of the catalytic activity of NOS. The physiologic significance of Ang-1V-mediated increased expression of calreticulin and calreticulin-mediated activation of NOS may help restore impaired NO production due to diminished or reduced catalytic activity of NOS associated with a variety of pulmonary diseases and/or injuries.

IL -51

**NITRIC OXIDE PARTICIPATION IN DOPAMINE NEURODEGENERATION:  
FACT OR FALLACY**

**Mohanakumar KP.**

Division of Neurosciences, Indian Institute of Chemical Biology, 4, Raja S C  
Mullick Road, Calcutta.

Evidences accumulated during the past one decade on the involvement of nitric oxide in dopaminergic neurodegeneration are not unequivocal. While direct evidences are hardly presented, indirect evidences including neuroprotection against 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine (MPTP)-neurotoxicity by nitric oxide synthase (NOS) inhibitors and resistance of transgenic animals deficient in NOS are, at the least, debatable. Evidences in favour of oxidative stress in animal models of Parkinson's disease (MPTP, Fe-citrate, rotenone, etc) and the influence of antioxidants including nitric oxide (NO), NOS inhibitors and NO donors are reviewed in the light of our results. Systemic administration of MPTP caused generation of hydroxyl radical (OH) in vivo in the striatum in a dose dependent manner in mice and OH scavengers protect dopaminergic neurons from this insult. Similarly, intranigral infusions of MPP+, rotenone or Fe- citrate also cause OH generation in the nigral region. On the other hand the role of NO in MPTP-neurotoxicity is controversial, and hitherto no direct evidence for the involvement of NO in MPTP neurotoxicity has been forthcoming. MPTP does not affect inducible-NOS mRNA levels and its expression in SN or the striatum, and nitroglycerine, an NO donor, can attenuate MPTP-induced dopamine depletion in the striatum by virtue of its OH scavenging action. Several other NO donors have also been shown to scavenge OH generated following Fenton chemistry in vitro and protect against in vivo dopaminergic neurotoxicity following the small mass iron complex. In our studies with rotenone, we have observed OH generation following intranigral infusion of the toxin and degeneration of dopamine neurons, which could be protected by OH scavengers and by NO. These evidences suggest that NO renders protection against OH-mediated nigrostriatal lesions, acting as an antioxidant.



OP-19

**SIGNIFICANCE OF THE ACTIVATION OF THE PLATELET NITRIC OXIDE SYNTHASE (NOS) BY ACETOXY POLYPHENOLS.**

Khurana P\*, Raj H G\*, Dwarkanath BS\*\*\*, Adhikari JS\*\*, Rohil V\*, Kumari R\*, Gupta G\*, Bose, M\*, Parmar V\*\*, Olsen CE\*\*\*\*

\*V.P.Chest Institute and \*\*Chemistry Deptt. University of Delhi, Delhi. \*\*\*Institute of Nuclear Medicine and Allied Sciences, Lucknow Road, Delhi. \*\*\*\*Royal Veterinary and Agricultural University, Copenhagen, Denmark.

**Objective:** We have reported earlier the hyperbolic activation of microsomal NADPH cytochrome C reductase by the model compound 7,8-diacetoxy-4-methyl coumarin (DAMC) catalyzed by a novel enzyme, DAMC: protein transacetylase (TAase) discovered in our laboratory for the first time. Similar observations were made with reductase activation in platelets. Since NADPH cytochrome C reductase forms an important domain of NOS efforts were made to examine whether platelet NOS was activated by DAMC and related polyphenols.

**Methods:** Platelets were employed as the system to assay NOS based on the oxidation of dichlorofluorescein diacetate using flowcytometry. Platelets were pre-incubated with DAMC followed by the addition of arginine and the fluorescent dye, incubated for 30 minutes at 37 degrees and increase in fluorescence was taken as the measure of NO production.

**Results:** TAase activity was assayed and characterized in platelets. Platelets incubated with 100  $\mu$ M DAMC were found to generate NO from arginine many folds higher as compared to the controls. Positive correlation was found to exist between the catalytic activity of TAase and NO formation by DAMC. The studies were extended to various acetoxy polyphenols including 7-acetoxy 4-methylcoumarin, 7-acetoxy 4-methylthiocoumarin, 1,4-diacetoxy xanthone.

**Conclusion:** The fact that 7,8-dihydroxy 4-methylcoumarin failed to enhance NO formation in platelets postulated the possible acetylation of active site amino acid residues of the reductase domain of NOS by DAMC catalyzed by TAase. Polyphenols were found promising as the TAase catalyzed NO producers in platelets.

# ***Symposium X***

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## **Pharmacology in India : Future perspective**

- Date** : 28-11-2002  
**Time** : 1200 -1300  
**Venue** : **Committee Room**
- Invited Lectures** : Dr. Shoibal Mukherjee  
Dr. A Sankaranarayanan  
Dr. N Mahalaxmibala  
Dr. Suresh Menon
- Co-ordinator** : Dr. Shoibal Mukherjee
- Sponsor** : **Pfizer India Ltd., Mumbai**



**IL -52**

**EMERGING ROLES FOR PHARMACOLOGISTS IN INDIA: AN OVERVIEW.**

**Mukherjee S.**

Pfizer, Mumbai, India.

The topic will provide an overview of the emerging environment in relation to growth of drug discovery and development work in India and its impact on clinical research activities, regulatory reform and health care delivery. The speaker will discuss the emerging role of pharmacologists in this context and emphasize the need for educational programmes to cater to these requirements.

**IL -53**

**DRUG DISCOVERY AND DEVELOPMENT: STATUS AND FUTURE.**

**Sankaranarayanan A.**

Torrent, Ahmedabad, India.

The speaker will provide a summary of approaches to drug discovery and the drug development process and discuss issues related to the cost, time and uncertainties associated with bringing new drugs to the market. A round-up of the current drug discovery and development effort within the country will be made. Use of India as a drug manufacturing base, research hub and development centre, and the implications for pharmacology as a specialty will be discussed.

**IL -54**

**GROWTH OF CLINICAL RESEARCH IN INDIA.**

**Mahalaxmibala N.**

Quintiles, Mumbai, India.

The topic will provide an overview of clinical research for drug development, emphasizing the need for GCP compliance, regulatory control, and quality assurance. The current status of clinical research in India will be discussed and future growth prospects will be outlined. The imperatives that make the emergence of clinical research in India a necessity will be emphasized and implications for the country elaborated.

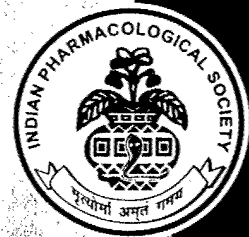
**IL -55**

**PHARMACOECONOMICS: EMERGING NEED.**

**Suresh Menon.**

Fulford, Mumbai, India.

The speaker will give an overview of expected changes in healthcare delivery in the country with the emergence and growth of the private sector healthcare industry and health insurance with third party payment. The implications of these changes and the expected effect of patent protection on the pattern of drug use will be discussed. The need for pharmacoeconomics and outcomes research in providing an insight into public health economics on the one hand and for formulation of drug usage policies on the other will be elucidated.



# ***Scientific Sessions***

**XXXV ANNUAL CONFERENCE OF  
INDIAN PHARMACOLOGICAL SOCIETY**

**IPS  
2002**



# ***Scientific Session I***

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## **Indigenous drugs I**

**Date** : 27.11.2002  
**Time** : 1400-1545  
**Venue** : Hall-B

**Oral Presentation** : OP 20 - OP 27

**Chairpersons** : Dr. P V Diwan  
Prof. R Mathur





OP - 20

**ADAPTOGENIC ACTIVITY OF GLYCO-PEPTIDO-LIPID FRACTION FROM THE ALCOHOLIC EXTRACT OF *TRICHOPUS ZEYLANICUS* GAERTEN. (PART II)**

**Singh B**, Chandan BK, Sharma N, Singh S, Khajuri A, Gupta DK, Suri OP.  
Department of Pharmacology and Natural Products Chemistry, Regional Research Laboratory, Canal Road, Jammu Tawi - 180016.

**Objective:** To develop herbal therapy as an adaptogen. The plant based drugs have emanated on the basis of therapeutic activity. Standardized herbal preparations have better therapeutic potential, efficacy, less toxic and inexpensive.

**Methods:** A new glyco-peptido-lipid fraction isolated from the plant *Trichopus zeylanicus* gaerten. was evaluated for its adaptogenic potential against the chemical and physical stress induced in rats and mice. The parameters studied to assess the anti-stress activity viz. Adjuvant-induced trauma in rats and RBC induced trauma in mice; Antigen (SRBC) induced humoral Immune response in normal and immunosuppressed mice; Chemical (GalN) and physical (immobilization) stress induced hepatic function in rats.

**Results:** The glyco-peptido-lipid fraction (12.5-100 mg/kg, p.o.) showed significant anti-stress activity. The % inhibition observed - in adjuvant-induced trauma injected paw 22.33-66.66% and RBC induced trauma in mice DTH response was 22.80-106.14%, where as humoral antibody study showed a significant increase in primary antibody synthesis in normal mice 14.84-73.75% ; Secondary antibody synthesis 23-63%; and immuno- stimulation in immunosuppressed mice 33.49-84.30%. It has significantly inhibited the severity and incidence of gastric ulceration. It has reversed the chemically and physically stress Induced hepato-pancreatic functions. It did not show any obvious manifestation of acute toxicity observed for 72 hours and finally up to 15 days and appeared safe up to 3 g/kg, p.o. administered in mice.

**Conclusion:** The studies reveal that glyco-peptido-lipid fraction is capable to increase the capacity to tolerate non-specific stress in experimental animals as evident from the results and it does not interfere with the normal physiological functions of the body, this study validate the use of *Trichopus zeylanicus* gaerten as rejuvenator and health tonic.

OP - 21

***TINOSPORA CORDIFOLIA* IN CHRONIC BRONCHITIS: A RANDOMISED CONTROLLED STUDY.**

**Hannan AG**, Baig SM, Dahat SH, Deshpande VY.  
Department of Pharmacology, Government Medical College, Aurangabad & Grant Medical College, Mumbai.

**Objectives:** To evaluate efficacy of aqueous extract of *Tinospora cordifolia* as adjuvant therapy in patients of chronic bronchitis.

**Methods:** 60 patients of chronic bronchitis attending medicine OPD for acute exacerbation were enrolled after obtaining informed written consent and were randomly assigned to receive- *Tinospora Cordifolia* (30) or placebo (30). Patients were evaluated every 15 days for 60 days by Pulmonary function tests, Clinical symptom score and QOL.

**Results:** *Tinospora cordifolia* significantly ( $p < 0.05$ ) increased FEV1 and PEF at the end of 60 days. Number of episodes of acute exacerbations during the study period was significantly ( $p < 0.05$ ) less in study group ( $2.06 \pm 0.41$ ) compared to placebo ( $3.9 \pm 0.79$ ). Clinical symptom scores and QOL scores improved in the study group as compared to placebo. Immunomodulatory and anti-inflammatory properties of *Tinospora Cordifolia* may be responsible for the beneficial effects observed in the study group.

**Conclusion:** *Tinospora Cordifolia* when given as adjuvant therapy improves QOL, clinical symptom score and PFT's in patients of chronic bronchitis.

OP - 22

### EVALUATION OF A HERBAL PREPARATION (HIMAMI'S BOROPLUS CREAM) IN DIFFERENT SKIN DISEASES.

Ram AK, Das AK, Maity RN, Bhattacharjee K, Chanda M.

Deptt. of Pharmacology, Deptt of Community Medicine and Department of Dermatology unit, Calcutta National Medical College and Hospital, Calcutta.

**Objective:** Skin diseases like miliaria rubra, seborrhoea, dermatitis, impetigo and intertrigo are common in lower socio-economic group of population. Though many antifungal and anti-bacterial preparations of modern medicines are available, but they are neither affordable nor without any adverse effects. Hence there is a need to explore clinical benefits of herbal medicine in skin diseases. This is a short term study to determine the benefits of herbal preparation containing neem, tulsi, liquorice, sandal wood and turmeric in the treatment of above skin diseases.

**Method:** 200 patients suffering from one of the above skin diseases were selected from the patients and their guardians attending Immunization Clinic of Department of Community Medicine and out patient department of Dermatology Unit of Calcutta National Medical College and Hospital were randomised into two groups and received either drug or placebo externally twice daily for 4 weeks. Clinical assessment of the skin lesions were done weekly for number, extent, itching, pain and signs of inflammation for 4 weeks.

**Result:** The herbal drug has significant superiority in relieving itching, pain and signs of inflammation and in reducing number and extent of lesions as compared to placebo.

**Conclusion:** Though clinical improvement is seen, separate study with large number of population are required to evaluate the affect of the herbal preparation in individual skin diseases which are in progress.

OP - 23

### EFFECT OF TOPICAL INDIGENOUS FORMULATION IN RELIEF OF JOINT PAIN.

Bose S, Biswas H, Maiti RN, Chaudhuri SB, Ram AK, Das AK.

Deptt of Physical Medicine and of Pharmacology, Calcutta National Medical College and Hospital, Calcutta.

**Objective:** The indigenous formulation comprising of *Mentha arrensis*, *Trachyspermum ammi*, *Cinamomum camphora*, oil of *Eucalyptus globulus*, oil of *Gaultheria procumbens*, oil of *Pinus roxburghi* and oil of *Syzigium taromaticum* has been in use as an ointment for somatic pain. The present study is undertaken to ascertain the effectiveness and safety of the above formulation in joint pain.

**Method:** 100 patients between 18-50 years suffering from joint pain are randomly selected from the patients attending Physical Medicine O.P.D. of Calcutta National Medical College and Hospital. They are randomly assigned to apply the active drug and identical placebo ointment over the affected joint 3 times daily for 4 weeks in a double blind fashion. Besides this, patients are allowed to consume only Nimesulide (100 mg) as and when required. The patients are evaluated once weekly for 4 weeks for severity of pain (pain score by visual analogue scale), number of nimesulide (100 mg) tablet consumed per day, subjective feeling and any adverse effect produced.

**Result:** Statistically significant superiority is observed in the pain score, number of NSAID consumed, and subjective feeling of the patient. No significant adverse effect is observed in the drug treated group.

**Conclusion:** Camphor, menthol, eucalyptus oil present have cooling, local anaesthetic and counter irritant effect which alter the emotional concomitance of the pain and thereby lower the feeling of pain.

OP - 24

**A CASE REPORT OF ADR DUE TO MIS-IDENTIFICATION BY AN INDIGENOUS DRUG.**

Rahman SZ\*, Latif A\*\*, Singhal KC.\*

Department of Pharmacology, J. N. Medical College and \*\*Dept. of Ilmul Advia, A. K. Tibbia College, Aligarh Muslim University, Aligarh -202002.

Roots of *Ruta graveolens* Linn. (Common name Suddab) is used in Unani System of Medicine for the treatment of vitiligo. During phase IV clinical trial conducted at A. K. Tibbia College (AMU, Aligarh), adverse drug reactions of *R. graveolens* Linn were monitored. The plant roots were procured from local suppliers, washed for any extraneous material, dried and pulverized. Patients of vitiligo were administered 2-3 gm root powder orally (dose related to extent of disease) twice a day with water. The powder mixed with vinegar was also applied locally over the affected parts of body and patients were asked to take sunbath for 4-5 minutes after application. No other drug was administered simultaneously or applied locally. Twenty-one patients developed adverse reactions. These include epistaxis in 12 patients (all males, 15-25 years), nausea/vomiting in 8 patients (both sexes, 30-40 years) and nematuria in 1 patient (female 10 years). Dechallenge was positive in all patients. Rechallenge was not attempted. The plant is in use since long for the treatment of vitiligo and no adverse reactions were ever noticed or reported. Pharmacognostic evaluation revealed that *Euphorbia dracunculoides*, which closely resembles *R. graveolens* Linn was being marketed as replacement of the later. Thus the adverse reactions observed were due to *E. dracunculoides* and occurred because of mis-identification.

OP - 25

**PERSPECTIVES OF INDIGENOUS DRUGS AS FEMALE CONTRACEPTIVE.**

Prakash AO.

Laboratory of Contraceptive Research & Reproductive Health, School of Studies in Zoology, Jiwaji University, Gwalior - 474011.

Population control has remained a burning global issue and in spite of enormous efforts made in this direction by demographers, media, scientists and administrators, the increasing trend is still prevailed in most of the countries especially the underdeveloped ones. Although number of approaches like hormonal, intra-uterine devices (IUD's), surgical, barrier and traditional methods are being used but a woman tolerates these contraceptive methods at some cost. History of Indian Traditional Medicinal Plants is very old and midwives were having the knowledge of using medicinal plants for contraception, abortion and inducing labour. However, their modus operandi was lacking scientific support. Since long time efforts are being made by various scientific bodies including World Health Organization to initiate screening of Medicinal Plants for antifertility activity in males and females. Ministry of Health & Family Welfare has also established its testing centres and during last forty years thousands of plants have been tested at different testing centres including of WHO sponsored ones using a standard protocol. Investigations carried out at different laboratories vary due to the variation in the collection of plants, storage and preparation of extract. Although number of plants have been listed under the potent anti-fertility plants but their scope in the area of new drug development is faint. Till date no single plant or its active constituent is yet available which may be marketed as a potent, safe and economic herbal contraceptive agent for women. Nevertheless, none of these potent plants have yet passed through the clinical trials which is considered as a pre-requisite for a drug controller to release the drug for formulation. Studies, scope and limitations of these medicinal plants will be discussed in relation to their development as potent contraceptive agent.

OP - 26

### WORMICIDAL ACTIVITY OF LATEX OF *CALOTROPIS PROCERA*.

Kumar VL, Shivkar YM.

Department of Pharmacology, All India Institute of Medical Sciences, New Delhi - 110029.

**Objective:** To investigate the anthelmintic activity of dried latex (DL) of *Calotropis procera* on earthworms.

**Methods:** Latex was collected from aerial parts of the plant and was used either fresh or after drying in shade. Earthworms, *Lumbricus terrestris*, four each were placed in a Petri dish containing either aqueous extract of DL (5, 10, 50, 100 mg/ml) or different dilutions of fresh latex (1, 5, 20, 50, and 100%). The worms were observed for their spontaneous motility (paralysis) and evoked responses to pinprick which were scored from 0 to 4. The paralytic score was recorded at different time intervals. Immediately after inhibition of response to pinprick, the worms were placed in fresh water and observed for recovery. Duration required for final recovery or death was noted. Mean paralytic score was plotted against time and compared with piperazine (3% solution) as reference standard.

**Results:** Both fresh as well as aqueous extract of dried latex exhibited a dose-dependent inhibition of spontaneous motility and evoked responses to pinprick. The paralytic effect was evident at 90 min while higher concentrations produced death within 60 min. Piperazine on the other hand produced grade 3 paralysis within 30 min and the effect could be reversed on placing the worms in fresh water.

**Conclusion:** The results show that latex possesses wormicidal activity.

OP - 27

### EVALUATION OF ANTIULCER PROPERTY OF *CYNODON DACTYLON* IN PYLORIC LIGATION MODEL OF RATS.

Gowda Veerabhadra, Holla Rajendra.

Department of Pharmacology, International Centre for Health Sciences, MAHE, Manipal-576119.

**Objective:** To evaluate antiulcer property of *Cynodon dactylon*

**Methods:** : In male albino rats, peptic ulcers were induced by pyloric ligation method. Animals were divided into 3 groups with 8 animals in each group. One hour before pyloric ligation, normal saline, Famotidine and solution of lyophilized powder of *C. dactylon* were administered to Group I (control), Group II (standard) and Group III (Test) respectively. Animals were sacrificed 22 hours after ligation and abdomen was cut opened. Parameters observed are: Ulcer index, volume of gastric juice, pH of gastric juice, free acidity and total acidity.

**Results:** Famotidine produced a significant reduction in mean ulcer size, ulcer number and ulcer index. Volume of gastric juice secretion, free acidity, and total acidity were also reduced significantly. *Cynodon dactylon* produced a significant reduction in mean ulcer number, ulcer index and, volume of gastric acid secretion where as reduction in mean ulcer size free acidity and total acidity were not statistically significant

**Conclusion:** *C. dactylon* produced a significant reduction in the ulcer number, ulcer index and volume of gastric juice. However reduction in ulcer size, free acidity and total acidity of gastric juice was not significant. Hence, *C. dactylon* may have antiulcer activity.

## ***Scientific Session II***

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### **Cardiovascular pharmacology and Anti-inflammatory agents**

**Date** : 27.11.2002  
**Time** : 1400-1545  
**Venue** : Hall

**Invited Lectures** : Dr. Kazim Husain  
Dr. R K Goyal

**Oral Presentation** : OP28 - OP36

**Chairpersons** : Prof. M K Ticku  
Dr. D Parmar



**IL-56****PHYSICAL CONDITIONING AND NITRIC OXIDE DEFICIENT HYPERTENSION.****Husain Kazim.**

Division of Cardiothoracic Surgery, Department of Surgery, Southern Illinois University School of Medicine, Springfield, IL, 62794-9638, USA.

**Objective:** Hypertension is a substantial health problem in the US affecting millions of individuals. However, the molecular mechanism of nitric oxide-deficient hypertension is not well studied. Therefore, the study objective was to investigate the interaction of physical training and chronic nitric oxide synthase (NOS) inhibitor (Nitro-L-Arginine Methyl ester, L-NAME) treatment on blood pressure (BP) and associated molecular changes in cardiovascular system of the rat.

**Methods:** Fisher 344 rats were divided into four groups and treated as follows: 1) Sedentary control, 2) Exercise training (ET) for 8 weeks. 3) L-NAME (10 mg/kg, s.c. for 8 weeks) and 4) ET + L-NAME. BP was monitored with tail-cuff method. The animals were sacrificed 24 hr post treatments and thoracic aorta and heart were isolated and analysed.

**Results:** Physical conditioning increased cardiovascular NO system as well as vascular endothelial growth factor (VEGF) gene expression. Training enhanced cardiovascular GSH/GSSG ratio and up-regulation of antioxidant enzymes. Training also caused depletion of cardiovascular malondialdehyde (MDA) and protein carbonyls. Chronic L-NAME administration resulted in depletion of cardiovascular NO system, VEGF gene expression, GSH/GSSG ratio and down-regulation of antioxidant enzymes. L-NAME administration elevated BP, xanthine oxidase, MDA and protein carbonyls. Interaction of training and L-NAME resulted in normalization of BP and up-regulation of antioxidant defense system.

**Conclusion:** Physical conditioning attenuated the oxidative injury caused by chronic NOS inhibition by up-regulating the cardiovascular antioxidant defense system, VEGF gene expression and lowering the BP in rats.

**IL-57****ROLE OF 5-HT<sub>2A</sub> RECEPTORS IN CARDIOVASCULAR COMPLICATIONS ASSOCIATED WITH DIABETES MELLITUS.****Goyal RK.**

Dept. of Pharmacology, L.M College of Pharmacy, Ahmedabad - 380 009.

The association between 5-Hydroxytryptamine (5-HT) and its role in glucose control has been a subject of controversy for last couple of decades. It is however, known that mania and positive schizophrenia are associated with hyperglycemia and hyperserotonergia, whereas, depression and negative schizophrenia are associated with hypoglycemia and hyposerotonergia. Initial data from our laboratory indicated the hyperglycemic effect of 5-HT involving 5-HT<sub>2A</sub> and 5-HT<sub>3</sub> receptors. Diabetes co-exists with incidences of heart failure and development of cardiomyopathy and 5-HT regulates cardiovascular function through central as well as peripheral mechanisms. The beneficial effects of 5-HT antagonists however, have not been studied except for anti-thrombotic effects of sarpogrelate in diabetic situation. In view of the importance of glucose carriers in cardiac function and considering critical role of 5-HT<sub>2A</sub> receptors in cardiovascular pathophysiology in diabetes, we studied the effect of chronic treatment with 5-HT<sub>2A</sub> antagonist sarpogrelate in STZ diabetic rats with a view to project 5-HT<sub>2A</sub> receptors as a potential target for anti-diabetic drugs. It was found that 5-HT<sub>2A</sub> receptors are not only involved in glucose transport mechanisms but also that increase in glucose transporters in cardiomyocytes by sarpogrelate may be independent of insulin. Based on our results it is suggested that 5-HT<sub>2A</sub> receptors may be looked upon as a novel target to develop anti-diabetic drugs to prevent the cardiovascular complications associated with diabetes mellitus considering (a) the close association between 5-HT<sub>2A</sub> receptors and glucose transporters, (b) the beneficial effects of 5-HT<sub>2A</sub> receptor antagonists like sarpogrelate in cardiovascular abnormalities and (c) the link between cardiac dysfunction and glucose metabolism.



OP - 28

### COMPARATIVE STUDY OF ANTI-HYPERTENSIVE ACTION OF LOSARTAN AND CANDESARTAN IN MILD TO MODERATE HYPERTENSION.

Das AK<sup>1</sup>, Hazra A<sup>1</sup>, Maity AK<sup>2</sup>, Bhattacharyya D<sup>1</sup>.

<sup>1</sup>Department of Pharmacology, University College of Medicine, Kolkata - 700020;  
<sup>2</sup>Department of Cardiology, Institute of Postgraduate Medical Education and Research, and Seth Sukhlal Karnani Memorial Hospitals, Kolkata - 700020.

**Objective:** Comparison of antihypertensive efficacy and tolerability of candesartan with losartan.

**Methods:** A prospective, single-blind randomized controlled trial with two parallel treatment groups was carried out at the cardiology clinic of IPGME & R, Kolkata. Subjects included were male aged 25-65 y or postmenopausal females up to 65 y age, with sitting diastolic blood pressure (BP) 90-110 mm Hg. Written informed consent was obtained. Major exclusion criteria were secondary, severe or complicated hypertension, severe systemic diseases and concomitant confounding medication use. Eligible subjects were randomized to receive either candesartan 8 mg once daily or losartan 50 mg once daily orally and follow-up every 2 weeks. Up titration to double the starting dose was done in subjects not responding adequately (i.e. diastolic BP > 90 mmHg). Treatment was for 8 weeks. Sitting BP was recorded at each follow-up visit and at study end. Routine biochemistry was done at screening and concluding visits. Adverse events reported spontaneously, detected at clinical examination or gathered from the trial diary were recorded to assess safety profile. All subjects were evaluated for safety. Efficacy analysis was carried out for subjects who reported for at least 2 follow-up visits.

**Results:** There were 31 efficacy-evaluable patients in the candesartan group and 32 in the losartan group. Mean changes in systolic and diastolic BP were - 21.1 mmHg and - 11.9 mmHg ( $p < 0.001$ ) respectively in candesartan and -17.4 mmHg and -14.8 mmHg ( $p < 0.001$ ) respectively in losartan-treated patients. Between group differences were not significant. Candesartan group had serum triglyceride reduction of 16.5% ( $p = 0.037$ ) and losartan group had serum uric acid reduction of 7.3% ( $p = 0.024$ ) from baseline. Adverse events were generally mild and similar in both groups. Possibly drug-related events forced 3 withdrawals in the candesartan and 1 in the losartan group.

**Conclusion:** Candesartan was a well-tolerated antihypertensive comparable in efficacy to losartan.

OP - 29

### THE EFFECT OF NABUMETONE, A SELECTIVE COX-2 INHIBITOR NSAID ON RENAL EXCRETION OF WATER AND SODIUM IN RATS.

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Physiology Department, Medical School, USM, 16150 Kubang Kerian, Kelantan, Malaysia.

Non-steroidal anti-inflammatory agents (NSAIDs) are known to produce deleterious side effects on renal function. The discovery of the COX-2 iso enzyme has led to believe that COX-2 selective inhibition would provide the potent therapeutic effects of the traditional NSAIDs without the side effects. The purpose of this study is to investigate the effects of Nabumetone, a selective COX-2 inhibitor NSAID on renal handling of sodium and water in conscious rats. Twenty male Sprague-Dawley rats weighing between 200-220 gm were housed in metabolic cages for a total duration of 5 weeks. The study period consisted of four phases, namely, acclimatization phase (1 week), control phase (1 week), experimental phase (2 weeks) and recovery phase (1 week). Food and water were provided *ad libitum*. All animals were treated identically during the acclimatization, control and the recovery phases. During the experimental phase, however, the animals in the Nabumetone group ( $n = 10$ ) received 3 mg/ 200 g body weight/day of Nabumetone dissolved in 0.5 ml of saline orally. Animals in the control group ( $n = 10$ ) received only 0.5 ml of saline orally. 24 hour water intake, urine output, osmolality, osmolal output and urinary sodium were estimated in all animals. Statistical analysis was performed using analysis of variance for repeated measurements. There were no significant differences in all parameters in all phases. From the data it appears that Nabumetone has not produced any deleterious side effects on renal function in conscious rats.

OP - 30

**COMPARISON OF ACUTE ANTI-INFLAMMATORY ACTIVITIES OF OCIMUM SANCTUM, AZADIRACHTA INDICA AND DICLOFENAC IN RATS.**

Seshadri J, Kakkeri RH, Ramabhimaiah S.  
M.R. Medical College, Gulbarga - 585105.

**Objectives:** To compare the acute anti-inflammatory activities of *Ocimum sanctum*, *Azadirachta indica* and Diclofenac in rats.

**Methods:** Wistar albino rats (body weight 120 - 150 g) were divided into 3 groups, with each group containing 5 rats. All drugs were given orally. First group was control group, receiving no drug. Second group received Diclofenac (4.5 mg/kg), third group received *Ocimum sanctum* 2 ml fourth group received *Azadirachta indica* 2 ml, an hour before subplantar injection of 1% carrageenin. Paw volume was measured plethysmographically in each group at zero and 3 hours.

**Results:** Diclofenac showed 55 % inhibition of rat paw edema, whereas *Ocimum sanctum* showed 9% inhibition of rat paw edema, while *Azadirachta indica* did not show any inhibitory activity.

**Conclusions:** Diclofenac has significant anti-inflammatory activity ( $P < 0.05$ ). *Ocimum sanctum* has little anti-inflammatory property ( $P > 0.05$ ) and *Azadirachta indica* has no anti-inflammatory activity.

OP-31

**PREDICTION OF CARDIOVASCULAR EVENTS: CORRELATION WITH CARDIOVASCULAR RISK FACTORS.**

Bargaje RS, Gupta A, Shah V, Kaliya D, Manjrekar K, Khan M, Joshi R, Rao SN, Deshmukh YA.  
Department of Pharmacology, TNMC and BYL Nair Chest Hospital, Mumbai.

**Objective:** To find an association between known cardio-vascular risk factors and ischaemic stroke in Indian population.

**Methods:** Retrospective, unicentric study conducted involving 201 patients who have suffered from ischaemic stroke from 1997-2001. The modifiable risk factors (HT, DM, Total Cholesterol levels and Personal habits) were analysed for their risk in ischemic stroke.

**Results:** (1) Uncontrolled HT were twice as compared to controlled HT (64.82% vs 35.18%); (2) Uncontrolled DM were 5 times as compared to controlled DM (78.95% vs 21.05%); (3) Hypercholesterolemia ( $>200$  mg %) was found in 45% of the patients; (4) Smokers, Alcoholics and tobacco chewers accounted for 15.84%, 23.77% and 20.79% respectively; (5) The mean age was  $55.19 \pm 13.72$  yrs with males twice at risk (67.33% vs 32.66%).

Multiple logistic regression revealed greatest impact of HT and hypercholesterolemia of all the factors studied.

**Conclusion:** Modifiable risk factors have established role in CHD. These risk factors hold considerable amount of probability for ischemic stroke also, hence must be controlled to reduce the risk for development of ischemic stroke.

OP-32

### ANTIOXIDANT- ACTIVITY OF FOLIC ACID IN HYPERCHOLESTEROLEMIC MODEL.

**Khanna N\***, Arora D\*, Mahajan P\*, Sharma SB\*\*.

\*Department of Pharmacology; \*\*Department of Biochemistry, University College of Medical Sciences & GTB Hospital, Shahdara, Delhi- 110095.

**Objective:** To study the antioxidant activity of Folic Acid (FA) in hypercholesterolemic rabbits.

**Methods:** Sixteen male albino rabbits were made hypercholesterolemic after feeding cholesterol (500mg/animal/day) for 8 weeks after which the animals were randomly assigned to two groups. Group 1 received normal saline and Group 2 received FA (0.5mg/kg/day) for 6 weeks. Erythrocyte superoxide dismutase (SOD) and catalase (CAT) as well as lipid peroxide (MDA) levels in serum and platelet rich plasma (PRP) were measured at 0, 8 and 14 weeks.

**Results:** FA administration decreased serum and PRP MDA levels significantly ( $p < 0.001$ ). Erythrocyte SOD and CAT activities were raised in the drug treated group ( $p < 0.001$ ).

**Conclusions:** Our study suggests an antioxidant activity of FA in hypercholesterolemic model. This action may be one of the mechanisms involved in improvement of endothelial function by FA in coronary artery disease.

OP-33

### EFFECT OF RDH- 1 ON EXPERIMENTALLY INDUCED HYPERTENSIVE ANIMALS.

**Tamhankar K**, Balaraman R.

Pharmacy Department, Faculty of Technology and Engineering, Kalabhavan, M.S.University of Baroda, Baroda- 390010.

**Objective :** To study the effect of RDH-1 on experimentally induced hypertensive animals.

**Method:** RDH-1(250 mg/kg/day, p.o ) and Amlodipine (500  $\mu$ g/kg/day, p.o) for 4 weeks was given to DOCA salt-treated hypertensive rats and CdCl<sub>2</sub> treated hypertensive rats as well as to normotensive rats. The blood pressure and pressor responses to adrenaline, noradrenaline (1 and 2  $\mu$ g/kg) and isoprenaline (1  $\mu$ g/kg) were recorded in these rats.

**Results :** Treatment with RDH-1 (250 mg/kg/day, p.o ) or Amlodipine (500  $\mu$ g/kg/day, p.o) for 4 weeks, reduced the blood pressure of unilaterally nephrectomised DOCA salt- treated hypertensive rats. Similar reduction in blood pressure was also observed in the CdCl<sub>2</sub> (1 mg/kg/day, i.p ) for 2 weeks treated hypertensive rats. The pressor response to adrenaline, noradrenaline (1 and 2  $\mu$ g/kg) was reduced by chronic administration of RDH-1 or Amlodipine in these hypertensive animals. However RDH-1 (250 mg/kg/day, p.o) or Amlodipine (500  $\mu$ g/kg/day, p.o) administered to normotensive albino rats for 4 weeks did not alter the mean blood pressure and the pressor response to adrenaline, noradrenaline(1 and 2  $\mu$ g/kg) and isoprenaline (1  $\mu$ g/kg).As the research work is in progress the results for in vitro studies would be discussed at the time of presentation.

**Conclusion:** Part of this study demonstrates that RDH-1 has antihypertensive effect.

OP - 34

### EVALUATION OF SOME AZOLES ON WOUND HEALING IN ALBINO RATS.

Girish MB, Muppayyanavarmath SS, Patil PA.

Department of Pharmacology and Pharmacotherapeutics, J.N. Medical College,  
Nehru Nagar, Belgaum - 590010.

**Objectives:** To investigate the influence of metronidazole and tinidazole on resutured incision and dead space wounds in albino rats.

**Materials and methods:** Resutured incision and dead space wounds were induced in Wistar rats of either sex under light ether anaesthesia, taking aseptic precautions. Control animals received normal saline and other groups received metronidazole (108 mg/kg) and tinidazole (180 mg/kg) body weight for a period of 10 days. On 11<sup>th</sup> day after estimating breaking strength of resutured incision wounds (under anaesthesia) animals were sacrificed and granulomas were removed for estimating breaking strength. Quantification of granulation tissue and their biochemical as well as histological studies in control and treated groups were done.

**Results:** Both metronidazole and tinidazole significantly enhanced breaking strength of incision wound, dry weight and hydroxy-proline content of granulation tissue when compared to control group.

**Conclusion:** Metronidazole and tinidazole promote wound healing.

OP-35

### A SIMPLE MODIFIED METHOD FOR RECORDING ANTI-INFLAMMATORY EFFECT ON DOG PAW OEDEMA.

Sharma AB, Sharma RK, Misraulia KS.

Department of Veterinary Medicine, College of Veterinary Science and Animal Husbandry, Mhow - 453446.

A simple modified method for recording dog paw oedema has been devised using common glassware available in the laboratory. Two pipettes of 25 ml capacity were connected by means of plastic tube at the bottom of assembly. The proximal end of right side pipette was connected by means of pressure tubing to glass vessel of 5 cm diameter and distal end of left side pipette was connected by means of pressure tubing to a 50 ml glass syringe. About 67 ml of mercury was filled in the pipettes and connecting tube (bottom) and mark zero in the pipette, which was connected to glass vessel, with the help of glass syringe. The space between the zero mark in the right side pipette and the fix mark on the glass vessel was filled with water.

**ANTI-INFLAMMATORY ACTIVITY OF SERRATIOPEPTIDASE AND ITS COMBINATION WITH DICLOFENAC SODIUM IN RATS.**

**Turankar AV**, Motghare VM, Dakhale GN, Pashu Shaikh, Khobragade LR, Satyajit Jagtap.

Dept. of Pharmacology, Govt. Medical College, Nagpur- 3.

**Objective:** The present animal study was planned to find out the anti-inflammatory activity of serratiopeptidase alone and in combination with diclofenac sodium.

**Materials and methods:** Albino rats of either sex weighing between 100-200 grams were divided into 4 categories (groups of 6 rats each). Acute inflammation was produced by sub planter injection of 0.1 ml carrageenin in normal saline in the right hind paw of the rats. The following groups were kept. Group - 1 (Control; normal saline 0.3 ml/100 gm intraperitoneally), Group - 2 (Serratiopeptidase 20 mg/kg orally), Group - 3 (Diclofenac sodium alone 2.5 mg/kg), Group - 4 (both Serratiopeptidase orally and Diclofenac sodium i.p). The change in volume of hind paw was measured between 3 hr and 0 hr and between 4 hr and 0 hr.

**Results:** The analysis showed serratiopeptidase alone and diclofenac sodium alone and their combination produced anti-inflammatory (edema reducing) activity up to 3 hrs as compared to control and the combination of serratiopeptidase and diclofenac sodium was longer acting up to 4 hrs. There was no statistical difference between serratiopeptidase alone and diclofenac sodium alone when compared with each other. The combination of serratiopeptidase and diclofenac sodium was having statistically more significant anti-inflammatory activity than serratiopeptidase alone at 3 hrs. However, the combination of serratiopeptidase and diclofenac sodium did cause more reduction in edema as compared with diclofenac sodium alone.

**Conclusion:** Our study on animals has shown that oral serratiopeptidase has anti-inflammatory action, which is nearly equivalent to diclofenac sodium at 3 hrs. The combination of serratiopeptidase and diclofenac sodium is showing more reduction the hind paw edema of rats as compared with control, serratiopeptidase alone but equivalent to diclofenac alone at 3 hrs and is longer acting showing reduction in edema up to 4 hrs.

# ***Scientific Session III***

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## **Rational use of drugs**

**Date** : 27.11.2002  
**Time** : 1600-1800  
**Venue** : Hall - A

**Oral Presentation** : OP37 - OP47

**Chairpersons** : Prof. V Dadkar  
Prof. N S Parmar



OP - 37

### A STUDY ON SELF-MEDICATION PRACTICES IN AND AROUND POKHRA SUB-METROPOLITAN CITY, WESTERN NEPAL.

Shankar PR, Partha P, Shenoy NK.

Departments of Pharmacology and Internal Medicine, Manipal College of Medical Sciences, Pokhara, Nepal.

**Objectives:** The main objectives of our study were: 1) to obtain baseline data on self-prescribing in Pokhara city and the surrounding villages, 2) to obtain information on the factors influencing self-prescribing, 3) to note an association, if any between self-prescribing and demographic factors.

**Methods:** 242 respondents selected by simple random sampling were interviewed in the first fortnight of February 2002 using a semi-structured questionnaire. Demographic information and information on drugs used for self-medication was collected.

**Results:** 128 respondents (52.9 %) were male while 114 (47.1 %) were female. 129 respondents were aged between 20 to 39 years. 174 respondents stayed within 30 minutes walking distance of a health post/medical store. 59.1 % had taken some form of self-medication in the 2 month period preceding the study. Paracetamol, other analgesics, cold remedies and herbal preparations were commonly used. The reasons for self-medication were mild illness, previous experience of treating a similar illness and non-availability of health personnel. A significantly higher proportion of male respondents and young (< 40 years) respondents had used self-medication.

**Conclusions:** Self-medication was common. Drugs, especially antimicrobials, were not taken for the proper duration and were stopped on symptomatic improvement. Education to help patients decide on the appropriateness of self-medication is required.

OP - 38

### MEDICATION USE IN EARLY PREGNANCY: A STUDY IN A TEACHING HOSPITAL IN WESTERN NEPAL.

Sarkar C<sup>1</sup>, Das B<sup>1</sup>, Datta A<sup>2</sup>, Bohra S<sup>2</sup>

<sup>1</sup>Department of Pharmacology, Manipal College of Medical Sciences, P.O. Box 155, "Deep Heights", <sup>2</sup>Department of Obstetrics and Gynecology, Manipal Teaching Hospital, Fulbari, Pokhara, Nepal.

**Objectives:** The question of prescription quality of gynecologists & practitioners and drug use by women has not been adequately addressed by the occasional studies conducted. The aim of the present study was to investigate the pattern and extent of drug use in early pregnancy in the context of a large teaching hospital situated in western Nepal.

**Methods:** Medication use was assessed from 595 prescriptions (for early pregnancy) collected at random from the antenatal care (ANC) in obstetrics out-patient department (OPD) at Manipal Teaching Hospital (MTH), Nepal for this study.

**Results:** The mean maternal age and haemoglobin concentration were 25 years and 13.2 g/dL, respectively. Out of 595 prescriptions analysed, 30% were non-drug prescriptions. 28%, 35% and 7% prescriptions contained one, two and three medications, respectively. 26.8% of women had attended obstetrics OPD owing to maternal disorder other than routine antenatal check-up (73.2%). Problem oriented drug use was due to nausea/vomiting (12.8%), dyspepsia (3.5%), per vaginal spotting/bleeding (3.4%), mainly. Total number of drugs prescribed was 701. Average number of drugs/prescription was 1.2. The most commonly prescribed drugs were nutritional supplements like iron, folate, calcium, vitamins (65.5%) followed by gastrointestinals (11.7%) and antimicrobials (8.3%), etc.

**Conclusions:** Though, the selection of drugs was rational in most of the cases, some anomalies were observed and discussed with the clinicians. Our data reflect the general extent and prescribing pattern for those Nepalese pregnant women attending hospital in western Nepal.



OP - 39

### A STUDY OF DRUG USE DURING PREGNANCY IN A TEACHING HOSPITAL IN WESTERN NEPAL.

Das B<sup>1</sup>, Sarkar C<sup>1</sup>, Datta A<sup>2</sup>, Bahra S<sup>2</sup>.

<sup>1</sup>Department of Pharmacology, Manipal College of Medical Sciences, P.O. Box 155, 'Deep Heights', <sup>2</sup>Department of Obstetrics and Gynecology, Manipal Teaching Hospital, Fulbari, Pokhara, Nepal.

**Objectives:** Information on the use of drugs during pregnancy is scarce and rather anecdotal. Careful consideration of the benefit to the mother and the risk to the fetus is required when prescribing drugs during pregnancy. The aim of this study was to gain knowledge on this issue in Western Nepal.

**Methods:** 2156 prescriptions of pregnant women were collected at random from the antenatal care (ANC) in obstetrics out-patient department (OPD) at Manipal Teaching Hospital (MTH), Nepal and analysed for this study.

**Results:** The mean maternal age and haemoglobin concentration were 25 years and 12.21 g/dL, respectively. 23% women attended obstetric OPD due to maternal disorders other than routine ANC (77%). Problem oriented drug use was due to nausea/vomiting (4 - 7%), dyspepsia (3.1%) and per vaginal spotting/bleeding (3.4%), mainly. Most of the women got 2-3 drugs and commonly included nutritional supplementation and tetanus toxoid. The average number of drugs/prescription was 2.0. 15.37% and 64.8% drugs were prescribed by generic name and as fixed dose combinations, respectively. The most commonly prescribed drugs were nutritional supplements like iron, folate, calcium, vitamins (72.8%) followed by tetanus toxoid (12.4%), gastrointestinals (5%), antimicrobials (4.6%), etc.

**Conclusions:** Though, the selection of drugs was rational in most of the cases, some anomalies were observed and discussed with the clinicians. Our data reflect the general extent and prescribing pattern for those Nepalese pregnant women attending hospital in western Nepal.

OP - 40

### STUDY OF PATTERN OF NON-PRESCRIPTION DISPENSING.

Barve RM, Ghongane BB, Radha Yegnanarayan.

Department of Pharmacology, B.J. Medical College, Pune - 411001.

**Objective:** To study pattern of non-prescription dispensing by interviewing customers visiting chemist's shop to purchase medicines.

**Methods:** Three retail pharmacies in suburban areas of Pune were selected. The customers visiting these shops for purchasing the drugs were interviewed. A proforma which was used for the study included age, sex, serial number of customers, drug-name (generic/brand), drug -quantity and ailment. Non prescription dispensing pattern was determined in terms of its percentage, class of drugs and the cost of dispensed drugs.

**Results:** Out of 600 customers interviewed 216 (36%) customers were having non-prescription Dispensing. Average age of customer using non-prescription medicines was 33.94 yrs. Out of 216 customers 56.5% were males and 43.5% were females. Commonest classes of non-prescription dispensed drugs were analgesics (20.6%) and antibiotics (20.2%). The commonest ailments for which non-prescription dispensing was done were gastrointestinal disorders (22.7%), painful conditions (20.8%) and respiratory disorders (19.0%). Average cost of non-prescription dispensed drugs for single customer was Rs.16.67. **Conclusion:** The incidence of non-prescription dispensing is 36% analgesics and antibiotics are common among them.

**OP - 41**

**SURVEILLANCE OF ANTIMICROBIAL AND OTHER DRUG PRESCRIPTIONS IN INDOOR PATIENTS OF IGMCH, NAGPUR.**

**Badar VA, Shrivastava MP, Bansod KA.**

Department of Pharmacology, Indira Gandhi Medical College, Nagpur - 440018.

**Objective:** Surveillance of antimicrobial and other drug prescribing in indoor patients of Medicine of IGMCH, Nagpur.

**Methods:** Data was collected from records of patients admitted in medicine wards of IGMCH; for the period of 1<sup>st</sup> May to 30<sup>th</sup> June 2002. A total number of 112 records of patients were studied regarding patient's name, age, sex, reg. No., diagnosis, antimicrobial and other treatment received. The parameters of antimicrobials studied were drug dose, route, frequency and duration of administration. Analysis of rationality of administration of antimicrobials was done by modified Kunin's criteria.

**Results:** The total number of drugs prescribed in 112 patients was 694, on average 6 drugs per patient. The range of drugs prescribed per patient was 1 - 15. The most frequently prescribed group of drugs were antimicrobial agents. Ampicillin was most commonly prescribed antimicrobial agent, which constitute 61.6 %, followed by Metronidazole 37 % and Gentamycin 33 %. The duration of AMAs ranged from 3 - 15 days. Only 5 patients were treated according to the culture sensitivity report. According to modified Kunin's criteria, use of antimicrobial agents was inappropriate in 38 % patients.

**Conclusion:** Periodic therapeutic audit is necessary to rationalise the use of drugs.

**OP - 42**

**INTENSIVE ADR MONITORING OF OLANZAPINE IN 100 PATIENTS - A PHARMACOVIGILANCE STUDY AT NATIONAL PHARMACOVIGILANCE CENTRE.**

**Pradhan S, Gupta, SK, Berry N.**

Department of Pharmacology, All India Institute of Medical Sciences, New Delhi-110029.

Olanzapine is, an atypical antipsychotic agent of the thienobenzodiazapine group. Because of its unique pharmacological profile, it is widely being used as a first line antipsychotic drug in the management of schizophrenia and bipolar affective disorder. In view of worldwide reports of metabolic abnormalities associated with its use, National Pharmacovigilance Centre, All India Institute of Medical Sciences, New Delhi, conducted a study to assess the adverse effect profile of olanzapine. The resident doctors of Department of Pharmacology in association with the department of Psychiatry, were involved in the intensive monitoring of 100 inpatient and outpatients over a 3-month period. Changes in weight ECG, lipid profile and blood glucose estimation were included in the adverse drug reaction monitoring. Analysis of the adverse effects revealed that olanzapine induced weight gain, hypertriglyceridaemia and hyperglycemia is a significant cause for concern that is likely to affect the health of such patients. One case report of Neuroleptic Malignant Syndrome associated with the use of olanzapine highlights the fact that though incidence of extra pyramidal symptoms with olanzapine is less, physicians need to be vigilant about this potentially life threatening ADR.

OP - 43

### PRESCRIBING PATTERN OF LIPID LOWERING DRUGS (LLD) IN NORTH INDIA: ANALYSIS OF RATIONALITY.

**Goyal P**, Sharma G, Bal BS\*, Singh J, Pandhi S, Singh Jagjit, Randhawa GK.  
Department of Pharmacology and Department of Medicine, and Government Medical College, Amritsar.

**Introduction:** The presentation of dyslipidemia and atherogenic risk factors in South Asians is unique. There has been controversy over the applicability of the National Cholesterol Education Programme (NCEP) guidelines to the South Asians. The objective was to study the pattern adopted by Indian physicians for prescribing lipid-lowering drugs (LLDs).

**Methods:** This observational study was carried out (from June to August 2000) in 200 patients at the Department of Medicine of a teaching hospital in North India. The baseline serum levels of total cholesterol(TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), triglycerides (TG) and lipoprotein (a)[Lp(a)] were recorded. The pattern of prescribing LLD was compared with the NCEP and other guidelines.

**Results:** The mean  $\pm$  SD levels (mg%) were: TC ( $223 \pm 22$ ), LDL-c ( $132 \pm 27$ ), TG ( $258 \pm 61$ ), HDL-c ( $40 \pm 8.9$ ) and Lp(a) ( $45 \pm 27$ ). The LLDs prescribed were fibrates (53.55%) and statins (46.5%). 40% prescriptions of LLDs did not meet the US NCEP-II criteria for initiation of LLD therapy.

**Conclusions:** The prescribing pattern of LLDs was considerably different from that observed in the west. The pattern was not in accordance with the then prevalent US NCEP-II guidelines. However it was in accordance with the specific recommendations made for the South Asians and also with the US NCEP-III Guidelines.

OP - 44

### PRESCRIBING TRENDS OF ANTIMICROBIAL AGENTS FOR THE PATIENTS OF UPPER RESPIRATORY TRACT INFECTION IN NAGPUR.

**Dakhale GN**, Turankar AV, Khobragade LR, Motghare VM, Khanzode SD,  
Dept. of Pharmacology, Govt. Medical College, Nagpur -3.

**Objective:** Present study was undertaken to define the prescription rate of antimicrobial agents for the patients of upper respiratory tract infection(URI) in Govt. medical college, Nagpur.

**Methods:** 226 prescriptions of patients suffering from URI from out patient department (OPD) of medicine, ENT and paediatrics were collected between Jan 2002 to March 2002. This information was compiled and subjected to critical evaluation using WHO drug indicators.

**Results:** Out of 226 prescription audited, 204 prescription (90%) contained antimicrobial agents for URI patients. In paediatric OPD, out of 100 prescriptions screened, among the different classes of antimicrobials agents, amoxycillin remained the most frequently (59%) prescribed agent. Sulfonamides were also found to be prescribed but to a lesser extent (2%). Nine percent of patients received ampicillin whereas 12% did not receive any antibiotic. It was a remarkable observation, that not a single audited prescription did include any floroquinolone group antibiotic prescription. Fifty eight prescriptions were screened from ENT OPD. Most common antimicrobial prescribed was amoxycillin (74%), followed by ciprofloxacin (7%) and erythromycin (5%). No antibiotic was received for seven patients. Sixty eight prescriptions of patients suffering from URI were edited from the medicine OPD. Amoxycillin was prescribed for 82 % of patients. Other patients received erythromycin (6%)and septran (4%). Three patients (4%) did not get any antibiotic for URI.

**Conclusion:** The results indicate that there is an overuse of antibiotic for the treatment of URI. Prescription rate can be reduced for reducing the cost of treatment and for preventing antibiotic resistance. This initial audit report is aimed at providing feedback to the drug prescribers and such periodical audit of drug prescribing is desirable in rationalizing prescribing practices.

OP- 45

### STUDY OF PRESCRIBING TRENDS IN ASTHMA IN A TERTIARY CARE HOSPITAL.

Shah V, Khan M, Bargaje R, Nerurkar RP, Gupta A, Joshi R, Pednekar S.  
Dept. of Pharmacology, T.N. Medical College and B.Y.L.Nair. Ch Hospital, A. Nair Road, Mumbai Central, Mumbai-400008.

**Objective:** To compare the prescribing pattern in bronchial asthma in a tertiary care hospital in Mumbai with the guidelines laid down in National Institute of Health (NIH) on severity and treatment of bronchial asthma.

**Methods:** Patients diagnosed as Bronchial Asthma attending Asthma OPD of B.Y.L. Nair hospital from July 10, 2002 onwards were interviewed. Relevant information was obtained from these interviews and from patients' OPD paper. Antiasthmatics prescribed patterns was analysed and compared with NIH guidelines

**Results:** Sixty four patients out of 68 were on combination therapy. According to NIH classification, number of patients in Step 2 (PEF > 80%), Step 3 (PEF > 60% - < 80%), Step 4 (PEF < 60%), were 10, 50 and respectively. Simple tablets of salbutamol and aminophylline were the most frequently prescribed drugs. Only 44 patients were on inhaled steroids. This was in variance with NIH guidelines.

**Conclusion:** Anti asthma drugs prescribing pattern in our hospital is governed more by the availability of the drugs in the hospital pharmacy than by the NIH recommendations. Simple tablets of salbutamol and aminophylline are the only drugs on the hospital schedule. It will be desirable to add sustained release oral methyl xanthines or long acting  $\beta_2$  agonists so that it is in concordance with the NIH guidelines.

OP- 46

### ANTIMICROBIAL DRUG UTILIZATION IN OBSTETRICS AND GYNAECOLOGY IN A TERTIARY CARE HOSPITAL.

Mujtaba Khan, Joshi R, Gupta A, Kirti M, Deepali K, Shivanand D, Vishal Shah, Bargaje R, Amol G, Anand P, Pandit PR.  
T.N.M.C and B.Y.L. Nair Chest Hospital, Mumbai - 400008.

**Objective:** To assess and evaluate the antibiotic prescribing pattern in obstetric and Gynaecology department in a tertiary care hospital in Mumbai. This study also aims to assess the quality of care given with respect to the standards of medical treatment at all levels of a health care system.

**Methods:** The study is designed as a prospective prescription data collection study without interfering in the treatment provided. The following data regarding the antimicrobial agent would be recorded: Dose, Route of administration, Dosage schedule, duration of treatment, culture report, co-relation, source and whether generic or trade name has used in the prescription. The data will be analysed as to the percentage of drug prescribed and the pharmaco-economic aspect.

**Result:** It is an ongoing study that is scheduled to be completed by mid November so that the results and conclusion of the study will be discussed at the time of presentation.

**PRESCRIPTION TRENDS IN RESPIRATORY DISORDERS IN NORTH GUJARAT.****Patel Natvarlal J\***, Patel Jignesh L\*, Goyal Ramesh K\*\*.

\*Shree S.K. Patel College of Pharmaceutical Education and Research, Ganpat Vidyanagar, Kherva, Mehsana-382711. \*\*L.M. College of Pharmacy, Ahmedabad - 380009.

Respiratory diseases are responsible for a major burden of morbidity and the lungs are often affected in multi system diseases. Irrational use of drugs and inappropriate prescribing are the two common phenomenons in the developing countries, which cause a big problem for providing effective health care facilities. Present work was undertaken to study the prescription trend for respiratory diseases. A profile of 615 doctors prescription were evaluated at retail outlet in urban and rural areas of North Gujarat. Punctuality in professionalism by doctors with respect to mentioning their own name, degree, patients name and diagnosis was higher in urban than rural areas. Doctors in rural and urban area prescribed two or more categories of drugs. Number of partial purchase of drugs as per the prescription was found to be higher in rural than urban area. Lack of money was one of the reasons for partial prescription. Prevalence of asthma was found to be higher in both rural (36.2%) and urban (41.4%) respectively. In all respiratory disorders antimicrobials were in majority of the prescriptions (79.3%). Use of antimicrobial agents was found to be highly irrational. 37 samples of sputum from the patients with bronchial asthma analysed for culture sensitivity test. 21 were found to be positive with respect to presence of bacteria. Various bacteria detected in samples were *Staph. aureus* (16), *proteus* (2), *pseudomonas* (2) and *streptococci* (1). In sputum culture sensitivity test, antimicrobials, which are most commonly prescribed, found to be less sensitive or resistant. Penicillin group of antibiotics particularly ampicillin, amoxycillin, or their combination were found. to be prescribed more in both rural (56%) and urban (48%) area. Sensitivity studies of organisms revealed that sensitivity to commonly prescribed. ampicillin and amoxycillin is only 31.25%. Sensitivity against erythromycin was found only 6.66%. Among fluoroquinolons sensitivity to ciprofloxacin was lower (37.5%) as compared to perfloxacin and ofloxacin. In conclusion use of antimicrobial agents as self-medication as well as through doctors prescription order was found to be highly irrational in patients with respiratory disorders particularly in patients with bronchial asthma. In many cases of bronchial asthma antimicrobials are either not required or many a time the antimicrobial having resistance to particular organism is being used.

## ***Scientific Session IV***

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### **Indigenous drugs II**

**Date** : 27.11.2002  
**Time** : 1600-1800  
**Venue** : Hall - B

Oral Presentation : OP48 - OP58

Chairpersons : Dr. Ram Raghuvir  
Dr. J R Behari



OP - 48

### COMPARISON OF EFFICACY OF FENUGREEK SEEDS AND GLIBENCLAMIDE ON BLOOD SUGAR AND SERUM LIPIDS IN ALBINO RATS.

Gokhale PM, Muppayyanavarmath SS, Patil PA.

Department of Pharmacology and Pharmacotherapeutics, J. N. Medical College, Nehru Nagar, Belgaum - 590010.

**Objective:** 1. To elucidate hypoglycemic and hypolipidemic action of fenugreek seeds in normal and diabetic rats. 2. To study the food drug interaction between fenugreek and glibenclamide.

**Methods:** Male Wistar rats (150 - 200 g) were divided into different groups [n = 6] to receive FGS (2g/kg and 8 g/kg), Glibenclamide (0.9 mg/kg and 0.45 mg/kg) and combination of FGS (2 g /kg) with GLB (0.9 mg/kg). Control group received equal volume of gum acacia suspension. The treatment was given to non-diabetic and alloxan induced diabetic animals and blood sugar greater than 200 mg % was taken as a criterion of diabetes. Blood glucose and lipid profile estimation was done. The body weight and the food intake of the animals were also monitored.

**Results:** In non-diabetic animals FGS (2 g/kg) produced significant hypolipidemia but did not decrease the sugar in contrast to 8 g/kg dose which lowered both the parameters significantly. GLB significantly lowered glucose and increased lipid level. In diabetic animals both doses produced significant hypoglycemia. On the other hand glibenclamide produced significant hypoglycemia but didn't correct the dyslipidemia associated with diabetes. Combination of FGS and GLB produced significant ( $p < 0.05$ ) hypoglycemia without hyperlipidemia in non-diabetic and diabetic animals.

**Conclusion:** The results of the study firmly establish the hypolipidemic and hypoglycemic effects of fenugreek and show its beneficial effects in combination with glibenclamide.

OP - 49

### EVALUATION OF ANTIDIABETIC ACTIVITY OF *GINKGO BILOBA* IN RATS.

Shankar Pinakini K, Vasanth kumar A, Rao Namita.

Department of Pharmacology, International Centre for Health Sciences Manipal - 576119.

**Objective:** To evaluate the antidiabetic activity of Ginkgo biloba and to probe into the mechanism of action.

**Methods:** In albino Wistar rats diabetes was induced by administration of streptozotocin. Animals were divided into 4 groups of 10 animals in each. Gum acacia, Troglitazone, Ginkgo biloba 50 mg/kg, Ginkgo biloba 100 mg/kg, were administered to group I (control), group II (standard), group III and group IV (test) respectively. After 10 and 15 days of drug administration the following parameters were estimated for all the groups: Fasting blood sugar (FBS) and blood glutathione (GSH).

**Results:** Troglitazone, a known antidiabetic and antioxidant produced a significant reduction in FBS and increased blood GSH levels. *Ginkgo biloba* in a high dose of 100 mg/kg produced a significant reduction in FBS and increase in blood GSH where as in a low dose of 50 mg/kg produced no significant change.

**Conclusion:** *Ginkgo biloba* a known antioxidant decreased FBS and increased blood GSH levels in a dose dependent manner. Hence Ginkgo biloba may have antidiabetic activity that can be attributed to its antioxidant activity.



OP - 50

### ASSESSMENT OF GLUNORM™ IN HEALTHY VOLUNTEERS.

Das D, Grover JK, Ammini AC.

Department of Pharmacology, A.I.I.M.S. New Delhi - 110029.

Antihyperglycemic effect but not hypoglycemic effect is required from any drug for treating diabetes mellitus. In the present study, we tested whether a commercially available Ayurvedic anti-diabetic drug Glunorm™ has a potential to cause hypoglycemia. Eleven healthy volunteers with age ranging (20-30 years) and body-weight (55 to 80 kg) were included in the study after obtaining informed consent. The basal data regarding LFT, RFT and lipid profile was taken. Glunorm™ (constituents *Patol* 10.0 g, *Methika* 0.5 g, *Tila* 1.12 g, *Karvellak* 10.0 g, *Laksmāna* 1.6 g, *Amaliki* 0.6 g, *Triphala* 0.6 g, *Baheda* 0.6 g, *Bilba* 0.5 g, *Baingan* 0.4 g) 2 capsules BO was administered for 1 week. Fasting and postprandial blood sugar was measured before and after taking drug. Results showed no significant differences in fasting ( $81.9 \pm 13.2$  versus  $80.81 \pm 14.5$ ) and post prandial ( $90.63 \pm 11.82$  versus  $86.81 \pm 18.7$ ) blood sugar levels after Glunorm™. No change in body weight, LFT, RFT and lipid profile was seen after 1 week of therapy. None of the volunteer reported any adverse effect. Thus, Glunorm™ did not produce hypoglycemia in healthy volunteers and therefore does not carry a risk of hypoglycemia when used for the treatment of diabetes.

OP - 51

### POTENTIAL ANTIFILARIAL AGENTS FROM HERBAL SOURCES

Singhal KC.

Consultant WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden. Professor, Department of Pharmacology, J.N. Medical College, A.M.U., Aligarh - 202 002.

Lymphatic filariasis, known as elephantiasis, puts at risk more than a billion people in more than 80 countries. Over 120 million have already been affected by it, over 40 million of them are seriously incapacitated and disfigured by the disease. One third of the people infected with the disease live in India. The high incidence of filariasis, its endemicity in our country, non-availability of an ideal anti filarial agent, lack of proper understanding of physiology and neurohumoral and neuromuscular transmission, lack of proper understanding of the immunological response of the host to the infection, lack of understanding of the role of ions and ionic channels in filarial parasites and related issues are stumbling block in finding an effective tool to eradicate the disease. *Setaria cervi*, a cattle filarial parasite has, been used as a basic model by the spontaneous motility of the whole worm, and nerve muscle preparation of *Setaria cervi*, survival of micro filariae *in vitro* and *Setaria-abino* rat system, which have been developed by the author as a tool for screening potential anti filarial agents and used as the basic model for experimental filariasis. The object of chemotherapeutic research is the development of new and more effective therapeutic tool to control and contain filarial infection. No serious efforts have so far been made to explore plant source to find a suitable therapeutic tool for filariasis. Large number of plant extracts were screened using above models for finding potential anti filarial agent. Extracts of root/ stem / leaves or fruits of twelve plants were found to have ability to modify the movements of whole worm and /or the nerve-muscle preparation of *Setaria cervi* (either flaccid or spastic paralysis) and also to adversely affect the survival time of microfilariae *in vitro*. The plants which were found effective and the part of the plant which contained substances which could adversely affect *Setaria cervi* are given below.

*L. cephalotes* - Flower, Stem ; *Asparagus adscendens* Roxb - Root ; *Saxifraga stracheyion* - Root extract; *Argyria speciosa* - Leaves ; *Streblus asper* - Whole plant; *Sencio nudicaulis* Buch Ham - Leaves; *Mallotus philippensis* LAM - Leaves; *Mimusops elengi* - Leaves; *Melia azedarach* - Fruit, Leaves, stem; *Mirabilis jalapa* - Roots; *Pongamia pinnata* - Fruits, Leaves; *Psoralea corylifolia* - Seeds;

These observations are likely to provide a lead to find a suitable remedy from plant sources for incapacitating disease like lymphatic filariasis.

OP - 52

### EVALUATION OF CERTAIN PLANT EXTRACTS FOR ANTIMALARIAL ACTIVITY.

Selvam DT, Manisha Nivsarkar, Sanjay Kumar, Kaushik MP, Batra HV, Gogoi HK<sup>1</sup>, Das SC<sup>1</sup>

Defence Research & Development Establishment, Jhansi Road, Gwalior-474002; <sup>1</sup>Defence Research Laboratory, Tezpur.

Malaria is the most important parasitic disease that affects the mankind. Every year more than 300 million people suffer from this disease and one million die due to this illness. The death is mostly caused by *Plasmodium falciparum* the species that causes cerebral malaria. Chloroquine is the drug of choice for the treatment of malaria in most parts of world and the development of resistance to this commonly used antimalarial as well as development of multi drug resistant *Plasmodium falciparum* strains have necessitated the need for the development of new antimalarials. Due to the high mutational rate and the resulting adaptation of malaria to newer geographical regions there is an urgent need for the development of new antimalarials. The crude extracts of *Vitex peduncularis* and *Gomphocentrum purpuria* collected from various parts of the country were checked for antimalarial activity. The crude extract of these plants showed 74.5% and 81.0% inhibition respectively against in vitro cultures of *Plasmodium falciparum*. When checked on to in vivo mouse model against *Plasmodium berghei* an inhibition of 52.5% and 60% was observed. Further work on to characterization of the bioactive components of these plants is under progress.

OP - 53

### PRELIMINARY STUDIES ON THE ANALGESIC AND ANTI-INFLAMMATORY EFFECTS OF *LIGUSTRUM ROBUSTUM*.

Usham DM, Chakraborty A, Rajkumari BD, Thokchom IS.

Department of Pharmacology, Regional Institute of Medical Sciences, Lamphelpat, Imphal -795004.

**Objective:** To evaluate the analgesic and anti-inflammatory effects of the aqueous extract of *Ligustrum robustum* (ALR) in experimental animal models.

**Methods:** ALR at 200 mg/kg, i.p. was tested for analgesic activity by the Tail Flick method in albino rats as described by Sheth et al (1972). Pethidine hydrochloride, 16 mg/kg, i.p. and distilled water, 10 ml/kg, i.p. were used as standard and control drugs respectively. The anti-inflammatory activity of ALR at 200 mg/kg, p.o. was studied in carrageenan induced rat paw oedema by the method of Winter et al (1956). Aspirin, 100 mg/kg, p.o. and normal saline, 10 ml/kg, p.o. were used as standard and control drugs respectively.

**Results:** The reaction time at 30 mins. and 1 hour after the administration of the test drug were  $8.0 \pm 0.77$  ( $p < 0.01$ ) and  $8.6 \pm 0.71$  ( $p < 0.001$ ), standard  $9.16 \pm 0.54$  ( $p < 0.001$ ) and  $9.33 \pm 0.27$  ( $p < 0.001$ ), control  $4.25 \pm 0.38$  and  $4.16 \pm 0.27$  respectively. The mean increase in paw volume were  $0.52 \pm 0.08$ ,  $0.32 \pm 0.05$  ( $p < 0.02$ ) and  $0.22 \pm 0.01$  ( $p < 0.001$ ) in control, test and standard groups respectively. The percentage of inhibition of oedema in test and standard groups were 39 and 58 respectively.

**Conclusion:** Aqueous extract of *Ligustrum robustum* shows significant analgesic and anti-inflammatory effects.

OP - 54

## ETHNOPHARMACOLOGICAL SEARCH FOR DRUGS USED IN WOUND HEALING IN NORTH EAST INDIA.

Barua CC<sup>1</sup>, Barua AG<sup>2</sup>, Khanikor HN<sup>1</sup>.

<sup>1</sup>Department of Pharmacology & Toxicology, CVSC, <sup>2</sup>Deptt. of Vety. Medicine, Public Health & Hygiene. AAU, CVSC, Guwahati -781022.

North Eastern India comprises states of Arunachal Pradesh, Assam, Manipur, Meghalaya, Nagaland, Sikkim and Tripura. Due to its unique tribal customs, manners and values, NE India has attracted many anthropologists, socialists, educationists, economists and ethopharmacologists. The local people (specially tribal) use a variety of plants as medicine for various ailments which is unique. Most common disease of animals of these regions are worm infestation, wound or cut injury, bronchitis, skin disease, bone fracture, snake bite etc. A survey was made for the use of ethnoveterinary medicines in healing of wound in different states of NE India. Wound healing itself is a complex phenomena and no such pharmacological agent is developed until now as many factors are involved in it. Use of ethnoveterinary medicine by the livestock owner is very common in the rural areas as they do not have access to allopathic medicine and high cost also deters them from using. The survey revealed some of the plants used in more than one states for the same ailment or infection and some used for more than one ailments. The data collected, authenticated from literature. Some of the commonly used plants preliminarily screened for their anti microbial property and analgesic activity in laboratory animals were *Azadiracta indica*, *Ocimum sanctum*, *Ageratum conyzoides*, *Bauhinia prupurea*, *Casia fistula*, *Clitorea ternatea*, *Celosisa argentea*, *Coleus aromaticus*, *Tilenthera ficoides*, etc. Some of these are well documented and they possess anti microbial activity. After antimicrobial, antifungal and histopathological study in laboratory animals, these plants can be ideally used for wound healing either singly or as a polyherbal preparations.

OP - 55

## INVESTIGATION OF ANXIOLYTIC-LIKE EFFECT OF ANTIDEPRESSANT ACTIVITY OF *BENINCASA HISPIDA*, METHANOL EXTRACT.

Rukmani R, Nidhiya ISR, Suresh Nair, Anil Kumar.

Department of Pharmacology and Toxicology, C.L. Baid Mehta College of Pharmacy, Chennai - 600096.

**Objective:** To investigate the antidepressant property and anxiolytic effect of methanol extract of *Benincasa hispida* fruit in various animal models.

**Methods:** The antidepressant activity of the extract was evaluated using modified forced swim test. Mice were administered with methanol extract of *Benincasa hispida* (MEBH 0.2-1 g/kg, i.p.) or imipramaine (30 mg/kg, i.p.) thrice (24,12 and 1/2h) and to another set of mice MEBH (0.2-1 g/kg, i.p.) 30 min before behavioural assessment. The duration of immobility of last 240 s of 6 min period was measured. In marble burying test, mice were administered (0.2-1 g/kg, i.p.) or haloperidol (0.5 mg/kg, i.p.) or diazepam (2 mg/kg, i.p.). In marble burying test, MEBH (0.2-1 g/kg, i.p.) haloperidol (5 mg/kg, i.p.) or diazepam (2 mg/kg, i.p.) was administered 30 min before the mice is placed individually in a mice cage in which 10 marbles equally distributed on top of a 5 cm saw dust. After 1 h, the number of visible and unburied (i.e. less than 2/3 covered by saw dust) marbles were counted. In social interaction test, paired rats after familiarizing the arena for a period of 8 min consecutively for 2 days were administered with MEBH (0.05,0.2,0.6 and 1g/kg, i.p.), diazepam (2 mg/kg, i.p.) 30 min before the pair of unfamiliar rats were placed together. The time spent by the rats in social interaction was noted in 5 min period.

**Results:** In forced swim test, MEBH (0.6 and 1g/kg administered thrice and only once) showed significant reduction in immobility. In marble burying test, MEBH (0.2-1g/kg) in a dose dependent manner increased significantly the number of visible marbles. MEBH (0.05-1g/kg) significantly reduced the social interaction time.

**Conclusion:** MEBH exhibited significant antidepressant activity in forced swim test along with anxiolytic property in marble burying test. Whereas in social interaction test MEBH showed anxiogenic activity. The results are agreeable with the clinically used antidepressants.

OP- 56

**ANTI-ULCER AND ANTIOXIDANT ACTIVITY OF DHC-1, A HERBAL FORMULATION.**

**Balaraman R,** Bafna PA.

Pharmacy Department, Faculty of Technology and Engineering, The M.S.University of Baroda, Baroda - 390001.

**Objective:** To study the anti-ulcer and antioxidant activity of DHC-1, a herbomineral formulation in rats.

**Methods:** The anti-ulcer effect of DHC-1 was tested in acute (pylorus ligation) and chronic (ethanol treated) ulcer models in rats. DHC-1 was investigated at four dose levels of 125 mg/kg, 250 mg/kg, 500 mg/kg and 1000 mg/kg body weight, p.o. The parameters such as ulcer index (both acute & chronic methods), volume and pH of gastric fluid, acidity and pepsin activity (acute method) were determined. The levels of superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), lipid peroxidation (MDA), membrane bound enzymes like Ca<sup>2+</sup>ATPase, Mg<sup>2+</sup>ATPase, Na<sup>+</sup>K<sup>+</sup>ATPase and total proteins were estimated in stomach and gastric fluid.

**Results:** The formulation significantly reduced the ulcer index in both acute and chronic models; decreased the volume, acidity and pepsin activity of gastric fluid and also increased the pH of gastric fluid (acute method) which proved its anti-ulcer activity. Inhibition of lipid peroxidation and enhancement of antioxidant enzymes by DHC-1 was also observed.

**Conclusion:** Thus it can be concluded that DHC-1 possesses significant anti-ulcer activity which can be attributed to its antioxidant mechanism of action.

OP - 57

**NOOTROPIC ACTIVITY OF METHANOL EXTRACT OF *BENINCASA HISPIDA* FRUIT.**

**Anil Kumar,** Nirmala V.

Department of Pharmacology and Toxicology, C.L.Baid Mehta College of Pharmacy, Chennai - 600096.

**Objective:** To investigate the cognitive function enhancing effect of methanol extract, fruit of *Benincasa hispida* (Thunb.) Cogn., in mice using Y maze and elevated plus maze.

**Methods:** Spatial working memory in mice was evaluated by using Y maze. Mice were administered (i.p.) with methanol extract of *Benincasa hispida* (MEBH 0.6-1 g/kg) or piracetam (150 mg/kg), scopolamine (3 mg/kg) or MEBH (0.6-1 g/kg) + scopolamine (3 mg/kg) or saline (0.1ml/10g). The number of entries and percentage of entries was calculated in a 8 min session. Spatial working memory was evaluated by latency test using elevated plus maze. Similar dosing regime as described above were followed both on the 1 and 2 day. Latency to enter from open to close arm was noted on 1 and 2 day.

**Results:** In Y maze test, MEBH (0.6- 1 g/kg) significant reduction in number of entries and increase in percentage of alteration. In latency test, MEBH at 0.6 and 0.8 mg/kg, significantly reduced the latency period. In both the models, MEBH was significantly able to antagonize the amnesic effect of scopolamine.

**Conclusions:** MEBH exhibited prominent nootropic effect and anti-amnesic effect in both models of memory (spatial. working memory and long term memory of Y maze and latency test respectively).

OP- 58

**HEPATOPROTECTIVE EFFECT OF FRUITS OF *COCCINA INDICA* AGAINST  $CCl_4$  INDUCED HEPATIC DAMAGE IN ALBINO RATS.**

**Mohana Rao GR**, Viyakumar M. Arun B Joshi\*, Rawat, MS AKS Pushpangadan P.

Depts.of Pharmacognosy and Ethnopharmacology, Phytochemistry and Pharma-cognosy,NBRI, Lucknow; NGSM Institute of Pharmaceutical Sciences, Mangalore.

*Coccinia indica* (cucurbitaceae) is a indigenous herb used traditionally for jaundice, inflammatory diseases and is believed to promote positive health by increasing resistance against infections. The fresh fruits of this plant are commonly used as vegetables. In the present study the hepatoprotective activity of the 50% ethanolic extract of the fresh fruits were evaluated using carbon tetra chloride induced hepatotoxicity model in albino rats. Liver damage was induced in rats by carbon tetra chloride (0.6 ml/kg, i.p), every alternate day for seven days. 50% ethanolic extract of the fruits (300 mg/kg and 400 mg/kg) was given orally for one week. Silymarin was given as a reference drug. Levels of marker enzymes ie, GPT, GOT and ALP were estimated in serum. Histopathological studies were also done to confirm the biochemical changes. Treatment with 50% ethanolic extract (400 mg/kg) of the fresh fruits showed significant ( $p < 0.05$ ) reduction in serum GPT, GOT and ALP levels as compared to  $CCl_4$  treated groups. Histopathological examination of liver sections showed protective effect of fruit extract comparable to silymarin treatment. **Conclusions:** MEBH exhibited prominent nootropic effect and anti-amnesic effect in both models of memory (spatial, working memory and long term memory of Y maze and latency test respectively).

# ***Scientific Session V***

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## **Biochemical pharmacology**

- Date** : 27.11.2002  
**Time** : 1600-1800  
**Venue** : Hall - C
- Invited Lectures** : Dr. Louis Premkumar  
Dr. Anil Belapure  
Dr. S K Mishra  
Dr. Vickram Ramkumar
- Oral Presentation** : OP 59 - OP67A
- Chairpersons** : Prof. Anna B Fischer  
Dr. Louis Premkumar



**IL-58****MODALITIES OF NOCICEPTION AND THE UNDERLYING MOLECULAR MECHANISMS.****Louis Premkumar, Jeremy Van Buren.**  
SIU School of Medicine, Springfield, IL-62702, USA.

Pain is a complex sensation designed to avoid harmful environment. However, in certain circumstances, the elements involved in generation, transduction, and processing of the pain sensation are sensitized contributing to hyperalgesia and chronic debilitating pain. This review focuses on the molecular mechanisms that underlie these complex phenomena. The capsaicin or vanilloid receptor (VR) plays an important role in transducing thermal and inflammatory pain. The VR is a nonselective cation channel that possesses a high permeability to  $Ca^{+}$ , exhibits strong outward rectification, and desensitizes following repeated stimulation (tachyphylaxis). Generally, VRs are distributed in peripheral sensory nerve endings and are involved in the perception of noxious stimuli. The activation of VR depolarizes the sensory nerve endings and evokes a train of action potentials that propagates to the spinal cord and brain. Mice lacking the VRI gene have deficits in thermal or inflammation induced hyperalgesia but are sensitive to noxious heat, which largely confirms a role in certain modalities of nociception. Multiple intracellular messenger pathways integrate either to activate or to sensitize the VRs (Premkumar, PNAS 98: 6537-6539). In a recent study (Premkumar and Ahem, Nature 408: 985-990), we have shown that activation of protein kinase C (PKC) induces VRI channel activity at room temperature in the absence of any other agonist. We also observed this effect in native VRs from sensory neurons, and phorbol esters induced a vanilloid-sensitive calcium rise in these cells. Moreover, the pro-inflammatory peptide bradykinin and the putative endogenous ligand anandamide respectively induced and enhanced VR activity in a PKC-dependent manner (Premkumar and Ahem, Nature 408: 985-990). These results suggest that PKC may link a range of stimuli to the activation of VRs.

**IL-59****PRIMARY OR CELL CULTURE FOR DRUG RESEARCH - WHAT IS THE RIGHT CHOICE?****Balasure AK.**  
Tissue Culture laboratory, NLAC, Central Drug Research Institute, Lucknow - 226001.

In the era of Biotechnology in India where the investment is slated to reach \$1.6 billion during this decade, the area of Tissue and Cell Culture as adjunct/alternative to animal usage cannot be ignored. The seeds of this technique were sown in the West during the beginning of 20<sup>th</sup> Century when Organ and Tissue Culture emerged following which techniques were discovered for their dissociation into cells and their subsequent culture. This laboratory is engaged in utilizing both the elements of Tissue and Cell Culture for screening and defining the molecular mechanism of action of estrogens/antiestrogens since a decade. In elegant studies, we have utilized both the culture of rabbit endometrial explants (Primary Culture) and MCF-7 Human Breast Cancer Cell Line (Cell Culture) for investigating antiestrogens. Studies have been conducted using simple and state-of-the-art tools such as Histology, Electron-Microscopy, Biochemistry, Molecular Biology and F ACS analysis etc. for demonstrating the unequivocal action of estrogen and the screening of antiestrogens. An overview of the progress made by us in relation to international certification of the data accomplished will be presented.



**IL-60****STRUCTURE AND FUNCTION OF T - TYPE  $\text{Ca}^{2+}$  CHANNELS.****Mishra SK, Raviprakash V.**Division of Pharmacology and Toxicology, Indian Veterinary Research Institute,  
Izatnagar - 243122.

Voltage-dependent  $\text{Ca}^{2+}$  channels (VDCC's) constitute an important pathway for the influx of  $\text{Ca}^{2+}$  into cells and thereby regulate a variety of cellular processes such as, muscle contraction, excitation-secretion coupling, neuronal development, fertilization and gene expression. Based on biophysical properties of  $\text{Ca}^{2+}$  currents, VDCCs have been classified as low voltage-activated (LV A) and high voltage-activated (HV A)  $\text{Ca}^{2+}$  channels.  $\text{Ca}^{2+}$  ions passing through LVA channels generate T - type currents that have the characteristic features of fast inactivation, slow deactivation and small conductance. The most important pharmacological property of these channels is that they are resistant to block by dihydropyridines, but can selectively be blocked by milbepradil, nickel and kurtoxin. Although their physiological functions are still not clearly understood, they are thought to play an important role in neuronal burst firing, pacemaker activity in heart, aldosterone secretion, atrial natriuretic factor release and fertilization. An increase in T - type  $\text{Ca}^{2+}$  channel expression has been observed in several pathological conditions like, cardiac hypertrophy, hypertension and epilepsy. In contrast, suppression of T - type  $\text{Ca}^{2+}$  channels has been related to morphological transformation of fibroblasts by oncogenes. It is, therefore, believed that T - type  $\text{Ca}^{2+}$  channel could be an important therapeutic target in the clinical management of pathological states like, hypertension, cardiac hypertrophy, angina pectoris and epilepsy. In recent years, three different genes encoding T - channel pore subunits have been identified and designated as  $\alpha_{1G}$  ( $\text{Ca}_v 3.1$ ),  $\alpha_{1H}$  ( $\text{Ca}_v 3.2$ ) and  $\alpha_H$  ( $\text{Ca}_v 3.3$ ). Northern blot studies provide evidence that all mRNA is restricted to CNS, while  $\alpha_{1G}$  and  $\alpha_{1H}$  are ubiquitous. How the  $\alpha$ -subunit structure of different T - channel isoforms relates to the channel function will be discussed.

**IL-61****MODULATION OF OXIDATIVE STRESS BY ADENOSINE.****Vickram Ramkumar.**

Southern Illinois University School of Medicine, Springfield, IL62702.

The nucleoside adenosine is released in response to various stressors, such as ischemia, chemotherapeutic agents and biological toxins, and mediates cytoprotection by interacting with various adenosine receptor (AR) subtypes. In the central nervous system the protective action of adenosine is mediated by reducing the release of glutamate and limiting excitotoxicity, by reducing the influx of  $\text{Ca}^{2+}$  into the cell and by a recently identified antiinflammatory action. Adenosine plays important physiological roles in the peripheral auditory pathway and in the kidney. The chemotherapeutic agent cisplatin is known to induce permanent hearing loss and nephrotoxicity through generation of reactive oxygen species. During this presentation, I will discuss data demonstrating an acute cytoprotective action of adenosine mediated via the  $A_1$ AR against cisplatin- toxicity in the cochlea and renal proximal tubular epithelial cells. Furthermore, I will provide evidence that the generation of ROS is involved in *de novo* synthesis of the  $A_1$ AR through activation of nuclear factor kappa B, thereby conferring longer term protection of these tissues against oxidative stress.

OP - 59

## FERMENTOR AND BIOREACTOR : A TOOL FOR DRUG RESEARCH AND DEVELOPMENT.

Shyamal Pal

Chemito Instruments Pvt. Ltd., 8, Mohata Bhawan of Dr. E. Moses Road, Worli, Mumbai - 400018.

Bioreactor and Fermentor plays an important role in drug research and development specially in recombinant DNA technology, microorganisms based vector research where it is very essential to control all possible biochemical and physiochemical parameters which directly and indirectly triggers biochemical and physiological activities of the selected organisms like bacteria, fungi, yeast and mammalian cells and other unicellular organisms. Design of bioreactor is also made accordingly as per the nature of biological reaction. Selections of vessel like size, material of construction, length and breadth ratio of vessel are very critical aspects while designing any bioreactor or fermentor. This paper highlights few operational conditions like control and monitor of all possible options like pH, dissolved oxygen, foam level, temperature, O<sub>2</sub>/CO<sub>2</sub>/N<sub>2</sub> rich environment; *in-situ* sterilization and its utility in long run where a highly sterile environment and stringent monitoring is essential to give best possible support to organisms or cells to get desired and effective results. A SCADA-PLC-PC based system which correlates all possible factors, which are directly, and indirectly affects the growth, biochemical activities and performance of the selected organisms are taken into consideration.

OP-60

## EGFR/MAPK DOWN REGULATION MAY EXPLAIN ENHANCED HEPATOTOXICITY OF THIOACETAMIDE IN DIABETIC RATS.

Devi SS, Mehendale HM.

Department of Toxicology, College of Pharmacy, The University of Louisiana at Monroe, Monroe, LA, USA.

**Objective:** To test the hypothesis that cellular signalling is down regulated in diabetic (DB) rats after thioacetamide (TA) treatment explaining inhibited liver tissue repair.

**Methods:** On day 0, male Sprague-Dawley rats were treated with streptozotocin (60 mg/kg, i.p.) or respective control. On day 10, rats were treated with TA (300 mg/Kg, i.p.). TNF- $\alpha$  and IL-6 were assessed by ELISA, while epidermal growth factor receptor (EGFR), and mitogen activated protein kinases (MAPKs) [ERK1, ERK2, and p38] were measured by Western blot analysis.

**Results:** TNF- $\alpha$  and IL-6 mediated pro-mitogenic signalling in TA-treated DB rats is higher than TA-treated NDB rats. However, EGFR is significantly down regulated in the DB rats and it is further down regulated after TA treatment. Down stream signalling through MAPKs were also down regulated in the DB rats. After TA treatment MAPKs were further down regulated in DB rats.

**Conclusion:** These data indicate that the problem is not at the level of cytokine signalling. Down regulation of MAPK signal transduction pathway via EGFR may explain failed tissue repair, leading to unfavorable toxic outcome of TA treatment in DB rats. (Supported by Kitty DeGree Endowed Chair and LBRSF.)

OP - 61

## GENETIC BASIS OF DIABETES INSIPIDUS AND FUTURE PROSPECTS FOR THERAPY.

Gota V, Tyagi MG.

Department of Pharmacology, Christian Medical College, Vellore - 632 002.

**Objectives:** The objective of this study was to evaluate the genetic basis of diabetes insipidus (DI) and future prospects for its treatment.

**Methods:** This study is based on a review of distinguishable clinical features and mutational analysis of the genes responsible for DI.

**Results:** The identification, characterisation and mutational analysis of genes provide the basis for understanding of three different hereditary forms of DI namely, the Autosomal dominant neurogenic DI, X-linked nephrogenic DI and Autosomal recessive nephrogenic DI. Numerous mutations within the AVP gene have been identified in patients with familial neurohypophysial DI. The mutations are distributed throughout the precursor protein and include missense, nonsense and point mutations within the signal sequence, the AVP peptide and the neurophysin (NP) domain. More than 90% of cases of nephrogenic DI are X-linked and are secondary to AVPR<sub>2</sub> mutations which result in the dysregulation of V<sub>2</sub> receptor. About 10 % cases of DI also occur due to AQP 2 (Aquaporin 2) gene mutations.

**Conclusion:** Recent evidence shows that defects in V<sub>2</sub> receptor coupling or a water channel underlie nephrogenic DI. The development of non-peptide vasopressin receptor antagonists and newly synthesised vasopressin agonists which are able to activate mutated V<sub>2</sub> receptor responsible for DI and gene therapy using adenoviral transfection hold good prospects for future therapy of DI.

OP - 62

## EFFECTS OF MIBEFRADIL ON UTERINE CONTRACTIONS OF PREGNANT RAT.

Asokan KT, Sarkar SN, Mishra SK, Ravi Prakash V

Division of Pharmacology and Toxicology, Indian Veterinary Research Institute, Izatnagar - 243122.

**Objective:** Calcium (Ca<sup>2+</sup>) channel blockers have often been used as tocolytic agents for treating preterm labour. Mibefradil, a nondihydropyridine Ca<sup>2+</sup> channel antagonist, has been extensively studied for its antianginal and antihypertensive effects, but little is known about its actions on uterine smooth muscle. Therefore, we examined its effects on isolated pregnant rat uterus.

**Method:** Longitudinal strips (approx. 3 x 10 rpm) from the mid-horn region of each uterus, isolated from 19-day old pregnant rats, were mounted in an organ bath containing Ringer Locke solution. Isometric tension was measured in an ink-writing polygraph through a force displacement transducer.

**Results:** Mibefradil (10<sup>-8</sup> - 3 x 10<sup>-6</sup> M), added cumulatively, caused concentration-dependent inhibition of spontaneous contractions of isolated uterine strips. The IC<sub>50</sub> values of mibefradil to inhibit the amplitude and frequency of rhythmic contractions were 8.83 x 10<sup>-7</sup> M and 1.03 x 10<sup>-6</sup> M, respectively. Pretreatment of tissues with 3 μM mibefradil shifted the Ca<sup>2+</sup> concentration-response curve (elicited on K<sup>+</sup> depolarized tissues) to right and decreased the maximal response by about 52 %. Similarly, nifedipine (10 nM) shifted the Ca<sup>2+</sup> concentration-response curve to right with a marked inhibition of the maxima. Mibefradil (3 μM) also antagonized the oxytocin (10<sup>-5</sup> - 10<sup>-1</sup> IU) - induced contractions in low Ca<sup>2+</sup> (0.3 mM) solution. In Ca<sup>2+</sup> - free solution, mibefradil (3 μM) significantly reduced oxytocin (3 x 10<sup>-2</sup> M) induced contraction.

**Conclusion:** The results show a significant tocolytic effect of mibefradil on pregnant rat uterus. The tension experiments provide an indirect evidence of L-type Ca<sup>2+</sup> channel antagonism as well as intracellular Ca<sup>2+</sup> release by mibefradil.

OP - 63

**KINETICALLY ALTERED ACETYLCHOLINESTERASE IN MALATHION RESISTANT *CULEX QUINQUEFASCIATES*.**

Gopalan N, Prakash S, Battacharaya BK.

Defence Research and Development Establishment, Jhansi Road, Gwalior-474002.

Organophosphorous esters (OP), carbamates and pyrethroids are neurotoxic and exert their deleterious effect by inhibiting the enzyme acetylcholinesterase (AChE). Several insects develop resistance against these compounds by modification in kinetic parameters of AChE. AChE enzyme from resistant individuals is much less sensitive to inhibition than that from susceptible individuals. In this study we have developed malathion resistant *Culex quinquefasciatus* upto 25th generation and estimated AChE and modified AChE activities from larvae and adult mosquitoes and also field collected mosquito samples. AChE inhibitors like Mipafox, Praoxon, DFP, Propoxur, O-ethyl S-benzyl phenyl phosphorothioate, O-methyl S-methyl phenyl phosphorothioate and O-methyl S-ethyl phenyl phosphorothioate were studied for their differential inhibition kinetics. Both inhibition 50 percent ( $IC_{50}$ ) and enzyme kinetic studies ( $K_m$  and  $V_{max}$ ) were carried out in susceptible and malathion resistant strains. The  $IC_{50}$  values obtained showed a range from 0.45  $\mu$ M to 23.44  $\mu$ M and ratio between susceptible vs resistant ranged 1.26 to 5.1  $K_m$  values of AChE for acetylthiocholine from the susceptible individuals ranged between 28.57 mM to 66.6 mM and that of resistant samples ranged between 20 mM to 200 mM. The  $V_{max}$  values showed an increase in resistant mosquito samples. It is inferred that alteration in  $IC_{50}$  values for the inhibitors increase in  $K_m$  for substrate makes the enzyme from resistant species less sensitive to OP inhibition and change in kinetic parameters is a physiological adaptation phenomenon.

OP-64

**POTENTIATION OF MORPHINE INDUCED ANXIOLYTIC EFFECT IN  $\alpha$ -MSH IMMUNO-NEUTRALIZED MALE RATS.**

Harle UN, Kokare, DM, Chopde CT, Subhedar NK.

Department of Pharmaceutical Sciences, Nagpur University Campus, Nagpur - 440010.

**Objective:** To study the role of  $\alpha$ -MSH in the mediation of anxiolytic effect produced by morphine.

**Methods:** Agents administered:  $\alpha$ -MSH and antiserum against  $\alpha$ -MSH by intracerebroventricular (icv) route and morphine by intraperitoneal (ip) route. Following protocols were employed: (1)  $\alpha$ -MSH (1, 2.5 or 5  $\mu$ g/rat) or morphine (0.1, 0.5 or 1 mg/kg, ip), (2) morphine (0.5 or 1 mg/kg ip) prior to  $\alpha$ -MSH (5  $\mu$ g/rat, icv), (3) icv administrations of  $\alpha$ -MSH antiserum (1: 100 dilution in 3  $\mu$ l volume) to immunoneutralize the endogenous  $\alpha$ -MSH, and (4)  $\alpha$ -MSH immunoneutralized rats treated with morphine (1 mg/kg, ip). Anxiety was evaluated in elevated plus maze and open field test.

**Results:**  $\alpha$ -MSH treatment showed the anxiogenic response, while morphine caused significant anxiolytic effect. Morphine significantly blocked the  $\alpha$ -MSH induced anxiety ( $P < 0.05$ ). Although  $\alpha$ -MSH immunoneutralized rats did not show significant anxiolytic effect ( $P > 0.05$ ), morphine challenged  $\alpha$ -MSH immunoneutralized rats showed the significant potentiation of its anxiolytic effect ( $P < 0.05$ ).

**Conclusion:** Mediation of melanocortin system in the morphine induced anxiolytic effect is suggested. (\*Supported by ICAR and DST, New Delhi).

OP-65

### EFFECT OF NIMESULIDE IN MODEL OF INFLAMMATORY BOWEL DISEASE IN RATS.

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R & D Division, Panacea Biotec Ltd., P.O. Lalru, Chandigarh Road, Punjab - 140501.

**Objective:** Inflammatory Bowel Disease (IBD) is relapsing inflammation of intestine involving increase in COX products such as prostaglandin (PGE<sub>2</sub>) and LOX products such as leukotriene (LTB<sub>4</sub>). Nimesulide, a preferential COX-2 inhibitor was evaluated for its efficacy against experimental colitis in two different models (acetic acid-induced and LTB<sub>4</sub>-induced IBD) in rats.

**Methods:** Inflammatory Bowel Disease was induced in overnight fasted animals by a single administration of acetic acid or LTB<sub>4</sub> into colon using a polyethylene tubing. On day 4 animals were sacrificed, the isolated colon was observed for presence of surface macroscopic changes (ulceration, inflammation) and altered muscle contractility to receptor independent potassium chloride (KCl) challenge was recorded. Myeloperoxidase enzyme activity was also performed. In drug treated animals, nimesulide (9 and 18 mg/kg, once daily, p.o) / sulphasalazine (reference drug, 100 mg/kg, once daily, p.o) was administered starting from day 1 after inflammogen challenge till day 4.

**Results:** The isolated colon segment of control animals (acetic acid and LTB<sub>4</sub> treated) provoked significant ( $p < 0.05$ ) ulceration, inflammation, increased myeloperoxidase (MPO) activity and altered (increased) muscle contractility to receptor independent potassium chloride (KCl) challenge. Daily administration of nimesulide (9.0 mg/kg and 18.0 mg/kg, p.o.) significantly prevented development of inflammatory changes, decreased MPO activity, and also restored the contractility response of the isolated colon to KCl in both the animal models. The effect was comparable to that of sulphasalazine.

**Conclusion:** The results suggest the involvement of both cyclo-oxygenase and lipo-oxygenase mediated proinflammatory agents in colonic inflammatory process associated with IBD. Further, this study suggests such therapeutic interventions may be looked as targets for the treatment of hypomotility /constipation associated with Inflammatory Bowel Disease.

OP-66

### PHARMACOLOGICAL EVALUATION OF NOVEL INSULIN SENSITIZING AGENTS.

Sharma Rashmi, Sharma Ajay, Singh Manjeet.

Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala.

The present study has been designed to investigate the antidiabetic effect of alpha-substituted phenoxy propanoic acid compounds RSR-14 and RSR-15. The compounds RSR-14 and RSR-15 were used for evaluation of their antidiabetic activities on Diabetic and nondiabetic mice. Their antidiabetic effect was compared with pioglitazone as standard insulin sensitizing agent. Oral glucose tolerance test was conducted in overnight fasted nondiabetic mice. Test compounds were administered at various dose levels along with glucose just before starting oral glucose tolerance test. Blood glucose was estimated at various time intervals during oral glucose tolerance test. Overnight fasted diabetic mice were administered the test compounds and their blood glucose was estimated 30 minutes after administration of test drugs. The antihyperglycaemic effect of the compounds RSR-14 and RSR-15 observed in diabetic and Nondiabetic mice were comparable to the antihyperglycaemic effect produced pioglitazone insulin sensitizing agent. The antihyperglycaemic effect of compounds RSR-14 and RSR-15 confirms that they may act as insulin sensitizing agents like pioglitazone.

**OP-67****KINETIC BEHAVIOUR OF TAMM HORSFALL GLYCOPROTEIN [A HETEROGENOUS NUCLEATOR OF CRYSTAL FORMATION] IN HYPERTENSIVES BEFORE AND AFTER VITAMIN E THERAPY.****Sumitra K, Selvam R, Varalakshmi P.**

Department of Medical Biochemistry, Dr.A.L.M.PGIBMS, University of Madras, Taramani, Chennai.

An independent association has been established between hypertension and urolithiasis. Though metabolic dissections have been unravelled between the two groups the role of macromolecules, which could act as promoters and/or inhibitors of calcium oxalate crystallization has not been taken up as a topic of study to link the two diseases. One such macromolecule is Tamm Horsfall glycoprotein [THP] a well-established marker protein in the pathogenesis of renal stone formation. Thus our present study was focussed on the kinetic behaviour of this protein isolated from hyperoxalurics and hypertensives before and after Vit E therapy. The patient groups were administered Vit E as evion 400 mg/day, the follow up period was for a total of 9 months, the 24 hr urine sample collection was done at the end of every third month, hypertensive patients presented hyperoxaluria, hypercalciuria, hyperuricosuria and hypocitraturia. THP was isolated from both the patients before and after treatment and subjected to kinetic studies such as spectrophotometric crystallization assay, CaOx filter binding assay, in vitro calcium oxalate crystal growth assay and light microscopic crystal interaction studies [COM & COD]. The protein was assessed for sialic acid content, carbonyl content and thiol content. Results indicated a loss of inhibitory activity in the hypertensive and hyperoxaluric patients as when compared with the control subjects' protein, which exhibited inhibitory activity. The protein also ultimately showed decreased sialic acid, thiol content and increased carbonyl content. The protein kinetic behaviour neared normal following therapy with vit E. These results are suggestive that normalization of the activity was partly due to restoration of sialic acid, thiol content and decrease in the carbonyl content which is a form of oxidative injury to the protein. Thus antioxidant therapy should be a must in any form of disease.

**OP-67A****ADENOSINE RECEPTOR ACTIVATION PROTECTS AGAINST HIV-L INDUCED CYTOTOXICITY.****Sandeep Pingie<sup>1</sup>, Daniel Hallam<sup>1</sup>, Adriana Marcuzzi<sup>1</sup>, Sanjay Maggirwar<sup>2</sup>, and Vickram Ramkumar<sup>2</sup>.**<sup>1</sup>Department of Pbarmacology. SIU School of Medicine, Springfield IL-62702,USA..<sup>2</sup>Department of Microbiology & Immunology, University of Rochester Medical Center. Rochester NY

Patients with advanced human immunodeficiency virus (HIV-I) disease develop a syndrome of cognitive and motor dysfunction described as HIV -associated dementia (HAD), which forms one of the AIDS-defining illnesses. The various pathogenic mechanisms in HIV-1 induced neuronal damage include release of neurotoxins and inflammatory cytokines from macrophages/microglia, increase in intracellular Ca<sup>2</sup> levels in neurons and the generation of free radicals such as superoxides, nitric oxide and peroxyxynitrite, the action of all of which culminates into neuronal apoptosis. The nucleoside adenosine, acting via the A<sub>1</sub> adenosine receptor (A<sub>1</sub> AR) subtype, serves a neuroprotective role. In the current study, we wanted to investigate whether A<sub>1</sub> AR could protect against HIV induced toxicity and if so, to delineate the mechanism underlying protection. We specifically used the HIV-1 protein Tat, which is increased in the brains of patients with HAD. We utilized rat pheochromocytoma (PC12) cells, an in vitro model widely used by investigators to study the mechanisms underlying HIV dementia. Initial experiments indicated that in PC12 cells, HIV-I Tat induced apoptosis, which was significantly reduced when cells were incubated with the non-hydrolyzable analog of adenosine R-phenylisopropyladenosine (R-PIA). In studying the mechanisms involved in adenosine-mediated cytoprotection, we observed that HIV-1 Tat increased intracellular Ca<sup>2+</sup> levels in PC12 cells, predominantly by mobilization of Ca<sup>2+</sup> from its internal stores. This response was inhibited by co-incubation R-PIA, acting via the A<sub>1</sub> AR. Further, R-PIA reduced Tat-mediated iNOS induction and NO release, by inhibiting the transcription factor nuclear factor (NF) KB. These findings suggest a potential cytoprotective effect of adenosine against HIV-1 Tat-induced neurotoxicity, mediated through the A<sub>1</sub> AR. A better understanding of the interactions between adenosine and HIV proteins could aid in the development of novel treatment strategies for HIV dementia.



## ***Scientific Session VI***

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### **Chemotherapy of cancer and Chemotherapy of microbial infections**

- Date** : 28.11.2002  
**Time** : 1100-1300  
**Venue** : Hall -A
- Invited Lectures : Dr. S P S Monga  
Maj. Gen. T Rabindranath  
Dr. BS Dwarakanath  
Dr. GBKS Prasad
- Oral Presentation : OP68 - OP74
- Chairpersons : Maj. Gen. T Rabindernath  
Dr. K Husain





**IL-62****THERAPEUTIC  $\beta$ -CATENIN INHIBITION: A NOVEL STRATEGY TO CONTROL LIVER GROWTH.****Monga SPS.**

Cellular and Molecular Pathology, Pittsburgh Cancer Institute, and McGowan's Institute of Regenerative Medicine, University of Pittsburgh, School of Medicine, Pittsburgh, PA 15261, USA.

Others and we have previously demonstrated the role of  $\beta$ -catenin, a key component of the Wnt signal transduction pathway, in liver growth. Stabilization of  $\beta$ -catenin protein is implicated in etiopathogenesis of several cancers. We have also shown its role in liver development and liver regeneration where we observed an early increase in  $\beta$ -catenin protein and its nuclear translocation followed by significant decreases in its protein due to the activation of its degradation complex. We have utilized several approaches to identify novel regulators of this pathway during liver development as well as in adult liver. Studies were performed in primary hepatocytes, cancer cell lines and transgenic animals to investigate the effect of HGF, EGF and Erythropoietin on  $\beta$ -catenin. We also utilized a novel strategy utilizing an antisense phospho-morpholino oligomer (PMO) to  $\beta$ -catenin to inhibit  $\beta$ -catenin synthesis in an *in vivo* and *in vitro* environment. We found HGF and EGF to promote  $\beta$ -catenin nuclear translocation and its signalling. We also identified a novel Met- $\beta$ -catenin complex at the hepatocyte membrane that is regulated by HGF and appears to be independent of the Wnt or E-cadherin interactions. *In vivo* analysis suggests differences in mechanisms of  $\beta$ -catenin regulation in liver. Also tissue specific differences were detected in  $\beta$ -catenin regulation following analysis in kidney. Erythropoietin demonstrated a strong inhibitory role in  $\beta$ -catenin regulation in the hepatocytes and cancer cell lines due to activation of  $\beta$ -catenin degradation by ubiquitination. Finally, the antisense PMO was an effective means of decreasing  $\beta$ -catenin levels. We demonstrate a role of  $\beta$ -catenin in early lineage specification in developing liver utilizing embryonic liver culture system. Antisense PMO administration significantly decreased liver regeneration following hepatectomy owing to a compromise in  $\beta$ -catenin protein and cell proliferation. Thus we have identified potent inhibitors of the Wnt/ $\beta$ -catenin pathway that may have therapeutic implications in later years. We can also conclude that down-regulating specific targets such as  $\beta$ -catenin is a useful way to regulate growth and novel strategic measures need to be identified to customize cancer treatments.

**IL-63****DEVELOPMENT OF IMMUNOSPECIFIC RADIOPHARMACEUTICALS FOR DIAGNOSIS AND THERAPY OF CANCER.****Rabindranath T, Mishra AK.**

Institute of Nuclear Medicine and Allied Sciences, Brig. S K Mazumdar Road, New Delhi - 110054.

The advent of hybridoma technology in 1975 enabled mass production and isolation of monoclonal antibodies better known as immunospecific pharmaceuticals, of predetermined specificity and high quality with 100 % immunoreactivity. The successful application of radiolabelled monoclonal antibodies in the diagnosis and therapy of human diseases is the final result of a long and intensive research. First clinical studies were reported with I-131 labeled anti-CEA antibodies. Due to limitations of I-131 attention was diverted to In-111. However, several disadvantages like high liver uptake and high cost complicated the labelling procedures. The convenient, safe and stable labelling of antibodies with Tc - 99m paved the way for using a whole battery of new antibodies for detection of various cancers as well as for imaging of non-malignant diseases. Therapy using radiolabelled antibodies has been effective in the treatment of breast, lungs, prostate, hepatocellular carcinoma and lymphomas. Their use as vectors for cytotoxic and cytostatic substances has initiated the use of different radio nuclides for labelling of antibodies, which may be produced at reasonable costs by cyclotrons or reactors. Molecular engineering is becoming more and more important to overcome the patient response to murine antibody administration and chimeric antibodies are a real breakthrough in this field. Here we report the excellent ways to overcome the problems associated with the direct labelling of biological molecules by introducing bifunctional chelating agents to load the radio nuclides of our choice for the diagnosis and therapy of various types of tumours of human origin.

IL-64

## IMPROVING CANCER THERAPY WITH 2-DEOXY-D-GLUCOSE.

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The success of contemporary cancer therapy is restricted by the resistance of tumour cells to the cytotoxic effects of therapeutic agents on the one hand and limited tolerance of the normal tissue on the other. While the poor response to radiotherapy is generally attributed to the presence of hypoxic tumour cells, resistance due to an efficient p-glycoprotein mediated drug efflux is mainly responsible for the multiple drug resistance. Furthermore, efficient DNA and cellular repair processes are responsible for the resistance offered by tumour cells to many cytotoxic agents including ionizing radiation. Therefore, strategies directed towards differentially enhancing radiation damage in tumour cells, while protecting normal tissues could significantly improve the efficacy of cancer therapy.

Experimental studies in a number of *in vitro* and *in vivo* model systems have shown that the glucose analogue, 2-deoxy-D-glucose (2-DG) can selectively inhibit energy dependent DNA repair and cellular recovery processes in cells with high rates of glycolysis (like the cancer cells), leading to an enhancement in mitotic as well as apoptotic cell death. Interestingly, under similar conditions, 2-DG has been found to protect normal cells, possibly by reducing the mis-repair and fixation of primary lesions, resulting in the reduction of cytogenetic damage as well as apoptosis. Subsequent studies have shown that metabolic inhibitors like hematoporphyrin derivatives and 6-aminonicotinamide that impairs respiratory and/or alternate metabolic pathways of energy production could significantly enhance the radiosensitizing effects of 2-DG. More recently, 2-DG has also been shown to significantly enhance the cytotoxic effects of anticancer agents like topoisomerase inhibitors (etoposide and camptothecin) and a radiomimetic drug (bleomycin) in established human and murine tumour cell lines. Therefore, combinations of 2-DG and DNA damage causing cytotoxic agents like ionizing radiation or chemotherapeutic agents provide a unique therapeutic regimen to selectively destroy tumours, while sparing the normal tissues.

Phase-I/II clinical trials carried out in cerebral glioma patients have shown that the combined treatment of 2-DG plus radiotherapy (RT) is well tolerated without any acute toxicity or late radiation damage to the normal brain tissue. A significant increase in the median survival (29 months), with improved quality of life observed in these studies is significantly higher than the survival (~13 months) reported with other therapeutic regimens. Multi-centric clinical trials to evaluate the efficacy of this treatment are currently in progress. Development of approaches for individualization of the combined therapy (2-DG + RT) is going to be a greater challenge in the future.

IL-65

## POTENTIAL APPLICATION OF STEM CELLS IN CELL THERAPIES.

Prasad GBKS.

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The development of stem cell lines, both pluripotent and multipotent, that may produce many tissues of the human body is an important scientific breakthrough in biomedical research. Perhaps the most important application of human pluripotent stem cells is their application in "cell therapies." Several human diseases and disorders result from destruction of tissues of the body and auto grafts or allografts are often used to replace ailing or destroyed body tissue. Pluripotent stem cells, stimulated to develop into specialized cells, offer the possibility of a renewable source of replacement cells and tissue to treat different diseases and disabilities and would include Parkinson's and Alzheimer's diseases, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis and rheumatoid arthritis. Recent published reports on the isolation and successful culturing of the first human pluripotent stem cell lines have generated great excitement and have brought biomedical research to the edge of a new frontier. Due to the potential of stem cells in the treatment of human diseases, significant attention has been generated regarding the origin of stem cells (ES versus adult), nuclear reprogramming, cloning, and organogenesis. Stem cells have now been identified in a variety of adult tissues such as bone marrow, blood, skin, liver, muscle and even brain. These adult-derived stem cells, cultured under the specific conditions, may be suitable for treatment in vivo of genetic or degenerative disorders. There would be many advantages of using adult multipotent stem cells for transplantation. The use of adult stem cells for such cell therapies would certainly reduce or even avoid the practice of using embryonic or fetal stem cells and there is evidence that length of human lives may be determined by the toughness of stem cells. Until recently, there was little evidence in mammals that multipotent cells such as blood stem cells could change course and produce any cell other than a blood stem cell or a specific type of blood cell. In animals, it has been shown that some adult stem cells previously thought to be committed to the development of one line of specialized cells are able to develop into other types of specialized cells. The stem cell research could dramatically change the way the drugs are developed and tested for safety. For example, new medications could be initially tested using pluripotent stem cells. Only the drugs that are both safe and appear to have a beneficial effect in cell line testing would be permitted further testing in laboratory animals and human subjects. Given the enormous promise of stem cells to the development of new therapies for the most devastating human diseases, stem cell research has the potential to revolutionize the practice of medicine and improve the quality and length of life. This paper discusses the latest developments in stem cell therapy.

**OP - 68**

**EFFECT OF PIPERINE ON ALTERED MITOCHONDRIAL ANTIOXIDANT SYSTEM IN BENZO (a) PYRENE INDUCED EXPERIMENTAL SMALL CELL LUNG CARCINOMA.**

Selvendiran K, **Senthilnathan P**, Sakthisekaran D.

Department of Medical Biochemistry, University of Madras, Taramani Campus, Chennai - 600113.

Alkaloid compounds are present in dietary and medicinal plants and beverages in high concentrations. They have been reported to exhibit a variety of biological effects, including anti-inflammatory, antioxidant, and antimutagenic activities. In the present study, our goal was to investigate the impact of piperine, a principle ingredient of pepper, on alterations of mitochondrial antioxidant system and lipid peroxidation. Benzo(a)pyrene [B(a)P] induced experimental small cell lung carcinoma. Oral supplementation of piperine (50 mg/kg body weight) effectively suppressed lung carcinogenesis in B(a)P induced mice as revealed by the decrease in the extent of mitochondrial lipid peroxidation and concomitant increase in the activities of enzymatic antioxidants (superoxide dismutase, catalase and glutathione peroxidase) and non enzymatic antioxidant (reduced glutathione vitamin E and vitamin C) levels when compared to lung carcinoma bearing animals. Our data suggest that piperine may exert its chemopreventive effect by modulating lipid peroxidation and augmenting antioxidant defense system.

**OP - 69**

**REHABILITATING ROLE OF CURCUMIN AGAINST N-NITROSO-DIETHYLAMINE INDUCED EXPERIMENTAL HEPATOCELLULAR CARCINOMA WITH REFERENCE TO GLUTATHIONE METABOLISM.**

Thangavel M, **Magesh V**, Sakthisekaran D.

Department of Medical Biochemistry, University of Madras, Taramani Campus, Chennai - 600113.

Cancer is a genetic disorder involving dynamic changes in the genome leading to uncontrolled cell growth, ability to invade and metastasis. Hepatocellular Carcinoma (HCC) is a common malignant tumor. The prognosis for patients with HCC is affected greatly by liver failure due to intra hepatic metastasis and carcinoma invasion rather than lymph node and distant metastasis. Curcumin is a (3-diketone constituent of the spice turmeric that possesses anti-carcinogenic properties in several chemical models. Adriamycin (ADR; Doxorubicin) is a potent antitumor antibiotic drug known to cause cardiotoxicity, nephrotoxicity and neurotoxicity. We have evaluated the effect of curcumin along with adriamycin on N-nitrosodiethylamine (DEN) induced hepatocellular carcinoma. In the present study, the antioxidant and anti-cancer effect of curcumin along with adriamycin on DEN induced HCC with reference to glutathione metabolizing enzymes (Glutathione-S-transferase, glutathione reductase and glutathione) were targeted.

**OP - 70**

**APIGENIN PROTECTION AGAINST THE N-NITROSODIETHYLAMINE INDUCED AND PHENOBARBITAL PROMOTED HEPATOCELLULAR CARCINOGENESIS IN WISTAR ALBINO RATS WITH REFERENCE TO MEMBRANE BOUND ATPASES.**

Prince Vijeya Singh J, Venkatesan PN, Sakthisekaran D.

Department of Medical Biochemistry, University of Madras, Taramani Campus, Chennai - 600113.

Flavonoids are polyphenolic compounds ubiquitously present in vegetables and fruits of vascular plants. Apigenin is a nonmutagenic and nontoxic plant flavonoid, which is having three hydroxyl groups in their 4, 5 and 7<sup>th</sup> positions. Research in recent years has strengthened the association between reduction in cancer rates and apigenin consumption. It is a flavone subclass of flavonoid that has been ascribed with anti-inflammatory, anticarcinogenic and antioxidant properties. N-nitrosodiethylamine (DEN) is a potent environmental carcinogen, which primarily induces tumours of liver. Phenobarbital (PB) is a well known liver tumour promoter and so both has been wide spread used as an experimental model in the field of experimental liver carcinogenesis in male Wistar albino rats. Present study was focussed on the protective role of apigenin against DEN induced and PB promoted liver carcinogenesis. We have observed the reduction in the activities of membrane bound ATPases in DEN and PB administered rats. Interestingly the activities of these enzymes were counteracted by the potency of apigenin.

**OP - 71**

**PROTECTION OF APIGENIN AGAINST N-NITROSODIETHYLAMINE INDUCED AND PHENOBARBITAL PROMOTED EXPERIMENTAL HEPATOCELLULAR CARCINOGENESIS WITH REFERENCE TO LIVER CANCER MARKERS.**

Prince Vijeya Singh J, Venkatesan PN, Sakthisekaran D.

Department of Medical Biochemistry, University of Madras, Taramani Campus, Chennai - 600113.

Apigenin, a common dietary flavonoid is a non-toxic, non mutagenic and antioxidant flavone subclass of flavonoid. It is a substantial component of the human diet and has been shown to possess a variety of biological activities including tumour growth inhibition and chemoprevention. Recent studies in several biological systems have shown that apigenin induces tumour growth inhibition, cell cycle arrest and apoptosis. N-nitrosodiethylamine (DEN) is a potent environmental carcinogen primarily induces tumours of liver. Changes in ploidy of cells, free radicals, non-oxidising species and associated DNA damages have been frequently coupled with carcinogenesis. In the present study some liver markers were examined in DEN induced and phenobarbital (PB) promoted experimental albino rats. Our results show that apigenin inhibited the elevation of these markers. Based on these results we suggest that apigenin may be developed as a promising chemotherapeutic agent against the development of chemical carcinogenesis

OP - 72

**PROTECTIVE EFFICACY OF PIPERINE AGAINST BENZO (a) PYRENE INDUCED GENOTOXICITY IN SWISS ALBINO MICE.**

Selvendiran K, Venkatesan PN, Sakthisekaran D.

Department of Medical Biochemistry, University of Madras, Taramani Campus, Chennai-600 113.

A wide variety of naturally occurring substances have been shown to have cancer chemopreventive properties. Many bioactive compounds present in edible as well in herbal plants have revealed their cancer chemopreventive potential. Some plant products are also used in traditional medicine. These factors elicit considerable antimutagenic and anticarcinogenic effects against experimental mutagenesis and carcinogenesis induced by various chemical carcinogens. In the present study, piperine a traditional plant products exerts modulatory effects on the in vivo genotoxicity of Benzo(a)pyrene [B(a)p]. Genotoxic effects were assessed in the mouse bone marrow by micronucleus test. The results obtained suggest that pre, simultaneously as well as post treatment with piperine can significantly inhibit the genotoxicity of B(a)p. Our results of the present investigation revealed that piperine has genoprotective potential against B(a)p induced mutagenesis in Swiss albino mice.

OP - 73

**LEUCOVORIN RESCUE SCHEDULES IN CHILDREN FOLLOWING TREATMENT WITH HIGH DOSE METHOTREXATE IN ACUTE LYMPHOCYTIC LEUKEMIA (ALL).**

Shafiq AT, Wafai S, Mushtaq A \*

Departments of Clinical Pharmacology and \*Medical Oncology, SKIMS, P.B. 27, Srinagar - 190011.

**Objective:** High dose methotrexate (HDMTX) treatment with leucovorin (L V) rescue has been found to improve the final outcome in acute lymphocytic leukemia (ALL). Monitoring of plasma methotexate levels during high dose therapy is useful in determining leukovorin dosage required to prevent severe methotrexate associated toxicity as well a sub-therapeutic effect of MTX and also to use amounts of LV that are adequate but not excessive so that normal but not tumour cells will be rescued. The aim of the study was to find out the amount of calcium leucovorin (CALV) required to achieve non-toxic MTX levels ( $< 0.2 \mu\text{mol/L}$ ) after high dose, MTX in patients of ALL.

**Methods:** 12 children (10 males and 2 females), with mean age of 11 years, (range 6-18 years), admitted in Medical Oncology ward, were subjected to this study. The average HDMTX was given from 2 to 4.8 gms according to surface area of the patient in combination therapy according to U. K. ALL protocol XII. After 36 hours of HDMTX, CaLV was given ( $15 \text{ mg/m}^2$ ) at different time intervals according to protocol. Patient's blood samples were collected at 24, 48, 72, 96 and 102 hours. Methotrexate levels were estimated by EMIT assay.

**Results:** The results showed variability in the total number of doses of GaL V required to achieve MTX non toxic levels ( $\frac{1}{2} 0.2\mu\text{mol/L}$ ). The time taken in all 12 children to reach serum MTX ( $< 0.2\mu\text{mol/L}$ ) varied from 46 to 102 hours. No severe toxic effect except mild mucositis was observed in one patient.

**Conclusion:** Each patient on HDMTX followed by GaLV needs individual therapeutic drug monitoring since there was a marked individual variation in serum MTX levels before and after LV administration.

OP - 74

**EFFECT OF PLANT EXTRACT (IVR - 1A) ON THE RHYTHMICITY OF *FASCIOLA GIGANTICA*.**

**Raje AA**, Kumar Dinesh, Rao, GS, Tripathi, HC.

Division of Pharmacology and Toxicology, Indian Veterinary Research Institute, Izatnagar - 243122.

**Objective:** To investigate the effect of IVR-1A (petroleum ether extract of plant of IVR-1A) on the rhythmicity of *Fasciola gigantica*.

**Methods:** *Fasciola gigantica* were freshly collected from local abattoir in an insulated container, containing Heldon-Fleig (H - F) solution. The effect of IVR - 1A (petroleum ether extract of rhizome of a plant) was studied on the rhythmicity of fluke, suspended in an organ bath ( $38 \pm 1^\circ\text{C}$ , containing H - F solution). The extract was added at cumulative log doses (100, 300, 1000 and 3000  $\mu\text{g/ml}$ ) on suspended helminths and motility (amplitude and frequency of contraction) was recorded isometrically on polygraph.

**Results:** IVR - 1A at 100, 300 and 1000  $\mu\text{g/ml}$  concentration reduced the amplitude and frequency of contractions. Significant reduction in amplitude ( $P < 0.05$ ) and frequency ( $P < 0.01$ ) was observed at 1000  $\mu\text{g/ml}$  concentration. At 3000  $\mu\text{g/ml}$  concentration IVR - 1A caused complete and irreversible paralysis of *Fasciola gigantica*.

**Conclusion:** IVR - 1A (petroleum ether extract of rhizome of a plant) possessed significant fasciolicidal activity *in vitro*.





## ***Scientific Session VII***

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### **Neurodegenerative disorders and Neuropharmacology - I**

**Date** : 28.11.2002  
**Time** : 1100-1300  
**Venue** : Hall - C

**Invited Lectures** : Dr. S K Kulkarni  
Dr. O N Tripathi

**Oral Presentation** : OP 75- OP 81

**Chairpersons** : Prof. K D Gill  
Dr. S P S Monga

THE UNIVERSITY OF CHICAGO  
DIVISION OF THE PHYSICAL SCIENCES  
DEPARTMENT OF CHEMISTRY  
5780 SOUTH CAMPUS DRIVE  
CHICAGO, ILLINOIS 60637

**IL-66****AN INSIGHT INTO TARDIVE DYSKINESIA.****Kulkarni SK, Naidu PS.**

Pharmacology Division, University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh -160 014.

Schizophrenia is a devastating psychiatric disorder that affects 1 % of population worldwide. Neuroleptics are the major class of drugs used in the treatment of schizophrenia. Neuroleptics are associated with wide variety of extrapyramidal side effects such as akathisia, dystonia, neuroleptic malignant syndrome, Parkinsonism and Tardive dyskinesia. Despite of the awareness that neuroleptics could cause EPS, these drugs remain the most effective means of treating schizophrenia and Tourette syndrome and for the management of behavioural disorders in developmentally disabled individuals. Tardive dyskinesia is a complex hyperkinetic syndrome consisting of choriform, athetoid or rhythmic abnormal involuntary movements. The face, mouth and tongue are most frequently involved (orofacial type), but a variety of less frequent motor abnormalities of the upper and lower limbs and of the trunk may also occur. Estimates of the prevalence rate of TD in patients receiving neuroleptics range from 0.5%-70% with an average prevalence rate of 24%. Despite much research, the pathogenesis of TD remains elusive. So far various neurochemical hypothesis have been proposed for the development of TD. Those include dopaminergic hypersensitivity, disturbed balance between dopamine and cholinergic systems, dysfunctions of striatonigral GABAergic neurons and excitotoxicity. Similarly, different suppressive agents have been tried with limited success. Recently role of oxidative stress and structural abnormality in the pathophysiology of TD has gained much impetus. This hypothesis has been supported by numerous reports that chronic neuroleptic treatment increases free radical production and causes structural damage. More recently the genetic vulnerability for the predisposition for the development of TD i.e. pharmacogenetic aspect of TD also gaining impetus in the tardive dyskinesia research.

**IL-67****NEW INSIGHTS INTO MOLECULAR MECHANISM OF ACTION OF CALCIUM CHANNEL BLOCKERS.****Tripathi ON.**

Central Drug Research Institute, Lucknow -226001.

Calcium channel blockers (CCBs) produce their pharmacological effects by binding to the  $\alpha_1$ -subunit of L-type ( $\alpha_{1C}$  or  $Ca_{v1.2}$ ) Ca channels leading to block of channel activity. This block is generally expressed in terms of Ca channel state model, viz resting (RCB), open (OCB) or inactivated (ICB) channel blockers. The mechanism of block determines the specific therapeutic profile of a CCB and often serves as a basis for their classification. Patch-clamp studies have offered valuable insights into the putative receptive sites for CCBs on  $\alpha_1$ -subunit. OCBs (e.g., verapamil and fendiline - FEND) bind to sites deep into the pore, while ICBs (e.g., nifedipine) act near the external mouth of the pore RCBs (e.g., nifedipine and diltiazem) also bind to sites close to the outer opening of the pore. Cloning and splicing studies on  $\alpha_1$ -subunit have helped in identifying motifs of amino acid sequences of these sites. Our patch-clamp studies on whole-cell  $Ca_{v1.2}$  channel currents in rat ventricular myocytes, using Na as the charge carrier, have revealed that some CCBs like Fend have multiple sites of action, including Na channels and calmodulin (CAM). Na channel block by Fend contributes to its therapeutic advantage. CAM antagonistic activity of FEND, applied intracellularly by cell dialysis, altered the kinetic behaviour of  $Ca_{v1.2}$  channels revealing role of novel cytosolic sites of CAM-dependent pathways in the pharmacological effects of CCBs. These novel molecular mechanisms are likely to need important considerations for new drug discovery.

OP - 75

### HYPOGLYCEMIC CONVULSIONS IN MICE: ROLE OF CENTRAL NEUROTRANSMISSION.

Anuradha K, Bhargava VK, Debasish H, Pandhi P.  
Department of Pharmacology, PGIMER, Chandigarh.

**Objective:** To determine the effects of blockade and enhancement of central neurotransmission on insulin induced hypoglycemic convulsions.

**Methods:** Swiss albino mice of 23-28 g of either sex were used. Insulin (bovine) was administered in graded doses (2, 4, and 8 IU/kg, s.c). Latency of onset of seizures, duration, number of seizures, animals with seizures and mortality were observed over a period of 2 hrs. Drugs like nimodipine (50 mg/kg), L-dopa (100 mg/kg), reserpine (2.5 mg/kg for 3 consecutive days), nicorandil (0.1 mg/kg) and glibenclamide (0.1 mg/kg) were used. Blood sugar estimation was done prior to and after treatment with insulin.

**Results:** Insulin in increasing doses produced convulsions with increasing severity. Blood sugar levels were lowered after insulin administration. Despite the presence of hypoglycemia dopamine and nicorandil prevented the development of insulin induced seizures. While reserpine, glibenclamide and nimodipine potentiated the same.

**Conclusion:** Our results showed that insulin induced seizures involve central neurotransmission mediated through dopamine, potassium and calcium channels. However further studies will be required to ascertain the exact mechanism of hypoglycemic seizures.

OP - 76

### NEUROPROTECTIVE POTENTIAL OF CURCUMIN IN FOCAL ISCHEMIA.

Thiyagarajan M, Sharma SS.

Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research (NIPER), S.A.S. Nagar, (Mohali) - 160062.

**Objective:** Free radical mechanisms are continuously active in the aggravation of neuronal injury during ischemia and reperfusion. Several in vitro and in vivo studies proved the antioxidant potential of curcumin and its metabolites. However neuroprotective potential of curcumin has not been investigated in cerebral ischemia.

**Methods:** Stroke was developed by occluding the middle cerebral artery with a 3-0 nylon monofilament (Ethilon) inserted from external carotid artery through the internal carotid artery for a distance of 18 mm. Blood flow to the ipsilateral and contralateral hemisphere of brain was monitored continuously with the Periflux 4001 multi channel laser doppler system with a rectangular probe. 120 min. after occlusion reperfusion was done by completely withdrawing the filament. Effect of curcumin was studied at the doses of 30-300 mg/kg, i.p. It was administered 30 min before reperfusion.

**Results:** About eighty percent reduction in the blood flow was observed on occluding with 3-0 nylon monofilament resulted in the 29 % infarction. Curcumin treatment (100 and 300 mg/kg, i.p.) produced 26 and 40 % neuroprotection respectively ( $p < 0.05$ ). Ischemia induced cerebral edema was also reversed. A dose dependent reduction in the neurological score was observed on curcumin treatment.

**Conclusion:** These results clearly show the neuroprotective potential of curcumin in cerebral ischemia.

OP - 77

**REVERSAL OF DIABETIC NEUROPATHIC PAIN BY ADENOSINE A2 RECEPTOR AGONIST IN RATS.**

**Kumar S \***, Pawar R, Kaul CL, Sharma SS.

Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research (NIPER), S.A.S. Nagar (Mohali) -16002.

**Objective:** Diabetic neuropathy is most common late order complication of diabetes mellitus. Most of the agents that are used for counteracting the symptoms of diabetic neuropathic pain are not clinically effective. In the present study, we investigated the effect of adenosinergic agents in diabetic neuropathy.

**Methods:** Diabetic neuropathy was developed by STZ (65 mg/kg, i.p.). Diabetic neuropathic pain was assessed after 6 weeks of STZ administration using cold immersion, hot immersion and formalin test. Diabetic neuropathy was also confirmed by reduction in motor nerve conduction velocity (MNCV) and nerve blood flow. Effect of adenosinergic agents, A2 receptor agonist (CGS 21680) and A3 receptor agonist (CL-IB-MECA) was studied in diabetic neuropathic pain.

**Results:** Streptozotocin caused significant decrease ( $p < 0.001$ ) in tail flick latency in cold and hot immersion test. Adenosine A2 receptor agonist, CGS 21680 (0.5-2 mg/kg.i.p.) produced dose dependent reversal of diabetic neuropathic pain. A2 receptor antagonist, ZM 211385 (3 mg/kg) completely blocked effects of CGS 21680. Adenosine A3 receptor agonist CL-IB-MECA (0.5-1 mg/kg) could not reverse allodynia in cold and hot immersion test but produced reversal of formalin induced hyperalgesia. Effect of adenosinergic agents on MNCV and nerve blood flow is in progress.

**Conclusion:** Adenosine A2 receptor agonist reversed the diabetes induced neuropathic pain in STZ-induced diabetic neuropathy in rat.

OP - 78

**OLFACTORY ENSHEATHING CELLS ENHANCE FUNCTIONAL RESTORATION IN RAT MODEL OF PARKINSON'S DISEASE: CO-TRANSPLANTED WITH FETAL VENTRAL MESENCEPHALIC CELLS (VMC).**

**Agrawal AK**, Shukla S, Seth K, Seth PK.

Developmental Toxicology Division, Industrial Toxicology Research Centre, P.O. Box 80, M.G. Marg, Lucknow -226001.

Transplantation of fetal ventral mesencephalic cells (VMC) to the adult striatum has been considered promising therapeutic approach in Parkinson's disease, yet its clinical use is limited due to non-availability of fetal brain and ethical concern. Different strategies have been worked out to promote survival of transplanted fetal VMC cells using various trophic and non-trophic supports. Olfactory ensheathing cells (OECs) derived from olfactory bulb shares the properties of Schwann cells / astrocytes and express high level of neurotrophic factors including NGF, bFGF, GDNF and NT3, known to play important role in functional growth and regeneration of DA neurons. An attempt has been made to study functional restoration following co-transplantation of VMC and OEC (cultured from olfactory bulb) in striatal region of 6-OHDA lesioned rats. Functional restoration was assessed using neurobehavioural, neurochemical, immunohistochemical approach. Twelve weeks post transplantation, a significant recovery in apomorphine induced circling behaviour (72%) and spontaneous locomotor activity (76%) was evident in co-transplanted animals when compared with 6-OHDA lesioned animals. A significant restoration in  $^3\text{H}$ - spiperone binding (88%), DA level (67%) and DOPAC level (73%) was observed in animals co-transplanted with OEC and VMC as compared to either OEC or VMC alone. A significantly high expression of tyrosine hydroxylase (TH) positive cells in striatal region of co-transplanted animals further confirmed the supportive role of OEC in viability of dopaminergic cells leading to functional restoration due to co-transplantation. The results suggest that co-transplantation of OEC and VMC may be a better approach for long term functional restoration in 6-OHDA induced rat model of Parkinson's disease.

OP - 79

**SUBSTANCE P IN ATTENUATION OF STRESS INDUCED BEHAVIOURAL DESPAIR AND CATECHOLAMINE DEFICITS.**

Vij AG\*, Satija NK\*\*, Flora SJS\*\*\*, Mathur R \*\*\*\*

DIPAS, Lucknow road, Timarpur, Delhi-110 054. \*\* CSE. Core 6A. India Habitat Centre. N Delhi-110 003. \*\*\* DRDE. Jhansi Road, Gwalior- 474002. \*\*\*\* SOS in Zoology, Jiwaji University, Gwalior - 474002.

**Objective:** To investigate the effect of peripheral administration of neuropeptide substance P (SP) on behavioural and neurochemical responses to stress.

**Methods:** Adult male albino rats pre-trained on Morris Water Maze (MWM) were co-exposed to multiple stressors namely immobilization, electric shock, vibration, light flashes and pre-recorded gun noise for 30 min. daily for three consecutive days following single intra-peritoneal injection of saline or SP (125 or 250 µg/kg/bw). Behavioural measures were carried out daily prior to and after the stress exposure. All the rats were sacrificed on the fourth day immediately after 30 minutes of stress exposure along with the controls. Catecholamine levels, metabolites and enzymes involved in their synthesis and deamination were assayed.

**Results:** Animals exposed to stress were hypo-kinetic and took more time to locate the platform whereas the animals receiving SP displayed neither the stress induced hypokinesia nor behavioural deficits in acquisition scores on MWM performance. Pre-treatment with SP abolished peripheral as well as cerebral depletion of norepinephrine in stress exposed rats and increased cerebral as well as adrenal dopamine levels.

**Conclusion:** Stress reducing effect of SP may be mediated by activation of catecholaminergic synthesis and/or inhibition of catecholamine degradation.

OP - 80

**EFFECT OF ELECTRICAL FOOT SHOCK STRESS DURING ADULT AGE ON SUBSTANTIA NIGRA IN ALBINO MICE..**

Prakash Babu B, Muddanna S Rao, Ramachandra Bhat K.

Department of Anatomy, Kasturba Medical College, Manipal - 576119.

Brain is a highly dynamic and plastic structure and is affected by malnutrition, environmental toxins. Research in past few years has shown that stress is one of the social factor which affects the brain and behaviour to a significant extent in all ages. Aim of the present experiment was to study the effect of electrical 'foot shock' stress during adult age on the dendritic morphology of substantia nigral neurons of mice. In the present experiment albino mice of 271 days old were given foot shock stress (80-90 volts, 50 Hz at 5-min intervals) for 3 hr/day in a foot shock apparatus for 5, 21 and 60 days. After the stress, mice were sacrificed along with age matched controls. Substantia nigra was dissected and processed for Golgi staining. In mice subjected to 5 days stress there was significant - decrease in dendritic intersections at 80 µ concentric circle. In 21 days stress group there was a significant decrease in (a) dendritic intersections at all concentric circles except at 20 µ concentric circle (b) total number of dendritic branching points and (c) branching points at 20-40 µ, 40-60 µ concentric zones. In 60 days stress group there was a significant decrease in total number of dendritic processes, dendritic, intersections at all concentric circles up to 100 µ concentric circle. In the same group of experimental animals there was also significant decrease in total number of dendritic branching points and dendritic branching points at all concentric zones except at 60-80 µ zone. These results suggest that stress during adult age affects the nigral neurons in mice and may cause behavioural changes in them.

**SPASTIN SEQUENCES IMPLICATED IN PROTEIN PHOSPHORYLATION HARBOUR MUTATIONS IDENTIFIED IN HEREDITARY SPASTIC PARAPLEGIA.****Ghosh T\***, **Bhaduri N\***, **Nandagopal K\*\***.

\*Institute of Molecular Medicine, \*\* Chembiotek-Research International, Block BN, Plot 7, Sector V, Salt Lake, Kolkata - 700091.

**Objective** To examine the Spastin protein sequence for motifs implicated in protein phosphorylation and verify thereby whether the loss of function phenotype observed in Hereditary Spastic Paraplegia (HSP) derives from impaired Spastin phosphorylation.

**Methods:** We utilized the NetPhos(2.0) software program to identify the sequence context, associated probability scores and regional distribution of Ser/Thr phosphoacceptor residues in Spastin. The PhosphoBase pattern search program was then used to identify consensus sequences for substrate phosphorylation mediated by various kinases. This aided the assignment of kinase family to a given sequence context. The PhosphoBase and NetPhos score-dependent predictions were evaluated for biological significance by searching orthologous sequences for similar motifs. The role (s) of evolutionary conserved sequences was then examined with respect to pathogenic mutations in Spastin.

**Results:** The consensus sequence (X-S/T-P-X-R/K) for CDC2 kinase mediated phosphorylation maps to <sup>40</sup>PPPESPHKR<sup>48</sup> in the N-terminus of Spastin. Though the associated NetPhos score (0.364) is low, we note that a sporadic missense mutation (S44L) occurs within this sequence. Protein kinase C (PKC)-mediated phosphorylation occurs when the consensus sequence is X-SIT-X-R/K. Several such sequences were identified in multiple regions of Spastin with a wide range of NetPhos scores (0.575-0.988). The sequence context <sup>454</sup>EHDASRRLK<sup>462</sup> is interesting. This is conserved between Spastin and its mouse and Drosophila orthologues. R460L missense Spastin mutation disrupts the consensus recognition sequence for PKC-dependent phosphorylation. The consensus sequence (X-SIT -X-X-D/E) for Casein kinase II (CKII)-mediated phosphorylation maps to multiple regions of Spastin and robust NetPhos score (0.878) indicates high probability of phosphorylation. The sequence context associated with S207 (<sup>203</sup>PFSKSQTDV<sup>211</sup>) is of particular significance. It is deleted in the KIAA 1083 splice variant, reported to be preferentially expressed in the corpus callosum and Spinal cord.

**Conclusion** Spastin sequences implicated in protein phosphorylation harbour mutations identified in Hereditary spastic paraplegia.



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## ***Scientific Session VIII***

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### **Toxicology and safety evaluation**

- Date** : 28.11.2002  
**Time** : 1400-1545  
**Venue** : Hall -A
- Invited Lectures** : Dr. Anna B Fischer  
Dr. P Balakrishna Murthy  
Dr. P B Deshmukh  
Dr. Pravin Kumar  
Dr. D Parmar  
Dr. S Das Gupta
- Oral Presentation** : OP82 - OP87
- Chairpersons** : Dr. Steven Baskin  
Dr. Balakrishna Murthy



**IL-68****TOXICOLOGICAL EVALUATION OF PEPPER SPRAY CONTAINING CAPSAICIN.****Anna Barbara Fischer**Institute of Hygiene and Environmental Medicine, Friedrichstr. 16,35392  
Giessen, Germany.

In the US, some European countries and recently also in some German federal states pepper spray is used by the police as a "less dangerous" weapon and has proved to be efficacious when directed against single person. In a review of the literature the mode of action of the irritant substance capsaicin and its possible health effects are described and assessed. The reviewed literature consists of scientific publications as well as reports by police agencies and by an American civil liberties union. Aerosol use constitutes usually single short exposures of skin, eyes and respiratory tract. Skin and eye effects appear to be transitory. In studies with human volunteers following inhalation exposure cough and a transient airway constriction were recorded; the reactions of asthmatic persons did not differ from those of non-asthmatics. An unclear point concerns, the reports on death cases following capsaicin use by the police. In most cases "positional asphyxiation" was diagnosed as the immediate cause of death. In three cases a cardiac disease in connection with stress and pepper spray, led to death. Whether persons with such underlying diseases are at special risk, is to date unclear. When licencing pepper spray, users should be informed about potential health hazards and should be trained in the treatment of affected persons. Adequate training can be given to police forces, but the release of the spray for private use is more - problematical. The synthetic analogue pelargonic acid vanillylamide (PAVA) should be preferred to the natural capsaicin derived from capsicum plants, because concentrations can be prepared and analysed more accurately.

**IL-69****ISSUES OF GLP IN REGULATORY TOXICOLOGY STUDIES.****Balakrishna Murthy P.**

International Institute of Biotechnology and Toxicology, Padappai - 601301.

Relevant Indian registration acts require all companies and manufacturers of new pesticides, drugs and pharmaceuticals and biotech products to submit detailed toxicological data on active and the formulated product, covering various end-points of toxicity before they are granted registration for import/indigenous manufacture and sale by appropriate authorities. Registration of each of the above products is a part of the relevant acts and rules for registration with necessary toxicology protocols are prescribed by the registration committee/statutory body of Government of India and amended from time to time. Generation of toxicological data as per the protocols prescribed by these authorities warrant sufficient quality checks on various aspects of experimentation to ensure the reliability of the data submitted. One potential lacuna of Indian registration acts is that due to lack of global cooperation/agreement, foreign based animal GLP data may not be acceptable many times due to deviations in test protocols. Consequently, most of the time toxicological studies are repeated in our country which could have been avoided if only Indian registration rules of products accept foreign based GLP test report as a part of the mutual acceptance of data MAD system of international/global registration process. This paper discusses the advantages of GLP study in animal toxicity studies in risk assessment to human health and environment.

**IL-70****TOXICOLOGY WITH GLP COMPLIANCE.****Deshmukh PB.**

Jai Research Foundation, P.B. No. 30, G.I.D.C., Vapi - 396195.

Product safety regulations all over the world are formulated to safeguard human health and its environment. We are constantly exposed to a large number of chemicals, which may cause an unreasonable risk to health or environment. The regulators have to rely heavily on the toxicology principles and the experimental data for their evaluation of the substances, which enables them to make critical decision so as to approve the product for marketing. The whole concept of Good Laboratory Practice and its evolution is the outcome of such demand from various regulatory agencies. Any company who wants to export their product, have to generate the required data in a GLP compliant laboratory which is acceptable to the regulatory agencies in most of the countries of your interest. Government of India also accepted DECO principles of GLP and very soon, we will also have Indian GLP.

**IL-71****SENSORY IRRITATION POTENTIAL AND ACUTE TOXICITY OF CAPSAICIN AND ITS ANALOGUES.****Pravin Kumar, Mathur R., Dangi RS, Vijayaraghavan R. Malhotra RC, Kaushik MP, Swamy RV.**

Division of Pharmacology and Toxicology, Defence R &amp; D Establishment, Jhansi Road, Gwalior - 474002.

**Objective:** Sensory irritation potential and acute toxicity of E-capsaicin and its ten analogues were evaluated in male mice to assess their efficacy as riot control agent.

**Methods:** Capsaicin (8-methyl-N-vanillyl-6-nonenamide; E-isomer) and its ten analogues were synthesized and characterized by elemental analysis, IR, <sup>1</sup>H NMR and mass spectral analysis (purity of the compounds >99% by GC analysis). For the determination of sensory irritation potential through inhalation, an all glass static inhalation exposure assembly (6 L) was used. The respiration of male mice were sensed, amplified, recorded and analysed using a polygraph coupled with computer. For each concentration (n=4), mean of percent respiratory rate during the exposure was calculated considering the pre-exposure rate as 100%. The graph was plotted using mean value of each point against corresponding air concentration (nominal concentration) of the compound. Fifty percent depression of the respiratory rate (RD<sub>50</sub>) was determined by obtaining the linear curve fitting equation and putting the value of 'Y' = 50. Solutions of the compounds were prepared in propylene glycol and were fed to 3-4 hours fasted male albino mice (25-31 g) and LD<sub>50</sub> was calculated by method of moving average.

**Results:** The nominal concentration of the compounds in air which induces respiratory depression by 50% (RD<sub>50</sub>) are as follows: E-capsaicin, 50.9(15.5); VC-7, 192.7(82.5); VC-8, 229(91.9); VC-9, >320; VC-10, 26.3(12.6); VC-11, 40.8(23.0); VUC-9, >320; VEC-9, >320; OVC-9, 290.9(119.1); VTU, >320 and VSO-8, >320 mg.m-3. Values in the parenthesis depicts actual concentration of the compound in air. LD<sub>50</sub> was found to be, E-capsaicin, 200; VC-7, 100; VC-8, 119; VC-9, 178.2; VC-10, 141.4; VC-11, 449; VUC-9, 141.4; VEC-9, 1600; OVC-9, 2268; VTU, 141 and VSO-9, 635 mg.kg<sup>-1</sup>.

**Conclusion:** The results suggest that E-capsaicin and two of its analogues VC-10 and VC-11 could be considered as potential future riot control agents pending further studies.

**IL-72****TOXICOLOGICAL CONSEQUENCES OF MODULATION OF BRAIN CYTOCHROME P450 EXPRESSION BY ENVIRONMENTAL CHEMICALS.****Parmar D, Yadav S, Dhawan A, Seth PK.**

Developmental Toxicology Division, Industrial Toxicology Research Centre, P.O. Box 80, M.G. Marg, Lucknow - 226 001.

Cytochrome P450s (P450s) have been identified as the functional enzymes in the brain, enabling the central nervous system (CNS) to catalyse the oxidative metabolism of substrates present in or reaching there. Due to the varied physiological functions of this vital organ, the nature and functions of the P450s may possibly be different in brain than the liver. Molecular cloning has led to the identification of P450s novel to the brain and have indicated the role of P450s in the physiology of brain. Significant regional and cellular differences have been reported in the distribution of P450s within the brain, with neurons in some specific brain areas exhibiting high local P450 activity. Brain P450s have been shown to catalyse the metabolic activation of deltamethrin, a synthetic pyrethroid insecticide and lindane, an organochlorine insecticide. The induction in the activity of brain P450s was found to correlate with the symptoms of neurobehavioral toxicity induced by these chemicals. Our data have further provided evidence that modulation of the levels of P450s significantly influences the neurobehavioral toxicity of deltamethrin and lindane. Furthermore, significant region specific induction in the P450s was observed after exposure to these insecticides suggesting that differences in the induction of P450s amongst the different brain regions could play a role in regulating the response of brain to the environmental chemicals by modulating their concentration *per se* or of their active metabolites at the target sites.

**IL-73****AN OVERVIEW ON THE MECHANISTIC BASIS OF ORGANOPHOSPHATE TOXICITY WITH REFERENCE TO ITS TREATMENT.****Dasgupta S.**

Centre for Applied Science and Technology, Kolkata.

Organophosphorus compounds elicit their primary effects by phosphorylating or phosphonylating the serine hydroxyl at the active site of the enzyme acetylcholinesterase causing essentially irreversible inhibition of the enzyme resulting in accumulation of excess acetylcholine at various cholinergic sites causing toxic manifestations. The inhibited enzyme can be reactivated by various cholinesterase reactivators / oximes. But till to-date there is no single oxime or an universal antidote which could protect against the lethality of different nerve agents like soman, sarin, VX and tabun. Different countries prefer different oximes for reasons still unknown. The decision on the drug of choice is only possible on the basis of experimental evaluation. This paper gives an overview on various antidotes both conventional and novel oximes synthesised in the Division of Chemistry at Defence R & D Establishment, Gwalior which have been evaluated against various nerve agents in experimental animals along with different adjuncts like bronchodilators, anticonvulsants, cholinoytics and calcium channel blockers. The spin off benefits from these studies have led to the development of an indigenous disposable and a reusable auto injector to counteract nerve agent poisoning.

OP - 82

**A NEW REAGENT FOR THE EFFICIENT SYNTHESIS OF DISULFIDES, A PRECURSOR OF SULFINE, POTENTIAL SENSORY IRRITANT.**

Polshettiwar Vivek, Nivsarkar Manisha, Acharya Jyotiranjan, **Kaushik MP**  
Process Technology Development Division, Defence R&D Establishment,  
Gwalior-474002.

Disulfides are versatile building blocks for the synthesis of various organo-sulfur compounds and they also play important role in biological and chemical processes. Disulfides are precursor of sulfine which has potential of sensory irritant. Various methods are reported in the literature for the synthesis of disulfides from thiols and alkylhalides. But all these methods involves multistep process and transformation are usually effected at 70-90°C for a longer period of time to give moderate yields of the corresponding disulfide. There is a current interest in sulfur containing compounds of molybdenum and tungsten essentially because of their implication in bio-inorganic chemistry and catalysts. Molybdenum sulfur complexes have generated interest in both synthetic and theoretical chemists, as very few studies have been reported on reactivity with organic reagents. In this communication, we report our initial findings, on the most efficient sulfur transfer reaction of Tetracosythiohepta molybdate  $MO_7S_{24}^{6-}$  with alkylhalides. We have synthesised a new reagent  $[(C_6H_5CH_2NEt_3)_6MO_7S_{24}]$  (1) which can be prepared from the commercially available ammonium heptamolybdate and the reaction of 1 with variety of organic halides (1:0.0183) in dichloromethane at room temp. (30°C) afforded the corresponding disulfide in excellent yields.

OP - 83

**INCIDENCE OF INTERMEDIATE SYNDROME IN FATAL ORGANOPHOSPHATE POISONING.**

**Kumar Mohan TS**, Palimar Vikram.  
Department of Forensic Medicine, Kasturba Medical College, Manipal - 576119.

Organophosphate insecticides that are used extensively in agriculture and horticulture accounts for the majority of pesticide related deaths in India. Following suicidal or accidental exposure, these organophosphates lead to three well-defined neurological syndromes viz., initial life threatening acute cholinergic crisis, Intermediate syndrome characterised by cranial nerve palsies, proximal muscle and respiratory muscle weakness, and delayed polyneuropathy. Sixty two cases of organophosphate poisoning admitted to Kasturba Medical College Hospital, Manipal, over a period of two years (from Jan 2000 to Dec 2001), who later succumbed to it were studied for intermediate syndrome. The results were compared with available data in the literature.

**OP - 84****SHORT-TERM EFFECT OF DELTAMETHRIN ON CERTAIN BIOCHEMICAL AND PATHOLOGICAL PARAMETERS IN RATS.****Mondal TK\***, Bhattacharyya D, Sukumar M.

Dept. of Pharmacology, University College of Medicine, Calcutta University, Kolkata - 20, \*Dept. of Pharmacology and Toxicology, West Bengal University of Animal and Fisheries Sciences, Belgachia, Kolkata.

Deltamethrin is a type II synthetic pyrethroid, widely used in crop protection as well as protects the human and animal health. The oral LD<sub>50</sub> of deltamethrin dissolved in DMSO was determined to be 150 mg/kg. Two groups male rat (Wistar) aged about 6 weeks, comprising 10 animals each were taken for this experiment. One group was served as control and were fed only DMSO (1 ml) each and other group was fed deltamethrin dissolved in DMSO (1 ml) 15mg/kg (1/10th LD<sub>50</sub>) for 60 days. On day 61 both of the groups were euthanised under ether anaesthesia and blood was collected for estimation of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), and glucose, and the liver was dissected out, homogenized with normal saline for estimation of lipid peroxidation (MDA), superoxide dismutase (SOD), reduced glutathione (GSH), catalase (CAT), and glycogen. The tissues like brain, heart, lungs, liver, spleen, stomach, intestine and testes were dissected out and some portion of the tissue were put immediately in 10 % buffered formalin and used for histopathological examination. The remaining portions of tissues were used for deltamethrin residual analysis by GC-ECD. The results showed that deltamethrin increased significantly (P<0.05) serum AST, ALT, ALP, LDH, and glucose level and tissue (liver) MDA, and glycogen level, but decreased (P<0.05) significantly the tissue activity of (liver) SOD, CAT, and GSH. The considerable amount of deltamethrin was present in all above tissues following short-term administration. Histopathological findings showed that marked congestion in brain, heart, spleen and testes, and severe haemorrhages in lungs, stomach and intestine. Necrosis was observed in liver. Short-term effect of deltamethrin produced moderate histopathological and biochemical changes in rats.

**OP-85****STUDIES ON THE TOXICODYNAMICS OF AMINOPHYLLINE-INDUCED SEIZURES IN MICE..****Gulati K**, Wardhan N, Anand S and Ray A

Department of Pharmacology, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi -110007.

In recent years, there has been a resurgence in the interest in methylxanthines like theophylline in the treatment of bronchial asthma, but the narrow therapeutic index of the drug, resulting in theophylline toxicity, has precluded its wider use. The present study thus evaluated the possible mechanisms involved in theophylline-induced neurotoxicity with a view to identify a viable antidote. Aminophylline (50, 100 and 250 mg/kg) induced convulsions in mice in a dose related manner, the dose of 250 mg/kg being most potent in inducing both tonic-clonic convulsions and mortality. The antioxidant, melatonin (50, 100 and 200 mg/kg) antagonized aminophylline seizures, the dose of 100 mg/kg being most effective. The nitric oxide (NO) synthase inhibitors, L-NAME and 7-nitroindazole (10 and 50 mg/kg) also attenuated aminophylline convulsions. In combination with melatonin, the effects of both NO synthase inhibitors were potentiated. Further, subconvulsive doses of aminophylline (100 mg/kg) when combined with subthreshold levels of electroshock, induced seizures and these were antagonized by both melatonin and the NO synthase inhibitors. The results are suggestive of the possible involvement of NO and related free radicals in the convulsigenic and proconvulsant effects of aminophylline.



OP - 86

**A STUDY OF THE IMMUNO - THERAPEUTIC VALUE AND POTENTIAL USE OF CHICKEN EGG YOLK (IgY) POLYCLONAL ANTIBODY DIRECTED TO WHOLE SNAKE VENOM.**

**Rajendra Prabhu R<sup>\*</sup>, Yogeewaran G<sup>\*\*</sup>, Nalini Ramamurthy<sup>\*</sup>, Nagarajan B<sup>\*\*\*</sup>, Thilagavathy Krishnan<sup>\*</sup>, Lalitha C. Pillai<sup>\*</sup>.**

<sup>\*</sup>King Institute of Preventive Medicine, Chennai - 600032. <sup>\*\*</sup>Sri Ramachandra Institute of Biomedical Sciences, Technology and Research, Sri Ramachandra Deemed Medical University, Chennai - 600 041, <sup>\*\*\*</sup>Department of Microbiology and Tumor Biochemistry, Cancer Institute, Chennai - 600 020.

The transfer of maternal antibody to the progeny in avians is through the egg-yolk, and predominantly the IgG antibody crosses the oviduct barrier and is termed as IgY, which accumulates in the yolk sac. Studies have shown that each egg contains approximately 100 mgs of total IgY, of which the antigen specific antibody varies from 1 % to 10 %. Many workers have raised abundant, inexpensive and non-invasive polyclonal egg-yolk (IgY) antibodies in avians. This study is aimed at the production of avian IgY antibodies against Cobra venom. Egg laying hens were immunized with graded dose of venom. The egg was purified by a step-wise precipitation method using sodium sulphate and polyethylene glycol to isolate the IgY (anti-venin). The purified immunoglobulin was analysed by immuno diffusion and venom neutralization tests. Interestingly, the anti-venin was also found to block phospholipase-AZ activity and to have neutralizing action against the toxic and lethal properties of Cobra venom. In depth, research work has to be carried out before considering the possibility of its use in humans and animals, to treat snakebite victims. The advantage envisaged is a cut in cost of production of antsnake venom and avoiding the use of large animals for production.

OP - 87

**COMPARATIVE EVALUATION OF CN, CS AND OLEORESIN AS RODENT REPELLENTS.**

**Ganesan K, Santosh Kumar, Dangi RS, Shri Prakash, Kaushik MP.**  
Defence R & D Establishment, Gwalior - 474002.

Rodents are not only carriers of diseases but also cause enormous damage to agricultural crops and stored materials. The conventional methods used on large scale to deal with rodent problems include chemical control through wide variety of rodenticides as well as trap and kill technique. Rodents are sensitive to odours and tastes and it has been shown that a number of chemical substances are found to possess repellent properties. Thus, the quest for benign, environmentally sensitive, yet effective means of vertebrate pest management has led to an increased interest in the use of nonlethal chemical repellents for the control of rodents. The application of conventional methods is not feasible in airfield conditions where rodents have been reported to damage multi-element nylon tapes used as aircraft arresters which block the forward momentum of the aircraft from overshooting the runway during its emergency landing or reject take-off. These nylon nets remains in open ground all the time, thus damaged by rodents leading to decrease in the service time and efficiency of the nylon nets. In the present study, laboratory evaluation of sensory irritants such as CN, CS and oleoresin for the protection of nylon tapes against rodents attack were carried out and it was observed that these irritants provide protection for the nylon tapes even under stringent conditions in the laboratory experiments.

# ***Scientific Session IX***

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## **Clinical pharmacology I**

**Date** : 28.11.2002  
**Time** : 1400-1545  
**Venue** : Hall - B

Invited Lecture : Dr. A Sankaranarayana

Oral Presentation : OP 88 - OP 94

Chairpersons : Dr. DS Dwarakanath  
Dr. Anil Belapure

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PROFESSOR J. H. GOLDSTEIN  
AND  
ASSISTANT PROFESSOR R. A. FIESCHER

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**NEW DRUG TARGETS FOR DIABETES.****Sankaranarayanan A.**

Torrent Research Centre, Bhat - 382428.

In New Drug Discovery, one of the critical steps for success is the choice of appropriate drug targets. In any discovery programme, the rigour with which the target is identified would have the greatest influence on the quality of lead molecules generated. Product failures - particularly in the late stages of discovery and development would impact greater loss of time and resources. Several pharmaceutical research institutions are striving to discover and develop new drugs for type 2 diabetes. The major driving force for this is the alarming increase in the prevalence of the disease; it has been predicted to afflict 200 - 300 million people by the year 2010. Currently available drugs are far from ideal due to limited efficacy and their potential for side effects. In this presentation, newer drug targets for type 2 diabetes would be reviewed and few of the interesting ones would be discussed at the meeting. The increased understanding of the biochemical abnormalities and the pathogenesis of type 2 diabetes has led to intensified attempts to identify and exploit drug targets for newer therapeutic approaches. The drug targets for diabetes may be broadly classified into those related to insulin resistance, insulin signalling pathways, insulin secretion and hepatic glucose output.

Abnormal fatty acid metabolism leading to accumulation of triglycerides and long chain fatty acyl-CoA can inhibit the metabolic actions of insulin in the liver and muscle. In the pancreatic islets this causes impairment of insulin secretion. This 'lipotoxicity' is reduced by increased fatty acid oxidation and inhibition of fatty acid synthesis. AMP-activated kinase is an important target in this regard as it has been shown to reduce lipid synthesis and increase fat oxidation through inactivation of acetyl-CoA carboxylase. Its activation decreases hepatic glucose output and increases glucose uptake by the muscle. Adipocyte complement-related protein 30 (Acrp 30), an adipocyte specific protein also stimulates tissue fatty acid oxidation and thereby brings in beneficial metabolic effects. The other target that has come into prominence with the introduction of thiazolidinediones is the peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ). Studies on PPAR- $\gamma$  activation reveal a wealth of targets downstream of its activation. Pyruvate dehydrogenase kinase 4, 11(3-hydroxysteroid dehydrogenase type 1, Acrp30 and Cbl-associated protein are just a few examples. Finally, the important role played by obesity in insulin resistance implies that drug targets for treating obesity itself would be useful in treatment of type 2 diabetes.

The insulin receptor and its signalling pathways present a variety of targets to improve the insulin action and inhibit insulin resistance. Protein tyrosine phosphatases (PTP-) are known to interfere with insulin signalling. PTP-1B knock out mice show increased sensitivity to insulin and, interestingly, also become resistant to obesity. Inhibitors of PTP-1B are therefore being actively developed for the treatment of diabetes and defects of energy metabolism. Other targets of interest in the insulin signaling pathways are glycogen synthase kinase-3, SH2-domain containing inositol 5-phosphatase type 2 and IKK kinase. The other possibility pursued actively is the direct stimulation of insulin receptors by small molecules.

Several newer developments are taking place on targets available to modulate the insulin secretion itself. Glucagon-like peptide (GLP-1) secreted by endocrine cells of the intestinal mucosa activates specific receptors on the pancreatic  $\beta$  cells and increase the glucose-stimulated insulin secretion. Exogenous administration of GLP-1 has been shown to benefit diabetics on clinical trials, though ideally small molecules could be developed for this task. The other approach had been to develop molecules to inhibit dipeptidylpeptidase -IV which physiologically inactivates GLP-1. The glucose output by the liver plays a major role in postprandial glucose levels. Several enzyme systems involved in glycogenolysis and gluconeogenesis are being examined as possible targets to control this hyperglycemia. Inhibition of glycogen phosphorylase, fructose-1, 6-bisphosphatase and glucose-6-phosphatase are few such examples. Glucagon secreted by the pancreatic  $\alpha$  cells also increase hepatic glycogenolysis and gluconeogenesis. Since high glucagon levels are observed in type II diabetics, glucagon antagonists would be potentially beneficial. New drugs discovered based on these targets are all under various stages of development and already limitations of some of these approaches are being appreciated. Intensive research efforts on these would hopefully lead to development of newer safe and effective therapies for the emerging wave of diabetes and related disorders in the new millennium.

**EFFICACY OF 14 DAYS PRIMAQUINE THERAPY AS ANTI-RELAPSE FOR *PLASMODIUM VIVAX* MALARIA IN MUMBAI (BOMBAY), INDIA.**

Rajgor DD, Gogtay NJ, Kadam VS, Kamtekar KD, Dalvi SS, Chogle AR, Aigal U, Bichile LS, Kain KC, Kshirsagar NA.

Dept. of Clinical Pharmacology and Dept of Medicine, Seth GS Medical College and KEM Hospital, Parel; Kasturba Hospital, Sat Rasta; Toronto General Hospital, Canada.

**Objective:** To compare the efficacy in patients treated with 14 days (15mg/day) primaquine versus without primaquine.

**Methods:** This was a comparative, open, randomized and parallel group study. Ethics committee permission and patient consent was obtained prior to study. Patients diagnosed as *Plasmodium vivax* malaria on peripheral blood (PB) smear and fulfilling inclusion - exclusion criteria were admitted. Blood was collected for G6PD, hemoglobin and polymerase chain reaction- single strand conformational polymorphism (PCR-SSCP) analysis. The patients were randomized into 2 groups after completion of 25 mg/kg chloroquine over 3 days; one without primaquine (PQ) and another given supervised 5 mg/day primaquine for 14 days and were discharged on day 4 and 14 respectively. All patients were followed upto 6 months at monthly interval and or whenever they got fever. During follow-up, PB smear was prepared and scanned. If smear showed *Plasmodium vivax*, blood was collected for PCR - SSCP. These pre and post treatment samples were analyzed by PCR-SSCP.

**Results:** A total of the 213 patients were enrolled in the study. Out of which 142 were in no primaquine group and 131 received 14 days primaquine. 12 relapses occurred in no primaquine group, relapse rate 9.1 % and 6 relapses in primaquine group, relapse rate 4.58%. PCR-SSCP analysis of the primaquine treated group showed, 3 true relapses whereas 2 re-infections and 1 sample did not amplify. Thus the true relapse rate is 2.29 % (3/121).

**Conclusion:** Increasing incidences of relapse with 14 days PQ suggest that there is need for either different regimens of PQ or of new antirelapse drugs i.e., bulaquine and tafenoquine with proven efficacy in controlled trials.

**A STUDY OF SERUM, ZINC AND COPPER IN HEALTH AND DISEASE.**

Nasiruddin M, Khan RA.

Department of Pharmacology, J.N. Medical College, A.M.U, Aligarh - 202002.

Trace elements play an important role in different metabolic activities in human body. An alteration in their concentration leads to altered metabolic processes resulting in various disorders. To observe the relation of trace elements especially zinc and copper in various diseases, several studies had been conducted at J.N. Medical College in the last two decades (1980-2000). The studies included 596 controls (healthy individuals, males 300, females 296) and 1616 patients (males 802, females 814) of various diseases. In these studies serum levels of zinc and copper ( $\mu\text{g/dl}$ ) were estimated on atomic absorption spectrophotometer (GBC-902) and were compared to their controls. The present study is done to compile the data of all these studies to evaluate the role of serum zinc and copper in health and disease. The study revealed mean serum zinc and copper levels as  $124.5 \pm 30.3$  and  $116.2 \pm 13.1$  respectively, Zn : Cu = 1.07. In diseased conditions the mean serum levels varied, Zinc:  $80.4 \pm 9 - 207.5 \pm 11.7$  and copper:  $56.0 \pm 2.0 - 194.8 \pm 14.1$ . It was observed that serum zinc level was lowest in malignancies (80-87) followed by submucous fibrosis, cataract and pregnancy (100-110), where as it was increased in hypertension, burn, epilepsy, urolithiasis and vitiligo (140, 145, 168, 199, 207.5) respectively. The copper levels observed were lowest in burn (56) followed by cataract and pregnancy 114 and 116 respectively. The copper levels were found elevated in epilepsy, vitiligo, ischaemic heart diseases, hypertension (123, 127, 148, 158) and various types of malignancies (174-590). It was inferred from the finding that zinc copper ratio remained nearer to control (1.07) in cataract, pregnancy and hypertension (0.91, 0.95, 1.05), increased in epilepsy and vitiligo (1.37, 1.64) where as it was highly decreased in malignancies (0.54 - 0.15).

OP-90

**A DOUBLE-BLIND, RANDOMIZED, COMPARATIVE TRIAL TO DOCUMENT: THE SAFETY, EFFICACY AND TOLERABILITY OF NIMESULIDE DS IN COMPARISON WITH COMBINATION OF IBUPROFEN AND PARACETAMOL IN THE TREATMENT OF SOFT TISSUE INJURY AND HAIRLINE FRACTURE.**

\*Patil RA, \*Maroli S, \*Ghai H, \*\*Goregaonkar AB.

\*Dept. of Pharmacology, LTMMC & LTMGH Sion, Mumbai 400 022. \*\*Dept. of Orthopaedics, LTMMC & LTMGH, Sion, Mumbai - 400022.

**Objective:** To determine the efficacy and safety and tolerability of Nimesulide DS (200 mg) in comparison with a combination of Ibuprofen and Paracetamol in the treatment of soft tissue injury and hairline fracture.

**Methods:** 99 patients were enrolled on the basis of clinical evidence of soft-tissue injury (evidenced by pain, swelling, and mobility) and radiological evaluation (for confirmation of fractures) after a written informed consent was taken. They were then randomized into the study and given the medication after evaluation for either a maximum of 7 days in case of soft-tissue injuries and 14 days in case of fractures. At the end of treatment for each patient, there was overall global evaluation for efficacy and tolerability of treatment by the patient as well as investigator.

**Results:** In this study 90% of total patients from Nimesulide and 81.6% among Ibuprofen + paracetamol group had an excellent improvement. 18.3% of patients from Ibuprofen + paracetamol treatment group had side effects which was on higher side as compared to only 6% in the Nimesulide group. Side effects included nausea, vomiting, and heartburn in the Ibuprofen and paracetamol group while the Nimesulide group included only heartburn and gastritis.

**Conclusion:** According to the results obtained in this study, Nimesulide has equal efficacy as compared to combination of Ibuprofen + Paracetamol in the treatment of soft tissue injury and hairline fracture. The advantage of Nimesulide was its better tolerability.

OP-91

**PATTERN OF ANTIMICROBIAL USE IN NEONATAL INTENSIVE CARE UNIT.**

Ambavane VR, Ghai H, Gawde A, Patil R, Maroli S.

Department of Pharmacology, L TMM College & L TM G Hospital, Sion, Mumbai - 400022.

A retrospective drug utilization review study was carried out to record all medications administered to patients admitted to the neonatal intensive care unit of LTMG hospital, registered during a three-month period (April-June 2002). Only 2 (0.7%) of the 258 neonates admitted were not given any drug at all. Respiratory tract infections were the commonest condition (41.47%) followed by primary septicemia (24.41 %). Cifran, amikacin and ceftazidime were the commonest antibiotic used singly (4.65%). Most of the neonates received antibiotics in combination, mainly Cifran + amikacin (46.37%), followed by cefotaxime + amikacin (22.09%), taxim + amikacin (9.3%), augmentin + amikacin (5.81%). Many neonates also received supplementary antibiotics in addition to the primary antibiotics used, augmentin (25.58%), metrogyl (20.93%), ceftazidime (15.11%), fluconazole (9.3%). Almost all neonates received medications intravenously. Cultures were done in 207 patients. 36.23% had positive cultures and *staphylococcus aureus* was the commonest organism isolated (18.84%), followed by klebsiella (7.24%). 6 neonates (2.89%) die due to complications of the primary conditions. In all the neonates, in whom cultures were positive, antibiotics were given in accordance with the culture sensitivity report. Average duration for which the neonates received medications was 10.44 days. Although the prescription pattern was quite rational, almost 100% of the drugs were prescribed using trade names and not generic names.

OP-92

### ERECTILE DYSFUNCTION: HUMAN BEHAVIOR, INCIDENCE AND TREATMENT.

**Romesh Joshi**, Anurag Gupta, Kirti Manjrekar, Deepali Kaliya, Shivanand Dhanure, Vishal Shah, Rahul Bargaje, Mujtaba Khan, Amol Galge, Anand P, Rajan Nerurkar.

Department of Pharmacology, TNMC & BYL Nair Ch. Hospital, Mumbai -400008.

**Objective:** Pilot study to identify the hidden cases of erectile dysfunction (ED) and their knowledge regarding erectile dysfunction and its treatment.

**Methods:** The international index of erectile function (IIEF) questionnaire was administered in 3 languages to 51 subjects attending medicine OPD of our institute, after voluntarily written informed consent. They were queried on sexual function whether they felt they had ED, or talked to their physicians, and their knowledge about treatments, and whether they wished oral sildenafil. The data was recorded and descriptive analysis was done.

**Results:** 8/51 subjects refused filling the form, with 70% stating no particular reason for refusal. 60.5% subjects wouldn't speak voluntarily about their sexual problems to their doctor. 42% subjects felt shy, 26.9% stated no particular reason, and the rest (31.1%) refused to reveal. 20.9% subjects felt they had sexual dysfunction, with 93.5% of them declined taking any treatment, but 66% stated that they wished for a confidential treatment.

**Conclusion:** 37% subjects knew about sildenafil from health magazines and friends. 6 subjects were detected to have ED and were thus referred accordingly. The incidence of 11.8% of ED was in concordance with that reported by Kinsey et al, (1948). The social taboo still hinders appropriate treatment.

OP-93

### COUGH FORMULATIONS IN THE INDIAN MARKET: A SURVEY.

**Roy V, Bansal A.**

Department of Pharmacology, Maulana Azad Medical College, New Delhi -110002.

**Objectives:** To determine the number and composition of the cough formulations available in the Indian market. To study their pharmacological rationale.

**Methods:** A survey of the cough formulations listed in the Drug Today Year Book, 2001, was done. The preparations available were studied under the following headings: number, single or combination, dose range of the constituents and the composition.

**Results:** The total number of cough formulations available in the Indian market are 762. Out of which 689 (90.4%) are combination preparations. The number of constituents in combination preparations ranged from 2 to 16. The constituents included pharyngeal demulscents, expectorants, antihistamines, bronchodilators, decongestants, analgesics, antipyretics, vitamins, minerals, herbal products and miscellaneous products. The total number of formulations with more than one constituent of the same class was 388(44.4%). The percentage range of the amount of the same constituent in different cough formulations ranged from 50 to 10,000%.

**Conclusion:** There are too many cough formulations available in the Indian market. The scientific rationale for the number and composition of the various cough preparations is not established. There is an urgent need to establish a criteria for formulating and marketing of cough preparations in India. The scientific validity of the same needs to be established by means of randomized, controlled clinical trials.



OP-94

## EFFICACY AND TOLERABILITY OF TOPICAL CYCLOSPORINE IN ORAL LICHEN PLANUS.

Annabelle Rajasekharan, **Purushothaman S** , Parvathavarthini S , Shirley Suresh\* , Jorgen Seldrup\* , Poon Choy Yok\* .  
Madras Medical College, Chennai - 600003; \*CTERU , Singapore.

**Introduction:** Oral Lichen Planus considered a premalignant condition is a disease which exhibits as reticular, papular, bullous, atrophic and erosive sub-types. The efficacy and tolerability of topical Cyclosporine in Oral Lichen Planus in Indians was evaluated. The objective of this study was: (a) to evaluate the response of oral lichen planus using Thongprasom Scale; (b) To evaluate alleviation of pain and burning sensation using Visual Analogue Scale; (c) to monitor adverse drug reactions which may be caused during the trial period; (d) to monitor the level of Cyclosporine.

**Methods:** An open study in which 12 patients of histologically proved oral lichen planus were recruited, after obtaining informed consent was done in the Clinical Pharmacology unit of the Madras Medical College. Cyclosporine Oral solution 100 mg/ml was used. Patients were instructed to apply this with their fingers three times a day for 8 weeks. Standard treatment for oral lichen planus was used after 8 weeks till all the lesions subsided. Clinical scoring was done using Thongprasom scoring. Pain and burning sensation were assessed using a visual analog scale; Tolerability: Adverse effects were monitored. Estimation of cyclosporine was done using homogenous EIA - Recombinant DNA Technology. All patients were followed up for one year at 12, 24, 36 and 48 weeks. Results were statistically analysed.

**Results:** Cyclosporine treatment was found to be effective. Cyclosporine levels were found to be below toxic levels. None complained of adverse effects due to cyclosporine.

**Conclusion:** Cyclosporine as a topical application is effective in the treatment of oral lichen planus and is well tolerated.

## ***Scientific Session X***

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### **Neurodegenerative disorders and Neuropharmacology II**

- Date** : 28.11.2002  
**Time** : 1600-1800  
**Venue** : Hall - C
- Invited Lectures** : Dr. Ram Raghbir  
Dr. S K Agarwal
- Oral Presentation** : OP95 - OP102
- Chairpersons** : Dr. B P Doctor  
Prof. N A Adibatti

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**IL-75****CEREBRAL ISCHEMIA AND GENE EXPRESSION.****Raghubir R .**

Division of Pharmacology, Central Drug Research Institute, Lucknow - 226001.

Cerebral ischemia is a process of delayed neuronal death, which results due to decrease in cerebral blood flow leading to hypoxia. The diminished cerebral blood flow initiates an ischemic cascade which leads to neuronal destruction. There are several mechanisms implicated in ischemic neuronal damage including expression of a number of genes in the ischemic brain. These may be immediate early genes (IEGs) of the c-fos and c-Jun family, intermediate genes, heat shock proteins (HSP) and late responsive genes (trophic factors). Intracellular signal transduction mechanisms are activated by ischemia and these in turn modify the mechanisms of gene expression. There seems to be interrelationship between induction of c-fos and c-jun and synthesis of other stress proteins, indicating an important association of IEGs and HSP-70 with neuronal survival following cerebral ischemia and reperfusion. In addition to IEGs a host of other genes are also induced by cerebral ischemia. Gene expression of trophic factors and their receptors are regulated by ischemia. Further, expression of neurotransmitter and their receptors is also affected by ischemia. The mechanisms responsible for the possible induction of late response genes by IEGs are being investigated. Cerebral ischemia is a potent stimulus for gene regulation. Rapid changes occur in IEGs. However, it is not known how IEGs affect the fate of neurones after cerebral ischemia. Alterations in gene expression may affect recovery process after cerebral ischemia, hence future therapy targeting gene expression may be specifically directed at genes that mediate apoptosis and recovery processes.

**IL-76****CALCIUM, CALCINEURIN IN WHITE MATTER ISCHEMIC INJURY.****Agrawal SK.**

Section of Neurosurgery, Department of Surgery, University of Nebraska Medical Center, Omaha, Nebraska, USA.

White matter of brain and spinal cord is vulnerable to ischemia. Ischemia can cause rapid energy depletion, which would lead to a cascade of events coupled with severe K<sup>+</sup> depletion that will lead to depolarization, influx of Na<sup>+</sup> and the subsequent reverse operation of the Na<sup>+</sup>-Ca<sup>2+</sup> exchange, intracellular Ca<sup>2+</sup> overload and irreversible axonal injury. The excessive accumulation of Ca<sup>2+</sup> in turn activates various Ca<sup>2+</sup>-dependent enzymes, such as calpain, phospholipases, protein kinase C and calcineurin, resulting in irreversible damage to axons. Hypoxia alone can mobilize internal Ca<sup>2+</sup> stores, as control of internal Ca<sup>2+</sup> pools is lost, excessive release from this leads to axonal damage. Reoxygenation causes deterioration in central axons possibly due to severe mitochondrial Ca<sup>2+</sup> overload. Astrocytes are far more resistant to oxygen deprivation than oligodendrocytes and myelinated axons. Astrocytes, oligodendrocytes can be damaged by Ca<sup>2+</sup> influx, although the mechanism by which Ca<sup>2+</sup> enters into these cells is not completely understood. These concepts may also apply to other white matter axonal injuries for e.g. brain and spinal cord trauma. Taken together, our results allow us to suggest that ischemia induces a complex cascade of events, involving several signaling pathways. The evidence of calcium influx into cells to be responsible for initiating the "final pathway" to cell death in neuronal tissue after traumatic or ischemic injury will be presented.

OP - 95

**ANOXIA-INDUCED DEPRESSION OF THE SPINAL SYNAPTIC TRANSMISSION INVOLVES NMDA DEPENDENT MECHANISM.**

**Jha Archana, Deshpande Shripad B.**

Department of Physiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005

The effects of aglycemia (glucose free) and ischemia (glucose free + O<sub>2</sub> lack) on the spinal reflexes were evaluated. The stimulation of the dorsal root evoked monosynaptic (MSR) and polysynaptic (PSR) reflexes in the segmental ventral roots of isolated spinal cords from the neonatal rats. Aglycemia and ischemia produced time-dependent depression of the spinal reflexes and abolished them within 35 min. The aglycemic depression began after 15 min whereas, the ischemic depression began immediately. The 50% depression of the reflexes occurred around 25 and 15 min, for aglycemia and ischemia, respectively. In the presence of Mg<sup>2+</sup>, the aglycemia-induced depression of MSR was completely attenuated but, the attenuation of ischemic response was partial as the reflex was abolished by 80 min. The results indicate that the aglycemia-induced depression of the synaptic transmission involves N-methyl-D-aspartate (NMDA) dependent (Mg<sup>2+</sup> sensitive) mechanism, while ischemia-induced depression involves mechanisms in addition to NMDA..

OP - 96

**PTYCHODISCUS BREVIS TOXIN ENHANCES - FREQUENCY DEPENDENT DEPRESSION IN NEONATAL RAT SPINAL CORD.**

**Singh JN<sup>a</sup>, Deshpande SB<sup>a</sup>, Dube SN<sup>b</sup>, Das Gupta, S<sup>b</sup>.**

<sup>a</sup>Department of Physiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, <sup>b</sup>Defence Research and Development and Establishment, Gwalior - 474002.

The effects of *Ptychodiscus brevis* Toxin (PbTx) on frequency-dependent depression (FDD) of the monosynaptic reflex (MSR) in isolated spinal cords from the neonatal rats was examined. The stimulation of dorsal root at different frequencies (0.1-2.0 Hz) produced a depression of MSR in a frequency-dependent manner. The PbTx at lower frequencies attenuated the FDD while at higher frequencies, enhanced the FDD in a concentration-dependent manner. The enhancement of FDD corresponded to the depression of MSR. In the presence of Mg<sup>2+</sup> (1.3 mM), the FDD-induced depression was much greater as compared to Mg<sup>2+</sup>-free medium. The PbTx-induced alterations in FDD were not seen in the presence of Mg<sup>2+</sup>. The present results indicate that the PbTx-induced enhancement of FDD was sensitive to Mg<sup>2+</sup> (NMDA). The attenuation of FDD at lower frequencies indicate the possibility of an additional mechanism.

OP-97

**ADAPTATION OF MICE TO THE RESTRAINED STRESS INDUCED IMMUNO-SUPPRESSION (IMSP) THROUGH CENTRAL 5 HT RECEPTORS.**

**Chattopadhyay M, Cardozo Z, Wanjari MM, Johrapurkar AA, Zambed SP, Umathe SN.**

University Department of Pharmaceutical Sciences, Nagpur University Campus, Nagpur - 440010.

**Objective:** Since, most of the behavioral manifestations of stress are often attenuated on repeated subjection what happens to the stress induced IMSP is investigated in mice and the involvement of centrally situated 5 HT receptors is envisaged.

**Method:** The mice were treated with ritanserin (RT) ( 5HT 2a/2c agonist) / fluoxetine (FLU) (SSRI) prior to and during the single and multiple restraint stress (RS). The primary (I) and secondary (II) antibody titer levels (ATL) respectively on day 7 and 14, to SRBC were assessed by haemagglutination method.

**Results:** The mice subjected to a single RS and those treated with FLU, both exhibited marked decline in the I and II ATL which was blocked by RT whereas no decline in the II ATL could be seen in those who were subjected to repeated stress. On the contrary, II ATL was found to be further ameliorated by FLU and this effect of FLU remained unaffected by RT.

**Conclusion:** The stress induced IMSP mediates through 5 HT 2a/ 2c receptors and involvement of 5 HT is substantiated by the fact that FLU alone produced IMSP. Repeated stress eliminated IMSP and FLU further activated immunosuppression. This suggests involvement of 5HT receptors other than 2a/2c in the observed adaptation.

OP-98

**ANTIDEPRESSANT ACTIVITY OF BIOFLAVONOID QUERCETIN IN STREPTOZOTOCIN -INDUCED DIABETIC MICE.**

**Anjali S, Anjaneyulu M, Chopra K.**

Pharmacology Division, University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh - 160014.

**Objectives:** To investigate the antidepressant activity of a bioflavonoid, quercetin, in STZ-induced diabetic depression model in mice as compared with some antidepressants.

**Methods:** Male Laka mice (20-30g) bred in Central Animal House facility of Panjab University was used in the present study. Diabetes was induced by single intraperitoneal injection of STZ (200 mg/kg) and mice were used 6 weeks after induction of diabetes. After 1hr of drug administration i.e. fluoxetine (5 mg/kg, i. p), imipramine (15 mg/kg, i. p) and quercetin (50 and 100 mg/kg, i. p), both age matched control and diabetic mice were subjected to forced swimming test for 6 min in an individual glass jar (25 x 12 x 25 cm) containing water up to 15 cm in height and maintained at room temperature  $22 \pm 3^\circ$  and immobility period was noted.

**Results:** Diabetic mice presented longer immobility duration during the test as compared with age matched control mice. Quercetin, dose dependently produced the antidepressant activity in diabetic mice, effects similar to fluoxetine and imipramine. All the above three drugs do not produce any *per se* antidepressant activity in age matched control mice.

**Conclusions:** The results of the present study demonstrate that quercetin produces significant antidepressant activity in STZ-induced diabetic mice similar to that of antidepressants. So it can be useful in the treatment of diabetic depression. However the exact mechanism of its antidepressant activity should be further evaluated.

**OP-99****REVERSAL OF DIAZEPAM TOLERANCE AND WITHDRAWAL- INDUCED HYPERACTIVITY AND ANXIETY IN MICE BY QUERCETIN.**

Joshi D, Singh A, Naidu PS, Kulkarni SK.

Pharmacology Division, University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh-160 014.

**Objectives:** Long term treatment with diazepam, a selective allosteric modulator of GABA-A receptors, incurs the risk of physical dependence and induces withdrawal symptoms on discontinuation such as enhanced anxiety, reduced seizure threshold and alteration in motor behavior. Quercetin a flavanoid isolated from many plants, including Quercus Mongollca Fish, Apocynum Venelim Linu and Hypericum Ascyron L. has wide ranging pharmacological actions on cardiovascular, anticancer and free radical scavenging activity. The aim of the present study was to explore the role of quercetin in recovery from diazepam withdrawal induced hyperlocomotor activity and anxiety in mice.

**Methods:** Animals were made BZD dependent by administration of diazepam (20 mg/kg ip) for consecutive 21 days. Development of BZD tolerance was assessed 30 min after the last injection of diazepam, and the spontaneous drug withdrawal was started 24 h after the last injection. Quercetin was co-administered along with diazepam for 21 days and the treatments were reversed on the last day to observe any *per se* effect of the drug. Diazepam withdrawal induced hyperlocomotor activity and anxiety (using a mirror maze) were assessed on the third day of the withdrawal.

**Results:** Long-term administration of diazepam resulted in tolerance to behavioral actions, sedation and anxiolytic effects. Abrupt discontinuation of diazepam after 21 days induced withdrawal reactions manifested as hyperlocomotor activity and severe anxiety. The peak withdrawal activity was observed on the third day of diazepam withdrawal. Quercetin when co-administered prevented the development of tolerance and withdrawal induced hyperlocomotor and severe anxiety.

**Conclusions:** Quercetin could be used in the treatment of benzodiazepine tolerance and dependence, though its mechanism remains to be explored further.

**OP-100****ROLE OF QUERCETIN IN PTZ- INDUCED KINDLING EPILEPSY.**

Kumar G, Singh A, Naidu PS, Kulkarni SK.

Pharmacology Division, University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh-160 014.

**Objectives:** Chemical kindling is an experimental model of epilepsy and eliptogenesis in which repeated application of initially subconvulsive chemical stimulation induces progressive seizure activity. Quercetin a flavonoid isolated from many plants, including Quercus Mongollca Fish, Apocynum Venelim Linu and Hypericum Ascyron L. has shown that quercetin has wide ranging pharmacological actions on cardiovascular, anticancer and free radical scavenging activity. Its CNS activity, particularly, role in kindling epilepsy has not yet been explored. The aim of the present study was to explore the role of quercetin in PTZ-induced kindling epilepsy.

**Methods:** Kindling epilepsy was induced in mice by injecting PTZ (40 mg/g i.p.) alternatively for nine days in a twelve-day study. Quercetin (50, 100 and 200 mg/kg p.o) was administered on all the twelve days of the study. After each PTZ injection the convulsive behavior was assessed for 15 min.

**Result:** The repeated administration of subconvulsant dose of PTZ (40 mg/kg i.p.) resulted in progressive increase in susceptibility to seizures which resulted in maximum cumulative score on the twelfth day in control group. Quercetin (50, 100 and 200 mg/kg p.o) dose dependently prevented the progression of the seizures, when assessed on the twelfth day of the study.

**Conclusions:** Quercetin may have role in the effective treatment of kindling epilepsy though its exact mechanism remains to be explored.

OP-101

**A STUDY ON BRAIN ACETYLCHOLINESTERASE ACTIVITY AND PASSIVE AVOIDANCE LEARNING IN OVARIECTOMIZED RATS.**

**Nath C, Das A, Dikshit M, Srivastava UK\*, Srivastava SR\*.**

Divisions of Pharmacology and Endocrinology\* Central Drug Research Institute, P.O. 173, Lucknow 226001

**Objective:** To investigate the effect of ovariectomy and estrogen treatment on the brain acetylcholinesterase activity and learning in rats.

**Methods:** The passive avoidance test (PACS 30 system) was employed to assess learning and memory functions in ovariectomized and control rats. Specific activity of acetylcholinesterase (AChE) was assayed spectrophotometrically in salt soluble (SS) and detergent soluble (DS) fractions of various brain areas.

**Results:** In the single trial passive avoidance test all the groups showed significant learning and retention of memory as evident by the increase in transfer latency time on 2<sup>nd</sup> trial as compared to 1<sup>st</sup> trial. No transfer response was significantly increased in the estradiol dipropionate (1.0 µg/rat, s.c daily for 8 days) treated ovariectomized (80%) and non-ovariectomized (60%) group as compared to ovariectomized (30%) group. The effect of ovariectomy and estradiol dipropionate was varied in both the fractions of AChE in these brain areas. Estradiol dipropionate treatment could restore AChE activity to the control level only in DS fraction of hypothalamus and SS fraction of hypothalamus, thalamus and medulla in ovariectomized rats.

**Conclusion:** The results indicate that ovariectomy alters acetylcholinesterase activity in the brain areas but not in a uniform manner and affects only qualitative aspects of learning and memory function, which could be improved by estrogen supplementation. Thus, on the basis of observations of the present study it emerges that only qualitative aspects of cognitive function are vulnerable to estrogenic influence, which may be unrelated to changes in the AChE activity in brain areas.

OP-102

**CLOBAZAM: EFFICACY AS ADD ON THERAPY IN EPILEPTIC PATIENTS RESISTANT TO PHENYTOIN AND INFLUENCE ON PHARMACOKINETIC PROFILE OF PHENYTOIN.**

**Khan Yasmeen R, Gupta Usha, Puri Vinod\*, Mallika V.\*\***

Department of Pharmacology, Maulana Azad Medical College and Associated Hospitals, New Delhi - 110002; \*Department of Neurology, G.B Pant Hospital, New Delhi - 110002; \*\*Department of Biochemistry, G.B Pant Hospital, New Delhi - 110002.

**Objective:** To evaluate the efficacy of clobazam (a 1,5 benzodiazepine) as add on therapy to phenytoin in epileptic patients resistant to phenytoin. Since, phenytoin has a narrow therapeutic range, the influence of clobazam on its serum levels and pharmacokinetic profile was also assessed.

**Methods:** 20 epileptic patients resistant to phenytoin monotherapy (less than 50 % improvement in seizure status despite taking maximal permissible dose of phenytoin) were included in this ethically approved study after obtaining written informed consent. The patterns of seizures included were generalised tonic clonic seizures and complex partial seizures. Clobazam was initiated in a dose of 10 mg twice daily. Seizure status was assessed and venous blood samples obtained before adding clobazam, on day 0 and on follow up days, 7, 21, 35, 65 and 95. In 7 out of 20 patients, a detailed pharmacokinetic study was performed on day 0 and day 21. The serum concentration of phenytoin was assessed by the EMIT assay kit using the automated autoanalyser.

**Results:** 75% of patients became completely seizure free by the end of the 3-month follow up period. The mean frequency of seizures decreased from 2.2/week on day 0 to 0.45/week on day 95. This decrease over the 3 month follow up period was highly significant ( $p \leq 0.01$ ). The most common adverse effect seen was drowsiness in 85% of patients, but tolerance developed to it gradually, by the 2nd month of treatment. The mean serum concentration of phenytoin increased to non significant proportions on all the follow up days except on day 21. There was no significant difference in the pharmacokinetic profile after the addition of clobazam.

**Conclusions:** Clobazam has good efficacy as add on treatment to phenytoin in refractory epileptic patients. Clobazam does not alter the serum levels of phenytoin to a significant extent so as to produce any toxicity.



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# ***Scientific Session XI***

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## **Teaching methods and psychopharmacology**

**Date** : 29.11.2002  
**Time** : 0900-1045  
**Venue** : Hall - B

**Invited Lectures** : Dr. G Palit  
Dr. R Raveendran  
Dr. B Gitanjali  
Dr. M Srivastava  
Dr. V N Puri

**Oral Presentation** : OP 103 - OP 109

**Chairpersons** : Dr. O N Tripathi  
Prof. Sushma Mengi



**IL-77****STRESS - BEHAVIORAL AND BIOCHEMICAL MANIPULATIONS IN THE BODY.****Gautam Palit**

Division of Pharmacology, Central Drug Research Institute, Lucknow - 226001.

Stress is an internationally recognized phenomenon and it has been realized that stress is playing a causative role in precipitating several diseases. The present experiment was carried out to understand the stress induced alterations in the behavioural, biochemical and histopathological parameters after different natures of stresses. The stress was given in the form of immobilization for 150 minutes once only in acute stress (AS) where as repeated for seven consecutive days in chronic predictable stress (CS). In chronic unpredictable stress (CUS) the rats were treated with two different stressors for seven consecutive days in an unpredictable manner. Immediately after stress regime the animals were sacrificed and blood was collected through cardiac puncture. Brain, adrenal gland and stomach were dissected out immediately for estimation of respective neurotransmitter levels, histopathological changes and ulcer index. Exploratory behaviour was studied with the help of Digiscan animal activity monitor. The serum was separated out and the level of serum glucose, triglyceride, cholesterol and creatine phosphokinase (CPK) was estimated using Beckman CX-5 auto-analyzer. There was a significant reduction in the exploratory behaviour after AS, CS and CUS in comparison to the control group. The stress exposure leads to significant gastric ulceration in CS and CUS. There was a significant increase in the adrenal gland weight in all stress groups. The serum glucose and insulin levels were significantly increased in acute stress only but the serum triglyceride and cholesterol level was decreased after CS and CUS. Serum CPK activity level was significantly high in all the stress groups. The levels of biogenic amines in different brain regions were significantly increased. The histopathological studies revealed that the AS as well as CUS induced adrenal hypertrophy is the result of the medullary region of adrenal gland with high vascularity in CUS. CS leads to the hypertrophy in the cortex.

Therefore, stress research in laboratory animals has assumed an important role in understanding the biological and behavioral consequences of stress and undoubtedly assumed a prime importance in the management of health and disease.

**IL-78****MANUSCRIPT PEER REVIEW.****Raveendran R.**

Dept of Pharmacology, JIPMER, Pondicherry - 605006

Almost all scholarly journals have set up a peer review system to assess the manuscripts submitted. Review of manuscript by peers (external experts in the area dealt by the manuscript) is an important step in manuscript processing as it helps the editorial team to remove chaff from wheat. As the internal review alone may not be adequate, journals seek the help of external peer reviewers. COPE (Committee On Publication Ethics) defines that "Peer reviewers are external experts chosen by editors to provide written opinions/with the aim of improving the study". They play a major role in improving the quality of a journal. But good reviewers are not easy to find. Apart from being an expert in his/her field(s) of interest/ a good reviewer should be able to critically analyse the work and be willing to spend considerable time with the manuscript to be reviewed. He / she should suggest ways to improve the study/manuscript rather than simply advising the editor to either accept or reject. This talk will cover different systems/procedures adopted for peer review process, guidelines for better reviewing pit falls and ethics of peer reviewing.

IL-79

## PLAGIARISM: THE EMERGING PLAGUE..

Gitanjali B.

Dept of Pharmacology, JIPMER, Pondicherry - 605006

Plagiarism is one of the commonest and serious forms of scientific misconduct. It is a form of intellectual theft and is the act of passing off another person's words, ideas or work as one's own, without proper acknowledgement of the original source, in a form which is acceptable to the medium of expression. It undermines the very fabric of scientific thought and scholarly discourse. Plagiarism is not new to science. Of late, there is a growing body of concern, that it could be contributed to a lack of knowledge on the ethics of scholarly writing rather than an erosion of scientific values. With the growing use of computers to prepare documents, the extent of plagiarism at the postgraduate dissertation/thesis level and in the papers being submitted for publication as review articles has increased. Writing skills have to be nurtured and developed along with ethical practices of how to write a scientific paper/thesis. The postgraduate curriculum should include courses in scientific writing and correct methods of referencing should be given due importance. In this talk, I shall discuss the types of plagiarism, the problems associated with it, the acceptable methods of referencing and the initiatives of the editors of various medical journals to combat this menace at National and International levels.

IL-80

## PAPER AND PENCIL METHODS IN CLINICAL PHARMACOLOGY.

Meena Shrivastava.

Dept. of Pharmacology, Indira Gandhi Medical College, Nagpur - 440018.

**Introduction:** Clinical pharmacology (CP) is an integral part of the Pharmacology Department. It encompasses a vast field of clinical research related to human being. It is hence necessary to boost up the research related to this area, with the available resources.

**Methods:** In spite of non-availability of the sophisticated instruments, studies can be planned in CP. The suggested areas are as follows- 1) Drug surveillance and drug audit - Prescribing habits in Govt and private hospital setting can be taken up. We have done studies related to use / misuse of antibiotics, analgesics, topical antibiotics & corticosteroids, sedatives, hypnotics, antiulcer agents & vitamins in out door & in door patients of various departments of our hospital, cardiology clinic, Surgical and Medical ICU, operation theaters etc. Studies can be done to find expenditure on various items purchased for the hospital and cost effectiveness can be assessed. The clinicians can be given the feedback of the same. 2) Human Pharmacodynamics - The Pharmacodynamics of different psychopharmacological agents (antipsychotics, anti anxiety, sedative, hypnotics) and analgesics can be studied in objective and subjective manner. Subjective Visual Analogue Scales are excellent tools to do such type of studies. 3) ADR monitoring - ADR monitoring studies can be planned in different hospital settings and in return provide a useful information to the clinicians. 4) Studies related to DRUG PROMOTION- Influence of drug advertising on prescribing habits of clinicians in public and private hospitals, critical study of various promotional literatures can be planned 5) Drug information services to the clinicians, fellow Pharmacologists, students and community- This can be done by circulars, bulletins, anecdotal articles and presentation of data, questionnaire etc can be planned.

**Conclusion:** The research in clinical pharmacology can be done in various areas using simple paper pencil techniques.

IL-81

## PHARMACOLOGY POLICY PLANNING.

Puri VN.

Division of Pharmacology, Central Drug Research Institute, Lucknow - 226001.

Scientific democracy has direct linking with a welfare state which is headed by President. In Indian context several democratically elected presidents have dynamically helped this country in achieving positive mile stones eg. Agriculture and Space sciences. In biomedical sciences eg. Pharmacology track record is not very clean. Pharmacology has played a very important role in health care delivery systems of humans and animals. Global investments in this field are going to be very high. Educational support has been according to the socioeconomic needs of the country. Developed nations have from time to time revised their teaching and training in pharmacology. You will have tough time to find out a kymograph in medical, pharmacy or veterinary schools in U.S.A. In India, Medical Council of India (MCI) inspectors will not issue accreditation certificates till large number of kymographs are procured. As president of Indian Pharmacological Society (IPS) I have written and requested for changes to MCI, Health Ministry and none has responded. Only ray of hope is that planning commission has acknowledged the letter. I have requested in this letter if atleast 4 centres of excellence in the discipline of pharmacology may be established. The key objective is to improve teaching and training in pharmacology so as to extract best for medical care and Pharma industry. Our policies at international levels are also very depressing. Indian National Science Academy (INSA), biological section has hundred's of members who are spreading scientific-terrorism. Recent example is XIV World Congress of Pharmacology at Sanfrancisco, U.S.A. I requested president of INSA to know the method and names of selecting Indian Pharmacologist. Letter was replied by secretary and contents were depressing. As IPS president I do not know what were deliberations like, how our younger pharmacologists are going to get some positive benefits. How retired and retiring professionals are going to provide momentum to young institutions. IPS is at cross roads and trying hard to make sound policies and execute them so that we can make globally acceptable drugs and produce pharmacologists who may serve industry, medical, veterinary, pharmacy institutes so as to make India a strong player in pharmacology.

OP-103

**SURVEILLANCE OF PSYCHIATRIC MORBIDITY AND THE PRESCRIBING TRENDS IN PSYCHIATRY OPD OF A TERTIARY CARE TEACHING HOSPITAL IN UTTARANCHAL.**

**Patnaik Shaktibala, Sharma Taruna, Dhasmana DC, Mishra KC.**  
Department of Pharmacology, Himalayan Institute of Medical Sciences, Jolly Grant, Dehradun.

**Objective:** To study the prevalence of psychiatric illness and the prescribing pattern of drugs in a tertiary care teaching hospital, attached to a Medical college, Dehradun.

**Methods:** Prescriptions were collected at random from the psychiatry OPD (No. 414) over a period of 6 months. Diagnosis done according to ICD-10 criteria and were analysed for following parameters (a) age, (b) sex, (c) socioeconomic status (d) religion, (e) occupation, (f) residence, (g) disease prevalence, (h) patterns of drug used.

**Results:** Total no of prescriptions 414, Total no of drugs 1106, male 209, female 205, < 15 years 19, < 30 years 158, < 45yrs 128, >45 yrs 109. High SES 82, Middle SES 292, Low SES 40. Professionals 61, Non Professionals 230, Farmers/labourers 52, Students 71, Hindu 357, Muslims 45, Sikhs 10, Christians and others 2. Residents of Uttaranchal 273, Non-Residents of Uttaranchal 141. Schizophrenic 40, Major Depression 118, MDP 110, Anxiety 72, Others 75. Out of 1106 no of drugs antipsychotics-246 antidepressants-179, anxiolytics-185, antimanic-9, antiepileptic-77, anticholinergics- 99, sedatives-10, hormones-19, fixed dose combinations-65, miscellaneous-21. Tialoperidol (44.7%) was the most commonly used antipsychotic. where as Sertaline (35.2%) and Clonazepam (52.9%) in antidepressants and anxiolytics group respectively. Among other categories group of drugs valproate (96.1%), Trihexyphenidyl (85.8%) from antiseizure and anticholinergic group of drugs .

**Conclusion:** This preliminary study may help us identify the type of psychiatric morbidity prevalent in Uttaranchal. Feed back to the prescribers may help them to rectify any lacunae in their prescribing habit as well as in decision making based on which future intervention studies can be planned.

OP-104

**A STUDY OF PRESCRIBING TRENDS IN MAJOR DEPRESSION IN PSYCHIATRY OPD OF TERTIARY CARE TEACHING HOSPITAL OF UTTARANCHAL.**

**Sharma Taruna, Patnaik Shaktibala, Dhasmana DC, Mishra KC.**  
Department of Pharmacology, Himalayan Institute of Medical Sciences, Jolly Grant, Dehradun, Uttaranchal.

**Objectives:** Rational prescribing is the need of the hour. Objective is to study the prescribing pattern in major depression in psychiatry OPD.

**Methods:** Prescriptions from psychiatry OPD were collected randomly over a period of 6 months. Relevant information were entered into the Preformed Proforma and were analysed. Patients suffering from only major depressions were diagnosed according to ICD-10 criteria were included in this study.

**Results:** Total no of patient in Major depression: 118. Total no of drugs prescribed :363, Average no of drugs per prescription: 3.1, Fixed dose combination: 8, No. of parenteral drugs:24, No. of oral drugs: 338. Out of total 363 drugs commonly prescribed drugs were antidepressants-111 (30.6%), antipsychotics- 43 (11.8 %), anxiolytics- 99 (27.3%) and multi vitamins and minerals-83 (22.9%). Among antidepressants SSRIs (44.1%), sertraline (35.1%) was most commonly prescribed drug followed by SNRIs (Venlafaxine-32.4%). Among anxiolytics Clonazepam-47 (47.5%) was most commonly prescribed drug.

**Conclusion:** This preliminary study may help us to identify the pattern of drugs used in prescribing and therapeutics decision making based on which future intervention studies may be planned to promote rational use of drugs.

OP-105

**A STUDY OF PRESCRIBING PATTERN OF DRUGS USED IN ANXIETY DISORDERS IN PSYCHIATRY OPD OF TERTIARY CARE TEACHING HOSPITAL IN UTTARANCHAL.**

**Bhardwaj R, Sharma Taruna, Patnaik Shaktibala, Dhasmana DC, Mishra KC**  
Department of Pharmacology, Himalayan Institute of Medical Science,  
Deharadun -248140.

**Objective:** Psychotropic drugs are widely prescribed but how new classes of psychotropic medications have affected prescribing pattern has not been well established. Present study was conducted to find out the prescribing pattern in psychiatry practice.

**Methods:** Prescriptions were collected at random from psychiatry OPD of a tertiary care teaching hospital (n=72) over a period of 6 months. Patients suffering from all type of anxiety disorders diagnosed according to ICD-I criteria were included in this study.

**Results:** Total no of patients in anxiety disorder:72, Total no of drugs prescribed :169, Average no of drugs per prescription:2.3, Fixed dose combination: 17, Out of 169 drugs, commonly prescribed drugs were anxiolytics-53 (31.4%), Anti psychotics-9 (5.3%), Anti depressants-28 (16.6%), Vitamins and minerals 37 (21.9%): Among anxiolytics Clonazepam (62.3%) was most commonly prescribed drug followed by Alprazolam (11.3%). Among antidepressants Sertraline (35.7%) was most commonly prescribed drug.

**Conclusion:** This preliminary study may help us to promote rational use of drugs which could be facilitated by periodic feed back to the prescribers.

OP-106

**OXIDATIVE STRESS INDUCED IMPAIRMENT OF SPATIAL LEARNING IN MICE ON EXPOSURE TO LOW FREQUENCY ELECTROMAGNETIC FIELD (EMF).**

**Dixit PV, Kulkarni AP, Wanjari MM, Joharapurkar AA, Zambad SP, Urnathe SN.**  
University Department of Pharmaceutical Sciences, Nagpur University,  
Nagpur - 440010.

**Objective:** Since EMF generated free radicals and neurodegenerative diseases are often attributed to the oxidative stress. It is proposed to investigate the influence of EMF on cognitive function and to delineate its relation to oxidative stress in mice

**Method:** The mice were treated daily with either Vitamin E or Piracetam or vehicle and concurrently exposed to EMF (50Hz) for 28 days. The learning and memory function was assessed by Morris Water Maze (MWM) and Elevated Plus Maze (EPM). On 28th day the brain levels of super oxide dismutase (SOD), Catalase, reduced glutathione (GSH) and lipid peroxidation (LPO) were assessed.

**Results:** The 28 days exposure of EMF significantly impaired the learning whereas no influence on long-term retention of memory was observed. Similarly the EMF exposure caused a significant rise in SOD and catalase with decrease in GSH and no change in LPO. The daily Vitamin E treatment not only prevented the changes in markers of oxidative stress but also prevented the EMF induced impairment of learning. Piracetam did not influence any of the parameters.

**Conclusion:** Long-term exposure to low frequency EMF impairs the spatial learning and it is subsequent to the induction of oxidative stress.



OP-107

**REVERSAL EFFECT OF *TINOSPORA CORDIFOLIA* IN COLCHICINE INDUCED ALZHEIMER'S DISEASE IN RATS.**

Samuel A, Malini S, Mudanna and Shanbhag R.

Department of Pharmacology, Kasturba Medical College, Manipal- 576 119.

**Objective:** To study the reversal effect of aqueous and alcoholic extracts of *Tinospora cordifolia* (Tc) ICV colchicine induced cognitive deficit rats.

**Methods:** Male albino rats of Wistar strain weighing 200 - 250 gms were selected for the study. To each animal colchicine was injected to the ventricles by stereotaxis. These rats were randomly divided into 4 groups (n=8/group) and treated with vehicle, donepezil (0.45 mg/kg), Tc aqueous extract (100 mg/kg) or alcoholic extract of Tc (200 mg/kg). The assessment of learning and memory was done using Hebb William Maze test and Passive Avoidance task on 14<sup>th</sup> and 30<sup>th</sup> day following ICV colchicine administration. The locomotor activity was assessed by open field chamber. Histopathological studies of the brain was done. Data was analysed by one way analysis of variance followed by Post Hoc Scheff's test.

**Results:** Colchicine increased the learning scores in Hebb William Maze and decreased the latency to enter dark compartment in Passive avoidance task. Tc aqueous and alcoholic extracts decreased the learning scores in Hebb William Maze test and increased the latency to enter the dark compartment in Passive Avoidance task. Histopathologically the extracts partially protected the neurodegeneration induced by colchicine.

**Conclusion:** Tc reversed the cognitive impairment induced by colchicine

OP-108

**VALIDITY OF MCQ TYPE OF QUESTIONS BY ITEM ANALYSIS.**

Jagtap Rohini P, Joshi AA, Radha Yegnanarayan.

Department of Pharmacology, B.J. Medical College, Pune - 411001.

**Objectives:** MCQ (Multiple choice questions) and SAQ (Short answer questions) are part of the examination being conducted by M.U.H.S. MCQ amounts to 30% of total marks which makes it essential to have questions with good discrimination power. Short answer type of questions permit the assessment of coherence of an argument and generation of logical line of thought. The objective is to have a valid MCQ and to study the correlation between MCQ and SAQ.

**Methods:** Records of results of MCQ and SAQ tests of second MBBS students (1999-2000) for midterm, terminal and preliminary examinations were studied. Item analysis, reliability index, correlation coefficient scores and frequency distribution of scores were calculated.

**Results:** Reliability index and correlation coefficient were significantly high for both MCQ and SAQ type of examinations. Mean scores obtained in MCQ tests were significantly different from mean scores obtained at SAQ tests.

**Conclusion:** MCQ is an asset to the educational spiral and MCQ and SAQ tests are supplementary to each other.

OP-109

**BLUNDER LECTURE - AN ACTIVE LEARNING STRATEGY FOR LARGE GROUP OF STUDENTS.**

**Nayak Satheesha B\***, Somayaji SN\*, Ramnarayan K\*\*.

\*Department of Anatomy and \*\*Pathology, International Centre for Health Sciences, Manipal - 576119.

**Introduction:** Active learning strategies are becoming popular in medical education today. It is difficult to incorporate active learning strategies for large groups of students. We attempted to incorporate one active learning strategy in the form of 'blunder lectures' for large group of students

**Methods:** Large group of students were asked to come prepared for certain topics. During a lecture, students were asked to identify the blunders. A lecture was taken for about 45 minutes, where more than 50% of the information given was wrong. At the end of the lecture, adequate time was given to students to discuss among themselves and identify and rectify the blunders.

**Results and conclusion:** The sessions were found to be enjoyable and provided opportunity to revise, recall and self-evaluation.



## ***Scientific Session XII***

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### **Pharmacokinetics and drug delivery**

**Date** : 29.11.2002  
**Time** : 1400-1545  
**Venue** : Hall - B

Invited Lecture : Prof. M U R Naidu

Oral Presentation : OP 110 - OP 117

Chairpersons : Prof. M U R Naidu  
Prof. N R Biswas



**IL-82****FAST TRACK DRUG DEVELOPMENT.****Naidu MUR.**

Dept. of Clinical Pharmacology and Therapeutics, Nizam's Institute of Medical Sciences, Hyderabad.

The molecular revolution in biology and medicine already had an enormous effect upon the drug discovery process and has a similar impact upon development. Between 1960s and mid 1980s, the drug discovery was limited due to less clearly identified biological targets. Why we should make most from early human trials: Due to continuous increase in time and cost of drug development and the considerable amount of resources required by the traditional approach, one can no longer afford to continue upto late phase III trial with a drug which is unlikely to be therapeutically effective. The future challenge is to slash research cost by achieving significant reduction in failure rate, for drug entering late clinical phase, and to reduce development time, and to increase a probability of success.

Use of pharmacogenomics has contributed extensively in drug selection, use and marketing. Now it is possible to do the modelling and stimulation experiment to understand the probable outcomes of preclinical and clinical trials. Calculation and interpretation of correct PK data gives more accuracy of dose selection, dosing frequency and drug distribution. New techniques and insights into genomics and the progressive characterization of the human genome, have broadened the scope of pharmacogenetics beyond the classic causes of pharmacokinetic variability. The influence of genetic polymorphism as it underlies etiologically distinct, but phenotypically similar, disease, subtypes is of divergent etiology (eg: ApoE in Alzheimer's disease) studies should investigate any allelic association with observed variability in compound activity. The previously distinct functions of drug discovery, lead optimization and exploratory clinical development are converging. Micro dosing strategies that combine very highly sensitive detection processes with 'homeopathic' doses may allow safe human exposure. This allows to learn and confirm cycle to be shortened, and may enable lead candidate selection to be made in humans.

**OP-110****PHARMACOKINETICS OF ORAL IBUPROFEN IN PREMATURE INFANTS.****Sharma PK, Garg SK, Narang A\*.**

Department of Pharmacology and Pediatrics\*, Post Graduate Institute of Medical Education and Research, Chandigarh-160012.

**Objective:** To study the single dose pharmacokinetic of oral ibuprofen in premature infants

**Methods:** 20 premature infants admitted to neonatal unit were enrolled in study. Ibuprofen was administered in a single oral dose of 10 mg/kg and blood samples were collected through an indwelling vascular catheter at time zero and 1, 2, 4, 8, 12, and 24 hours. Ibuprofen plasma concentrations were assayed by high performance liquid chromatography (HPLC).

**Results:** 20 infants, with gestational age,  $30.3 \pm 0.33$  weeks and birth weight,  $1262.5 \pm 55.4$  g; (values are given as mean  $\pm$  SEM) were studied. There was large inter individual variability observed for plasma concentrations, elimination half-life ( $t_{1/2}$ ) ( $15.72 \pm 3.76$  h) and area under plasma concentrations time curve ( $AUC_{0-\infty}$ ) ( $402.60 \pm 79.67$   $\mu\text{g}\cdot\text{h}/\text{mL}$ ) in these babies. Variables like gestational age, birth weight, and sex did not affect ibuprofen pharmacokinetic significantly ( $p > 0.05$ ).

**Conclusion:** Ibuprofen pharmacokinetics showed a wide variability in premature infants. These results may have enough reasons to consider dosing schedule in this group of patients.

**OP-111****INFLUENCE OF ACIDIC BEVERAGE (COCA-COLA) ON THE ABSORPTION OF PHENYTOIN IN RABBITS.****Kondal A, Garg SK.**

Department of Pharmacology, Postgraduate Institute of Medical Education and Research, Chandigarh - 160012.

**Objective:** To evaluate the effect of acidic beverage (Coca-Cola) on absorption of phenytoin in rabbits.**Methods:** In a cross over study, phenytoin was given orally in a dose of 30 mg/kg to New Zealand white rabbits (n=8) and blood samples were drawn at different time intervals from 0-24 h from marginal ear vein. After a washout period of 7 days, coca-cola in a dose of (5 ml/kg p.o.) was administered along with phenytoin (30 mg/kg) and blood samples were drawn from (0-24 h). To the same animals coca-cola (5 ml/kg p.o.) was continued for seven days. On the 8th day, Coca-Cola (5 mg/kg) and phenytoin (30 mg/kg) were administered simultaneously and the blood samples were drawn from 0-24 h. Plasma was separated and stored at -20°C until assayed for phenytoin by HPLC technique. Pharmacokinetic parameters were calculated.**Results:** In a single dose as well as multiple dose, Coca-Cola significantly increased the C<sub>max</sub> and AUC<sub>0-∞</sub> of phenytoin, while no difference was observed in T<sub>max</sub> and t<sub>1/2</sub>. The elimination half life was increased after single and multiple dose as compared to control group but was not statistically significant.**Conclusion:** Coca-Cola increases the extent of absorption of phenytoin. These results warrants the reduction of phenytoin dose when administered with Coca-Cola to avoid any toxicity.**OP-112****A STUDY OF SINGLE DOSE PHARMACOKINETIC INTERACTIONS OF LITHIUM WITH CHLORPROMAZINE, IMIPRAMINE AND DIAZEPAM IN NORMAL HEALTHY HUMAN VOLUNTEERS.****Malhotra S, Minocha KB\*, Kaur S\***

Department of Pharmacology, PGIMER, Chandigarh; \* DMC and Hospital, Ludhiana

**Objective:** To study the single dose pharmacokinetic interactions of three commonly used psychotropic agents - chlorpromazine, imipramine and diazepam with lithium in normal healthy human volunteers.**Methods:** In a cross-over study, 18 volunteers were given a single dose of 900 mg of lithium carbonate after an overnight fast and blood samples were drawn at 0, 0.3, 0.6, 1, 2, 4, 6, 12, 24 and 48 hours after drug administration. After a washout period of 4 weeks, the volunteers were randomized into three groups of six each. One group received 900 mg of lithium and 100 mg of chlorpromazine, the second group received 900 mg of lithium and 50 mg of imipramine and the third group received 900 mg of lithium and 5 mg of diazepam. Blood samples were collected at the same time points as above. Serum lithium levels were estimated by the flame photometric method and the pharmacokinetic parameters (C<sub>max</sub>, T<sub>max</sub>, AUC<sub>0-∞</sub>, t<sub>1/2</sub>) were calculated.**Results:** Single dose chlorpromazine reduced the C<sub>max</sub> and AUC<sub>0-∞</sub> (p < 0.01) and prolonged the T<sub>max</sub> (p < 0.001) of lithium whereas the t<sub>1/2</sub> was not significantly altered. Single dose imipramine reduced the C<sub>max</sub> (p < 0.05) and prolonged the T<sub>max</sub> (p < 0.01) of lithium. The AUC<sub>0-∞</sub> was reduced and the t<sub>1/2</sub> prolonged, but this was not statistically significant. Single dose diazepam did not significantly alter any of the pharmacokinetic parameters of lithium.**Conclusions:** Concomitant administration of chlorpromazine significantly reduced the bioavailability of lithium by interfering with its absorption, most likely because of its anticholinergic effects. Imipramine led to a delay in the attainment of the therapeutic levels of lithium. Diazepam did not have a significant pharmacokinetic interaction with lithium.

OP-113

### BIOAVAILABILITY OF TWO FORMULATIONS OF ZAFIRLUKAST 20 mg IN NORMAL, HEALTHY, MALE, HUMAN VOLUNTEERS.

Shobha JC\*, Naidu MUR\*, Hari Sankar#, Sita Raman#, Ananta Rao#.

\*Dept. of Clinical Pharmacology and Therapeutics, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad - 500 082.

#Dr.Reddy's Laboratories Limited, Clinical Development Department, Bachupally, Hyderabad.

**Objective:** To study the oral bioavailability of two formulations of Zafirlukast 20 mg in normal healthy, male, human volunteers.

**Methods:** Twelve healthy male human volunteers after fulfilling the inclusion and exclusion criteria entered into the study, after giving their written informed consent. This study was approved by the Ethical Committee of our Institute. After an overnight fast, on the day of the study each volunteer ingested 20 mg of tablet of Zafirlukast of either formulation as per randomization with 240 ml of water. 5 ml of Blood was collected at 0.0 (pre-dose) and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 14.0, 6.0, 8.0, 12.0, 24.0, 36.0 hours post dose. Plasma was separated and stored at - 20°C until analysis by HPLC. Crossover was done after 7 days washout period. Occurrence of any side effects was recorded during the study.

**Results:** The mean age of the volunteers was  $27.8 \pm 5.1$  years, mean height was  $169.3 \pm 3.9$  cm and the mean weight was  $64.3 \pm 7.1$  kg. Mean Zafirlukast peak concentration  $C_{max}$  was  $278.75 \pm 79.9$  ng/ml and  $282.45 \pm 74.63$  ng/ml with standard and test formulations respectively. The absorption of Zafirlukast was similar from both the formulations with the mean time to reach peak concentration ( $T_{max}$ )  $1.92 \pm 0.47$  with standard and  $2.4 \pm 0.8$  hours with test formulation. The mean area under the time concentration curve calculated upto  $0 - \infty$  with standard was  $848.54 \pm 232.94$  ng.h/ml and  $876.60 \pm 359.86$  ng.h/ml with test formulation. There was no statistically significant difference in any of these parameters. As compared to standard, the test formulation was found to be 103.31% bioavailable. All the volunteers tolerated both the formulations without any significant adverse effects.

**Conclusions:** The plasma concentration time profile, rate and extent of Zafirlukast absorption, were comparable between standard and test formulations. Bioavailability of test formulation was 103.31 % as compared to standard. Drug was tolerated well. With these findings it can be said that both the formulations are bioequivalent.

OP-114

### INTRAVENOUS PHARMACOKINETICS OF PEFLOXACIN IN BROILER CHICKENS.

Pant S, Rao GS, Sastry KVH\*, Tripathi HC, Jag Mohan\*, Malik JK.

Division of Pharmacology and Toxicology, Indian Veterinary Research Institute, Izatnagar, \*Division of Physiology & Reproduction, Central Avian Research Institute, Izatnagar - 243122.

**Objective:** To determine plasma concentrations and pharmacokinetics of pefloxacin in broiler chickens.

**Methods:** The plasma levels and pharmacokinetic properties of pefloxacin were determined in broiler chickens after single intravenous administration at a dose of  $10 \text{ mg.kg}^{-1}$  body wt. The drug was determined in plasma by using a reverse phase high performance liquid chromatography method and  $C_{18}$  column was used for separation. The mobile phase comprising of a mixture of acetonitrile and buffer consisting of 2.0 g sodium acetate, 2.0 g citric acid and 1.0 ml triethylamine in 1.0 L HPLC water (15: 85, v/v) was used at a flow rate of  $0.9 \text{ ml.min}^{-1}$ . The fluorescence detector excitation and emission wavelengths were adjusted at 278 and 440 nm, respectively.

**Results:** Following intravenous administration, pefloxacin concentration in plasma was  $19.69 \pm 3.20 \text{ } \mu\text{g.mL}^{-1}$  at 0.083 h which rapidly declined to  $2.67 \pm 0.47 \text{ } \mu\text{g.mL}^{-1}$  at 0.75 h. Thereafter, drug concentration in plasma gradually decreased to  $2.13 \pm 0.40$ ,  $1.62 \pm 0.34$ ,  $0.95 \pm 0.16$  and  $0.63 \pm 0.14 \text{ } \mu\text{g.mL}^{-1}$  at 2, 4, 8 and 12 h, respectively. The plasma drug concentration-time data were best fitted to a two-compartment open model. The distribution half-life, elimination half-life, volume of distribution at steady state, total systemic clearance and mean residence time of pefloxacin were  $0.08 \pm 0.04$  h,  $6.54 \pm 1.17$  h,  $3.73 \pm 1.6 \text{ L.kg}^{-1}$ ,  $0.406 \pm 0.08 \text{ L.h}^{-1}.\text{kg}^{-1}$  and  $8.06 \pm 1.68$  h, respectively. The tissue to plasma ratio was calculated to be  $40 \pm 12$ .

**Conclusion:** The results suggest that pefloxacin given intravenously may be useful in the treatment of susceptible bacterial infections in poultry.



**OP-115****EFFECT OF PROBENECID ON THE DISPOSITION KINETICS OF CIPROFLOXACIN IN GOATS.**

Ramesh S, Rao GS, Sastry KVH\*, Moudgal RP\*, Malik JK.

Division of Pharmacology and Toxicology, Indian Veterinary Research Institute, Izatnagar, \*Division of Physiology &amp; Reproduction, Central Avian Research Institute, Izatnagar - 243122.

**Objective:** The study was undertaken to determine the effect of probenecid on the subcutaneous pharmacokinetics of ciprofloxacin in goats.

**Methods:** The disposition kinetics of fluoroquinolone antimicrobial agent ciprofloxacin was investigated in goats given ciprofloxacin ( $7.5 \text{ mg.kg}^{-1}$ , s.c) alone or in combination with probenecid ( $40 \text{ mg.kg}^{-1}$ , s.c.). Blood samples drawn from jugular vein at predetermined time intervals were centrifuged to obtain plasma. Ciprofloxacin concentrations in plasma were determined by reversed phase high performance liquid chromatography. Fluorescence detector was used and its excitation and emission wavelengths were adjusted at 278 and 440 nm, respectively.

**Results:** Plasma ciprofloxacin concentrations were appreciably higher in goats from 0.5 h to 10 h and significantly higher at 12 and 24 h after concurrent administration of probenecid and ciprofloxacin. The plasma drug concentration-time data of ciprofloxacin in animals given ciprofloxacin alone or in combination with probenecid were analysed by a two-compartment open model. The median values of elimination half-life ( $t_{1/2\beta}$ , 3.5 h), area under the plasma concentration-time curve (AUC,  $6.66 \mu\text{g.h.ml}^{-1}$ ), mean residence time (MRT, 4.89 h), apparent volume of distribution ( $V_{d(\text{area})}$ ,  $3.79 \text{ L.kg}^{-1}$ , bioavailability (F, 59%) increased and total systemic clearance (CIB,  $1126 \text{ ml.h}^{-1}\text{kg}^{-1}$ ) decreased appreciably but nonsignificantly in animals given probenecid plus ciprofloxacin as compared to those given ciprofloxacin alone ( $Y/2jJ$ , 2.76 h; AUC,  $3.66 \mu\text{g.h.ml}^{-1}$ ); MRT, 3.55 h;  $V_{d(\text{area})}$ ,  $2.69 \text{ L.kg}^{-1}$ ; F, 33%; CIB,  $2050 \text{ ml.h}^{-1}\text{kg}^{-1}$ ).

**Conclusion:** The results tend to suggest that co-administration of probenecid may have some favourable effect on clinically important pharmacokinetic variables of ciprofloxacin.

**OP-116****PHARMAKOKINETICS OF SINGLE DOSE OF 200 mg OF ORAL NEVIRAPINE SUSPENSION IN HIV-1 INFECTED MOTHERS FOR PREVENTION OF VERTICAL TRANSMISSION IN MUMBAI.**

Thakur PA, Dalvi SS, Gogtay NJ, More BD, Gupta AH, Nandanwar YS, Kshirsagar NA.

Dept. of Clinical Pharmacology, Seth GS medical college and KEM Hospital, Parel, Mumabi - 400012.

**Objective:** To study pharmacokinetics of single dose of 200 mg oral Nevirapine suspension in HIV-1 infected mothers for prevention of vertical transmission in Mumbai.

**Methods:** Protocol was approved by institutional Ethics Committee and written informed consent was taken from all participating mothers who were screened during antenatal visits and selected as per the inclusion and exclusion criteria. At the onset of the labour, 200 mg single dose of oral Nevirapine suspension was given to the mother and blood samples were collected at specific time intervals from 0 hr (baseline) to 72 hours post drug, also at the time of delivery infant's cord blood was collected. Infant was given single dose of Nevirapine 2-mg/kg dose, within 72 hrs. of birth. Blood samples were analysed by high performance liquid chromatography for Nevirapine levels. For efficacy study, babies will be followed up on quarterly basis up to age of 18 months.

**Results:** A total of 20 patients have been studied so far. Single dose of Nevirapine was well tolerated by mothers and infants, and no adverse events were seen. Cord blood was available in 12 out of 20 infants and Nevirapine levels in all were above 100 ng/ml (10 times the *in vitro* IC<sub>50</sub>), ranging between 237 ng/ml to 1460 ng/ml.  $T_{\text{max}}$  (ranging between 3 hr - 6 hr),  $C_{\text{max}}$  (ranging between 600 ng/ml - 4790 ng/ml), AUC,  $T_{1/2}$  of Nevirapine are comparable with other reported studies.

**Conclusion:** 200 mg oral Nevirapine suspension was shown to achieve adequate plasma levels both in the mother as well as in infant.

OP-117

### DISPOSITION KINETICS OF CIPROFLOXACIN IN GOATS AFTER ITS INTRAVENOUS ADMINISTRATION.

Suresh Babu N, Verma MP, Thaker AM, Bhavsar SK, Patel HB.

Division of Pharmacology, College of Veterinary Science and. A.H., Gujarat Agricultural University, Anand Campus, Anand - 388001.

**Objective:** To determine the serum concentrations and pharmacokinetics of ciprofloxacin in goats after its intravenous administration.

**Methods:** Ciprofloxacin was given intravenously to healthy goats ( $5 \text{ mg.kg}^{-1}$ ) and the blood samples were collected at pre determined time intervals. Concentrations of ciprofloxacin in serum were determined by a reverse phased high performance liquid chromatography method on RP18 column. The gradient mobile phase consisted of buffer and methanol 3:1 V/V. The buffer contained 5.44 grams of potassium dihydrogen phosphate and 4 ml of tetra-n-butyl ammonium hydroxide as an ion pairing agent in one liter of water. The pH of buffer was adjusted to 2.5 by orthophosphoric acid. The flow rate was kept at  $1 \text{ ml.min}^{-1}$  and the UV detector wave length was set to  $280 \text{ }\mu\text{m}$ .

**Results:** Following intravenous administration the serum drug concentrations were  $7.73 \pm 0.18$ ,  $2.34 \pm 0.32$ ,  $1.15 \pm 0.10$ ,  $0.41 \pm 0.02$  and  $0.15 \pm 0.01$  at 0.33, 0.25, 1, 4, 8 h, respectively. Suggested therapeutic concentration of ciprofloxacin in serum ( $\geq 0.12 \text{ }\mu\text{g.ml}^{-1}$ ) persisted upto 8 h. The decline of ciprofloxacin concentration in serum after intravenous administration was best described by a bi-exponential equation and was fit into a two-compartment open model. Pharmacokinetic parameters, distribution half-life ( $t_{1/2\alpha}$ ) elimination half life ( $t_{1/2\beta}$ ) and the mean residence time (MRT) were  $0.08 \pm 0.01$ ,  $1.69 \pm 0.01$  and  $3.40 \pm 0.09$  h, respectively. The drug was widely distributed with apparent volume of distribution ( $V_{d_{\text{area}}}$ ) of  $2.07 \pm 0.20 \text{ L.kg}^{-1}$ . The area under serum concentration-time curve (AUC) and total systemic clearance ( $Cl_{\text{g}}$ ) of ciprofloxacin were  $6.00 \pm 0.26$ , ( $\text{Lg.h.ml}^{-1}$ ) and  $1399 \pm 57 \text{ ml.h}^{-1} \text{ kg}^{-1}$ , respectively.

**Conclusion:** Ciprofloxacin appears to be useful agent for treatment of goat diseases associated with pathogens that are sensitive to the drug.



# ***Scientific Session XIII***

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## **Clinical pharmacology II**

**Date** : 29.11.2002  
**Time** : 1100-1300  
**Venue** : Hall - C

Invited Lecture : Prof. D Sakthisekaran

Oral Presentation : OP 118 - OP 129

Chairpersons : Prof. Meena Srivastava  
Prof. K L Bairy



IL-83

**REHABILITATING ROLE OF ANTIOXIDANTS IN ANTICANCER DRUGS  
INDUCED CYTOTOXICITY.**

**Sakthisekaran D.**

Department of Medical Biochemistry, University of Madras, Taramani Campus,  
Chennai-600113.

Widespread scientific and clinical interest on antioxidants in the prevention and treatment of human diseases gained importance recently. Focus on vitamins like vit C, E, carotenes and micronutrients like selenium revealed their significance in chemotherapy as antioxidants in the prevention and scavenging of free radicals and lipid peroxidation. The rate of DNA damage is a major contributor to the development of common age related cancers. Agents decreasing such DNA damage should delay cancer development. Antioxidants like crocetin, curcumin and sodium selenite proved to be very effective in protecting the cells against free radical mediated damage. These antioxidants also possess anticancer effects and also minimise the side effects induced by the anticancer drugs like cisplatin and adriamycin during chemotherapy. The cytoprotective and the anticancer effects of the antioxidants will be presented.

OP-118

**PATTERNS AND PERCEPTIONS OF COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM) AMONG LEUKEMIA PATIENTS VISITING HAEMATOLOGY CLINIC OF A NORTH INDIAN TERTIARY CARE HOSPITAL.**

**Gupta M, Shafiq N, Kumari S, Pandhi P.**

Department of Pharmacology and Internal Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh - 160012.

**Objective:** The use of CAM cancer treatments is widespread with substantial numbers of patients deserting conventional cancer therapies in favour of unproved methods. The present study tended to discover the prevalence of use of CAM cancer therapies in leukemia patients visiting haematology clinic of a North Indian tertiary care hospital from May 2001 to Oct 2001.

**Methods:** 533 consecutive leukemia patients were interviewed. Information was gathered about patients demographics, types of CAM taken, sequence of seeking CAM and conventional medicine, sources of recommendation, reasons of opting CAM and areas of satisfaction and dissatisfaction associated with the use of CAM. Patients were also asked if they had informed their doctor about CAM use.

**Results:** Prevalence of CAM use in leukemia patients was found to be 56.6%. Ayurveda was the most commonly used CAM (33%). Most of the patients sought conventional medicine first (61%) followed by CAM therapies. 52% of the patients opted for CAM hoping for a miracle cure. 51 % were dissatisfied with these therapies while 33% were satisfied and 16% were neutral. Family members (54.5%) constituted major source of recommendation of CAM therapy. Only 3.8% of the patients had informed their doctors about CAM use.

**Conclusion:** A sizeable percentage of patients receiving conventional treatment for leukemia also use CAM therapies. Clinicians should not under estimate the value of hopeful attitude in their management of leukemia patients and ought to be conversant with popular forms of CAM cancer therapies.

OP-119

**CISPLATIN INDUCED OTOTOXICITY - A PILOT STUDY.**

**Ahmad R, Singhal K.C, Sharma, S.C**

Department of Pharmacology and Otorhinology, J.N. Medical College, A.M.U., Aligarh - 202002.

**Objective:** To study the different types of ototoxicity by cisplatin used in the treatment of head and neck malignancies.

**Method:** 100 patients of various head and neck malignancies with cisplatin therapy were included in the study and evaluated for various manifestations of ototoxicity by detailed questioning and local examination of ear. Type and degree of hearing impairment (H.I.) was confirmed by tuning fork examination and audiometry. A proforma was filled containing demographic details/other drug intake or illness/result of dechallenge and rechallange therapy and causality assessment.

**Result:** 64 out of 100 patients developed ototoxicity of various degree and types. Tinnitus was the commonest (58) manifestation followed by H.I. (24) and vertigo (10). Most of the patients with H.I. or vertigo were having tinnitus in early stage. H.I. was of sensorineural type and initially high frequency loss that subsequently extends to include the speech frequencies in severe cases.

**Conclusion:** Cisplatin causes both cochlear (tinnitus and R.I.) and vestibular (vertigo) toxicity. Cisplatin initially causes high frequency loss, so even a significant hearing loss cannot be detected by patient or even prescribing physician without audiometric evaluation in early stage and a significant damage had already occurred in most of the patients before H.I. becomes apparent.

OP-120

**SUBLINGUAL CETIRIZINE IN ALLERGIC RHINITIS: A DOUBLE BLIND COMPARATIVE STUDY.**

**Shankhe Sheetal**, Langade Deepak, Mhatre Devarsh, Deshpande VY, Dehadry Arun.

Department of Pharmacology & Department of Ear Nose and Throat, Grant Medical College, Mumbai - 400008.

**Objective:** To study the efficacy and onset of action of sublingual & oral cetirizine in allergic rhinitis.

**Methods:** 20 patients of allergic rhinitis attending the ENT OPD were randomly assigned to sublingual (10) or oral (10) cetirizine after obtaining written informed consent. Dummy tablets were used for blinding. Onset of action determined by measuring improvement in overall symptoms on a VAS after the first dose. Rhinorrhoea, nasal irritation, sneezing, post nasal drip and ocular irritation evaluated for a period of 7 days. Both patients and clinician independently opined about the efficacy of study medication on a 4-point scale:

**Results:** Mean onset of action for sublingual tablet was  $49.5 \pm 5.89$  and was  $66.0 \pm 18.97$  minutes for oral tablet, the difference being significant ( $p = 0.049$ , 't' test). Improvement in rhinorrhoea, nasal irritation, sneezing, post nasal drip and ocular irritation was comparable in the two groups. 3 patients in both the groups reported mild sedation during study period. There was no significant difference between two groups in patients and clinicians global assessment about the study medication.

**Conclusion:** Sublingual cetirizine provides faster symptom control in patients of allergic rhinitis and the overall efficacy is similar to oral administration.

OP-121

**GENETIC POLYMORPHISM OF CYP2C9 IN TAMIL NADU POPULATION.**

**Vasu S**, Adithan C, Shashindran CH, Gerard Nathalie\*, Krishnamoorthy R\*.  
Department of Pharmacology, JIPMER, Pondicherry - 605006 and \*INSERM U458, Hopital Robert Debre, Paris, France.

**Objective:** To identify the prevalence CYP2C9\*1/\*1, 2C9\*1/\*2, 2C9\*1/\*3 and 2C9\*2/\*3 genotypes in the Tamil Nadu population.

**Methods:** The study was conducted on 114 unrelated healthy human volunteers. Ten ml of blood was collected from each volunteer. DNA was extracted from the blood samples and was analyzed by the PCR protocol. The PCR product was digested with Nci, Kpn and Ava II enzymes by incubating at 3°C for overnight. The size of each digested product was determined electrophoretically using polyacrylamide gel. Bands were visualized by staining with ethidium bromide. The genotype of the subject was identified based on the size of DNA fragments.

**Results:** In this study the prevalence of 2C9\*1/\*1, 2C9\*1/\*2, 2C9\*1/\*3 and 2C9\*2/\*3 genotypes were identified to be 83, 5, 11 and 1 percent respectively. The distribution of CYP2C9\*1, CYP2C9\*2 and CYP2C9\*3 alleles were found to be 91, 3 and 6 percent respectively.

**Conclusion:** The prevalence of wild allele (CYP2C9\*1) in the Tamil Nadu population was identified to be 91 %. This is more than that of in the Caucasian population (81 %) but less than that of Oriental population (97 %). The prevalence of mutant alleles, CYP2C9\*2 (3 %) and CYP2C9\*3 (6 %) in Tamil Nadu population is lower than that of the Caucasian population (10 and 8.5 % respectively), but higher than that of the Oriental population (0 and 2 % respectively).



OP-122

### GENETIC POLYMORPHISM OF GLUTATHIONE S - TRANSFERASE IN TAMIL NADU POPULATION.

Naveen AT, Adithan C, Shashindran CR, Gerard Nathalie\*, Krishnamoorthy R\*. Department of Pharmacology, JIPMER. Pondicherry, and \*INSERM U458, Hopital Robert Debre, Paris, France.

**Objective:** To assess the distribution of the GSTM1 and GSTT1 null genotypes in Tamil Nadu population.

**Methods:** Leukocyte DNA was extracted from whole blood collected from healthy volunteers. DNA samples were amplified by PCR using primers simultaneously for GSTM1, GSTT1 and albumin (positive control). The PCR products were resolved using gel electrophoresis. GSTM1 and GSTT1 fragments were visualized as bands under UV light. The polymorphism was detected based on the fragments produced.

**Results:** We observed frequencies for null genotypes of GSTT1 and GSTM1 as 12.0% and 17% respectively. The double null genotype for both GSTM1 and GSTT1 was found in 9.0% of individuals studied. The observed allele frequency for GSTM1, GSTT1, GSTM1\*0 and GSTT1\*0 was 37.3%, 39.5%, 12.7% and 10.5% respectively.

**Conclusion:** The frequency of the GSTT1 and GSTM1 null genotype was identified in Tamil Nadu population. The double null genotype frequency was much higher in Tamil population (9%) when compared to Kerala population (0%) and also higher than that of Caucasians (7.5%) and African Americans (3.9%).

OP-123

### PLASMA VALPROATE MONITORING IN EPILEPTIC PATIENTS - A 2 YEAR EXPERIENCE.

Mhatre RB, Dalvi SS, Gogtay NJ, Ravat S, Kshirsagar NA. Dept. of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Parel, Mumbai - 400012.

**Objectives:** To evaluate the utility of plasma valproate monitoring in management of epileptic patients.

**Methods:** A retrospective analysis of 92 epileptic patients with 197 drug concentration measurements referred to clinical pharmacology therapeutic drug monitoring out patient department during the period April 1999 to May 2001 was conducted. Patients with age ranging from 1.5 yrs - 46 yrs receiving valproate monotherapy as well as polytherapy were analyzed from TDM OPD cards. Plasma levels from patients with more than one drug concentration measurement were evaluated for efficacy (50% reduction in seizure) and toxicity. Patients were excluded if history of noncompliance and steady state was not reached.

**Results:** Among 92 patients 16 (17.39%) had levels above the therapeutic range i.e ATR (50 - 100 µg/ml), 55 (59.78%) had within the therapeutic range i.e., TR and the remaining 21 (22.83%) had below therapeutic range i.e BTR. Seizure control was achieved in 4 (25%) patients with levels ATR, 32 (58.18%) with TR and 9 (42.86%) with BTR. Comparison of difference in the response between the TR group and ATR group showed that the difference was statistically significant ( $p < 0.05$ ), While the difference between the TR and BTR group was not statistically significant. 18/92 (0.195%) patients presented with signs and symptom of toxicity out of which 11 of them had levels in TR.

**Conclusion:** In this study patients who had levels in TR (49.54 - 100.14 µg/ml) achieved better seizure control than other groups and the range is in keeping with the conventional therapeutic range. Monitoring of valproate levels is helpful to keep a check on the compliance and toxicity and also to help the patient to achieve better seizure control.

OP -124

**BIODISTRIBUTION AND TOXICITY STUDIES WITH AEROSOLIZED LIPOSOMAL (L-Rif), PLAIN RIFAMPICIN (p-Rif) AND ORAL PLAIN RIFAMPICIN.**

**Kirodian BG**, Mhatre RB, Kshirsagar NA.

Dept. of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Parel, Mumbai - 400012.

**Objective:** To study the biodistribution and toxic effects of aerosolized liposomal Rifampicin (L-Rif), plain Rifampicin (pRif) and oral plain Rif in the tissues of mice.

**Methods:** Standard treatment of pulmonary Tuberculosis involves daily administration of 2 or more drugs for a period of 6 months or longer. However there are some disadvantages of oral drugs such as metabolic degradation and dilution of drugs before reaching their target site and toxicity. Non-compliance of patients leads to failure of therapy and development of multi drug resistant (MDR) strains. Liposome is a targeted drug delivery system. Rif entrapped in liposomes can be effectively delivered to the infection site minimizing hepatotoxicity. Sterile pyrogen free L-Rif conforming to quality control criteria was used for the study. Mice were exposed to 1 h aerosols of L-Rif and pRif and oral 10mg/kg dose of pRif. Estimation of Rif levels in lung, liver, kidney, spleen and blood was done using HPLC. Male and female mice were exposed to different time periods of aerosolized L-Rif, pRif and varying doses of oral pRif. The tissues were studied histopathologically and liver enzymes estimated.

**Results:** The concentration of Rif in lung after 1 h exposure of L-Rif aerosol was found to be higher as compared to inhaled or oral pRif. No changes evident of toxicity with aerosolized L-Rif were observed. Toxic changes were observed with inhaled and oral pRif.

**Discussion:** Aerosolized L-Rif can be used in the treatment of Tuberculosis where in the patient compliance can be improved owing to shortened duration of treatment and thereby reducing the emergence of MDR Tuberculosis. Studies on efficacy of aerosolized L-Rif in mouse model of Tuberculosis are in process.

OP-125

**ORAL ANTACID AND LIGNOCAIN IN RELIEVING ACUTE SYMPTOMS OF GASTRITIS, IN HUMAN VOLUNTEERS.**

**Dudhgaonkar SS**, Hatwar RD, Motghare VM.

Department of Pharmacology, Govt. Medical College, Nagpur - 440009.

**Objective:** To evaluate the efficacy of single dose oral lignocain and antacid, alone or in Combination, was evaluated in acute symptoms of gastritis in human volunteers.

**Methods:** OPD patients with symptoms of acute gastritis were randomly allocated to group 1, 2 and 3 (n = 40 per group). The groups were matched for age, sex and prior antigestritis treatments. Group 1 received 30 ml of antacid. Group 2 received 20 ml of 2 % lignocain (300 mg ) and Group 3 received 30 ml antacid and lignocain, as a single therapy. The study was patient blind and with written consent. All patients were asked to record pain score prior to and 30 min after respective treatments, on an 11 cm linear analog scale.

**Results:** Pain scores prior to treatment were  $6.1 \pm 5.5$  cm,  $6.4 \pm 12.8$  cm, and  $6.7 \pm 2.7$  cm in Gr 1, Gr 2 and Gr 3 respectively, while pain score after the treatments were  $1.2 \pm 2.6$  cm,  $0.9 \pm 2.9$  cm and  $4.0 \pm 3.4$  cm ( $p < 0.0001$ ) respectively. Two patients in Gr 3 reported constipation.

**Conclusion:** The combination of antacid and lignocain provide significantly greater pain relief than either antacid or lignocain, in patients with symptoms of acute gastritis.

OP-126

**A PROSPECTIVE STUDY TO EVALUATE THE EFFICACY OF 45 mg PRIMAQUINE AS A GAMETOCYTOCIDAL AGENT IN ADULT PATIENTS OF FALCIPARUM MALARIA.**

**Kamtekar KD, Gogtay NJ, Das SS, Karnard D, Kadam VS, Desai SA, Kshirsagar NA.**

Dept. of Clinical Pharmacology and Medicine, Seth .G.S Medical College and Hospital, Parel, Mumbai-400 012.

**Objective:** This study was carried out to assess the efficacy of single dose of 45 mg Primaquine as a gametocytocidal agent in falciparum malaria in adults in Mumbai.

**Methods:** The protocol for the study was approved by the ethics committee and written, informed consent was obtained from all subjects. Inclusion for the study was presence of gametocytes  $>55 \mu\text{l}$  within the first 72 hours. Patients were open randomized to 4 groups. Group A = uncomplicated falciparum malaria not treated with primaquine; Group B = uncomplicated falciparum malaria treated with primaquine; Group C = complicated falciparum malaria treated with Quinine or Quinine + Doxycycline without primaquine; Group D = complicated falciparum malaria treated with Quinine or Quinine + Doxycycline and primaquine. Patients were followed for gametocytaemia and exflagellation (to confirm viability) on DB, D15, D22, and D29.

**Results:** Only patients sensitive to schizontocidal drugs were analyzed. On day 29, 6/22 (27.27%) in A versus 1/24 (4.16%) in B group showed persistence of gametocytes ( $p < 0.05$ ). Similarly, 7/22 (31.81 %) in C versus 2/21 (9.52%) in D group showed gametocytaemia on day 15 ( $p < 0.05$ ).

**Conclusion:** The study shows inefficacy of primaquine as a gametocytocidal agent in 29.16 % cases of uncomplicated and 9.52% cases of complicated malaria and suggests a need to review the current dose schedule.

OP-127

**COMPARATIVE EFFECTS OF ENALAPRIL MALEATE AND LOSARTAN POTASSIUM ON HUMAN SPERM MOTILITY- AN IN VITRO STUDY.**

**Patil ARS, Deshmukh Y, Deshpande V.**

Department of Pharmacology, Topiwala National Medical College and Grant Medical College, Mumbai.

**Objectives:** To study and compare the effects of Enalapril maleate and Losartan potassium at different concentrations and time intervals on motility of ejaculated human spermatozoa.

**Methods:** The effect of the study drugs was evaluated on the motility of human spermatozoa in vitro in 30 healthy and normal male volunteers from patients attending out patients department for the treatment of infertility. Spermatozoal motility of the semen samples collected at the departmental laboratory was studied by microscopy (WHO manual) with 5 mM, 10 mM and 20 mM of the two study drugs on addition and at the end of 10, 30 & 60 minutes.

**Results:** All concentrations except 5 mM of Enalapril maleate and Losartan potassium inhibited the sperm motility significantly ( $p < 0.05$ ), 20 mM having a greater effect than 10 mM. 10 mM and 20 mM of Enalapril maleate caused more significant decrease ( $p < 0.05$ ) in sperm motility than Losartan potassium.

**Conclusion:** Enalapril maleate and Losartan potassium both have an inhibitory effect on the sperm motility, that of Enalapril maleate being faster and to a greater extent as compared to Losartan potassium.

OP -128

**EFFECTS OF TERFENADINE AND FEXOFENADINE ON ELECTRICAL AND CHEMICAL INDUCED SEIZURES.**

**Sangha RB**, Namrata Misra, Sheethal DU, Shilin Giri, Sridhar SB, Akhila J Shetty Gopala Krishna HN, Pai MRSM.

Department of Pharmacology, Kasturba Medical College, Mangalore - 576119.

**Objective:** To study the effects of terfenadine and fexofenadine on electrical and chemical induced seizures in mice.

**Methods:** Inbred albino mice weighing between 25-30 g were selected and divided into groups, each containing six animals. The standard drug sodium valproate and test drugs terfenadine and fexofenadine were suspended in 1 % gum acacia solution. Vehicle and drugs were administered intraperitoneally, forty five minutes prior to the exposure of animals to either maximal electrical shock (MES) or pentylenetetrazol (PTZ) administration.

**Results:** In MES seizure, terfenadine dose relatedly increased the duration of hind limb extension and with the highest dose tested it reduced the F/E ratio. On the other hand, fexofenadine did not alter any of the parameters studied significantly. In PTZ test, terfenadine in the highest dose tested reduced the time for onset of convulsion. Fexofenadine had no significant effect both on the onset and duration of convulsion with all the doses tested.

**Conclusion:** Present study indicates that terfenadine has proconvulsant activity and fexofenadine has no significant effect on seizures.

OP -129

**SCREENING FOR ANTI-ANXIETY ACTIVITY OF NR-ANX-C IN RATS.**

**Gopala Krishna HN**, Sangha RB, Namrata Misra and MRSM Pai.

Department of Pharmacology, Kasturba Medical College, Mangalore- 576119.

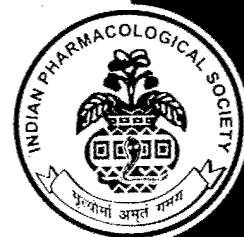
**Objective:** To study the effects of NR-ANX-C on anxiety-like behaviour in rats.

**Methods:** Male Wistar albino rats weighing between 180-200 g were selected and divided into six groups, each consisting of six to eight animals. The standard drug diazepam, and the test drug, NR-ANX-C, a herbal product supplied by Natural Remedies, Bangalore were suspended in 1% gum acacia solution. The vehicle (1 ml/kg;), diazepam (0.5 and 1 mg/kg) and NR-ANX-C (5, 10 and 20 mg/kg) were administered orally one hour prior to the exposure to experimental model-Elevated Plus Maze.

**Results:** The test compound NR-ANX-C in the doses tested increased the number of entries, time spent and the number of rears in open arms and also the percentile ratio of open arm to total arm entries. These behavioural changes are comparable to that produced by diazepam.

**Conclusion:** NR-ANX-C produced the behavioural disinhibition similar to the standard anxiolytic diazepam in the elevated plus maze model indicating that the test drug may have anxiolytic-like activity.





# PRIZE SESSIONS



XXXV ANNUAL CONFERENCE OF  
INDIAN PHARMACOLOGICAL SOCIETY

**IPS**  
2002



# **Prof. G Achari Prize**

**(PZA1 - PZA7)**

**Date** : 28-11-2002  
**Time** : 0900 - 1045  
**Venue** : Hall - A

**Chairpersons** : Prof. YK Gupta  
Prof. R Raveendran





PZA-1

**EFFECT OF *WITHANIA SOMNIFERA* ROOT EXTRACT ON HALOPERIDOL-INDUCED OROFACIAL DYSKINESIA: POSSIBLE MECHANISMS OF ACTION**

**Naidu PS**, Amanpreet Singh and Kulkarni SK.

Pharmacology Division, University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh - 160014.

**Objectives:** Haloperidol (HP) is a widely used neuroleptic drug for the treatment of acute and chronic psychosis. Use of atypical antipsychotics such as haloperidol is limited by their tendency to produce a range of extrapyramidal movement disorders such as Parkinsonism, akathisia, dystonia and tardive dyskinesia. Tardive dyskinesia (TD) which occurs in 20-40% of the patient population undergoing chronic neuroleptic therapy, is characterized by repetitive involuntary movements, usually involving mouth, face and tongue, and some times limb and trunk musculature. The present study investigated the role of oxidative stress in the pathophysiology of haloperidol-induced orofacial dyskinesia and evaluated the beneficial effect of *Withania somnifera* (Ws) root extract in the amelioration of haloperidol-induced vacuous chewing movements in the rat model for tardive dyskinesia.

**Methods:** Rats were treated chronically (for 21 days) with haloperidol (1 mg/kg, s.c.) for the induction of orofacial dyskinesia. The neuroleptic-induced vacuous chewing movements, viz., vertical jaw movements, tongue protrusions were counted during a 5-min observation period.

**Results:** Rats chronically treated with haloperidol (1.0 mg/kg i.p.) significantly developed vacuous chewing movements and tongue protrusions. Ws root extract dose dependently (100-300 mg/kg) reduced the haloperidol-induced vacuous chewing movements and tongue protrusions. Biochemical analysis revealed that chronic haloperidol treatment significantly reduced lipid peroxidation and decreased the glutathione (GSH) levels in the forebrains of rats. Chronic haloperidol treated rats showed decreased forebrain levels of antioxidant defense enzymes, superoxide dismutase (SOD) and catalase. Co-administration of Ws extract (100-300 mg/kg) significantly reduced the haloperidol-induced lipid peroxidation. Co-administration of Ws extract (100-300 mg/kg) significantly reversed the haloperidol-induced decrease in forebrain SOD and catalase levels in rats. However Co-administration of Ws root extract had no significant effect on the haloperidol-induced decrease in the forebrain GSH levels.

**Conclusion:** The major findings of the present study strongly suggested that oxidative stress might play a significant role in haloperidol-induced orofacial dyskinesia and *Withania somnifera* could be effective in preventing the development of neuroleptic-induced extrapyramidal side effects.

**ANTICONVULSANT ACTIVITY OF FLUOXETINE: INVOLVEMENT OF GABERGIC NEUROACTIVE STEROID ALLOPREGNANOLONE.**

Mittal Nutan S, Ugale Rajesh R, Hirani Khemraj, Chopde Chandrabhan T.  
Pharmacology Division, University Department of Pharmaceutical Sciences,  
Nagpur University Campus, Nagpur - 440010.

**Objective:** Modulation of the neuroactive steroid site on the GABA<sub>A</sub> receptor complex steroid is an important new direction for pharmaceutical interventions in epilepsy. Fluoxetine is known to selectively increase the brain concentration of allopregnanolone. However, there exists several controversies about pharmacological spectrum and mechanism(s) of action of fluoxetine. We report here the result of the investigation into the role of neuroactive steroid allopregnanolone in the anticonvulsant action of fluoxetine.

**Methods:** Anticonvulsant effect of fluoxetine or allopregnanolone was studied in male swiss mice (20 -25 g) against pentylentetrazol and picrotoxin induced seizures. Different groups of animals were either treated with neurosteroid biosynthesis inhibitors like 5 $\alpha$ -reductase inhibitor, finasteride; 3 $\beta$ -hydroxysteroid dehydrogenase inhibitor, trilostane; 3 $\alpha$ -hydroxysteroid oxidoreductase inhibitor, indomethacin or neurosteroidogenic drugs like 11 $\beta$ -hydroxylase inhibitor, metyrapone; neurosteroid precursor, progesterone or GABA<sub>A</sub> agonist muscimol before administration of fluoxetine. Group of isolated mice were treated with different doses of fluoxetine to study its effect on decreased endogenous allopregnanolone content. Further, pseudopregnant female rats were challenged with fluoxetine in model of perimenstrual catamania epilepsy to assess its effect on PTZ induced seizures.

**Results:** Fluoxetine protected the animals from PTZ or Picrotoxin induced convulsions. Furthermore, concomitant administration of subeffective doses of fluoxetine and drugs which advance neurosteroidogenesis like metyrapone, allopregnanolone, progesterone or GABA<sub>A</sub> agonist muscimol enhanced the anticonvulsant effect of fluoxetine. On the other hand, pretreatment with neurosteroid biosynthesis inhibitors, GABA antagonist bicuculline or negative modulators of GABA<sub>A</sub> receptor DHEA SO<sub>4</sub> blocked the anticonvulsant effect of fluoxetine. A higher dose of fluoxetine was required in protracted socially isolated mice to reverse the convulsions compared to group housed animals. Fluoxetine increased sensitivity in protecting against PTZ-induced convulsions in pseudopregnant rats unlike in pseudopregnant withdrawn group.

**Conclusions:** Present study provide evidences for vital role of allopregnanolone in the anticonvulsant action of fluoxetine and supports the hypothesis that modulation of GABA<sub>A</sub> receptors by neurosteroid mediates the anticonvulsant action of fluoxetine. The identifications of the neurosteroid intermediaries involved in fluoxetine action may lead to important advances in the field and the development of novel therapeutics in seizure-related disorders.

PZA-3

### EVALUATION OF ANALGESIC AND ANTIPYRETIC POTENTIAL OF THE ROOTS OF *RUMEX NEPALENSIS* SPRENG.

Datta L<sup>1</sup>, Chattopadhyay S<sup>1</sup>, Das J<sup>1</sup>, Saha BP<sup>2</sup>, Pal M<sup>2</sup>.

<sup>1</sup>Department of Pharmacology, University College of Medicine, Kolkata - 700020 and <sup>2</sup>Department of Pharmaceutical Technology, Jadavpur University, Kolkata - 700032.

**Objectives:** The roots of *Rumex nepalensis* Spreng. is claimed to be used in traditional medicine as an analgesic and antipyretic agent. The present study was undertaken to evaluate these potentials of the methanol extract of *Rumex nepalensis* (MERN) and thereby to substantiate the folklore claim.

**Methods:** MERN was evaluated for its analgesic activity in the following animal models: (a) central analgesic activity - tail flick method, tail immersion method, and hot plate method, (b) peripheral analgesic activity - acetic acid-induced writhing test. The antipyretic activity of MERN was evaluated by the study of the effect on yeast induced pyrexia. MERN was used in two doses of 200 and 400 mg/kg, intraperitoneally for the analgesic evaluation, and orally for the antipyretic evaluation. The standard drug used for the central analgesic activity was pethidin (12 mg/kg), for the peripheral analgesic activity was aspirin (100 mg/kg) and for the antipyretic activity was paracetamol (150 mg/kg). A control group was maintained in all the models.

**Results:** In the tail flick, hot plate and tail immersion methods, both the doses of MERN increased significantly in a dose dependent manner the paw licking/jumping time as well as the time for withdrawal of tail. In acetic acid induced writhing test the MERN significantly decreased the number of writhing responses to  $33.17 \pm 1.51$  and  $25.0 \pm 1.15$  respectively in 15 minutes from  $41.5 \pm 1.43$  in control group and thus exhibited significant analgesic activity. The subcutaneous injection of yeast suspension markedly elevated the rectal temperature after 19 hour of administration. MERN treatment at doses of 200 and 400 mg/kg body weight decreased the rectal temperature of rats in a dose dependent manner. The antipyretic effect started within 1 hour of extract administration and the effect was maintained for 4 hours after its administration.

**Conclusions:** The findings suggest that the MERN possess significant analgesic and antipyretic activity

PZA-4

**LEAD INDUCED OXIDATIVE STRESS AND ITS RESPONSE TO COMBINED ADMINISTRATION OF AN ANTIOXIDANT AND SUCCIMER IN RATS.**

**Ashish Mehta**, Manisha Pande, Flora SJS.

Division of Pharmacology and Toxicology, Defence Research and Development Establishment, Jhansi Road, Gwalior - 474002.

**Objective:** The study describes the therapeutic potential of two differently acting antioxidants, melatonin or N-acetylcysteine, when given in combination with DMSA in providing clinical recoveries in altered biochemical variables indicating oxidative insult and in the depletion of lead concentration from blood and soft tissues.

**Methods:** Male albino rats were exposed to 0.1% lead acetate in drinking water for 3 months. Lead exposed animals were treated with a single daily oral dose of 50 mg/kg, meso 2,3-dimercaptosuccinic acid (DMSA; succimer) either individually or in combination with melatonin or N-acetylcysteine (NAC) (50 mg/kg, i.p.) for 5 consecutive days.

**Results:** Administration of melatonin and NAC seems to decrease the susceptibility of antioxidant defence system towards lead. However, no marked effects on MDA and GSH were noticed on melatonin administration either alone or in combination suggesting, its effects as a free radical scavenger depend on tissue which has been examined and the dose applied. NAC a thiol containing antioxidant has been used under several clinical conditions with few adverse side effects has a high toxicity threshold and its wide therapeutic window enhances its utility. The antioxidant action is believed to be due to its direct interaction with reactive oxygen species (ROS) or its ability to stimulate Glutathione (GSH) synthesis. In this study, NAC supplementation resulted in an increased GSH/GSSG ratio and decreased MDA activity suggesting marked protection. The results also support the involvement of ROS in lead toxicity and a possible beneficial role for NAC in therapeutic implications of lead poisoning.

**Conclusion:** The present study implies that a thiol containing antioxidant is capable of mitigating lead induced oxidative stress. While a combined administration of antioxidant and thiol chelators provide a better choice for treating plumbism.

PZA-5

**FENOLDOPAM TREATMENT IMPROVES PERIPHERAL INSULIN SENSITIVITY AND RENAL FUNCTION IN STZ - INDUCED TYPE 2 DIABETIC RATS.**

**Dhananjay N, Umrani, Ramesh K. Goyal.**

Department of Pharmacology, L. M. College of Pharmacy, Ahmedabad - 380009.

**Objective:** To study the effect of six-week treatment with D<sub>1</sub> receptor agonist fenoldopam (1 mg/kg, ip, daily) on glucose, lipid and renal profile in streptozotocin (STZ) - induced (non-insulin dependent) type 2 diabetic rats.

**Methods:** Sprague Dawley rats were made diabetic by injecting STZ (90 mg/kg, ip) to 2 day old pups. At the age of 10 weeks, animals were screened for blood glucose and divided into control and treated groups. Treated animals received fenoldopam (1 mg/kg, ip, daily) for six weeks.

**Results:** STZ produced hyperglycemia, hyperinsulinemia, hyperlipidemia, hypertension, increase in serum urea and creatinine by the time animals were 10 week old. Treatment with fenoldopam significantly decreased serum glucose, insulin, cholesterol, triglyceride, urea, creatinine, and blood pressure. During oral glucose tolerance test (OGTT), diabetic rats showed increase in AUC<sub>glucose</sub> and AUC<sub>insulin</sub>. Fenoldopam significantly decreased AUC<sub>glucose</sub> in diabetic rats. Diabetic rats showed lower insulin sensitivity index (K<sub>ITT</sub>) that was significantly increased by treatment with fenoldopam in diabetic rats. Diabetic rats showed decrease in urinary sodium. Fenoldopam treatment significantly increased urine output as well as urinary sodium indicating reduced sodium retention.

**Conclusion:** Our data indicates fenoldopam treatment improves peripheral insulin sensitivity and renal function in STZ-induced type 2 diabetic rats.

PZA-6

**EFFECT OF FOLATE TREATMENT ON HOMOCYSTEINEMIA IN CARDIAC PATIENTS: A PROSPECTIVE STUDY.**

**Mehta KN**, Parikh KH<sup>\*</sup>, Chag MC<sup>\*</sup>, Shah UG<sup>\*</sup>, Baxi HA<sup>\*</sup>, Chandarana AH<sup>\*</sup>, Naik AM<sup>\*</sup> Goyal RK.

Department of Pharmacology, L.M. College of Pharmacy, PO Box No 4011, Navrangpura, Ahmedabad - 380009, and <sup>\*</sup>Department of Cardiology, Sterling Hospital, Gurukul, Ahmedabad - 380052.

**Objectives:** To establish the normal levels of serum Hcy in patients with CAD among Indians, to study the influence of diabetes mellitus on Hcy levels in patients with or without CAD, to study the effect of folate therapy on serum Hcy levels.

**Methods:** The study was a random, non-blind clinical trial carried out in 84 angiographically documented CAD patients and 40 controls (angiographically proved normal or TMT negative). Biochemical analysis of serum glucose, serum insulin, serum hcy, serum lipid profile and serum CRP were conducted in their serum samples. A treatment with folic acid (5 mg/day) for 3 months was given to patients with hyperhomocysteinemia and the Hcy levels were analyzed again after the treatment.

**Results:** The mean plasma Hcy level in normal Indian population was found to be  $17.85 \pm 1.4$   $\mu\text{mole/L}$ , which was significantly lower than those in CAD patients ( $24.69 \pm 2.8$   $\mu\text{mole/L}$ ). The levels were higher in non-diabetic patients ( $30.33 \pm 3.9$   $\mu\text{mole/L}$ ) as compared to non-diabetic controls ( $18.18 \pm 1.6$   $\mu\text{mole/L}$ ) as well as diabetic patients ( $14.53 \pm 1.43$   $\mu\text{mole/L}$ ), irrespective of presence of hypertension. No correlation was found between t-hcy levels and serum glucose, insulin, triglycerides, VLDL, LDL, HDL, cholesterol or CRP levels. A significant negative correlation was found between t-Hcy levels and age of the patients. The Hcy levels were highest in young age group of patients (30-40 years) ( $49 \pm 7.8$   $\mu\text{mole/L}$ ). There was a significant reduction in t-Hcy levels after the folate treatment in mild and moderate hyperhomocysteinemic patients but the reduction in severe hyperhomocysteinemic patients was not significant.

**Conclusions:** Hyperhomocysteinemia appears to be an independent risk factor for CAD in younger patients. Patients with diabetes mellitus show low levels of t-Hcy irrespective of presence of cardiac disease that might interfere the correlation of hyperhomocysteinemia and CAD. Folate decreases the t-Hcy levels in patients with mild and moderate hyperhomocysteinemia and hence can be used in treatment of hyperhomocysteinemia.

PZA-7

## EFFECTS OF SIMULTANEOUS PRENATAL EXPOSURE TO ANILOFOS AND ARSENIC IN RATS.

Agarwal M, Wangikar PB, Sarkar SN, Rao GS, Dinesh Kumar, Dwivedi P, Malik JK.

Division of Pharmacology and Toxicology, \*Division of Pathology, Indian Veterinary Research Institute, Izatnagar - 243122.

**Objective:** Arsenic, a metal of great toxicological importance, is believed to be a mammalian teratogen. Anilofos, an organophosphorus herbicide, is a new entrant in the field of herbicide. It is selectively used to control annual grassy weeds and sedges in transplanted rice. There is a possibility that effects produced by either of these environmental contaminants could be modified when animals are exposed to these chemicals concurrently. It seems, no report is available on teratogenic potential of the combined administration of anilofos and arsenic. We, therefore, planned to study the foetotoxic effects induced by the interaction between these metal and herbicide.

**Methods:** Thirty pregnant rats were randomly divided into 3 groups of 10 animals each. A - control (olive oil), B - arsenic (1 mg/kg/day) and C - anilofos and arsenic (100 and 1 mg/kg/day). These agents were administered by gastric intubation from gestation day 6 to 15 and animals were sacrificed on day 20 of gestation.

**Results:** None of the treatments caused mortality of dams. Incidence of resorption was significantly higher in group C ( $8.2 \pm 0.66$ ) compared to group A ( $0.1 \pm 0.10$ ) and group B ( $1.4 \pm 0.93$ ). Foetal body weight ( $0.39 \pm 0.26$  g) and crown-rump length ( $0.50 \pm 0.33$  cm) were significantly decreased in group C compared to group A ( $4.12 \pm 0.08$  g and  $3.74 \pm 0.10$  cm) and group B ( $3.24 \pm 0.55$  g and  $2.83 \pm 0.48$  cm). Gross foetal examination in groups A and B revealed no abnormalities, while the combination group showed protrusion of tongue, wrist drop, curling of tail, mid facial cleft, bulging of head, micromelia and anophthalmia.

**Conclusion:** Simultaneous prenatal oral exposure to arsenic and anilofos could induce more developmental toxicity in rats than arsenic given alone.





# **Prof. U K Sheth Prize**

(PZU 1 - PZU 7)

**Date** : 28-11-2002  
**Time** : 0900 - 1045  
**Venue** : Hall - B

**Chairpersons** : Prof. V N Puri  
Prof. Hardayal Singh



**PZU-1****PRESCRIBING TRENDS OF ORAL HYPOGLYCEMIC AGENTS IN NORTH INDIA, THEIR COSTS AND IMPACT ON QUALITY OF LIFE.**

**Geeta Sharma**, Gurpreet Kaur Randhawa, Jatinder Singh, Jagjit Singh, Pankaj Goyal, Kumra RK.

Dept. Pharmacology, Govt Medical College, Amritsar-143001.

**Objective:** To assess the prescribing trends of ORAs, their influence on glycemic control, QOL and cost and to analyze the relationship between HbA1c and QOL.

**Methods:** An open, prospective study was conducted in the Diabetic Clinic in a prominent tertiary care hospital of North India. Prescribing trend of ORAs was studied (213 prescriptions) and the patients were assessed for glycemic control and change in QOL over 90 days.

**Results:** In the study, life style modifications were advocated to 2% of the patients; SUs alone were prescribed to 41%, SUs and Metformin to 45%, Metformin alone to 9% of the patients. Glycemic improvement was significantly better with combinations than with SUs and Metformin alone. No direct, statistically significant correlation was found between HbA1c and QOL among various ORAs. Glibenclamide alone and the combination of Glibenclamide+Metformin emerged as the most cost effective agents among the ORAs.

**Conclusion:** The use of newer and more expensive ORAs in a significant number of patients indicates a trend that ignores the economics of drug prescribing. There is a need for modifying prescribing behavior for the treatment of NIDDM in poor countries like India.

**PZU-2****SURGICAL PROPHYLAXIS VERSES THERAPEUTIC USE OF ANTIBACTERIALS IN A TERTIARY CARE TEACHING HOSPITAL.**

**Goyal RR**, Desai SV.

Department of Pharmacology, Pramukhswami Medical Collge, Karamsad - 388325.

**Objectives:** To review the appropriateness of surgical prophylaxis and compare it with therapeutic use in a teaching hospital. At the same time to generate baseline data and compare it with national and international studies.

**Methods:** A prospective cross sectional study spread over 3 months in the wards of general surgery, gynecology - obstetrics and ENT departments. Emphasis was laid on: 1. Type of antibacterial use whether prophylactic or therapeutic, 2. Duration of treatment in relation to type of antibacterial use, 3. Cost analysis of drug treatment and 4. Outcome of patient management.

**Results:** Inappropriate use of antibacterials was 93.5% when they were used for prophylaxis whereas it was 25% when they were used for therapeutic purpose. Out of total cost spent on drug therapy 85.7% was spent on antibacterials alone. In gynecology - obstetrics department 83% of total cost spent on prophylactic use of antibacterials was inappropriate. In ENT and surgery departments it was 33% and 32.5% respectively. In all, the inappropriate prophylactic use caused 47.15 % of extra expenditure to the patients.

**Conclusion:** There is a strong need for antibiotic policy and awareness about antibiotic prescription guidelines. There should be clear distinction of where the prophylaxis ends and therapeutic approach should be started.

PZU-3

## EVALUATION OF TAMSULOSIN IN THE TREATMENT OF SYMPTOMATIC BENIGN PROSTATIC HYPERPLASIA.

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**Objectives:** Benign Prostatic Hyperplasia is a common disease in older men, characterized by an enlargement of the prostate gland, leading to bladder outlet obstruction, disturbed urinary outflow and retention. The currently available alpha 1 antagonists have potential to cause adverse effects when used in patients with BPH. Recent studies have revealed three subtypes of alpha 1 adrenoceptors namely alpha 1A, 1B, 1D. The alpha 1A subtype is present in the greatest concentration in the human prostate. Tamsulosin, a sulfamoylphenethylamine, is a new selective alpha 1A antagonist. The objective of this study is to evaluate the safety and efficacy of Tamsulosin in patients with symptomatic BPH.

**Methods:** 24 male patients in the age group of 40-80 years with BPH, having IPSS of more than 10 and maximum urinary flow rate of 5-15 ml/s for a voided volume of more than 150 ml and PSA between 4-10 were enrolled with prior written informed consent. This was an open-label noncomparative study initiated after requisite permission from Institute Ethics Committee. A detailed history, through clinical examination and necessary investigations were performed at the baseline. Patients received SR capsules of Tamsulosin (0.4 mg) once daily for 8 weeks. Efficacy parameters were assessment of total IPSS, obstructive and irritative symptom scores, uroflowmetry measurements and Residual urine. Students paired t test; nonparametric Wilcoxon's test and Fishers were used to measure changes in the uroflowmetry measurements, IPSS scores and adverse events as compared to the baseline respectively.

**Results:** The main and total IPSS scores, obstructive and irritative symptom scores improved with Tamsulosin ( $p < 0.001$ ). The main change in the Qmax and Qavg. At the end of 8 weeks were 3.8 and 2.7 ml/s respectively. The maximum voided volume increased and post-void residual volume decreased significantly. There were no significant changes in the blood pressure and pulse rate.

**Conclusion:** Tamsulosin is new prostate specific postsynaptic alpha 1A subtype receptor antagonist. In the present study, it showed a fast onset of action and the improvement in IPSS scores and urodynamic parameters were maintained through out the treatment period. The drug was very well tolerated without significant changes in the pulse rate and blood pressure. In conclusion, Tamsulosin is an effective and safe drug for the symptomatic management of benign prostatic hyperplasia.

**PZU-4****PHARMACOKINETIC STUDY OF BOSWELLIA SERRATA EXTRACT.****Sunita Sharma<sup>A</sup>, Vijay Thawani<sup>B</sup>, Lal Hingorani<sup>C</sup>, Meena Shrivastava<sup>A</sup>, Bhate VR<sup>D</sup>, Rajkumar Khiyani<sup>E</sup>.**<sup>A</sup>Dept. of Pharmacology, Indira Gandhi Medical College, Nagpur - 440018;<sup>B</sup>Govt. Medical College, Nagpur; <sup>C</sup>Pharmanza (India), Nagpur; <sup>D</sup>Indtech Analytical, Nagpur; <sup>E</sup>Govt. Ayurvedic College, Nagpur.

**Introduction:** *Boswellia serrata*, known as Gajabhakshya in Sanskrit, has been used in traditional medicine for treatment of inflammatory diseases since antiquity. However, human kinetic studies are lacking for this substance, and therefore to better elucidate its effects in humans, as well as to determine optimal dosing following kinetic study was planned.

**Methods:** Twelve healthy adult men volunteers were given capsule Wok Vel<sup>TM</sup> containing 333 mg of *Boswellia Serrata* Extract, orally, after seven days washout period. Venous blood samples were drawn through indwelling canula from each volunteer prior to drug administration and at 30, 60, 120, 150, 180, 210, 240, 300, 360, 480, 600, 720, 840 minutes after drug administration. Plasma obtained after centrifuge was analyzed to measure concentration of 11-keto-13-boswellic acid by HPLC. Various kinetic parameters were then calculated from the plasma concentrations.

**Results:** The results are expressed as mean  $\pm$  Standard Error of Mean. The peak plasma levels ( $128.17 \pm 8.68$ ) of BSE were reached at  $4.5 \pm 0.55$  h. The concentration declined with a mean elimination half life of  $5.97 \pm 0.95$  h. The apparent volume of distribution averaged  $142.87 \pm 22.78$  L and the plasma clearance was  $296.10 \pm 24.09$  ml/min. The AUC<sub>0- $\infty$</sub>  was  $1286.46 \pm 93.80$  ng/ml h.

**Conclusion:** Elimination half life of nearly six hours suggests that the drug needs to be given orally at the interval of six hours. The plasma concentration will attain the steady state after approximately 30 hours. BSE is a safe drug and well tolerated on oral administration. No adverse effects were seen with this drug when administered as single dose in 333 mg.

**PZU-5****MULTIPLE DROP INSTILLATION OF CENTBUCRIDINE COMPARED WITH LIGNOCAINE - A RANDOMIZED DOUBLE MASKED CONTROLLED CLINICAL TRIAL.****Biswas NR<sup>\*</sup>, Ghose S, Das GK, Sethi A, Verma B, Jhingan S<sup>\*</sup>, Pandey RM<sup>\*\*</sup>.**

Rajendra Prasad Centre for Ophthalmic Sciences, AIIMS, New Delhi - 110029;

<sup>\*</sup>Ocular Pharmacology, Dr. R.P. Centre for Ophthalmic Sciences, AIIMS;<sup>\*\*</sup>Biostatistics, AIIMS, New Delhi - 110029.

**Objective:** In the first phase of this study, the ocular surface anaesthetic and analgesic efficacies of 0.5% and 1% centbucridine in saline were compared with 4% lignocaine drops in normal healthy volunteers divided into three equal groups. In the second phase, 1% topical centbucridine was evaluated for minor nonintraocular ophthalmic procedures, along with 0.5% centbucridine injectable (in water for injection) in some eyes whenever necessary.

**Methods:** In phase 1 in 99 healthy eyes, keeping one eye as an unanaesthetised control, one drop of any of the above three coded drugs was instilled in the contralateral eye, followed by one more drop of the same drug in the same eye after 3 minutes. The onset of anaesthesia, achievement and duration of peak activity, total duration of action, the depth of analgesia, and period of burning sensation were all noted in this double-masked RCT with the various drug solutions. In 185 more eyes of phase 2, centbucridine 1% was instilled twice at an interval of 3 minutes, and for infiltration anaesthesia 0.5% centbucridine 1 to 2 ml was also injected in 23 eyes depending upon the requirements of the individual case.

**Results:** Total peak duration of anaesthetic as well as analgesic effects in the 99 healthy normal eyes in phase 1 were found to be the highest with centbucridine 1%, followed by 4% lignocaine and 0.5% centbucridine respectively. In the other 185 eyes of phase 2, all the minor ocular procedures were carried out easily under surface (and if necessary as in 23 eyes infiltration) anaesthesia with centbucridine, without any significant local or systemic side effects even with injectable centbucridine.

**Conclusions:** Centbucridine may be used as a viable and effective alternative local anaesthetic agent for ophthalmic procedures requiring surface or infiltration anaesthesia, with a wide margin of safety.

PZU-6

## CLINICAL PHARMACOKINETICS OF CENTCHROMAN.

Gupta RC, Lal J.

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Centchroman (Ormeloxifene) is a non-steroidal, once a week oral contraceptive developed by this Institute. Its clinical pharmacokinetic parameters were generated following single and multiple doses in normal and nursing females. A simulation and measurement approach study was carried out to generate an alternate dosing schedule using pharmacokinetic data from 30 mg single dose. The new regimen is economic, reduces the unnecessary exposure of the body to centchroman. Also it is user friendly and efficacious. Drug-drug interaction with commonly used antibiotic, tetracycline, which is known to interfere with steroidal oral contraceptives, was also studied. Centchroman pharmacokinetics follows a two-compartment model with half-life of approximately 7 days. It is widely distributed and repeated doses have no effect on the rate of absorption, distribution or elimination. Centchroman is a weak base and is excreted into breast milk. The maximum infant dose received via breast milk is less than 2% of the maternal dose per day and is unlikely to have any physiological consequences to breastfed infants. No adjustment in dosage regimen for nursing women is needed inspite of its excretion into breast milk. Both the pharmacokinetic and clinical evaluation studies showed that the new dosage regimen yielded clinically effective steady-state concentrations of 30 mg once weekly dosing immediately after a loading dose of a single 60 mg. Also, the distinct disadvantages encountered in the currently practiced dosage regimen (30 mg twice-a-week for 12 weeks followed by 30 mg once weekly) are minimized in this proposed schedule. Moreover, the new dosage regimen is devoid of unnecessary additional exposure to centchroman and was more convenient and efficacious. The clinical trials supported this regimen as it provided better pregnancy protection (Pearl index: 1.34) than the current regimen on the market. Tetracycline co-administration with and without lactic acid bacillus spores affected the absorption of centchroman. The other pharmacokinetic parameters were not affected with either of the treatments. Thus, tetracycline is unlikely to alter the contraceptive efficacy of centchroman as compared to steroidal oral contraceptives.

PZU-7

### DOSE RELATED DISULFIRAM ETHANOL REACTION

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Department of Pharmacology, Department of Psychiatry, JJM Medical College, Davangere - 577004.

**Objective:** To study the nature and severity of disulfiram ethanol reaction (DER).

**Methods:** Sixty seven male alcoholics otherwise healthy were randomly allocated into low and high dose disulfiram group. Patients assigned to high dose group were given a cumulative dose of 5 gm spread over 4 days. The low dose group were given a cumulative dose of 2.5 gm spread over 7 days. On fourth day in high and seventh day in low dose patients ethanol challenge was carried out. Details of DER were recorded on a checklist. Severity of DER was measured on a self devised rating scale.

**Results:** Common DER manifestations were flushing, drowsiness, vomiting, fall in blood pressure and raise in pulse rate, in addition both group had some more additional symptoms. Majority of patients developed severe DER in both groups and most of them recovered in about 6 to 8 hr. Severity of DER was independent of duration of alcohol use, dose of disulfiram and BMI.

**Conclusion:** The nature and severity of disulfiram ethanol reaction determines strength of negative reinforcement in deterrent therapy of alcohol dependence. Knowledge of nature of DER helps in following clinical progress of a patient, planning treatment of a patient ingesting alcohol while on disulfiram and in determining maintenance dose.



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# ***Gufic Prize***

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**(PZG 1 - PZG 19)**

**Date** : 28-11-2002  
**Time** : 1600 - 1830  
**Venue** : Hall - A

**Chairpersons** : Prof. S B Deshpande  
Prof. B Gitanjali



**PZG-1**

**SCREENING OF ANTI-INFLAMMATORY ACTIVITY OF A NEW COMPOUND JC-02.**

**Pardeshi Milind L, Radha Yegnanarayan.**

Department of Pharmacology, B.J. Medical College, Pune - 411001.

**Objective:** To study the anti-inflammatory activity of a new compound JC-02 on carrageenan induced hind paw oedema in rats.

**Methods:** Oedema was produced by injecting 0.1 ml of 1% carrageenan into the plantar surface of the right hind paw with the left hind paw acting as control. Paw volume was measured under light ether anaesthesia by plethysmography at baseline and 1 hr, 2.5 hrs and 4 hrs after injection of drug. Difference in the paw volume was taken as the indicator of the oedema of inflammation. The compound JC-02 was given by oral and intra peritoneal route at various dose levels (62.5, 125, 250, and 500 mg/kg). The anti inflammatory activity of JC-02 was compared with ibuprofen and diclofenac sodium.

**Results:** Compound JC-02 showed maximum inhibition of oedema with 125 and 250 mg/kg dose. The higher dose (500 mg/kg) produced more oedema suggesting proinflammatory action. There was no significant decrease in oedema with lower dose (62.5 mg/kg).

**Conclusion:** Compound JC-02 possesses anti-inflammatory effect in acute inflammation comparable to standard drugs.

**PZG-2**

**SCREENING FOR ANALGESIC ACTIVITY OF A NEW DRUG, JC-01.**

**Hiray RS, Radha Yegnanarayan.**

Department of Pharmacology, B.J. Medical College, Pune - 411 001.

**Objectives:** To screen for analgesic activity of the plant based product against different types of painful stimuli. To evaluate and compare the analgesic activity of the test drug (JC-01) with the standard analgesic drugs.

**Methods:** In radiant heat method and tail pinch method the test drug in doses of 250 mg/kg, 500 mg/kg, 750 mg/kg was compared with saline control and standard pentazocine. In writhing method, the test drug in the doses as above was compared with saline control and standard diclofenac.

**Results:** In radiant heat method, JC-01 raises the pain threshold in dose - dependent manner, the maximum effect is seen with 750 mg/kg. Analgesic effect with 250 mg/kg lasted up to 1 hr. with 750 mg/kg lasted up to 2hrs. With 500 mg/kg it lasted up to 2 hrs. with lesser intensity than 750 mg/kg.

**Conclusion:** The present study indicates that the plant based product, JC-01 has analgesic activity against different types of painful stimuli and it is as effective as standard drug in intensity and duration.

PZG-3

**EVALUATION OF ANTI-INFLAMMATORY PROFILE OF AN INDIGENOUS PLANT 'X01' IN EXPERIMENTAL ANIMAL MODELS.**

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**Objectives:** The medicinal plant 'X01' is widely used in indigenous system of medicine for treatment of inflammatory conditions like conjunctivitis and placation of boils. It was therefore decided to assess the anti-inflammatory profile of this plant.

**Methods:** 'X01' seed in powdered form was evaluated for anti-inflammatory activity using two acute inflammation models (carrageenan and dextran induced rat paw edema) and a subacute model (cotton pellet induced granuloma in rats). Indomethacin was used as standard drug in the dose of 10 mg/kg orally in these models. 'X01' was used in two doses 100 mg/kg and 200 mg/kg by oral route. In the acute model, the standard and the test drugs were given 30 minutes before administration of the phlogistic agent. In the subacute model, test drug was dosed daily for 5 days starting from the day of pellet insertion.

**Results:** Both doses of 'X01' exhibited significant ( $p < 0.001$ ) anti-inflammatory activity in acute inflammation models. At higher dose 'X01' exhibited maximal inhibition of 62.74% of paw volume in the carrageenan model while the standard showed inhibition of 66.67%, three hours after treatment. In the dextran induced paw edema model, higher dose of 'X01' suppressed edema by 45.71 %, while indomethacin produced inhibition of 62.85%. In the subacute inflammation model, 'X01' produced significant ( $p < 0.01$ ) reduction of granuloma weight. The higher dose of 'X01' exhibited 40.58% reduction whereas indomethacin caused 54.87% reduction.

**Conclusions:** 'X01' has significant anti-inflammatory activity in standard acute and subacute animal models of inflammation. Further exploration of its anti-inflammatory activity is necessary .

PZG-4

#### ANTINOCICEPTIVE ACTIVITY OF *VITEX NEGUNDO* LINN LEAF EXTRACT.

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Department of Pharmacology, M.G. Institute of Medical Sciences,  
Sewagram - 442102.

**Objective:** To evaluate the analgesic activity and mechanism of action of *Vitex negundo* leaf extract in rats and mice.

**Methods:** Tail flick technique in rats and acetic acid induced writhing test in mice were employed to study the antinociceptive activity of *Vitex negundo*. The mechanism of analgesic action was explored by observing its effect on interaction with naloxone in tail flick method, oxytocin induced contractions in rat uterus and oxidative stress. *Vitex negundo* extract was administered orally in graded doses (100, 250, 500 mg.kg<sup>-1</sup>) and the effect was compared with meperidine (40 mg.kg<sup>-1</sup> sc) in tail flick method and aspirin (50 mg.kg<sup>-1</sup> po) in writhing test as standard controls respectively.

**Results:** The test drug showed significant analgesic activity in dose dependent manner in both the experimental models. The Subtherapeutic dose (5 mg.kg<sup>-1</sup> po) of *Vitex negundo* potentiated the analgesic activity of meperidine (4 mg.kg<sup>-1</sup> sc) and aspirin (25 mg.kg<sup>-1</sup> po). Naloxone (1 mg.kg<sup>-1</sup> sc) did not show any reversal of analgesia of test drug in comparison to analgesia produced by it. *Vitex negundo* inhibited oxytocin induced contractions of rat uterus and plasma MDA level significantly.

**Conclusion:** These observations suggest that *Vitex negundo* possesses analgesic activity which appears to be due to prostaglandin inhibition and reduction of oxidative stress. Since naloxone did not reverse the analgesia induced by test drug, it indicates that central analgesic action is not mediated through opioid receptors.

PZG-5

### ANTI-ULCER ACTIVITY OF *CHLOROPHYTUM ARUNDINACEUM* IN RATS.

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<sup>1</sup>Dept. of Pharmacology, L.M. College of Pharmacy, Ahmedabad - 380009.

<sup>2</sup>Dept. of Pharmacognosy, L.M. College of Pharmacy, Ahmedabad - 380009.

**Objective:** The present study was designed to investigate the effect of 50% alcoholic extract of *Chlorophytum anandinaceum* (CAE) against ethanol- induced, pylorus ligation-induced and cold stress-induced experimental gastric ulcers.

**Methods:** The CAE was given in the dose of 100 mg/kg, p.o. in all the models and results of those were compared with that of Omeprazole 20 mg/kg, p.o. (reference standard) treated animals. Ulcer-index was a common evaluating parameter in all the models. In pylorus ligation model, acid secretory parameters (total acid, pepsin activity and total acid output) and mucoprotective parameters (total carbohydrate, total protein and mucin activity) were studied. In addition, lipid-peroxidation and anti-oxidant activity were specifically studied in cold stress-induced gastric ulcer model. Effects on vascular permeability as well as gastric emptying were also studied.

**Results:** The CAE has shown significant protection in gastric ulceration as evident from reduction ( $p < 0.05$ ) in ulcer-index in all the models. It has shown increased mucin activity in pylorus ligation model. In stress model, it showed antioxidant activity in gastric mucosal homogenate where it reversed the increase in lipid peroxidation and decreased the catalase levels, however, it did not produce any change in SOD levels, which was significantly increased by stress. Further it has shown significant reduction in vascular permeability and gastric emptying rate.

**Conclusions:** Hence, it is suggested that *Chlorophytum arundinaceum* possesses significant anti-ulcer activity. The mechanism of its activity is associated with strengthening of gastric mucosal barrier.

PZG-6

### SAFETY EVALUATION OF *EUPHORBIA HIRTA* IN RATS.

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Department of Pharmacology and Toxicology, College of Veterinary Sciences, Pantnagar - 263145.

**Objective:** Safety evaluation of aqueous extract of *Euphorbia hirta* in rats.

**Methods:** Male albino rats weighing 170-200 grams were used in this study. The dried aqueous extract of *Euphorbia hirta* was administered as an oral aqueous suspension in four equal divided doses appropriately spaced within the first 24 hours to attain a total dose of 15 gm/kg body weight. Cage side observations, biochemical and hematological parameters, histopathology, organ-body weight ratio and urine analysis were carried out to evaluate the effect of acute dose of *Euphorbia hirta*.

**Result:** In this study none of the animals died in 7 days experimental period. Body weight and feed intake of rats; hematological and biochemical parameters; organ-body weight ratio and urine analysis were within the normal range in both the treated and control on the 7th day. Histopathological examination of the target organs showed no evidence of lesions attributing to drug toxicity.

**Conclusion:** As the aqueous extract of *Euphorbia hirta* neither killed any animal nor showed any adverse side effect it can be concluded that the drug is practically non-toxic and hence safe.

**PZG-7****WITHANIA SOMNIFERA AS AN EFFECTIVE ADJUNCT TO L-DOPA IN DRUG- INDUCED CATATONIA IN RATS.**

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Pharmacology Division, University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh - 160014.

**Objectives:** L-dopa plus carbidopa treatment continues to be the first line therapy for Parkinson's disease, even though the therapy is not free from unwanted effects. To avoid such problems with L-dopa therapy, several agents have been tried as an adjunct therapy to L-dopa in Parkinson's disease. Therefore the present study was carried to investigate the role of *Withania somnifera* as an effective adjunct to L-dopa in drug-induced catatonia in rats.

**Methods:** Catatonia in rats was induced by administration of perphenazine (5 mg/kg i.p.) and reserpine (1.5 mg/kg i.p.) +AMPT (200 mg/kg) respectively. Catatonia in animals was assessed by bar test.

**Results:** *W. somnifera* dose dependently (25-100 mg/kg, p.o.) reversed perphenazine- as well as reserpine- induced catatonia in bar test. *W. somnifera* (50 mg/kg) when combined with an ineffective dose of L-dopa (100 mg/kg p.o.) plus carbidopa (10 mg/kg p.o.) potentiated the anti-catatonic effect of the latter combination. Pretreatment with a central COMT inhibitor OR-486 (3 mg/kg, p.o.) or a MAO-B inhibitor selegline (2.5 mg/kg, i.p.) also potentiated the actions of a sub-effective dose of *W. somnifera* (50 mg/kg, p.o.) against perphenazine and reserpine -induced catatonia. On the other hand adenosine (100 mg/kg i.p.), which is known to decrease the release of catecholamines through an action on pre-synaptic A<sub>1</sub> receptors, completely blocked the protective effect of *W. somnifera* against perphenazine-induced catatonia.

**Conclusions:** *W. somnifera* not only potentiated the anticatatonic actions of an ineffective dose of L-dopa but also OR-486 (a centrally acting COMT inhibitor and selegline (selective MAO-B inhibitor), thereby suggesting its role as an effective adjunct in L-dopa therapy in Parkinson's disease.

**PZG-8****EFFECT OF SIX WEEK TREATMENT OF ZINGIBER OFFICINALE IN STREPTOZOTOCIN INDUCED NIDDM RATS.**

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Department of Pharmacology, L. M. College of Pharmacy, Ahmedabad - 380 009.

**Objective:** To study the effect of fresh juice of *Zingiber officinale* in neonatal non insulin dependent diabetes mellitus (NIDDM) rats.

**Methods:** Sprague Dawley rats were made diabetic by injecting STZ (90 mg/kg, i.p.) to 2 day old pups. At the age of 12 weeks, animals were screened for blood glucose and divided into control and treated groups. Treated animals received fresh juice of *Zingiber officinale* (4 ml/kg, orally, daily) for six weeks.

**Results:** Fasting glucose and insulin levels in NIDDM rats were significantly ( $P < 0.05$ ) higher than control rats. Treatment with *Z. officinale* produced a significant increase in insulin levels and no change in fasting glucose levels in NIDDM rats. Results of oral glucose tolerance test (OGTT) showed that treatment with *Z. officinale* significantly decreased AUC glucose and increased AUC insulin values ( $P < 0.05$ ) in NIDDM rats. Treatment with *Z. officinale* also caused decrease in cholesterol and triglyceride levels and lowered blood pressure in NIDDM rats that were found to be higher in NIDDM rats as compared to control rats.

**Conclusion:** Our data suggest a potential antidiabetic activity of the fresh juice of *Z. officinale* in type II model of diabetic rats.



PZG-9

**THE IMMUNOMODULATORY ACTIVITY OF *HYPTIS SUAVEOLENS* (L.) POIT. FAMILY- LAMINACEAE.**

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<sup>1</sup>Institute of Pharmacy, Jiwaji University, Gwalior - 474011.

<sup>2</sup>Department of Pharmaceutical Sciences Nagpur University, Nagpur - 440010.

**Objective:** The *Hyptis suaveolens* (L.) Poit, family Laminaceae has been traditionally indicated in various infectious diseases. The volatile oil present in the leaves of this plant possesses anti-bacterial and anti-fungal activities. The plant *Ocimum sanctum* which is a well known immunomodulator also belongs to the same family. The immunomodulatory activity of several other plants has been attributed to their antioxidant property by TBARS method.

**Methods:** The dried alcoholic (90%) extract of the aerial parts of *H. suaveolens* was suspended in gum acacia for oral administration (75 mg/kg for 28 days) to the group of mice which has received pyrogallol (50 mg/kg for 05 days) in order to induce immunosuppression and oxidative stress. The humoral immune response (HIR) and cell mediated immune response (CMIR) were assessed by conventional immunological methods in *H. suaveolens* treated mice, who were antigenically challenged with SRBC. At the end of the experiment, the lipid peroxidation levels in blood were assessed by TBARS method. The control group received only the vehicle.

**Results:** Pyrogallol administration produces significant suppression of antibody formation and also prevented the % increase in paw volume, indicating the immuno suppressant effect of pyrogallol. It also produces extensive oxidative stress as indicated by the marked rise in lipid peroxidation levels. The treatment of pyrogallol treated mice with alcoholic extract of *H. suaveolens* not only prevented the pyrogallol induced suppression of HIR and CMIR, but also prevented the rise in lipid peroxidase enzyme (LPO) levels.

**Conclusion:** The alcoholic extract of *H. suaveolens* possesses immunomodulation as well as antioxidant property, and the latter property may be responsible for the amelioration of the immunosuppressant effect of pyrogallol. This activity substantiates its traditional anti-infective claim.

PZG-10

**ANALGESIC EFFECT OF *AZADIRACHTA INDICA* (NEEM) SEED OIL ON ALBINO RATS.**

**Sanjay Kumar, Rath Bandana, Patnaik Shantilata, Mukherjee Dipali:**  
Dept of Pharmacology, VSS Medical College, Burla - 768017.

**Objectives:** *Azadirachta indica* (Neem), an indigenous plant is reported to have antidiabetic, anti-inflammatory antifungal and several other medicinal properties. The present work is undertaken to study the analgesic activity of *A. indica* seed oil (Neem Seed Oil) on Albino rats.

**Methods:** Neem Seed Oil was obtained in pure form, from the Indian Herbs research supply Company Limited, Saharanpur, U.P. The analgesic activity was tested by the tail flick method using the analgesiometer (Techno). Neem seed oil in the doses of 0.25, 0.5, 1 and 2 ml/kg body weight was given intraperitoneally to different groups of rats. Tail flick latency was measured in seconds before and after the drug injection. Results were compared with Morphine and statistically analysed.

**Results:** Neem Seed Oil showed significant effect in the doses of 1 and 2 ml/kg body weight.

**Conclusion:** The study concludes that the Neem Seed Oil has dose dependent analgesic activity.

PZG-11

**EFFECT OF HD-LL 2 ON THE LIPID PROFILE OF NORMAL AND HYPERCHOLESTEROLEMIC RABBITS.**

**Ayar upendra, Balaraman R.**

Pharmacy Department, Faculty of Technology and Engineering, Kalabhavan,  
The M.S. University of Baroda, Baroda - 390001.

**Objective:** The herbal formulation HD-LL 2 was tested for its effect on the lipid profile in normal (normolipidemic) and hypercholesterolemic (hyperlipidaemic) rabbits.

**Method:** The rabbits were fed with HD-LL 2 (500 mg/kg, po) or Lovastatin (6 mg /kg, po) along with standard laboratory diet for 60 days. Control rabbits received SLD and suspending agent in saline. The levels of various lipids in serum, tissues and feces were estimated.

**Results:** HD-LL 2 and Lovastatin were found to lower the serum cholesterol, phospholipids, triglyceride, VLDL, LDL, Cholesterol:phospholipids ratio and atherogenic index, whereas they decreased the HDL level as compared to the normal control group. HD-LL 2 or Lovastatin treated normal rabbits also showed decreased in lipid profile of liver but did not produce significant reduction in heart or aorta as compared to the corresponding control group. The study of HD-LL2 in hypercholesterolemic (hyperlipidaemic) rabbits is under progress, and it will be discussed at the time of presentation.

**Conclusion:** The part of this study demonstrates that HD-LL 2 possesses anti-hyperlipidaemic activity.

PZG-12

**METABOLIC AND HISTOPATHOLOGICAL EFFECTS OF STREPTOZOTOCIN INDUCED DIABETES IN RATS: INFLUENCE OF MULBERRY (*MORUS INDICA L.*) LEAVES.**

**Andallu B, Varadacharyulu NC\***

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\*Department of Biochemistry, Sri Krishnadevaraya University, Anantapur - 515001.

**Objective:** To evaluate antihyperglycemic, hypolipidemic and pancreatic islet  $\beta$  cell protective effect of mulberry (*Morus indica L.*) leaves based on biochemical and histopathological observations.

**Method:** Streptozotocin (55 mg/kg bw.) induced male wistar diabetic rats were treated with mulberry leaves (25% in the diet) for 8 weeks; blood glucose, lipid profile and serum insulin (RIA) levels were determined; the pancreas was processed for histological examination and compared with that of controls.

**Results:** Streptozotocin caused significant elevation of fasting glucose, total cholesterol, triglycerides, phospholipids, free fatty acids, LDL and VLDL cholesterol and a significant decrease in serum insulin, HDL cholesterol levels and fecal bile acids in albino rats. Feeding of mulberry leaves corrected these changes. This was also reflected in the histological alterations in the islet  $\beta$  cells of Langerhans.

**Conclusion:** This investigation provides strong evidence of antidiabetic activity of mulberry leaves which protected pancreatic islet  $\beta$  cells in STZ- diabetic rats.

**PZG-13**

**A COMPARATIVE STUDY OF HERBAL TREATMENT VERSUS MODERN MEDICINE TREATMENT IN FISSURE-IN-ANO.**

**Langade D, Balakrishna S, Bakshi G, Sankhe S, Lad S, Davar G, Deshpande V.**

Department of Pharmacology and Department of Surgery, Grant Medical College, Mumbai - 400008.

**Objectives:** To study the efficacy and safety of herbal treatment in comparison with modern medicine treatment in patients of fissure-in-ano.

**Methods:** 37 patients of anal fissure attending the surgery OPD were randomly assigned to receive either study (19) medication (*Vaipani fissilax* ointment and *Vaipani relax* oral powder) or control (18) medication (lignocaine jelly application and oral liquid paraffin) after obtaining written informed consent. Clinical evaluation done by proctoscopy and PR examination for constipation, pruritus, bleeding PR, discharge and anal spasm for a period of 4 weeks. Pain was evaluated on VAS. Effect on renal and hepatic functions was evaluated by laboratory investigations.

**Results:** 17 patients from study group and 14 from control group completed the study. Pain scores significantly reduced on days 7, 14 and 28 with both the treatments ( $p < 0.05$ ) and the reduction was similar in both groups ( $p > 0.05$ ). Improvement in constipation bleeding and anal spasm was comparable in the two groups. Healing was similar in both groups at the end of study. 3 patients in the study and 2 in the control reported pruritus after starting medication. Hepatic and renal functions were unaltered in all patients.

**Conclusion:** *Vaipani fissilax* ointment and *Vaipani relax* powder provided significant symptomatic improvement in patients of fissure-in-ano which is comparable to the standard therapy.

**PZG-14**

**ACUTE OCULAR TOXICOLOGICAL STUDY OF NEEM OIL: A NEW HERBAL DRUG WITH ANTIMICROBIAL POTENTIAL.**

**Ghose S, Biswas NR, Nayak N, Ravi AK, Saxena M\*, Srivastava A\*.**

Dr. Rajendra Prasad Centre for Ophthalmic Sciences, AIIMS, and \*Department of Surgery, All India Institute of Medical Sciences, New Delhi - 110029.

**Objective:** An acute toxicological study on the eye with Neem\* Oil, an ayurvedic (herbal) drug from natural sources, was undertaken.

**Methods:** Keeping the left eye as control, a standardised drop of the crude undiluted oil was instilled into the conjunctival sac of the right eye of each of 10 healthy New Zealand albino rabbits of either sex weighing approximately 2.5kg each, as 1 drop hourly for 9 hours for 4 consecutive days, followed by 1 drop QID for 10 days. Before the study and as well as before the first instillation on each day, these eyes were examined with a direct ophthalmoscope and the reactions were graded according to a modified system for grading eye irritation by hazardous substances. The study was conducted according to the rules set forth in ARVO resolution on animal experimentations. The eye lid, conjunctiva, cornea, anterior chamber, iris and pupil were examined grossly as well as by slit lamp biomicroscopy.

**Results and Conclusions:** This acute toxicity study on rabbit eyes showed complete absence of any untoward reactions like lid oedema, conjunctival congestion, chemosis or discharge. The rabbit exhibited no signs of irritation on instillation of the drug. Further studies especially on its role as an antimicrobial agent, are in progress. Trials may then be undertaken on experimental and even in human eyes, both in health and disease.

**PZG-15**

**MODERN APPROACH IN ESTABLISHING TRADITIONAL FORMULATIONS AS POTENTIAL ANTIOXIDANT AGENTS.**

Sanjay Pandita, **Dinesh kumar\***, Neelam, Prasanna Krishna, Rajendera Prasad, Wahab Ur-Rehman\*, Kamala Krishnaswamy.

Food and drug toxicology research centre, National Institute of Nutrition, Jamai Osmania, Hyderabad - 500007; \*Government Nizamia General Hospital, Govt., Unani Medical College, Hyderabad.

**Introduction:** The recent escalation in the chronic diseases over the contagious communicable diseases is an alarming feature. The efforts, are therefore concentrated to evaluate substances having minimum toxic effects and maximum therapeutic efficacy. Indian heritage viz Ayurveda, Siddha, Unani etc., are now recognized as integrated system of medicine by WHO for the treatment and prevention of diseases. Osteoarthritis, described in unani medicine as thahajjar - u/- mafasi/ is common among the various degenerative diseases. The objective of the present study is to evaluate the effect of traditional formulations on osteoarthritis and oxidative stress.

**Methods:** 60 (45-60 yrs) subjects coming to the out patient department of Nizamia Hospital for the treatment of arthritis have been enrolled in the study. The osteoarthritis status was assessed by standard clinical procedure of Algo Function Frequency Index. In addition to the routine laboratory investigations the antioxidant profile was evaluated by Glutathione, Lipid peroxidation and Protein carbonyls activities. The subjects were randomly divided to receive the test formulations viz, (i. *surinjan + bozidan + aswaganda*; ii. *Mundi* - water extract; iii. Paracetamol - as placebo) 0.6.g twice daily for a period of 8 weeks using double blind clinical trial procedures.

**Results:** The traditional preparations have not only indicated to have potential anti-arthritis activity but also reduced oxidative stress (30 - 50%). There were no abnormalities in the routine laboratory investigations with special reference to liver and renal functions.

**Conclusion:** The preparations described in Unani and Ayurveda have demonstrated pharmacodynamic activity along with antioxidant potentials. The study of this nature not only has great relevance in clinical evaluation of pharmacodynamic activity but also in validating the potentiality of traditional medicine that facilitates in patenting.

**PZG-16**

**HEPATOPROTECTIVE ACTIVITIES OF CERTAIN MEDICINAL PLANTS FROM NORTH EAST REGION OF INDIA.**

Jagadeesan V\*, Kotoky J\*\*, Syed Quadri\*, Kamala Krishnaswamy\*.

\*National Institute of Nutrition, (ICMR), Hyderabad - 500007; \*\*Institute of Advanced Study in Science and Technology (IASST), Guwahati - 781022.

**Objective:** Certain plants extracts have been traditionally used by the tribals of North East Region for their hepatoprotective properties. In order to validate these observations scientifically, the present collaborative study was undertaken.

**Methods:** Paracetamol-induced liver injury model was adopted for this study. Extracts of *Leucos lewendulaefolia* or *Costos speciosus* plants at different doses were given to drug -administered groups immediately afterwards. Suitable controls were run simultaneously. After 48 hours, animals were sacrificed and biochemical and histological investigations in control, paracetamol fed and paracetamol + herbal extracts fed groups of animals were carried out.

**Results:** (i) There was a significant elevation in liver enzymes, SGOT (AST) and SGPT (ALT) on the administration of paracetamol, which decreased in response to herbal extracts, (ii) both plant extracts showed similar results to administration of different doses, and (iii) histopathology studies of the liver were strongly supportive of biochemical findings.

**Conclusions:** Results suggest that extracts from above herbal plants may be beneficial against liver damage. In order to understand the underlying mechanisms, studies are currently underway on the interrelationship between plant extract constituents and their antioxidant activities.

**PZG-17****ADAPTOGENIC EFFECT OF *BACOPA MONNIERA* (BRAHMI).**

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Division of Pharmacology and \*Toxicology, Central Drug Research Institute, Lucknow - 226001.

**Objectives:** As stress has been linked to many of diseases, searching an effective anti-stress agent (adaptogen) from plants has gained importance. We report the investigations on the adaptogenic property of a standardized extract of *Bacopa monniera* (Brahmi) containing  $55 \pm 5\%$  the major constituent, viz., bacosides at 40 and 80 mg/Kg, p.o. against acute (AS) and chronic stress (CS) models in rats. *Panax ginseng* (100 mg/kg, p.o.) extract was taken as a standard.

**Methods:** Male SD rats, weighing 180 - 200 g were exposed to the immobilization stress for 150 min. once only in AS where as for seven consecutive days in CS with the respective drugs fed 45 minutes prior to stress. Rats were sacrificed immediately after stress and blood was collected. The plasma was separated out for the biochemical estimation using Beckman CX-5 auto-analyzer. Adrenals, spleen and thymus were dissected out for organ weight and stomach for gastric ulcers score.

**Results:** AS exposure significantly increased the ulcer index, adrenal gland weight, plasma glucose, ALT, AST and CK but significantly decreased the spleen weight. Pretreatment with brahmi at 40 mg/kg significantly reduced the AS induced increase in ulcer index, plasma glucose and CK whereas at 80 mg/Kg significantly reversed the AS induced changes on adrenal gland weight, spleen weight, plasma glucose, ALT and AST. *Panax ginseng* significantly reversed the AS induced changes in ulcer index, spleen weight, plasma ALT, AS and CK. CS exposure resulted significant increase in ulcer index, adrenal gland weight, plasma CK and AST with a significant decrease in thymus and spleen weight, plasma triglyceride and cholesterol. Pretreatment with brahmi extract at low dose significantly reversed ulcer index and plasma AST only where as the pretreatment with higher dose significantly reversed CS induced changes in ulcer index, adrenal gland weight, CK, and AST. *Panax ginseng* significantly reversed CS induced increase in ulcer index; adrenal gland weight, CK and AST.

**Conclusions:** On the basis of our results it may be concluded that the standardized extract of brahmi possess a potent adaptogenic activity.

**PZG-18****RANDOMISED, DOUBLE-BLIND, PLACEBO CONTROLLED CROSS-OVER EVALUATION OF ORAL VALERIAN EXTRACT ON PSYCHOMOTOR PERFORMANCE IN HEALTHY HUMAN SUBJECTS.**

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Department of Clinical Pharmacology and Therapeutics, Nizam's Institute of Medical Sciences, Panjagutta, Hyderabad - 500082.

**Objective:** Valerian extract is extensively used as OTC for insomnia with CNS depressant activity (200 - 900 mg dose). The objective is to compare the effect of single oral dose of 200 and 400mg of valerian extract with placebo on psychomotor performance in healthy subjects.

**Methods:** Total 18 healthy male subjects participated after, written informed consent to IEC approved protocol. Each subject randomly received placebo 200 or 400mg valerian extract orally in fasting state, in 3 way crossover design with one week washout period. Cardsorting (CST), six letter cancellation (SLCT), Digit Symbol Substitution (DSST), Critical Flicker Fusion (CFFT), Choice reaction (CRT), tests were performed before and at 1.5, 3, 5 and 8 hr after treatment. Sedation, dryness of mouth (VAS Scale) and any ADR were simultaneously recorded.

**Results:** Placebo, 200mg did not produce any significant effect, while 400 mg valerian extract produced significant change in psychometric performance at 1.5 hours. CST increased from  $37 \pm 1.5$  to  $41.8 \pm 1.3$ secs. Corrected attempted in SLCT decreased from  $62 \pm 2.3$  to  $54 \pm 3$  and in DSST from  $62 \pm 1.6$  to  $55.8 \pm 0.96$  and CEFT by  $3.4 \pm 1.2$ . CRT increased from  $0.17 \pm 0.01$  to  $0.20 \pm 0.01$  msec. The apparent changes noted at 3, 5 and 8 hr were insignificant. Significant sedation and dryness of mouth were observed with 400 mg at 1.5 hrs.

**Conclusion:** Compared to placebo and 200 mg, single administration of 400 mg of valerian extract significantly altered psychomotor function and produced sedation dryness of mouth in healthy subjects.

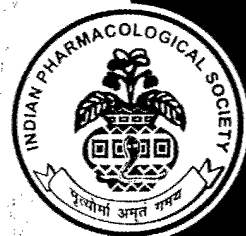
**PZG-19**

**DARL-2, AN EFFECTIVE HERBAL OINTMENT FOR THE TREATMENT OF ECZEMA.**

**Rawat PS, Verma GS, Pandey HK, Veer S, Kumar Narendra.**  
Defence Agricultural Laboratory, Pithoragarh - 262501.

Eczema or atopic dermatitis is an eruption of skin, characterized by pin head sized macules, papules, vesicles accompanied by intense itching followed by blisters formation and lichenization of skin. The aetiology of ailment depends upon various predisposing and determining causes with clinical features being erythematous skin, vesiculation, weeping, crustation, secondary infection, scale formation and lichenization. Allopathic and Indian system of treatments are available but are either effective to particular feature of eczema or have side effects. They have no effect on lichenized stage of eczema. Keeping in view the limitations of existing remedies, attempt was made to formulate a poly component broad spectrum effective herbal ointment which can address all clinical features of eczema. In the product ethanol isolates of nine plants have been taken for formulation which were found non toxic to Wistar rats and Albino rabbits. Clinical trial on volunteers were conducted, in which 3 cases were with lichenized skin, 3 with eczema psoriasis association, 15 cases up to secondary infection and 19 were in primary stage of erythema and papule formation. All these patients recovered within 5 to 60 days depending upon the severity, extent and clinical feature of disease. No side effects and relapse cases were observed.





# **Poster Sessions**

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**XXXV ANNUAL CONFERENCE OF  
INDIAN PHARMACOLOGICAL SOCIETY**

**IPS  
2002**





# **Prof. P C Dandiya Prize**

**(PPZ 1 - PPZ 26)**

**Date** : 28-11-2002  
**Time** : 0900 - 1300  
**Venue** : Training Centre  
**Co-ordinator** : Dr. S Dasgupta



PPZ - 1

**POSSIBLE ROLE OF NITRIC OXIDE IN ISONIAZID-INDUCED NEUROTOXICITY IN MICE.**

**Wardhan Neeta, Vijayan VK, Ray A.**

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Isoniazid (INH) is a potent antitubercular drug with documented neurotoxic and hepatotoxic effects. Involvement of free radicals in INH toxicity is known, and pharmacological and biochemical studies indicate that INH-nitric oxide (NO) interactions are possible. However, the role of NO and NO-related radicals in INH toxicity is not clearly defined. The present study therefore evaluated the possible role of NO in INH induced convulsions in mice. INH (50-200 mg/kg) induced tonic-clonic convulsions and mortality in mice in a dose related manner. Nitric oxide synthase (NOS) inhibitors, L-NAME (10 and 50 mg/kg) and 7-NI (10 and 50 mg/kg), both inhibited INH (200 mg/kg) convulsions and mortality. These anticonvulsant effects were more pronounced when the NOS inhibitors were combined with the free radical scavenger, melatonin. INH (100 mg/kg) also induced convulsions when combined with subthreshold electroshock (ES, 15 mA). L-NAME and 7-NI, both alone and in combination with melatonin, attenuated the convulsiogenic effects of INH + ES. These results are suggestive of the possible involvement of NO and NO-related free radicals in INH induced convulsions.

PPZ - 2

**DRUGS FOR MEDICAL TERMINATION OF PREGNANCY (MTP): CURRENT PRACTICE AND OPINION OF THE ABORTION SERVICE PROVIDERS IN AMRITSAR.**

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**Introduction:** There is scarcity of trained staff and infrastructure for conducting medical termination of pregnancy (MTP) by surgical methods. Various drugs now offer safe and effective alternative for MTP. The objective of this study is to find out the current practice and opinion of Obstetricians and Gynecologists (OBGs) of Amritsar about the drugs as medical option for MTP.

**Methods:** Thirty practising OBGs of Amritsar were interviewed and standardized questionnaire about their opinion about medical options for MTP was filled.

**Results:** 23% OBGs were unaware of the drugs as alternative for MTP. For <9 wk gestation 40 % OBGs used mifepristone and misoprostol for MTP. 58% of these OBGs and 61% of the OBGs not using these drugs doubted their efficacy. 31% OBGs considered it as a cheaper option. 50% used the dose of 200 mg mifepristone. 24% OBGs used misoprostol by oral route. 33% OBGs did curettage for bleeding per vagina even after using drugs.

**Conclusions:** There is lack of awareness amongst OBGs about the availability, dose/route for administration, efficacy and cost-effectiveness of drugs for MTP. The results can be improved by creating awareness. Using mifepristone in 200 mg dose; using misoprostol by intra-vaginal route and by waiting for the outcome, instead of a hurried curettage for bleeding per vagina.

PPZ - 3

### INTERACTION BETWEEN GLIBENCLAMIDE AND NICORANDIL IN CASES OF CHRONIC STABLE ANGINA.

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Department of Pharmacology<sup>1</sup>, Lady Hardinge Medical College, Delhi - 110001.

Department of Pharmacology<sup>2</sup> and Cardiology<sup>3</sup>, S.N. Medical College, Agra.

**Objective:** To study the interaction between Glibenclamide (a k<sup>+</sup> channel blocker) and Nicorandil (a k<sup>+</sup> channel Opener) in cases of chronic stable angina.

**Methods:** Sixty patients 30 - 35 years with chronic stable angina were divided into three groups of twenty each. Group I was of twenty non diabetic patients who received nicorandil only. Group II consisted of borderline NIDDM patients controlled by diet and given nicorandil. Group III, consisted of NIDDM patients receiving glibenclamide and nicorandil. Patients were kept on nicorandil 10 mg twice a day and glibenclamide; depending on patients blood sugar in the dose of 5 - 10 mg once/twice a day. Computerized treadmill exercise test was done before therapy and after six weeks of therapy with nicorandil.

**Results:** TMTs conducted on day zero and after six weeks of therapy showed that change in improvement in heart rate response was not significant; similar response was shown for blood pressure change in all three groups. The improvement seen in load attainment (METS), duration of exercise was maximum in Group I and II (p < 0.02) followed by Group III (p < 0.05). The ST segment depression on exercise showed a significant improvement in Group I followed by Group II (p < 0.02) and in patients of Group III (p < 0.05) was less comparatively. Number of patients who had to take additional nitrate support in a day was significantly reduced in all three groups. In ST segment response, downsloping of ST segment reduced in significant number of patients in all groups but less improvement was there in Group III (p < 0.05) as compared to Groups I and II (p < 0.02). Angina during exercise significantly decreased in all three groups.

**Conclusion:** Antianginal benefits of nicorandil are maximum in non diabetic patients or in patients taking only nicorandil. Glibenclamide does not abolish the actions of nicorandil but merely reduces the action marginally.

PPZ - 4

### NEUROPROTECTIVE EFFECT OF POLY (ADP-RIBOSE) POLYMERASE INHIBITION IN FOCAL CEREBRAL ISCHEMIA IN RATS.

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Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education and Research (NIPER), S.A.S. Nagar (Mohali) 160062.

**Objective:** Cell death after cerebral ischemia triggers cascade of events leading to excessive release of excitatory amino acids, calcium overload, generation of free radicals and over activation of poly (ADP-ribose) polymerase (PARP). In the present study neuroprotective effect of PARP inhibitors was investigated in middle cerebral artery occlusion (MCAO) induced focal ischemia in rat.

**Methods:** Focal ischemia was induced by MCAO for 2 hours and reperfusion for 22 hours. Neurological damage was assessed by infarct volume and neurological deficit measurement. Brain was isolated after 22 hours of reperfusion and 6 coronal section of frozen brain were prepared and stained with 2% 2,3, 5-triphenyltetrazolium chloride. Image analysis software was used for measurement of infarct volume from slices. Neurological deficit was measured after 22 hours of reperfusion. Effect of 1, 5-isoquinolindiol (ISO, 0.05 and 0.1 mg/kg, i.p), a PARP inhibitor was studied in focal ischemia. Effect of other PARP inhibitor 5(6H)-Phenathridindione is in progress.

**Results:** ISO at 0.05 mg/kg and 0.1 mg/kg i.p significantly decreased the percentage infarction to 16% (p < 0.05) and 12% (p < 0.01) respectively, as compared to vehicle treated group (30%). Similar protection was observed in neurological deficit 47% (p < 0.05) at 0.05 mg/kg and 53% (p < 0.05) at 0.1 mg/kg as compared to vehicle treated.

**Conclusion:** Inhibition of PARP was neuroprotective in focal cerebral ischemia.

**PPZ - 5****EFFECT OF TRANS RESVERATROL ON ICV STREPTOZOTOCIN MODEL OF ALZHEIMER'S TYPE DEMENTIA IN RATS.**

Sharma M, Gupta YK.

Neuropharmacology Lab, Department of Pharmacology, All India Institute of Medical Sciences, New Delhi-110029.

We have recently shown free radical generation is associated with cognitive impairment in intracerebroventricular (ICV) streptozotocin (STZ) model of sporadic dementia of Alzheimer's type in rats. Trans resveratrol is a polyphenolic compound and is known to have antioxidant activity. In the present study, the effect of trans resveratrol was investigated on ICV STZ induced cognitive impairment and oxidative stress in rats. Adult male Wistar rats were injected with ICV STZ bilaterally, on day 1 and day 3. The learning and memory behaviour was assessed using passive avoidance paradigms, elevated plus maze and the closed field activity test while the parameters of oxidative stress assessed were malondialdehyde [MDA] and glutathione. The rats were treated with trans resveratrol chronically at doses of 10 and 20 mg/kg,i.p. for 21 days starting from day 1 of STZ injection. Trans resveratrol, treatment significantly prevented ICV STZ induced cognitive impairment. There was a rise in brain glutathione and an insignificant increase in brain MDA in trans resveratrol treated ICV STZ rats as compared to significantly elevated brain MDA levels in the vehicle treated ICV STZ animals. The study demonstrates the effectiveness of trans resveratrol in preventing the cognitive deficits as well as the oxidative stress caused by ICV STZ in rats and it's potential in the treatment of neurodegenerative diseases such as Alzheimer's disease.

**PPZ - 6****PROTECTIVE ROLE OF ALPHA-TOCOPHEROL IN THE MACAO MODEL OF ACUTE ISCHEMIC STROKE IN RATS.**

Chaudhary G, Sinha K Gupta YK.

Neuropharmacology Laboratory, Department of Pharmacology, All India Institute of Medical Sciences, New Delhi- 110029.

Free radicals generated during ischemia reperfusion have been implicated for causation of neuronal injury and the depletion of endogenous antioxidants like ascorbic acid, alpha-tocopherol, protein thiols further contributes to the free radical induced neuronal injury. The present study was carried out to see the effect of acute administration of alpha-tocopherol in the middle cerebral artery (MCA) occlusion model of stroke in rats. Male Wistar rats in the weight range of 250-300 g were used. Rats were anaesthetized using chloral hydrate (400 mg/kg i.p.) and were subjected to 2 hours of transient ischemia. Alpha-tocopherol was administered at the dose of 125 and 250 mg/kg orally 1 hour prior to the occlusion of MCA. Motor performance test (grip test, foot fault test, rotarod performance test, spontaneous locomotor activity), markers of oxidative stress and TTC staining were carried out 24 hours after MCA occlusion. Vehicle treated group was run parallel. It was observed that alpha-tocopherol at the dose of 125 mg/kg did not improve neurological deficit, neither decreased the raised level of oxidative stress markers as compared to the MCA occluded rats. However higher dose of alpha-tocopherol afforded significant protection as evident by increase in motor performance tests and the decrease in the infarct volume. The raised levels of MDA were also significantly attenuated by alpha-tocopherol 250 mg/kg orally. The results demonstrate that exogenous administration of alpha-tocopherol is able to prevent the neuronal damage caused during ischemia reperfusion, which can be attributed to its antioxidant activity.

**PPZ - 7****NALOXONE REVERSIBLE ANALGESIA BY TRANS RESVERATROL IN RATS.****Briyal S, Sharma M, Gupta YK.**

Neuropharmacology Laboratory, Department of Pharmacology, All India Institute of Medical Sciences, New Delhi - 110029.

Trans resveratrol is an antioxidant that occurs naturally in grapes and some medicinal plants. Recently, it has been shown to decrease hyperalgesia induced by carrageenan in rat hind paw. In the present study, the effect of different doses of trans resveratrol on nociception was studied by hot plate in rats. Trans resveratrol at graded doses of 5, 10, 20 and 40 mg/kg, i.p produced dose dependent analgesia. The effect was more pronounced (% MPE  $34 \pm 8.4$  % and  $32 \pm 6.2$  % at 45 min) at the dose of 20 and 40 mg/kg, i. p respectively. However, there was insignificant difference between the % MPE of these two doses. Pretreatment (20 min) with opioid antagonist naloxone ( 1 mg/kg, i.p) blocked the analgesic effect of trans resveratrol (20 mg/kg, i. p). When the sub maximal dose of trans resveratrol (5 mg/kg i. p) was combined with a sub maximal dose of morphine (2 mg/kg, i. p), the analgesic effect was significantly potentiated as compared to the individual drugs alone. The findings suggest that trans resveratrol produces analgesia, which may be mediated via the opioidergic mechanism.

**PPZ - 8****NEUROPROTECTIVE EFFECT OF PEROXYNITRITE SCAVENGER IN MIDDLE CEREBRAL ARTERY OCCLUSION INDUCED FOCAL ISCHEMIA IN RATS.****Sharma SS, Shankar M, Kaul CL.**

Department of Pharmacology and Toxicology, National Institute of Pharmaceutical Education &amp; Research (NIPER), Sector-67, S.A.S. Nagar, Punjab - 160062.

**Objective:** Free radical production shown to be increased during cerebral ischemic reperfusion injury. Nitric oxide is a weak radical that combine with superoxide to form a more toxic species peroxynitrite leading to neuronal death. Peroxynitrite has been considered to be one of the potential target for stroke. Therefore in the present study effect of peroxynitrite scavengers was investigated in animal model of stroke.

**Methods:** Focal ischemia was induced in Male Sprague-Dawley rats (260 to 280 g) by occlusion of middle cerebral artery for 2 hrs and reperfusion for 22 hrs. Neurological damaged was assessed by volume of cerebral infarction and neurological deficits. Effect of peroxynitrite scavenger (FeTMPyP) was studied at the doses of 1 and 2 mg/kg, i.p. in focal ischemia.

**Results:** FeTMPyP administration at the doses of 1 and 2 mg/kg, i.p., 5 minutes before reperfusion produced significant reduction in the infarction volume 19 % ( $p < 0.05$ ) and 15 % ( $p < 0.01$ ) respectively, as compared to that of the vehicle treated group, 30%. Significant improvements in neurological deficits were also observed in a dose-dependent manner as compared to the vehicle treated group. We have also carried out combination studies with poly (ADP ribose) polymerase inhibitors. Results of these studies will also be discussed.

**Conclusion:** This study has shown the neuroprotective potential of peroxynitrite scavengers in stroke.

PPZ - 9

**EFFECT OF METOCLOPRAMIDE ON SCOPOLAMINE INDUCED WORKING MEMORY IMPAIRMENT IN RATS.**

Naveen K, Kohli K.

Department of pharmacology, Lady Hardinge Medical College, New Delhi - 110001.

**Objective:** Metoclopramide acts at multiple receptor sites. We investigated the effect of metoclopramide on scopolamine induced working memory deficits in rats by using the three-panel runway apparatus.

**Methods:** Trained male albino rats were randomly divided into groups of 6 animals each. The groups were administered saline, scopolamine in the doses of 0.1-0.56 mg/kg and metoclopramide in the doses of 0.1-5.0 mg/kg. All the metoclopramide doses were co-administered with scopolamine, in the dose of 0.56 mg/kg. The working memory errors and latency period of the session were recorded on the three-panel runway apparatus.

**Results:** Trained rats treated with scopolamine at the dose of 0.1 mg/kg did not result in any significant change in working memory errors or latency period. Scopolamine treatment in the dose 0.56 mg/kg resulted in a significant increase in the number of working memory errors and latency period. Concurrent administration of metoclopramide, in the dose of 0.1 and 1.0 mg/kg and scopolamine, in the dose of 0.56 mg/kg, resulted in a significant increase in working memory errors and latency periods as compared to the control. Rats co-administered with metoclopramide, in the dose of 5.0 mg/kg and scopolamine (0.56 mg/kg) failed to complete the trial run.

**Conclusion:** We conclude that scopolamine treatment resulted in working memory deficits on the three-panel runway apparatus and could serve as a model for human dementia. Metoclopramide treatment did not reverse or significantly aggravate the working memory impairment produced by scopolamine.

PPZ-10

**COGNITIVE ENHANCING AND ANTIOXIDANT PROPERTY OF CELASTRUS PANICULATUS IN MODEL OF ALZHEIMER'S DISEASE IN RATS.**

Veerendra Kumar MH, Gupta YK.

Neuropharmacology Laboratory, Department of Pharmacology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi - 110029.

**Objective:** We have earlier demonstrated that *Celastrus paniculatus* (CP) has cognitive enhancing and antioxidant property in normal rats. Oxidative stress or impaired endogenous antioxidant mechanism is an important factor that has been implicated in Alzheimer's disease (AD). Intracerebroventricular (ICV) streptozotocin (STZ) in rats causes the cognitive impairment and is associated with free radical generation. Therefore in the present study the effect of aqueous extract of CP (100, 200 and 300 mg/kg for 21 days once a day) was evaluated in ICV STZ induced cognitive impairment and oxidative stress in rats.

**Methods:** Male Wistar rats were injected ICV STZ (3 mg/kg) bilaterally on 1<sup>st</sup> and 3<sup>rd</sup> day. The cognitive behaviour was assessed using passive avoidance and elevated plus maze paradigms on 13<sup>th</sup>, 14<sup>th</sup> and 21<sup>st</sup> day. The rats were sacrificed on the 21<sup>st</sup> day for the estimation of oxidative stress parameters (malondialdehyde (MDA), glutathione, superoxide dismutase (SOD) and catalase) in the whole brain upon completion of the behavioural task.

**Results:** The rats treated with CP showed a dose dependent increase in the cognitive behaviour in both the paradigms. Significant lower level of MDA, and higher level of glutathione was observed in only 200 and 300 mg/kg CP treated rats.

**Conclusion:** The present findings indicate that aqueous extract of CP was effective in preventing the cognitive deficits as well as the oxidative stress caused by ICV STZ in rats.



**PPZ-11****ANTIOXIDANT ACTIVITY OF *OCIMUM SANCTUM* IN HYPERCHOLESTEROLEMIC MODEL.****Arora D\***, Khanna N\*, Mahajan P\*, Sharma SB.\*\*

Department of Pharmacology\*, Department of Biochemistry\*\*, University College of Medical Sciences and GTB Hospital, Shahdara, Delhi - 110095.

**Objective:** To study the antioxidant activity of aqueous leaf extract of *Ocimum sanctum* (OSE) in hypercholesterolemic rabbits.**Methods:** Sixteen male albino rabbits were made hypercholesterolemic after feeding cholesterol (500 mg/animal/day) for 8 weeks after which the animals were randomly assigned to two groups. Group 1 received normal saline and Group 2 received OSE (100 mg/kg/day) for 6 weeks. Erythrocyte superoxide dismutase (SOD) and catalase (CAT) as well as lipid peroxide (MDA) levels in serum and platelet rich plasma (PRP) were measured at 0, 8 and 14 weeks.**Results:** Administration of OSE decreased serum and PRP MDA levels significantly ( $p < 0.001$ ). Erythrocyte SOD and CAT activities were raised in the drug treatment group ( $p < 0.001$ ).**Conclusion:** Our study suggests that through an increase in antioxidant defense and a direct free radical scavenging action, *Ocimum sanctum* may have a beneficial role in atherosclerosis and coronary artery disease.**PPZ-12****EFFECTS OF GLIMEPIRIDE ON PLASMA INSULIN, PLASMA LEPTIN AND OTHER BIOCHEMICAL AND ANTHROPOMETRIC PARAMETERS IN TYPE 2 DIABETIC PATIENTS.****Madan M**, Mahajan P, Bhattacharya SK, Shastri S, Madhu SV\*, Ram BK\*, Chakrabarty AK\*\*, Tripathi AK.\*\*

Departments of Pharmacology, Medicine\* and Biochemistry\*\*, UCMS and GTB Hospital, Delhi - 110095.

**Objective:** Glimepiride, a new second generation sulphonylurea is an oral hypoglycaemic drug. The present study was undertaken to assess its effects on the glycaemic control, plasma insulin, plasma leptin and other parameters. The trial also aimed to monitor adverse drug reactions during therapy.**Methods:** Plasma insulin, plasma leptin, blood sugar, glycosylated Hb (GHb), lipid profile, body mass index (BMI) and waist hip ratio (WHR) were assessed in 30 type 2 diabetic subjects before and after 10 weeks of glimepiride administration after obtaining their informal written consent and approval of the Institutional Ethics Committee. The monitoring of the ADR's reported by the patients was done.**Results:** Glimepiride significantly reduced blood sugars and GHb as compared to the baseline values. A significant rise in plasma insulin levels from  $21.1 \pm 6.4 \mu\text{U/mL}$  to  $36.1 \pm 9.6 \mu\text{U/mL}$  was observed. Although the plasma leptin levels showed an increase from  $3.34 \pm 0.95 \text{ ng/mL}$  to  $3.79 \pm 1.79 \text{ ng/mL}$ , this was not statistically significant. The effects on BMI, WHR and lipid profile did not differ significantly from the control values. During the period of drug administration asthenia, fatigue, hypoglycaemic episodes and dizziness were reported by some subjects.**Conclusion:** Glimepiride is an effective oral hypoglycaemic drug. It increases plasma insulin levels. It has no significant effects on BMI, WHR, lipid profile and plasma leptin levels.

**PPZ-13****CALCIUM HOMEOSTASIS AND DICHLORVOS INDUCED NEUROTOXICITY IN RAT BRAIN.****Geetu Raheja, Kiran Dip Gill**

Dept. of Biochemistry, Postgraduate Institute of Medical Education and Research, Chandigarh - 160012.

The present study was designed to investigate the possible effects of chronic dichlorvos exposure on the various aspects of calcium homeostasis in rat brain. Chronic dichlorvos administration caused significant rise in the intrasynaptosomal calcium levels. The activity of major calcium expelling enzyme i.e.  $\text{Ca}^{2+}$  ATPase was also found to be declined. Also, the depolarization induced calcium uptake via voltage operated calcium channels increased significantly. Concomitant to the increase in intrasynaptosomal calcium, calpain activity was found to be increased. These results indicate that the toxic effects of dichlorvos could be mediated through modifications in the intrasynaptosomal calcium homeostasis which may lead to impaired neuronal function.

**PPZ-14****ANTIULCEROGENIC AND ULCER HEALING PROPERTIES OF *OCIMUM SANCTUM* LINN.****Dharmani P, Kumar KV, Maurya R\*, Palit G.**

Division of Pharmacology, \*Division of Medicinal Chemistry, Central Drug Research Institute, Lucknow - 226001.

**Introduction:** *Ocimum sanctum* Linn. (OS) commonly known as Holybasil or Tulsi is a potent adaptogen according to Ayurveda. OS is known to possess anti-inflammatory, analgesic anti-oxidant, anti-arthritis and anti-stress properties. Present study was undertaken to evaluate anti-ulcerogenic and ulcer healing properties of OS (methanolic extract) *in vivo* ulcer models.

**Methods:** Sprague-Dawley (SD) rats (150-170 gm) and guinea pigs (300-350 gm body weight) of either sex were pretreated with OS at a dose of 100 mg/kg/day x 3 days, p.o. Ulcers were induced in rats by CRU (immobilization at 4°C for 2 hrs), alcohol (AL, 1 ml/200 gm body weight, p.o, after 1 hr), while in guinea pigs by histamine (HST 0.25 mg/kg, i.m, every 30 min for 4 hrs). Healing property of OS was evaluated in acetic acid induced ulcer model (AC, exposure of serosal surface to 60  $\mu\text{L}$  of 20% acetic acid for 90 sec) in rats. Anti-ulcerogenic and ulcer healing properties of OS were compared with standard anti-ulcer agent omeprazole (OMZ, 10 mg/kg/day x 3 days, p.o).

**Results:** OS significantly ( $p < 0.05$ ) reduced ulcer index in all models showing protection index of 50.4, 43.8 and 70.79 % in CRU, AL and HST respectively, whereas OMZ produced 61.9, 64 and 76.4 % protection index. OS significantly healed ulcers in AC within 15 days.

**Conclusion:** These findings support the fact that OS possess anti-ulcerogenic and ulcer healing properties which may be due to its effect to strengthen defensive factors coupled with anti-secretory and antioxidant activities.

**PPZ-15****ROLE OF DOPAMINERGIC SYSTEM IN DICHLORVOS INDUCED DELAYED NEUROTOXICITY IN RAT BRAIN.****Pushpinder Kaur, Suresh Verma, Kiran Dip Gill.**

Dept. of Biochemistry, Postgraduate Institute of Medical Education and Research, Chandigarh - 160012.

Effect of dichlorvos (200 mg/kg bw) on the role of dopaminergic system in organophosphorus induced delayed neurotoxicity was studied in rat brain. Detail assessment of the dopaminergic neurotransmitter system comprising levels of Dopamine, Norepinephrine, activity of key synthetic and degradative enzymes viz., Tyrosine hydroxylase, Dopamine  $\beta$  Hydroxylase, Monoamine oxidase and Receptor binding studies in response to dichlorvos was made. The administration of dichlorvos caused increase in Dopamine and Norepinephrine levels as well as increase in the activity of Tyrosine Hydroxylase and Dopamine  $\beta$  Hydroxylase. It decreased the activity of Monoamine Oxidase. Scatchard plot analysis revealed decreased ligand receptor binding sites following dichlorvos exposure. This study reveals that dichlorvos may cause Organophosphorus Induced Delayed Neurotoxicity by the impairment of dopaminergic system.

**PPZ-16****POTENTIAL ROLE OF NEUROSTEROID ALLOPREGNANOLONE IN ANXIOLYTIC ACTION OF ETHANOL AND WITHDRAWAL INDUCED ANXIETY.****Sharma Ajay N, Hirani Khemraj, Ugale Rajesh R, Chopde Chandrabhan T.**  
Pharmacology division, University Department of pharmaceutical Sciences,  
Nagpur University Campus, Nagpur - 440010.

**Introduction:** Ethanol is known to increase the brain and plasma concentration of allopregnanolone (3 $\alpha$ -hydroxy-5 $\alpha$ -pregnan-20-one) that positively modulates GABA<sub>A</sub> receptor. Recent findings indicate that ethanol and allopregnanolone share common mechanisms of action and that allopregnanolone modulates some of the ethanol's abuse related effect. Aim of the present study was to investigate the potent role of neurosteroid in anxiolytic action of ethanol and withdrawal-induced anxiety.

**Methods:** Male Sprague-Dawley rats were treated intraperitoneally with various doses of 8% w/v ethanol alone or in combination with allopregnanolone, progesterone, 5 $\alpha$  DHP, metyrapone or GABAergic drugs bicuculline or muscimol and subjected to elevated plus maze (EPM). Rats in different conditions of low neurosteroid using neurosteroid biosynthesis inhibitors (trilostane, finasteride or indomethacin), socially isolated rats, adrenalectomised rats or pseudopregnant-withdrawn female rats were challenged with ethanol and subjected to EPM. For chronic studies rats received an ethanol containing liquid diet for 10 days and were tested for withdrawal induced anxiety at 0, 2, 4, 8, 12, 18, 24 or 36 hrs after termination of the diets. These animals were challenged with neurosteroid or drugs that promote steroidogenesis or acute ethanol during peak withdrawal time and subjected to EPM.

**Results:** Ethanol dose dependently increased percent time spent and percent entries in the open arms. This effect was enhanced by neurosteroidogenic drugs and attenuated in the low neurosteroidal conditions. Chronic ethanol produced tolerance to anxiolytic effect and upon withdrawal rats displayed less open arm activity and total arm entries than pair fed rats. Administration of allopregnanolone or neurosteroidogenic drugs but not ethanol showed heightened anxiolytic response in the ethanol withdrawn rats.

**Conclusions:** These results suggest the vital role of neurosteroidogenesis in anxiolytic effect of ethanol and support the hypothesis that neurosteroid by modulation of GABA<sub>A</sub> receptors mediate central effects of ethanol including tolerance to and dependence on ethanol. The identifications of the neurosteroid intermediates involved in ethanol action may lead to important advances in the field and the development of novel therapeutics in alcoholism.

**PPZ-17****INTRAOPERATIVE TRANSCORNEAL PENETRATION OF TOPICAL OFLOXACIN AND LOMEFLOXACIN EYE DROPS INTO THE HUMAN AQUEOUS.****Ravi AK, Biswas NR, Vajpayee RB, Titiyal JS, Verma L, Tewari HK, Gupta SK\*, Ghose S.**

Dr. Rajendra Prasad Centre for Ophthalmic Sciences and \*Department of Pharmacology, All India Institute of Medical Sciences, New Delhi - 110029.

**Objective:** A comparative two drops (single dose) study was undertaken to estimate the intraocular penetration of topically instilled ofloxacin and lomefloxacin eye drops in aqueous humor.**Methods:** 16 patients undergoing cataract surgery in one eye received either 0.3% ofloxacin topical eye drops (8 eyes) or lomefloxacin (in 8 eyes). The patients were administered two drops in a single dose of either drug ½ hour pre-operatively. The study was approved by the Institutional Ethics Committee and informed consents were obtained from the patients before being enrolled. Intraoperatively, 0.1 ml aqueous humor was aspirated from the anterior chamber and immediately stored at - 80°C deep freezer till the accurate estimation of ofloxacin or lomefloxacin by HPLC (high performance liquid chromatography).**Results:** MIC<sub>90</sub> of most of the ocular pathogens for ofloxacin and lomefloxacin are known to range from 0.12 - 0.50 µg/ml. Two drops of 0.3% topical ofloxacin achieved a mean aqueous concentration of 0.40 ± 0.09 µg/ml with a range of 0.29 - 0.55 µg/ml. Topical lomefloxacin gave a mean aqueous concentration of 0.27 ± 0.07 µg/ml with a range of 0.16 - 0.40 µg/ml. Using the Student's 't' test for comparison, the difference was highly significant (p = 0.009).**Conclusion:** Though both these antimicrobials gave aqueous concentrations with effective MIC<sub>90</sub>, ofloxacin achieved significantly higher concentrations than lomefloxacin in this study.**PPZ-18****COMPARATIVE CARDIOTOXICITY OF NEWER FLUOROQUINOLONES IN ANAESTHETIZED GUINEA PIG MODEL.****Pawar VD, Patil RT, Latad SB, Patil VB, Chugh Y, and Patel MV.**

Division of Pharmacology, Drug Discovery Research, Wockhardt Research Centre,

D-4, MIDC, Chikalthana, Aurangabad-431210.

**Objective:** To assess and rank the cardiotoxic potential of newer fluoroquinolones in anesthetized guinea pig model using escalated dosing protocol.**Method:** Guinea pigs of either sex were anesthetized with urethane. Blood pressure and Lead II ECG were monitored. 3, 5, 10, 30 mg/kg doses of test drugs (moxifloxacin, levofloxacin, gatifloxacin and sparfloxacin) were administered over 1 min from jugular vein after 30 min stabilization period at the interval of 30 min. Serum levels of test drugs were estimated by HPLC. Qtc- intervals were calculated using Bazette and Fridericia's formulae.**Results:** Of the four fluoroquinolones studied, moxifloxacin, sparfloxacin, and gatifloxacin had QT -interval prolongation effect at all the doses, while levofloxacin had minimal effect. Moxifloxacin, sparfloxacin, gatifloxacin and levofloxacin caused prolongation of QTc(f) interval ( mean ± S.D. in msec) by 6.6 ± 4.2, 5.7 ± 4.8, 4.5 ± 3.5, 1.0 ± 2.6 at 3 mg/kg, 10.7 ± 6.4, 13.3 ± 3.5, 5.7 ± 3.8, - 4.0 ± 6.1 at 5 mg/kg, 18.8 ± 4.4, 21.2 ± 8.5, 21.3 ± 15.0, -1.7 ± 8.0 at 10 mg/kg and 45.7 ± 12.2, 35.8 ± 11.0, 36.7 ± 9.6, 3.0 ± 5.6 at 30 mg/kg dose respectively. All the four compounds produced dose dependent fall in blood pressure to the same extent.**Conclusion:** Moxifloxacin was found to produce maximum QT prolongation, while levofloxacin had the least potential. Sparfloxacin and gatifloxacin were in second and third place. Using escalated dosing protocol, dose response curve could be generated in one animal.

PPZ-19

**STUDY OF IMMUNOMODULATORY ACTIVITY OF YASHTI-MADHU (GLYCYRRHIZA GLABRA).**

Daswani BR, Radha Yegnanarayan.

Department of Pharmacology, B. J. Medical College, Pune.

**Introduction:** Yashti-madhu is a common ingredient of several polyherbal preparations claimed to stimulate the immune system.

**Objective:** To evaluate the effects of yashti-madhu on some of the immunological parameters in an experimental study.

**Methods:** 3 doses of Yashti-madhu were given to rats/ mice (for different tests) orally, daily for 4 weeks [5 mg/kg; 50 mg/kg; 500 mg/kg in case of mice and 3.6 mg/kg; 36 mg/kg; 360 mg/kg in case of rats]. At the end of 4 weeks, the animals were subjected to immunological evaluation where total/ differential WBC counts, phagocytic activity of polymorphs and RES, delayed hypersensitivity to oxazolone and ability to counteract *E.coli* induced abdominal sepsis was studied using a fresh set of animals for each test.

**Results:** The lowest and the highest dose of yashti-madhu significantly enhanced the phagocytic activity of polymorphs and the cellular immunity. The lowest dose even increased the granuloplectic activity of RES. Contrary to our expectation, the intermediate dose did not show such stimulatory effect but rather reduced the percentage of neutrophils in blood. Mortality due to *E.coli* sepsis and total WBC counts were however not affected by any of the doses.

**Conclusion:** Thus, the present study so far indicates that yashti-madhu has the potential of being useful as an immunostimulant in a particular dose. The effect on humoral immunity is also being investigated.

PPZ-20

**PROTECTIVE EFFECTS OF CALCIUM CHANNEL BLOCKERS AGAINST FREE RADICAL INDUCED ANOXIC BRAIN DAMAGE IN RATS.**

Nischal A<sup>1</sup>, Saxena AK<sup>2</sup>, Shankar K<sup>2</sup>, Gurtu S<sup>2</sup>.

<sup>1</sup>Department of Pharmacology, Lady Hardinge Medical College, New Delhi - 110001. <sup>2</sup>Department of Pharmacology and Therapeutics, K.G. Medical College, Lucknow.

**Objectives:** To study the effects of calcium channel blockers (CCBs) against free radical induced brain damage following ischaemia-reperfusion in rat brain.

**Methods:** Ischaemia-reperfusion was produced in rats by bilateral carotid artery occlusion. The rats were sacrificed by decapitation at the end of 5 minutes of ischaemia and 20 minutes of reperfusion. Brain homogenate was used for the estimation of lipid peroxides using the thiobarbituric acid method of Esterbauer and Cheeseman (1990) with minor modification. The CCBs, Verapamil, Nimodipine and Flunarizine were administered in a dose of 20 mg/kg i.p. 1 hour prior to the induction of ischaemia. The data were expressed as means with standard errors. Differences between the control and treated groups were compared by employing Student's unpaired "t" test.

**Results:** All three CCBs inhibited the increase in lipid peroxides in the brain induced by ischaemia and reperfusion. Verapamil and Nimodipine but not Flunarizine produced a statistically significant decrease in the basal levels of malondialdehyde in the brain. There was no marked difference in the magnitude of protective effects of the three calcium channel blockers.

**Conclusions:** The protective effects of the CCBs could possibly be due either to a decrease in free radical generation or an augmentation of the activity of scavenging enzymes.

**PPZ-21****EFFECT OF ONDANSETRON AND SCOPOLAMINE ON THE WORKING MEMORY OF ALBINO RATS.**

Kela AK, Naveen K.

Department of Pharmacology, Lady Hardinge Medical College, New Delhi - 110001.

**Objective:** Effect of ondansetron, a 5-HT<sub>3</sub>-receptor antagonist was investigated on the scopolamine induced working memory impairment in rats by using the three-panel runway apparatus.

**Methods:** Trained male albino rats were randomly divided into groups of 6 animals in each. The groups were administered saline, scopolamine in the doses of 0.1-0.56-mg/kg and ondansetron in the dose of 1.0 mg/kg. Ondansetron in the doses of 0.01-1.0 mg/kg were co-administered with scopolamine, in the dose of 0.56 mg/kg. The working memory errors and latency period of the session were recorded on the three-panel runway apparatus.

**Results:** Trained rats treated with scopolamine at the dose of 0.1 mg/kg did not result in any significant change in working memory errors or latency period. Scopolamine treatment in the dose 0.56 mg/kg resulted in a significant increase in the number of working memory errors and latency period. Treatment with ondansetron in the dose of 1.0 mg/kg significantly reduced the scopolamine (0.56 mg/kg) induced working memory errors and latency period.

**Conclusion:** We conclude that scopolamine treatment resulted in working memory deficits on the three-panel runway apparatus and could serve as a model for human dementia. Ondansetron treatment in the dose of 1.0 mg/kg improved the working memory deficits induced by scopolamine.

**PPZ-22****PHARMACOKINETICS OF CEFAZOLIN IN GOATS FOLLOWING INTRAVENOUS, INTRAMUSCULAR AND SUBCUTANEOUS ADMINISTRATION.**

Ahuja V, Pardeep K, Bhandari P, Ashish Sachan, Mehta G, Ahmad AH.

Department of Pharmacology and Toxicology, College of Veterinary Sciences, Pantnagar - 263145.

**Objectives:** To determine the pharmacokinetics and dosage regimen of Cefazolin in goats following intravenous, intramuscular and subcutaneous administration.

**Methods:** The study was performed on six healthy goats subsequent to single dose i. v., i.m. and s.c. administration of Cefazolin (10 mg. kg<sup>-1</sup>). The concentration of Cefazolin in plasma was determined by HPLC. The plasma drug concentration time-profile were analysed by least-square iterative curve fitting computer programme 'statis- 3'.

**Results:** The peak plasma concentration of Cefazolin were 7.33 (i.v.), 2.56 (i.m.), and 1.93 (s.c.) µg.ml<sup>-1</sup> at 0.03, 0.17 and 0.25 h, respectively. The Cefazolin concentration could be detected up to 5 h following i.v. administration and up to 7 h following i.m. and s.c. routes of administration, respectively. The t<sub>1/2 p</sub> and V<sub>d</sub> were calculated to be 1.07, 1.70, 2.08 h and 2.92, 2.90, 2.08 L.kg<sup>-1</sup> following i.v., i.m. and s.c. routes of administration, respectively. C<sub>1β</sub> and AUC values were 1.97, 1.22, 1.02 L.kg<sup>-1</sup>.h<sup>-1</sup> and 5.12, 4.32, 4.58 µg.ml<sup>-1</sup> following i. v., i.m. and s.c. routes of administration, respectively.

**Conclusion:** An intramuscular and subcutaneous dosage regimen of Cefazolin in goats was calculated as 16 and 14 mg.kg<sup>-1</sup> b.wt. every 8 hours, respectively, with a minimum steady state concentration of 0.2 µg.ml<sup>-1</sup> which is within the range of MIC.

**PPZ-23****EFFECT OF ENALAPRIL ON PLATELET FUNCTION IN HYPERTENSIVE PATIENTS.**

Gupta S, Gupta VK\*, Dhamija RK\*\*, Kela AK.

Departments of Pharmacology and Medicine\*\*, Lady Hardinge Medical College, New Delhi - 110001, Department of Biochemistry\*, GB Pant Hospital, New Delhi.

**Objective:** To evaluate the effect of enalapril on platelet function in hypertensive patients.**Methods:** Newly diagnosed hypertensives (age group 30-60 years) were recruited. Written informed consent was obtained from all patients. Oral enalapril was administered and the dosage was titrated according to the control of blood pressure (BP). Platelet aggregability was determined on an automatic platelet aggregometer using ADP (10  $\mu$ M) and adrenaline (20  $\mu$ M) as agonists. Platelet malondialdehyde (MDA) production (basal and activated) was estimated by thiobarbituric acid reaction. Ratio of MDA:MDA-a was calculated. These tests were performed at the beginning of the study and at the end of 12 weeks of drug treatment**Results:** After 12 weeks of enalapril therapy, the systolic, diastolic and mean arterial pressures reduced significantly ( $p < 0.001$ ). Enalapril therapy reduced ADP-induced platelet aggregation from 64.04 % to 57.68 % and adrenaline-induced platelet aggregation from 60.19 % to 52.94 % ( $p < 0.05$ ); MDA from a pretreatment value of 109.36 to 98.35 ng/ml PRP ( $p < 0.01$ ); the reduction in MDA-a from 136.84 to 134.25 ng/ml PRP was not significant ( $p > 0.05$ ). Decrease in MDA:MDA-a from 0.81 to 0.74 was significant ( $p < 0.05$ ).**Conclusion:** The present study concludes that enalapril treatment favourably affects the platelet function status in hypertensive patients.**PPZ-24****EFFECT OF  $\alpha$ -KETOGLUTARATE ON CYANIDE INDUCED CHANGES IN VARIOUS BIOCHEMICAL VARIABLES IN RAT BRAIN AND LIVER.**

Raj Kumar Tulsawani, Jatav PC\*, Bhattacharya R.

Division of Pharmacology and Toxicology, and \*Animal Facility, Defence Research and Development Establishment, Jhansi Road, Gwalior - 474002.

With near ubiquity of cyanide in the environment, there is need for more complete understanding of its toxicology and antagonism. Cyanide being predominantly a neurotoxin, most of its effects have been associated with central nervous system or neuronal cells. However, information on its effects on other tissues, particularly liver is inadequate, considering that liver actively participates in the bio-transformation of cyanide to thiocyanate. This would enable designing of better antidotes. Commonly recommended treatment for cyanide poisoning are amyl nitrite and/or sodium nitrite (SN) with sodium thiosulfate (STS). However, there are many limitations of these antidotes. We have recently shown that oral administration of  $\alpha$ -ketoglutarate ( $\alpha$ -KG) conferred significant protection against acute potassium cyanide (KCN) poisoning in rodents and the protection was significantly enhanced by adjunction of SN and/ or STS. In the present study, pre-treatment, simultaneous treatment or post-treatment of  $\alpha$ -KG+STS were found to protect cyanide induced neurotoxicity, based on the levels of certain biochemical variables like brain cytochrome oxidase (CYTOX), reduced glutathione (GSH), oxidised glutathione (GSSG), glutathione peroxidase (GPx) and superoxide dismutase (SOD), and other motor activities. In liver only delayed effects of cyanide was observed on the levels of GSH and GSSG but not on sorbitol dehydrogenase (SDH). The changes in brain and liver were attenuated by  $\alpha$ -KG+STS. Protective efficacy of  $\alpha$ -KG against cyanide induced cytotoxicity was also studied *in vitro* in non-neuronal cells viz. cultured rat thymocytes. Treatment of 5 mM KCN for 6 hr significantly reduced the cell viability measured by Eosin Y exclusion, accompanied by leakage of lactate dehydrogenase (LDH) and mitochondrial dysfunction (MTT uptake). A 30 min pre-treatment or simultaneous treatment of 5 mM  $\alpha$ -KG prevented the cytotoxicity. The present study shows the promising role of  $\alpha$ -KG in preventing cyanide induced acute neurotoxicity and cytotoxicity. However, implication of cyanide in hepatic toxicity was not well expressed.

PPZ-25

**AMPLIFIED CCl<sub>4</sub> HEPATOTOXICITY IN TYPE 2 DIABETES DUE TO INHIBITED TISSUE REPAIR.**

Sawant SP, Dnyanmote AV, Mehendale HM.

Department of Toxicology, College of Pharmacy, The University of Louisiana at Monroe, Monroe, LA, USA.

**Objective:** To investigate the mechanisms of amplified CCl<sub>4</sub> hepatotoxicity in Type 2 diabetic rats.

**Methods:** Type 2 diabetes was induced in male SD rats by feeding high fat diet for 2 weeks and injecting streptozotocin (45 mg/kg, ip) on day 14. On day 24, blood glucose, insulin and insulin resistance (OGTT, 5mg/kg, po) were measured. Lethality and time course studies were done in diabetic (DB) and non-diabetic (non-DB) rats by administration of non-lethal dose of CCl<sub>4</sub> (2 ml/kg, ip). Liver injury was assessed by AL T, liver function by bilirubin & ammonia and tissue repair by <sup>3</sup>H-T incorporation.

**Results:** Elevated glucose, normoinsulinemia and insulin resistance confirmed type 2 diabetes. Administration of a CCl<sub>4</sub> yielded 100% mortality in the DB rats. A time course study revealed substantially higher liver injury in DB rats and death was due to hepatic failure as indicated by hyperammonemia and hyperbilirubinemia. Tissue repair was inhibited in DB rats after CCl<sub>4</sub> administration due to which injury progressed and resulted in death between 24 to 48 h. In contrast, non-DB rats exhibited robust repair response resulting in recovery and survival.

**Conclusion:** High fat diet yields a robust model of type 2 diabetes and CCl<sub>4</sub> hepatotoxicity is amplified due to inhibited tissue repair.

**Acknowledgements:** Kitty DeGree Endowment and LBRSP

PPZ-26

**BIOAVAILABILITY OF RIFAMPICIN AND ISONIAZID IN DRUG SENSITIVE AND MULTI DRUG RESISTANT TUBERCULOSIS.**

Chetna SM, Sushant HM, Shrivastava MP.

Dept. of Pharmacology, Dept. of Chest and Tuberculosis, Indira Gandhi Medical College, Nagpur-440018.

**Introduction :** Altered pharmacokinetic parameters or lowered bioavailability is just like inadequate dose administration by which MIC will not be achieved and there may be bacteriostatic action or no action on the bacilli leading to secondary acquired drug resistance. We attempted to find out contribution of pharmacokinetic parameter in development of drug resistance tuberculosis.

**Methods:** Ten patients with normal hepatic and renal function age between 14 -45 yrs. in each group of drug sensitive and multi drug resistant tuberculosis were selected. Serum drug, concentration at 0, 1, 2, 4, 6, 8, 12 and 24 hrs. were estimated for isoniazid and rifampicin by Edius and Little and Mac Connell method respectively.

**Result:** Values of pharmacokinetic parameter for drug sensitive and multi drug resistance tuberculosis were as follows respectively.  $t_{1/2}$   $4.29 \pm 1.5$  and  $5.3 \pm 1.02$  hrs;  $C_{max}$   $8.6 \pm 2.0$  and  $7.6 \pm 1.4$ ; AUC  $67.27 \pm 10.3$  and  $61.25 \pm 15.56$ ;  $K_{el}$   $0.184 \pm 0.08$  and  $0.1342 \pm 0.02$  and F/V  $1.13 \pm 0.31$  and  $0.815 \pm 0.23$

**Conclusion:** Host factors do not alter the bioavailability of isoniazid and rifampicin in drug sensitive and drug resistant tuberculosis patients.





## ***Poster Session I***

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(PP1 - PP60)

**Date** : 27-11-2002  
**Time** : 1630 - 1800  
**Venue** : Training Centre

**Co-ordinator** : Dr. Dinesh Kumar

## ***Poster Session II***

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(PP61 - PP113)

**Date** : 28-11-2002  
**Time** : 1400 - 1730  
**Venue** : Training Centre

**Co-ordinator** : Dr. Manju Gupta



PP - 1

## RECENT TRENDS IN ANTIMICROBIAL RESISTANCE PATTERN OF CLINICAL ISOLATES FROM PATIENTS OF URINARY TRACT INFECTIONS IN A TERTIARY CARE HOSPITAL.

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Dept of Pharmacology, Lady Hardinge Medical College, New Delhi.

\*Dept. of Microbiology, Kalawati Saran Hospital, Lady Hardinge Medical College, New Delhi - 100003.

**Introduction:** There has been an increase in antibiotic resistance due to the misuse, patient non-compliance, and lack of antibiotic policies in individual health set-ups in India. We studied the resistance pattern of clinical urinary isolates from suspected cases of urinary tract infections.

**Methods:** Out of 2000 urinary samples (collected over a six-month period from Oct 2001 to March 2002) screened to find out the antimicrobial resistance pattern, 280 urinary isolates were culture positive. *In-vitro* antibiotic sensitivity testing was done by disc-diffusion method (Stoke's) against the following antibiotics using standard potency discs: co-trimoxazole, gentamicin, ciprofloxacin, cefuroxime, ampi-sulbactam, ceftriaxone, cefotaxime, penicillin, erythromycin, amikacin, netilmicin, and norfloxacin.

**Results:** The predominant bacterial isolate was *E. Coli* (57.5 %) followed by *Klebsiella* (18.57 %), *Enterococcus* (8.21 %), *Acinetobacter* (6.42 %), *Proteus* (4.28 %), Coagulase negative *Staphylococci* and *Pseudomonas* (2.5 %) each, respectively. All strains were multi-drug resistant, showing maximum resistance to co-trimoxazole (75 %), followed by ciprofloxacin (60.71 %), cefotaxime (53.57 %), gentamicin (46.42 %), ampi-sulbactam (40.35 %), netilmicin (34.64 %), norfloxacin (30.35 %), amikacin (27.85 %), ceftriaxone (24.64 %), penicillin (7.5 %), erythromycin (6.78 %), and cefuroxime (3.21 %) respectively.

**Conclusion:** Co-trimoxazole has been used as one of the first line therapies for the treatment of urinary tract infections in the past. The emergence of alarming rates of resistance to co-trimoxazole and ciprofloxacin highlights the need for a more rational and restricted use of antimicrobials, in order to avoid antibiotic resistance. We recommend that physicians seek updated knowledge of the common antibiotic resistance patterns when starting antibiotic therapy.

PP - 2

## FATAL CUTANEOUS VASCULITIS BY HIGH DOSES OF PARENTERAL NOVALGIN - A CASE REPORT.

Singh SP\*, Arya TVS\*\*

\*Deptt. Pharmacology and Therapeutics, GSVM Medical College, Kanpur and

\*\*Deptt. Medicine, LLRM Medical College, Meerut.

**Objective:** To Study the toxic effect of Novalgin.

**Methods :** A young lady (27 yrs) injected with high doses of Novalgin was clinically observed for its toxic effects. She suffered from high fever (105° F) and hence reported to a practitioner, where she was immediately put on glucose-saline i.v. drip containing four ampules of Novalgin. Each ampule (5ml) contained Novalgin (analgin) 0.5 g/ml.

**Results:** By the time drip was over, she complained of generalised itching. Within hours rashes appeared all over the body. Symptomatic treatment was given but magnitude of itching and rashes kept on increasing. Six hours later, in the evening she was shifted to medical college hospital. Next day petechial subcutaneous haemorrhage with blisters appeared all over the body which kept on increasing. On 5<sup>th</sup> day many blisters sloughed. Patient's condition started deteriorating. Symptomatic management along with antibiotics were given but patient lost her life on 10<sup>th</sup> day. Sequential colour photographs will be presented and case will be discussed.

**Conclusion:** Novalgin an antipyretic analgesic drug may cause fatal cutaneous vasculitis in high doses.

PP - 3

**SERUM LEVEL CLINICAL RESPONSE RELATIONSHIP OF MOOD STABILIZERS: LITHIUM (LI), CARBAMAZEPINE (CBZ) AND VALPROATE (VPA) IN ACUTE MANIA.**

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**Objectives:** - The aim of the study was to evaluate the correlation between serum levels and clinical response of Lithium, Carbamazepine and Valproate.

**Methods:** 40 patients of acute mania were randomly treated with Li (n = 13); CBZ (n = 13) or VPA (n = 14) monotherapy. Dosage adjustments were done according to serum level or clinical response as indicated by Young Mania Rating Scale (YMRS). Through serum levels the YMRS was done every week for 4 weeks.

**Results:** The therapeutic range for Li, CBZ and VPA was 0.61 - 1.04 meq/ml, 2.6 - 9.4 mg/ml and 52 - 94 mg/ml respectively. There was no statistically significant correlation between serum level and clinical improvement in Li group. CBZ group showed a positive correlation between serum level in week 3 and fall in YMRS score in week 4, the time lag being consistent with delayed drug effectiveness. A positive correlation was also seen between the rise in serum level from baseline and fall in YMRS score from baseline at weeks 3 and 4 in VPA group.

**Conclusion:** Therapeutic drug monitoring of CBZ and VPA may be useful in predicting the clinical response in acute manic patients.

PP - 4

**COST-COMPARATIVE STUDY OF ANTI-TUBERCULAR DRUGS**

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**Objective:** Affordable supply of all the essential anti-tubercular drugs is the cornerstone for any effective tuberculosis treatment in a developing country. The present study compares the prices of first line anti-tubercular drugs in the Indian market.

**Methods:** A review of the drug prices mentioned in the July - September (2002) edition of Drugs Today was done. The consumer cost of a drug being manufactured by different companies in the same strength, dosage form and number was compared.

**Results:** A total of 74 formulations were compared. Variations in prices of all the drugs, ranging from 0.7 % to 277.1 %, were observed. Greater the number of companies manufacturing the drug, more was the variation in their prices.

**Conclusion:** The results of this study indicate that there exists a wide variation in prices of drugs manufactured by different companies. In the absence of comparative information on drug prices and their quality it is difficult for the physician to prescribe the most economical treatment. There is an urgent need to provide adequate information to physicians regarding cost, bioequivalence and quality of drugs.

PP - 5

### UTILIZATION OF PARENTERAL ANTI-INFECTION AGENTS IN THE EMERGENCY UNIT OF A TERTIARY CARE HOSPITAL.

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**Objective:** To investigate the pattern of use of parenteral anti-infective agents in the medical emergency unit of PGIMER, Chandigarh.

**Methods:** Data were collected from the in patient hospital charts of 400 patients, who were prescribed parenteral antimicrobials. The number of anti-infective agents in each prescription, the frequency of individual drug used, age, sex, the site of infection were noted. We also calculated the cost per patient. Drug were classified according to the Anatomical Therapeutic Chemical (ATC) Classification and we estimated the defined daily dose (DDD) for each drug.

**Results:** The mean (SD) and median (range) of the number of parenteral antimicrobials prescribed for patients was 1.9 (0.8) and 2 (1 - 4) respectively. The common site of infections comprising 73.4 % of drug usage were those of respiratory tract (21.3 %), central nervous system (20.1 %), abdomen (18.9 %) and sepsis (13 %). The four most commonly used therapeutic classes accounting for 94.4% of usage were penicillins and cephalosporins (42.5 %), amino glycosides (21.6 %), nitroimidazoles (17.7 %) and quinolones (12.6 %). Combination products of antibiotics (all of them included beta-lactamase inhibitors) constituted 5.3 % of total drug usage. The mean (SD) and median (range) of parenteral antibiotic cost per day was US\$ 3.8 (7.7) and US\$ 2 (1 - 85.7). The mean daily cost per patient was US\$ 7.6.

**Conclusion:** Patients admitted to the emergency unit had severe infections requiring the use of parenteral antimicrobials. Antimicrobials with less drug resistance potential were used in most instances. The choice of antibiotic was generally based on the prevalent microbial sensitivity patterns in the hospital. Further this drug utilization study provides us with a database which can be used to monitor the institutional antimicrobial policy.

PP - 6

### STUDY OF THE EFFECT OF INTRAVAGINAL MISOPROSTOL (PGE 1) IN INDUCTION OF LABOUR.

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**Objectives:** 1. To study the safety and efficacy of intravaginal Misoprostol in progress and induction of labour. 2. To study the maternal side effects and the foetal outcome.

**Methods:** Total 46 pregnant women aged between 21-25 yrs. with indication of labour participated in the study. 20 patients (control group, PGE 2) were administered 0.5 mg. Dinoprostone (PGE 2) intracervically 12 hourly while 26 patients (study group, PGE 1) were given Misoprostol (PGE 1) 100 µg 6 hourly intra vaginally.

**Results:** Mean induction of labour initiation interval was  $2.08 \pm 1.46$  hrs in study group and  $2.21 \pm 1.20$  hrs in control group. Induction delivery interval was  $6.92 \pm 4.01$  hrs in study group and  $12.54 \pm 7.73$  in control group. Vaginal route of delivery was 95 % in study group and 85 % in control group. Average dosage required were  $1.55 \pm 1.02$  in study group and  $1.30 \pm 0.46$  in control group. All these result were statistically significant. Very few maternal side effects were reported. There was no significant difference in foetal outcome in either group.

**Conclusion:** Misoprostol is easy to administer and is cheap, effective, safe and convenient drug for induction of labour.

PP - 7

**ESTIMATION OF SERUM ZINC, COPPER AND ZINC COPPER RATIO IN PATIENTS OF TUBERCULOSIS: IMPACT ON ANTITUBERCULAR THERAPY.**

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**Introduction:** The serum concentration of copper and zinc vary in tuberculosis and returns to their normal range as patients responds to antitubercular therapy.

**Methods:** Serum copper level, serum zinc level and serum zinc copper ratio was estimated in patient of tuberculosis before and after 4 weeks of anti-tubercular therapy. The estimation of serum level of these trace elements was done with atomic absorption spectrophotometer, ECIL AAS 400.

**Results:** In cases of tuberculosis the serum zinc levels were below normal ( $0.46 \pm 0.09$ ) and serum copper levels were above normal ( $4.49 \pm 0.66$ ) hence serum Zn / Cu ratio became below normal ( $0.11 \pm 0.06$ ). After 4 weeks of anti-tubercular therapy, the levels of serum Zn and Cu returned to normal range ( $0.58 \pm 0.09$  and  $2.45 \pm 0.76$  respectively). The return to normal range corresponded with the improvement in the symptomatology of patients.

**Conclusion:** The serial estimation of serum Cu and Zn levels, and serum Zn / Cu ratio may be used as a successful tool to monitor the effect of anti-tubercular therapy in patients of tuberculosis.

PP - 8

**CLINICAL EFFICACY AND SAFETY OF HISTAGLOBULIN AND FEXO-FENADINE IN PATIENTS OF CHRONIC IDIOPATHIC URTICARIA.**

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Department of Pharmacology, Dept. of Skin and STD, Govt. Medical College, Amritsar - 143001.

**Objective:** To investigate the clinical efficacy and safety of Inj. Histaglobulin and Tab. Fexofenadine in patients of chronic idiopathic urticaria.

**Methods:** 50 patients of chronic idiopathic urticaria aged 21-50 years were selected from the Department of Skin and STD of Govt. Medical College, Amritsar. They were administered Tab. Fexofenadine, 180 mg OD for 16 weeks and Inj. Histaglobulin, 2 ml sc, once weekly for first 3 weeks and once fortnightly for next 12 weeks. Follow-up was done at the beginning of 6th, 7th and 8th month. Prior written and informed consent was obtained from each patient.

**Results:** At 9th week, there was complete relief (76 -100%) in 6%, excellent improvement (51-75%) in 28%, very much improved (26-50%) in 54% and improved (1-24%) in 8% patients. At 17th week, complete relief was in 16%, excellent improvement in 58%, very much improved in 20% and improved in 4% patients. Complete relief was observed in 12%, 12% and 10% patients at the beginning of 6th, 7th, and 8th month respectively. Local and systemic drug events were not observed except exacerbation of wheals in 2 patients.

**Conclusion:** The combination of Inj. Histaglobulin and Tab. Fexofenadine given for 16 weeks provided excellent improvement in majority patients. The combination treatment is efficacious and appears to be safe.

PP - 9

**EFFECT OF CURCUMIN ON ERYTHROCYTE MALONDIALDEHYDE (MDA) LEVELS IN PATIENTS OF CHRONIC PANCREATITIS.**

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**Objective:** To assess the reduction of oxidative stress in chronic pancreatitis patients after administration of curcumin.

**Methods:** 10 patients of chronic pancreatitis were selected from gastroenterology department, for a study period of 6 weeks, after obtaining their consent and after approval from institutional ethical committee. The patients in the age group of 15- 45 of either sex who were clinically diagnosed as chronic pancreatitis were included and patients with the present or past history of gallstones, gastritis or gastric ulcer or hepatitis were excluded from the study. Patients were given capsules containing 500 mg of curcumin with 5 mg of piperine three times daily for 6 weeks. Fasting blood samples were collected before and after the treatment. Erythrocyte level of lipid peroxidation product was estimated by spectrophotometric method, measuring thiobarbuturic acid (TBA) reactivity and expressed as MDA in nmoles/gm of Hb.

**Results:** The MDA values before and after treatment are presented as mean  $\pm$  SD and compared using student t test. MDA levels (before treatment) -  $14.36 \pm 6.18$  nmoles/gm of Hb and (after treatment)  $8.52 \pm 2.50$  nmoles/gm of Hb (p value 0.02).

**Conclusion:** Though there is significant change in the erythrocyte MDA level, it has to be ascertained whether the biochemical improvement correlates with clinical improvement, if then, what should be the duration of treatment to have significant clinical improvement.

PP - 10

**PRECLINICAL EVALUATION OF ANTIDEPRESSANT ACTIVITY OF NR-ANX-C IN MICE.**

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**Introduction:** Depression is a chronic illness that affects people of all ages. Although there are many effective antidepressants available today, the current armamentarium of therapy is often inadequate, with unsatisfactory results in about one third of all subjects treated. This provides impetus in the search of newer and more effective antidepressants. In this direction a new compound, NR-ANX-C, developed by Natural Remedies is claimed to have antidepressant activity. The objective of the present study is to assess and compare the antidepressant effects of NR-ANX-C, a herbal product of Natural Remedies, Bangalore, with the standard drug imipramine in two experimental models-forced swim test and tail suspension test.

**Methods:** In bred male albino mice weighing 25-30 g were selected. The standard drug imipramine and the test drug NR-ANX-C were suspended in 1 % gum acacia solution. Vehicle (10 ml/kg), imipramine (1.5 and 3 mg/kg) and NR-ANX-C (5, 10 and 20 mg/kg) were administered orally, one hour prior to the experimental procedure. Duration of immobility was noted.

**Results:** Both imipramine and NR-ANX-C significantly reduced the duration of immobility of animals when compared to the vehicle treated group.

**Conclusion:** Reduction in the duration of immobility, in both the tests studied, similar to imipramine indicate that NR-ANX-C have antidepressant activity.



PP - 11

### EFFECT OF PHYTIC ACID ON GASTRIC ULCERS IN RATS.

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Phytic acid (PA), a nontoxic dietary constituent, is an antioxidant, energy store and a regulator of vesicular transport via binding to various proteins. PA inhibits Fenton reaction by complexing with Fe (II) and blocks the generation of OH<sup>\*</sup> radical. In our earlier study PA has shown potent anti-inflammatory activity. Gastric irritation being a common side effect of NSAIDs, anti ulcer activity of PA on ibuprofen, alcohol and cold stress-induced ulcers was studied in rats. PA showed significant protection at all the doses tested (90 - 450 mg/kg), with a maximum activity at 450 mg/kg. There was a significant increase in tissue malondialdehyde levels in alcohol treated rats but these levels fell following PA treatment. Moreover, pretreatment with PA significantly inhibited the various effects of ethanol on gastric mucosa, such as, reduction in the concentrations of proteins and nonprotein sulfhydryl groups, besides necrosis, erosions, congestion and haemorrhage. The results suggest that the gastro-protective effect of PA could be mediated by its free radical scavenging activity and cytoprotection of gastric mucosa.

PP - 12

### A PRELIMINARY STUDY ON THE EFFECT OF *WITHANIA SOMNIFERA* ON SIDE EFFECTS OF CHEMOTHERAPY IN CANCER PATIENTS.

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**Introduction:** Anticancer drugs often limit their full therapeutic dose because of their high toxicity profile e.g. gastrointestinal, haematological, renal etc. Though several palliative approaches are attempted to reduce the toxicity such as antiemetics, growth factors, antimicrobials etc, there still remains a need to have adjuvants for prevention of toxicity. Traditionally *Withania somnifera* (Hin: Ashwagandha) has been used as an adaptogen. Animal studies have shown that it possesses immunostimulatory, antitumour and anti-stress properties. Therefore, the study was conducted to evaluate the effect of *Withania somnifera* on side effects of chemotherapy in cancer patients.

**Methods:** A single blind, randomized, placebo controlled study was planned among 24 patients of cancer (8 each of AML, ALL, ovarian tumours). 12 of these patients were included in the test group while the rest were kept as controls. The test group will receive marketed preparation of *Withania somnifera* root powder (Stresscom, Dabur India Ltd) in a dose of 300 mg bid while the controls will be administered glucose filled capsules as placebo for two months in addition to the standard chemotherapy regime. The parameters to be studied are gastrointestinal toxicity (nausea, vomiting and stomatitis), haematological toxicity (haemoglobin, total leucocyte count, absolute neutrophil count, platelets), nephrotoxicity (serum urea and creatinine) and general performance indicator (Karnofski's Performance Index). Till now 8 patients-5 AML (3 control, 2 test group), 2 ALL (1 control, 1 test group) and 1 ovarian tumour (control group) have completed their follow up period of 2 months.

**Results:** In the 3 patients treated with *Withania somnifera*, there was a trend indicating a low incidence of secondary chest infections and stomatitis and better hemogram profile and general condition with respect to controls. No appreciable benefit was observed in the incidence of nausea, vomiting and renal functions test. The statistical analysis could not be done, as there was inadequate number of patients studied till now.

**Conclusion:** Although the study is at a very preliminary stage, a trend indicating an improvement in overall general condition has been noticed. The study warrants more number of subjects to reach a definite conclusion.

PP - 13

### A STUDY OF MOOD STABILIZERS IN PATIENTS OF BIPOLAR DISORDER: MONOTHERAPY VS COMBINATION THERAPY.

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**Objectives:** The study was carried out to assess the relative efficacy and tolerability of lithium (Li) and valproate (VPA) monotherapy and lithium-valproate (Li+VPA) combination therapy in patients of bipolar disorder over a follow up period of 12 weeks.

**Methods:** Patients of bipolar disorder (n=40, Li=13, VPA=14 and Li+VPA=13) who had recovered from an index manic episode were included in the study. Lithium was given in range of 900-1200 mg in Li group and valproate was given in range of 1000-1500 mg in VPA group. Lithium and valproate were given together in the above mentioned doses in Li+VPA group. Patients were followed for a period of 12 weeks. During the follow up period, the patients were assessed on Young Mania Rating Scale (YMRS), Clinical Global Impressions (CGI) and Hamilton Depression Rating Scale (HAM-D). Patients were also monitored for adverse events.

**Results:** No significant difference was found on the YMRS and HAM-D in the three groups. No patient in the study experienced a relapse. Li+ VPA and VPA groups were significantly better than Li group on CGI. No significant difference was found in the three groups in terms of adverse event scores.

**Conclusion:** Monotherapy as well as combination therapy with mood stabilizers is efficacious in bipolar disorder. However, combination therapy with lithium and valproate and monotherapy with valproate are superior to lithium monotherapy in terms of overall assessment of the patient. Combination therapy as well as monotherapy is well tolerated.

PP - 14

### EFFECT OF SIMVASTATIN IN COMBINATION WITH NIACIN AND ALONE ON LIPID PROFILE AND LP(A) LEVELS.

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**Objective:** To compare the effect of Simvastatin in combination with Niacin and alone in patients of hyperlipidemia.

**Method:** Fifty hyperlipidemic patients in the age group of 30-70 years were divided into two groups i.e. group I and group II. Group I patients were put on Simvastatin (20 mg/day) and group II on Simvastatin (10 mg/day) plus Niacin (500 mg/day). The lipid profile and Lp(a) levels were measured before the start of therapy and at 6 weeks and 12 weeks of treatment.

**Results:** It was seen that in group I (on simvastatin therapy) there was a decrease of  $15.45 \pm 18.90\%$  in triglyceride levels as compared to  $28.17 \pm 19.99\%$  in triglyceride levels in group II (on combination therapy) ( $p < 0.05$ ). There was a decrease of  $30.39 \pm 12.56\%$  and  $26.32 \pm 13.98\%$  in total cholesterol levels in group I and group II respectively ( $p > 0.05$ ). LDL decreased by  $40.77 \pm 15.21\%$  and  $34.34 \pm 19.27\%$  in group I and group II respectively ( $p > 0.05$ ). HDL increased by  $7.15 \pm 7.26\%$  and  $16.78 \pm 18.15\%$  in group I and group II respectively ( $p < 0.05$ ). Lp(a) levels decreased by  $17.66 \pm 23.61\%$  in group I and by  $25.84 \pm 22.40\%$  in group II ( $p > 0.05$ ). Both the drugs were tolerated well by patients in both the groups and there were no drop-outs.

**Conclusion:** Results show that combination therapy of Simvastatin and Niacin has better effects on triglycerides. HDL and Lp(a) levels whereas Simvastatin alone has better effect on total cholesterol level. Combination therapy is more suited for Indian population as Indians have elevated triglyceride and Lp(a) levels and low HDL levels.

PP - 15

**POLYMPHONUCLEAR LEUKOCYTE FUNCTION IN TYPE - 2 DIABETES MELLITUS PATIENTS AND ITS CORRELATION WITH GLYCAEMIC CONTROL.**

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**Objective:** The present study aimed to assess the glycaemic control achieved by glibenclamide as measured by blood sugar fasting (FBS) and postprandial (PPBS) and glycosylated haemoglobin (GHb). The study evaluated the effect of glibenclamide on polymorphonuclear leukocyte (pMNL) function Hydrogen peroxide ( $H_2O_2$ ) and superoxide anion ( $O_2^-$ ) and studied the relationship between the PMNL function and glycaemic control.

**Methods:** Thirty, type-2 diabetes mellitus patients were recruited from the diabetes clinic of GTB hospital after their informed written consent and approval of the institutional ethical committee. PMNL function, FBS, PPBS and GHb were assessed both before and after 10 weeks of treatment with glibenclamide.

**Results:** Glibenclamide reduced FBS, PPBS, and GHb significantly ( $P < 0.001$ ).  $H_2O_2$  and  $O_2^-$  production increased significantly after treatment. No correlation was seen between PMNL function and glycaemic control.

**Conclusion:** Glibenclamide improved Oxygen dependent bactericidal mechanism of PMNL. Further studies with a larger number of patients are needed to assess the correlation between the glycaemic control and PMNL function.

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**EFFECTS OF NITRERGIC AGENTS ON SOME NEUROBEHAVIORAL PARAMETERS IN : NORMAL AND STRESSED RATS.**

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The neurotransmitter/neuromodulator status of nitric oxide (NO) has been suggested and the present study evaluated the effects of some nitrenergic agents on neurobehavioral parameters in normal and stressed rats. In the elevated plus maze (EPM) test, the NO precursor, L-Arginine, dose dependently increased open arm entries and time spent in open arms when compared to controls. These effects were similar in both normal and restraint stress (RS) exposed rats, and were comparable to those of diazepam. On the other hand, the NO synthase inhibitor, L-NAME (10 and 50 mg/kg) showed differential, dose related effects on the EPM parameters, with lower and higher doses producing opposite effects. In the open-field (OF) test both diazepam and L-Arginine (a) reduced OF entry latency. and (b) increased ambulation and rearing, in normal and RS exposed rats. Whereas, L-NAME (10 and 50 mg/kg) showed opposite effects on the OF test parameters, in both normal and stressed rats. These results are discussed in light of the possible involvement of NO in stress .

PP - 17

**STUDY OF SENSITIVITY/RESISTANCE (S/R) PATTERNS OF MICROBIAL AGENTS IN A TEACHING HOSPITAL.**

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This study was carried out to study the S/R patterns of microorganisms against some of the commonly used antimicrobial agents (AMA). This was a prospective, observational study. A total of 262 specimens (pus, sputum, throat swabs, urine) received in the department of microbiology from Jan 2002 to May 2002 were studied. Culture-sensitivity (C/S) tests were performed by disc-diffusion method. Commonest microbe isolated from pus and throat swabs was staphylococcus (54% and 88% respectively). Sputum specimens mainly showed the growth of *staphylococci* (41%) and *klebsiella* (36%) while the common microbes isolated from urine cultures were *klebsiella* (45%) and *E.coli* (33%). *Staphylococci* were sensitive to cephalosporins (86%), methicillin (73%), amoxicillin (65%) and resistant to ampicillin (100%), cloxacillin (95%), cephaloridine (83%). *Klebsiella* was sensitive to ciprofloxacin (86%), cephalosporins (79%), gentamicin (75%) and resistant to amoxicillin (86%), cephaloridine (80%) while *E.coli* was sensitive to ciprofloxacin (80%), cephalosporins (78%) and resistant to cephaloridine (95%), amoxicillin (84%) and gentamicin (75%). The S/R patterns of microorganisms may vary from place to place. So it is very essential to study the S/R patterns of microbes against commonly used AMAs, at regular intervals. This will be helpful in the rational use of AMAs in the treatment of infections.

PP - 18

**PREVALENCE OF SELF-MEDICATION AMONGST THE URBAN LITERATE POPULATION OF A NORTH INDIAN CITY.**

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**Objective:** To assess the prevalence of self-medication, the reasons for its preference and preferred conditions for its usage.

**Methods:** A survey using a preformed structured multi response questionnaire was conducted amongst the urban literate population (100 persons) including bank employees, university students and teachers. They were asked questions about self-medication - prevalence, reasons for its preference and ailments for which it was used.

**Results:** About 72% of study population practised self-medication. The most common ailments for which self-medication was prevalent were headache (84%) and cough/cold (76%). Most commonly used drugs were NSAIDs (87%) followed by antihistaminics (51%). 43% of subjects took medicines which had been prescribed by a doctor in the past. 36% and 25% took medicines on the suggestion of parents/relatives and chemist respectively. The reasons for self-medication were minor ailment (48%), easy availability of drugs (37%) and that going to doctor was expensive (22%). 75%, 36% and 23% checked for date of expiry, exact spelling and intactness of packaging respectively before using the medicines.

**Conclusion:** The results show that there is a high degree of prevalence of self-medication especially for minor ailments. NSAIDs were the most commonly used drugs for self-medication and the commonest source of knowledge for self medication was an earlier prescription.

PP - 19

### PRESCRIBING PATTERN OF NSAIDS IN ORTHOPAEDIC PRACTICE.

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**Objective:** To study the prescribing pattern of NSAIDs in orthopaedic practice, according to WHO Complementary Drug Use Indicators.

**Methods:** 600 prescriptions from the orthopaedics OPD of SGTB Hospital attached to Govt. Medical College, Amritsar, were collected over a period of 6 months and the data collected was analysed for various parameters.

**Results:** Systemic NSAIDs were prescribed to 89.66% patients. Monotherapy was prescribed to 34.75% and FDC to 65.24%. In monotherapy, nimesulide was prescribed in 31.55%, rofecoxib in 29.94% diclofenac sodium in 18.18% and diclofenac potassium in 6.95% patients. Under FDC, 45.86% were prescribed combination of diclofenac sodium, paracetamol and chlorzoxazone; 21.65% combination of diclofenac sodium and paracetamol; 17.66% diclofenac sodium and serratiopeptidase combination and 8.83% combination of nimesulide and tizanidine. 5.83% prescriptions comprised of non-pharmacological therapy without any drug prescription. The average number of drugs per prescription was 3.09. Analgesic gel/herbal oil to be applied locally was prescribed in 57.5% in which diclofenac sodium gel was in 40.57%.

**Conclusion:** FDC was preferred to monotherapy. The combination of diclofenac sodium, paracetamol and chlorzoxazone was most commonly prescribed whereas nimesulide was the most commonly used drug as monotherapy. Diclofenac sodium gel was most commonly prescribed analgesic locally. No drug was prescribed by generic name.

PP - 20

### PRESCRIPTION AUDIT STUDY IN SRINAGAR (GARHWAL), UTTARANCHAL, INDIA.

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**Objective:** To study prescribing pattern in Srinagar (Garhwal), Uttaranchal, India.

**Methods:** This was a prospective, randomised, single blind survey of 400 prescriptions from Govt. Combined Hospital, Srinagar (Garhwal), Uttaranchal, India. Various WHO recommended and other prescribing specific indicators were studied.

**Results:** Randomly obtained 400 prescriptions were written for 59.25% males and 40.75% females. Average number of drugs 3.65 and about 51% drugs were prescribed by generic names. Most widely prescribed drugs belong to NSAIDs (89.75%), antibiotics (77.25%), and vitamins (59.74%). Proportion of fixed dose combinations was 59% and injection use was 7%.

**Conclusion:** Increased drug exposure and indiscriminate use of NSAIDs, antibiotics, and vitamins was observed in various clinical conditions. Further studies in different hospitals of this area should be carried out. It is recommended that well designed training programme should be conducted on rational drug use in this health facility and other health facilities of this area if similar lacunae are found by prescription survey.

**PP - 21****PHARMACOEPIDEMOLOGY AND RISK FACTORS OF HYPERTENSION IN WESTERN GUJARAT.**

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The present investigation was undertaken to evaluate the risk factors and pattern of drug usage in patients with hypertension. 920 subjects attending free BP camps organized jointly by our team at Sterling Hospital, Ahmedabad. After a detailed questionnaire filled by team of pharmacists, clinical parameters were recorded by cardiac specialists. It was found that out of 920 subjects evaluated, 53% had hypertension. However, only 36% of them were found to be taking drug treatment. Out of 36% of patients taking drug treatment, only 35% were reported to have an effective control of blood pressure. While non-compliance was found to be one of the reasons for ineffectiveness of the drug treatment, it was also observed that improper selection was also responsible for ineffectiveness of the drug. In conclusion, our data suggest that public awareness and proper selection of antihypertensives with involvement of pharmacist in counselling with patients is essential to have adequate control of blood pressure and thereby prevent incidences of Coronary Artery Diseases that is growing dangerously in India.

**PP - 22****PHARMACOKINETICS OF AN ANTI-ISCHEMIC AND ANTI-HYPERTENSIVE AGENT CDRI-93/478 IN RATS.**

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CDRI-93/478, a potent anti-ischemic and anti-hypertensive agent, is in advanced stage of preclinical trials. Its pharmacokinetic parameters were generated to aid its development as a potential anti-ischemic and anti-hypertensive agent. The study was carried out with adult male Sprague Dawley rats. The rats were fed an oral dose of 2 mg/kg dose of a solution formulation of the compound. Blood was withdrawn from 0.5 to 24 h post dose. Serum concentrations were determined using the validated HPLC assay. The method involved double extraction of serum samples with diethyl ether and the use of fluorescence detection at  $EX_{max}$  250 nm and  $EM_{max}$  at 372 nm the use of a cyano column, mobile phase (35% acetonitrile in acetate buffer, pH 3.5) pumped at a flow rate of 1 ml/min. Peak concentration  $C_{max}$  and its occurrence were directly read from the concentration-time data. Following 2 mg/kg oral dose, the compound was monitored up to 8 h. It exhibited two peak concentrations ( $C_{max(1)}$ ,  $478.4 \pm 90.8$  ng/ml and  $C_{max(2)}$ ,  $154.1 \pm 26.9$  ng/ml) after 0.5 and 3.0 h. Probably, the compound is undergoing enterohepatic recycling. Other pharmacokinetic parameters were determined on subjecting the concentration-time to non-compartmental analysis. It showed elimination half-life was 2.09 h. The clearance (C1/F) was 1.69 L/h/kg. The volume of distribution ( $V_d/F$ ; 5.08 L/kg) was much larger than the blood volume of rats, indicating rapid uptake of the compound by quickly perfused organs such as the liver and kidney.

PP - 23

**PHARMACO-ECONOMICS IN OCULAR PHARMACY PREPARATIONS - AN ANALYSIS.**

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**Objective:** Cost consideration has a special relevance in therapeutics perhaps more so in the developing countries like India. Ours is a tertiary care eye Centre attached to a major multi disciplinary hospital. At our Centre we manufacture and dispense some common ocular drugs for our out patients and in patients. The objective of this study was to calculate savings from the drugs manufactured in our Ocular Pharmacy as compared to the market prices of the same items.

**Methods:** We routinely prepare drugs like Homatropine, Artificial Tears, Sodium Sulphacetamide, Methylcellulose, Hypertonic Saline and McCarey-Kaufman's (MK) medium for corneal preservation. Based on our consumption, on calculating the annual expenditure for the above items against their corresponding market prices, the savings per year were analysed over the past 5 years.

**Results and Conclusion:** It was calculated that the annual savings were Rs. 5,16,228/-, Rs. 9,49,404/- and Rs. 10,96,404/- in the year 1997, 1999 and 2001 respectively. It is recommended that any hospital with one trained Pharmacist could cost-effectively dispense most common ophthalmic medications with significant savings.

PP - 24

**PRESCRIBING PATTERN OF ANTIHYPERTENSIVES IN A TERTIARY CARE TEACHING HOSPITAL AND ITS VARIATION WITH COMORBID CONDITIONS.**

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**Objective:** To study the variation in prescribing pattern in patients of hypertension alone and hypertension with comorbid conditions-diabetes mellitus, coronary artery disease or congestive heart failure; and compare it with WHO guidelines, 1999.

**Methods:** Prescriptions (n=406) for these patients were collected at random from the medical OPD of Guru Nanak Dev Hospital, attached to Government Medical College, Amritsar over a period of nine months. Prescribing trends for antihypertensives were analysed and compared with WHO guidelines.

**Results:** The average number of antihypertensive agents prescribed per patient was 1.42. ACE inhibitors were prescribed most often for patients with hypertension alone (59.52%), hypertension with diabetes mellitus (68.83%); and hypertension with CHF (75%) where they were usually given in combination with diuretics (87.5%). Beta-adrenergic antagonists (52.94%) and calcium channel antagonists (51.52%) were prescribed most often for patients with coexisting hypertension and CAD. Diuretics were prescribed least i.e. in 14.78% of total and only 4.76% of the group with hypertension alone. Low-dose aspirin was prescribed in 88.7 % of total patients. FDCs were used for 21.92 % patients.

**Conclusion:** The prescribing pattern largely conformed to guidelines laid down by WHO, except diuretics, which were used sparingly. WHO guidelines propose their use, especially in low doses, particularly for elderly patients.

PP - 25

### PRESCRIBING PATTERN OF ANTIMICROBIALS IN PATIENTS UNDERGOING ELECTIVE ABDOMINAL SURGERY IN A TERTIARY CARE HOSPITAL.

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**Objective:** To study the prescribing pattern of injectable / oral antimicrobials in the preoperative period.

**Methods:** Prescriptions of 450 indoor patients who had undergone elective abdominal surgery (Type II) at Guru Nanak Dev Hospital, Amritsar were collected over a period of six months and analysed.

**Results:** 86.6% of patients received a single dose of an antimicrobial as preoperative prophylaxis i.e Cefazolin, Cefuroxime, Ceftriaxone and Cefotaxime in 26.3%, 14.7%, 16.8% and 33.4% patients respectively at time of induction of anaesthesia. In the postoperative period, average no. of antimicrobials / patient were 2.9. No antimicrobial was administered to 8.9% patients. Commonly prescribed injectable antimicrobials were Gentamicin, Ampicillin, Cefotaxime and other Cephalosporins in 63%, 32%, 38% and 24.4% patients and oral antimicrobials were Ciprofloxacin, Cephalosporins and metronidazole in 49.7%, 21% and 4% patients respectively. Amongst the cephalosporins, 3rd generation agents were most frequently prescribed for preoperative prophylaxis as well as postoperatively in 50.2% and 89.3% patients respectively.

**Conclusion:** Cefazolin, which is the recommended drug according to the guidelines for prophylaxis in surgical procedures was being prescribed to 26.3 % patients. Members of the 3rd generation were preferred amongst the cephalosporins in the pre operative period.

PP - 26

### LINEZOLID, A NOVEL OXAZOLIDINONE: PRECLINICAL PHARMACOKINETICS.

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**Objective:** Linezolid (LNZ) is the first of a new class of antimicrobial agents, the oxazolidinones, to be developed for the treatment of gram positive infections. LNZ has a wide spectrum of activity against gram positive bacteria, including those resistant to other antibiotics. In the present work our objective was to establish the PK profile of LNZ in mouse and rat at different doses to determine the linearity and estimate the oral bioavailability.

**Methods:** Mouse doses: 5, 15 and 30 mg/kg po, and iv; Rat doses: 5, 15 and 30 mg/kg, po and iv. At all the doses blood samples were withdrawn at different intervals of time and the serum concentrations of LNZ were determined by in - house developed and validated HPLC method. In addition lung tissue concentrations were also determined in mouse. PK parameters were calculated by non compartmental analysis using WIN NONLIN software. Serum protein binding was determined by ultrafiltration.

**Results:** In both mouse and rat the absolute oral bioavailability of LNZ was 90 - 95%. In mouse up to 15 mg/kg dose there was a linear increase in  $C_{max}$  and AUC, but at 30 mg/kg dose level a non linear increase in AUC was seen. However in rat a linear increase in  $C_{max}$  and AUC was seen at all the doses. Serum protein binding in both the species was around 30 - 40%.

**Conclusion:** 1. LNZ achieves adequate serum concentrations at the tested doses which are higher than its MIC against MRSA and Strep. pneumoniae; 2. Adequate PK parameters found for LNZ combined with optimal serum binding would enable the drug to be used effectively against resistant gram-positive infections.



PP - 27

**LIPOIC ACID AS A RESCUE AGENT IN ADRIAMYCIN - INDUCED PEROXIDATIVE DAMAGES TO ERYTHROCYTES.**

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One of the most intriguing phenomenon observed during adriamycin (ADR) toxicity has been attributed to ADR - induced oxidative stress. The study was aimed to assess the protective effect of lipoic acid against ADR - induced erythrocyte membrane lipid peroxidation (LPO) and antioxidant status. Male albino rats (Wistar strain) were subjected to ADR (1 mg/kg body weight/day/rat, iv) once a week for a period of 12 weeks. These rats demonstrated enhanced erythrocyte membrane LPO and an onslaught in the antioxidant defense armory witnessed by lowered activities of superoxide dismutase, glutathione peroxidase, glutathione, vitamin A, vitamin C, vitamin E, along with a decline in the activities of phosphohydrolases. Hematological indices like hemoglobin levels and hematocrit were also lowered along with a marked increase in the activities of serum glutamate pyruvate transaminase and serum glutamate oxaloacetate transaminase. Pre-treatment with lipoic acid (35 mg/kg/body weight/day/rat, ip) intraperitoneally once a week for 12 weeks was effective in counteracting these biochemical disturbances thereby minimising the toxic side effects of ADR.

PP - 28

**EFFECT OF DOXYCYCLINE ON COLLAGENATION PHASE OF HEALING IN RATS.**

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**Objectives:** To find out if doxycycline could promote normal and dexamethasone depressed healing in experimentally inflicted wounds on rats.

**Methods:** Studies were conducted in male Wistar rats, 180 - 200 g. Two wound models namely incision and dead space were employed in the study to assess the effects of drugs on collagenation phase of healing. The parameters monitored were breaking strength (g) in incision wounds and breaking strength, dry weight and hydroxyproline content of granulation tissue harvested in 10-day old dead space wounds. Four groups of animals (n = 8) per model were used. While the first group received vehicle, the remaining groups received respectively doxycycline PO (4 mg/kg), dexamethasone (DXT) (0.17 mg/kg, im) and the combination of DXT plus doxycycline. Results were analysed by one way ANOVA followed by Scheffe's test.

**Results:** Doxycycline *per se* did not affect the breaking strength, and dry weight parameters. However, it significantly ( $p < 0.05$ ) enhanced hydroxyproline content of granulation tissues. On the other hand it significantly ( $p < 0.05$ ) reversed the dexamethasone depressed healing in incision and dead space wounds.

**Conclusion:** Doxycycline does not influence the normal healing. However, it may promote the healing in the healing-retarded situations, perhaps by inhibiting the collagenase activity.

PP - 29

### DRF 3644 - A NOVEL CYCLOOXYGENASE - 2 INHIBITOR.

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**Objective:** In search of selective COX-2 inhibitors as novel pharmacophores from plants, an alkaloid with indolizidine skeleton was isolated. In view of its structural similarities with known COX-2 inhibitors, a number of substituted indolizidine derivatives were synthesized and tested for COX-2 selectivity.

**Methods:** Initially all the compounds were evaluated *in vitro* at 100  $\mu$ M for COX-1 and COX-2 activity by spectrophotometric method. COX-1 activity was assessed using RAM seminal vesicles as a source of COX-1 enzyme. The COX-2 activity was assessed against COX-2 enzyme obtained from Sf9 Cells infected with baculovirus containing human COX-2 cDNA. The human whole blood assay was performed for both COX-1 and COX-2. Compounds that exhibited good COX-2 selectivity at 100  $\mu$ M were further evaluated and the IC<sub>50</sub> values were determined for COX-1 and COX-2. The most selective COX-2 compound (DRF3644) was selected and evaluated for *in vivo* potential using carrageenan induced rat paw edema, hyperalgesia and endotoxin induced pyrexia in rats. The ulcerogenic liability was tested in mice.

**Results and Conclusion:** DRF 3644 is a novel, selective COX-2 inhibitor exhibiting antiinflammatory activity (ED<sub>50</sub> = 6.48 mg/kg), analgesic activity (ED<sub>50</sub> = 4.3 mg/kg), and antipyretic activity (ED<sub>50</sub> 8.3 mg/kg) in experimental models.

PP - 30

### EFFECT OF INTRA VENTRICULAR METHOTREXATE ON SEROTONIN METABOLISM IN RAT BRAIN.

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**Introduction:** Intrathecal methotrexate in children with leukemia is known to cause seizures, leukoencephalopathy and cognitive dysfunction. Previous work suggested that methotrexate impairs the biosynthesis of brain amine, especially dopamine. We extend this study by measuring the serotonin and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) in various regions of the brain to understand the neurotoxic mechanism.

**Methods:** Four months male Wistar rats were given different doses (1.5 or 2 mg/kg) of methotrexate (3 doses) intraventricularly. The level of serotonin and its metabolite, 5-HIAA were estimated in different regions of the brain by HPLC method. The results were compared with control as well as sham operated group.

**Results:** The serotonin level declined significantly ( $P < 0.01$ ) at 2 mg/kg dose in all the regions estimated except in hypothalamus. Further the level of 5-HIAA reduced significantly ( $P < 0.01$ ) in all the regions investigated except in hypothalamus.

**Conclusion:** This study clearly demonstrates that methotrexate has altered brain serotonin metabolism. The seizures, leukoencephalopathy and cognitive dysfunction after methotrexate therapy may also involve serotonergic system. In view of the above finding in rats, children undergoing such treatment should be monitored for neurological disturbances. One has to consider both benefit and risk factor before selecting the dose, as prevalent therapeutic dose has been proved to be neurotoxic in the present study.

PP - 31

### INOSINE AMELIORATES EXPERIMENTALLY INDUCED HEART BLOCK.

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**Objective :** To evaluate the effect of inosine (a deaminated product of adenosine) in heart block induced by coronary artery occlusion and digoxin.

**Methods:** In phenobarbitone ( 30 mg/kg, iv) anaesthetised dogs main branch of coronary artery was ligated in 2 stages. Initial (control) and after MI, EKG ( Lead II) recordings were made to assess effect of drug on HR and rhythm. On the next morning (24 hrs after ligation) animals with II and III degree and complete heart block were selected and divided into 2 groups of 5 animals each. In group I inosine (25 mg/kg, iv) was given as a single bolus injection. Animals of group II received continuous iv infusion of inosine (1 mg/kg/min) for 30 min. In another series of experiments effect of inosine (inj. as well as infusion) was also evaluated on heart block induced by high doses of digoxin (100 µg/kg, in 3 divided doses).

**Results:** In animals with II, III degree and complete heart block, inosine bolus injection as well as infusion completely restored normal sinus rhythm. There was a significant increase in heart rate following inosine administration. Digoxin induced heart block was also completely abolished after inosine injection and infusion.

**Conclusion:** Inosine has good potential in the treatment of heart block after myocardial infarction and due to overdoses of digoxin.

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### LIPID LOWERING ACTIVITY OF TATA TEA - LEAF AND DUST.

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Tea leaf (*Camellia* species) extract has been reported to exert beneficial effects against platelet aggregation, cancer, tumor, hypercholesterolemia and atherosclerosis. Since heart diseases are directly related to disorders of lipid metabolism, the aim of the present study has been to investigate the mode of action of CTC leaf extract as well as Tea dust, manufactured by TATA Tea Co. Ltd., India as lipid lowering agent in normal and triton induced hyperlipemia in rats. Normal adult Charles foster rats were fed orally with tea extract at a dose of 100 mg/kg for 60 days and blood total cholesterol (TC), phospholipid (PL) and triglyceride (TG) were investigated after an interval of 30 and 60 days. These were found to be lowered significantly as compared to control. In another set up of experiment, hyperlipemia was induced by triton WR1339 (400 mg/kg). There was a marked increase in the level of the serum TC, PL, TG along with inhibition of post-hepatic lipolytic activity (PH LA). These levels were significantly reversed by the treatment of hyperlipemia in both extracts. It is concluded that lipid lowering activity of tea extract due to reactivation of extra hepatic lipases and anti-oxidant property of this natural product.

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### ANTIALLERGIC ACTIVITY OF A SYNTHETIC COMPOUND - 96/775

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**Objective:** A new compound 96/775 was synthesized in our Chemistry Division and evaluated for antiallergic activity by us.

**Methods:** Antiallergic activity of synthetic compound 96/775 was evaluated and compared with standard drug disodium chromoglycate (DSCG) using paradigms. Passive cutaneous anaphylaxis (PCA), mast cell stabilising activity in mice and rats and aerosol test in sensitized guinea pigs.

**Results:** Synthetic compound 96/775 at the dose of (25-50 mg/kg, po) in mice inhibited (65-75%) PCA activity. In rats this compound has shown dose dependent (25-50 mg/kg) anti-PCA activity (65-73%). The mast cell stabilising activity in rat at 10 mg/kg, po for 4 days showed 68% protection of mast cell degranulation. In sensitized G. pig induced by egg albumin also showed 68% protection. These results were comparable with disodium chromoglycate (DSCG). Thus our results suggest that synthetic compound 96/775 has promising antiallergic activity, which needs further evaluation.

**Conclusion:** It is concluded that compound 96/775 possess potent antiallergic activity comparable with that of DSOG, a clinically used antiallergic drug.

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### EFFECT OF OXYTOCIN IN FORMALIN - INDUCED PAIN RESPONSE IN MICE.

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**Objective:** Oxytocin a nemopeptide, is reported to play a role as a nemotransmitter/nemomodulator in the central nervous system. It has been shown to exert an antinociceptive effect in acute models of pain sensitivity. The present study investigates the effect of Oxytocin and its possible mechanism in formalin test, a model of continuous pain.

**Methods:** Male Swiss albino mice (25-30 gm) were divided into different groups of 8 animals each. They were injected with 0.1 ml of 1 % formalin in the right hind paw and the left hind paw was injected with an equal volume of normal saline. Two distinct phases of intense licking of right hind paw were observed during 0-5 min (early phase) and 20-25 (late phase) after formalin injection. These phases were scored separately for studying drug effect. Vehicle or drugs were administered intraperitoneally (i.p.) 30 min before formalin injection.

**Results:** Oxytocin, 100 µg/kg, produced a significant decrease in the licking response both during the early as well as the late phase, the effect being more marked during the late phase. Naloxone, an opioid antagonist in a low dose (1 mg/kg) failed to modulate the analgesic effect of Oxytocin. However, a higher dose of Naloxone 5 mg/kg attenuated the effect of Oxytocin during the early phase. Nimodipine, a calcium channel blocker when given in sub effective dose along with Oxytocin potentiated the antinociceptive activity of the latter drug.

**Conclusion:** Oxytocin exerts an analgesic effect during continuous pain probably by modulating voltage gated calcium channels. Role of opiodergic receptor mechanism in mediating Oxytocin induced antinociceptive effect is inconclusive.

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### INSULIN MIMETIC EFFECTS OF MACROCYCLIC BINUCLEAR OXOVANADIUM COMPLEXES ON STZ INDUCED EXPERIMENTAL DIABETES IN RATS.

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The vanadium complexes so far tested for their insulin mimetic effects are either mono or binuclear and contain only acyclic ligands. The leaching or hydrolysis of vanadyl ions from these complexes is much easier and hence they elicit side effects. In the present study binuclear macro cyclic oxovanadium complexes have been synthesized and their efficacy was studied on streptozotocin induced diabetic rats over a period of thirty days. The oral administration of the complexes normalizes the blood sugar level in the diabetic rats by modulating the carbohydrate metabolizing enzymes. The histological and patho physiological studies revealed that the complexes are not toxic to the system. The non-toxic nature of these complexes may be due to the presence of the vanadyl ions in an intact form. Further, the vanadyl ions present in the binuclear macro cyclic complexes are very close to each other and which may enhance the insulin-mimetic activity by synergic effect.

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### EFFECT OF SELECTIVE CYCLOOXYGENASE - 2 INHIBITORS ON ELECTRICALLY AND CHEMICALLY-INDUCED SEIZURES IN MICE.

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**Objective:** Conflicting results are reported on the role of prostaglandins, the cyclooxygenase (COX) metabolites of arachidonic acid, and their inhibitors in convulsive phenomenon. The present study investigates the role of selective COX-2 inhibitors on electrically - and chemically-induced seizures.

**Methods:** Swiss albino mice of either sex (20-25 g) were used. Maximal electroshock (MES)-induced seizure was used as a model for electrical convulsions. A 60mA current was delivered transauricularly for 0.2 sec in mice via small alligator clips attached to each pinna. To evaluate the effects of the drugs on the seizure severity, the duration of tonic hind limb extension (THLE) and mortality due to convulsions were selected as the parameters. Pentylentetrazole (PTZ), 70 mg/kg, i.p., was used for chemically-induced seizures. The onset to preclonic seizures, duration of clonus, incidence of THLE and mortality due to PTZ were recorded.

**Results:** Nimesulide (20 mg/kg), celecoxib (10 mg/kg) and rofecoxib (5 mg/kg) produced a significant ( $p < 0.001$ ) decrease in the duration of THLE in MES seizures. Nimodipine, a calcium channel blocker, also caused a statistically significant dose-dependent (20 and 40 mg/kg) decrease in the duration of THLE. A lower dose (10 mg/kg) of nimesulide, which alone could not significantly decrease THLE, caused a significant decrease in the duration of THLE when given in combination with a per se ineffective dose of nimodipine (10 mg/kg). Nimesulide (10 mg/kg) and celecoxib (10 mg/kg) enhanced PTZ - induced convulsions as shown by a decrease in the latency to onset of seizures, an increase in the duration of clonus, increased percent THLE and an increase in mortality. Nimodipine (40 mg/kg) and diazepam (0.5 mg/kg), a benzodiazepine, on the other hand, protected against PTZ - induced seizures as seen from the statistically significant ( $P < 0.05$ ) increase in the latency to onset of seizures, a decrease in the duration of clonus, decreased percent THLE and a decrease in mortality. Nimesulide, when given in combination with nimodipine or diazepam, reversed the anticonvulsant effect of nimodipine as well as diazepam.

**Conclusion:** The selective COX-2 inhibitors modulate different types of epilepsies in a differential manner, exerting protective effect in MES seizures but a deleterious effect in PTZ-induced seizures.

**PP - 37****EFFECT OF L-ARGININE ON OXALATE METABOLISM AND THE PROTECTIVE ROLE OF VITAMIN E IN HYPEROXALURIA IN RATS.****Prakash V, Selvam R, Varalakshmi P.**

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Oral supplementation of L-Arginine attenuates endothelial dysfunction. However, its role as an antilithic agent is yet to be explored. The present study was designed to assess the effect of L-Arginine in experimental hyperoxaluria. As L-Arginine is known to increase LPO and decrease thiol contents of the cell, Vit-E pre-treatment was also included in our study. Male albino rats of Wistar strain were divided into two major groups of 24 each. One group was pre-treated with Vit-E (40 mg/kg, bwt in olive oil) for 21 days. Each group was further divided into four subgroups. One subgroup acted as control, the II<sup>nd</sup> received L-arginine (1.25gm/kg, bw) for 28 days, III<sup>rd</sup> received EG (1 %) *ad libitum* for 28 days and the IV<sup>th</sup> received EG and L-Arg. Urinary and serum risk factors with respect to CaOx stone as well as oxalate metabolizing enzymes in liver and kidney were assessed at the end of 28<sup>th</sup> day. The increased urinary risk factors such as Ca<sup>2+</sup>, oxalate, urea and phosphorus in the EG treated rats were brought to normal by L-Arg. L-Arg - Vit E treatment. A similar trend was observed for serum risk factors. L-Arg along with Vit-E dramatically reduced CaOx retention in the kidneys. L-Arg/L-Arg+ Vit-E pre-treated hyperoxaluric rats exhibited low activities of oxalate synthesizing enzymes like LDRGAO, XO. These studies establish that L-Arg can be effectively used as an antilithic agent along with Vit-E.

**PP - 38****ANTI-CANCER EFFICACY OF TAMOXIFEN IS IMPROVED WHEN ADMINISTERED WITH ENERGY MODULATING VITAMINS ON EXPERIMENTAL BREAST CANCER IN RATS.****Saravana Perumal S, Sachdanandam P.**

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Tamoxifen, a non-steroidal antiestrogen, has been widely used in the hormonal treatment for breast cancer. Besides its anticarcinogenic potential, it also produces some adverse toxic side effects, while taking for a long time. In most cases, patients receiving chemotherapy die of medication rather than of disease. Hence, this study is aimed at reducing the contradiction of tamoxifen therapy, with energy modulating vitamins viz., riboflavin, niacin and co-enzyme Q10 supplementation. Female Sprague-Dawley rats were selected for the experimental study. Mammary carcinoma was induced by oral administration of 7,12- dimethylbenz(a) anthracene (DMBA) (25 mg/kg, body wt) dissolved in one ml of olive oil as vehicle. Body weight and tumour weight changes of treated and untreated animals were measured. Initially, there was no significant changes in the body weight. But finally, there was a sharp drop in the body weight of the mammary carcinoma bearing animals. Drug treated animals show a gradual increase in their body weight. There was a considerable tumour progression in the untreated animals, which can be seen from the weight gain. But in drug treated animals, the tumour did not disappear totally, but a significant regression was found. These results suggest that tamoxifen treatment is more effective during co-administration with energy modulating vitamins, which may open new avenues in cancer chemotherapy.

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### ROLE OF ENDOGENOUS $\alpha$ -MSH IN ANXIOLYTIC EFFECT OF ETHANOL.

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**Objective:** To assess the mediation of melanocortin system in anxiolytic effect produced by ethanol.

**Methods:**  $\alpha$ -MSH and antiserum against  $\alpha$ -MSH by intracerebroventricular (icv) route and ethanol 9 % w/v by intraperitoneal (ip) route. Following protocols were employed: (1)  $\alpha$ -MSH (1, 2.5 or 5  $\mu$ g/rat) or ethanol (1, 1.5 or 2 g/kg, ip), (2) ethanol (1.5 or 2 g/kg, ip) prior to  $\alpha$ -MSH (5  $\mu$ g/rat, icv), (3)  $\alpha$ -MSH antiserum (1:100 dilution in 3  $\mu$ l volume, icv) to immunoneutralize the endogenous  $\alpha$ -MSH, and (4) ethanol (2 g/kg, ip) given to  $\alpha$ -MSH immunoneutralized rats. Anxiety was evaluated by the elevated plus maze and open field tests.

**Results:** Rats treated with  $\alpha$ -MSH (5  $\mu$ g/rat, icv) or ethanol (2 g/kg, ip) produced anxiogenic or anxiolytic effects respectively. Ethanol (1.5 or 2 g/kg, ip) significantly suppressed the anxiogenic effect induced by  $\alpha$ -MSH (5  $\mu$ g/rat, icv). Immunoneutralized rats did not exhibit any anxiolytic effect per se ( $P > 0.05$ ), but potentiated the anxiolytic effect produced by ethanol ( $P < 0.05$ ).

**Conclusion:** Ethanol may produce anxiolytic effect by inhibiting endogenous melanocortin system.

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### EFFECT OF DIABETES ON HEMODYNAMIC FUNCTION AND NERVE CONDUCTION VELOCITY IN WISTAR RATS.

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**Introduction:** The objective of this study was to evaluate the magnitude and onset of micro and macro vascular complications of diabetes. We measured the effect of diabetes on nerve conduction velocity (NCV) and cardiac and hemodynamic responses for this purpose.

**Methods:** Blood pressure, +dp/dt in response to ACh and NCV were measured in Wistar rats (8 wks) made diabetic (24 h fasting glucose  $>15$  mmol/L) by injecting streptozotocin ( $n=5$ ) and age-matched non-diabetic controls ( $n=8$ ) after 24 wks of diabetes.

**Results:** Although there was no significant difference in the NCV between the normal and diabetic animals, there was a significant drop in both systolic ( $p \leq 0.0001$ ) and diastolic ( $p \leq 0.02$ ) blood pressure in response to ACh in the diabetic group as compared to normal controls. +dp/dt was also significantly ( $p \leq 0.003$ ) reduced in the diabetic group when compared to control animals both before and after administration of ACh.

**Conclusion:** Cardiac and endothelial dysfunction are evident from the changes in blood pressure and cardiac contractility in the diabetic group. These changes appear before onset of neuropathy. Hence, measurement of cardiac function and markers of endothelial dysfunction may be early indicators of diabetic complications.

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**ANTIOXIDANT ENZYMES IN PERITONEAL EXUDATE CELLS IN RESPONSE TO MYCOBACTERIUM HABANA VACCINE.**

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**Introduction:** *Mycobacterium habana*, a candidate vaccine had been developed in Central Drug Research Institute, Lucknow was found to provide protection against *M. tuberculosis*, *M. leprae* and *L. donovani* infection. *M. habana* induced macrophages also alters bio-chemical parameters. Detoxification of host generated RO's through antioxidant enzymes is regarded as one of the important mechanisms. The present study is to assess the production of antioxidant enzymes in mouse peritoneal macrophages after different days of *M. habana* vaccination.

**Methods:** Susceptible inbred female BALB/c mice were divided into different groups and administered with *M. habana* vaccine at 63.3 µg *M. habana* protein at 0, 30, 60 and 90 days and release of antioxidant enzymes were examined.

**Results:** The study shows the enhanced production of the antioxidant enzymes in vaccinated PEC. After 60 days (1<sup>st</sup> booster on 30<sup>th</sup> day) all enzymes studied were significantly higher. The release of enzymes were gradually declined after 90 days of vaccination.

**Conclusion:** It appears that *M. habana* vaccine releases these antioxidant enzymes which exert its prophylactic action to help the body defence mechanisms against the harmful effect of oxygen free radicals in biological system.

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**FACS ANALYSIS OF MCF-7 CELLS TREATED WITH ANTIESTROGENIC LIGANDS SUCH AS CENTCHROMAN AND TAMOXIFEN.**

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MCF-7 Human Breast Adenocarcinoma Cell Line is being extensively utilized in this laboratory to screen and explore the molecular mechanism of action of estrogens/antiestrogens. In continuation with our earlier studies wherein we have utilized these cells for evaluating the cytotoxic potential of antiestrogenic ligands, herein we have used FACS (Fluorescence Activated Cell Sorter with MODFIT-LT software) for defining the underlying molecular mechanism. Logarithmically growing cells harvested with trypsin at  $0.2 \times 10^6$  cells/well were plated in six-well plates for 24 h in DMEM under standard conditions. Centchroman and Tamoxifen were used as test compound and positive control respectively at 1-25 µM doses and the cells cultured for 48 h. Following harvestation, the cells were suspended in PBS, pH 7.4 containing Propidium Iodide (PI) at 40 µg/ml for assessing membrane permeability and cell size. For cell cycle studies, the cells were permeabilized with 70% chilled ethanol followed by the addition of PI. The resulting samples were analyzed by FACS. The data indicate a dose-dependent effect of ligands on the mentioned parameters which is commensurate with the earlier results of cytotoxicity studies which will, be discussed.



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### ASPIRIN AND CLOPIDOGREL PLUS ASPIRIN ON HEMATOLOGICAL AND BIOCHEMICAL PARAMETERS IN ACUTE ISCHAEMIC STROKE.

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**Objective:** The present study was planned to study the effect of aspirin and clopidogrel on haematological and serum biochemical parameters in patients of acute ischaemic stroke.

**Methods:** Thirty patients of acute ischaemic stroke presenting within 48 hours of onset were randomly divided into two groups. Patients in G I were given aspirin 325 mg daily while patients in G II were given aspirin 325 plus clopidogrel 300 mg on day 1 followed by aspirin 325 mg plus clopidogrel 75 mg daily. Patients in each group were clinically evaluated and haematological (Hb, TLC, DLC, platelet count) and serum biochemical parameters (Na<sup>+</sup>, K<sup>+</sup>, urea, creatinine, SGPT, bilirubin, glucose) were assessed at the time of admission and one month thereafter.

**Results:** Twenty nine patients completed one month follow up. 15 patients were in aspirin group and 14 patients were in aspirin plus clopidogrel group. There was no statistically significant change in haematological and biochemical parameters at one month follow up. No patients developed decreased platelet count or neutropenia. No patient had deterioration of neurological signs. Two patients in aspirin plus clopidogrel group developed G.I. hemorrhage. Disability assessment at end of month by Raskin score showed statistically significant difference (2.63 vs 1.96) (P < .05) in aspirin plus clopidogrel group compared to aspirin alone group.

**Conclusion:** There was no statistically significant change in hematological and biochemical parameters in both the groups. Outcome was slightly better in patients on aspirin plus clopidogrel as compared to those on aspirin alone.

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### EFFECT OF ANTI-INFLAMMATORY AGENTS ON THE RELEASE OF TUMOUR NECROSIS FACTOR AND NITRIC OXIDE DURING CHRONIC INFLAMMATION IN RAT.

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**Objective:** To study the effect of anti-inflammatory agents on the release of tumour necrosis factor (TNF) and nitric oxide (NO) at local inflammatory site and peripheral immune effector's cells during chronic inflammation.

**Methods:** Chronic inflammation was produced by injecting Freund's complete adjuvant (1 mg/100 µl) in right hind footpad of rat. TNF and NO were estimated in the stimulated (by Lipopolysaccharide) and non-stimulated peritoneal macrophage supernatant and paw homogenate. Celecoxib, indomethacin and curcumin were administered daily by oral route during the experiment.

**Results:** TNF release from non-stimulated peritoneal macrophages was significantly increased (28% and 69% at day 14 and 21 respectively) during chronic inflammation as compared to control. Drug treatment significantly reduced the increased level at day 14, but showed no effect at day 21. However, TNF release was unaffected in LPS-stimulated macrophages. In the inflamed paw homogenate, level of TNF increased by 90% and 61% at day 14 and 21 respectively, which was not affected by drug treatment. A significant increase in the release of NO from peritoneal macrophages was observed in stimulated as well as non-stimulated cells during chronic inflammation. Drugs significantly reduced the increase in stimulated cells only. In paw homogenate, NO level increased 3.5 times at day 14 and 1.5 times at day 21 during chronic inflammation. Drug treatment did not affect this increase.

**Conclusion:** During chronic inflammation TNF and NO release is increased at local inflammatory site as well as from the peripheral immune-effector cells. Standard anti-inflammatory agents have been effective only at peripheral immune-effector cells in inhibiting increased release of TNF and NO.

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**ROLE OF H<sub>1</sub> RECEPTORS IN ATTENUATING EFFECT OF L-HISTIDINE ON HYPERACTIVITY INDUCED BY AMPHETAMINE IN MICE.**

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**Objective:** To evaluate the role of H<sub>1</sub> receptors in attenuating effect of L-Histidine on hyperactivity induced by amphetamine in mice.

**Methods:** Male Swiss mice (25-30 gm) were used in the study. Psycho stimulation was induced by administering amphetamine (AMP) at a dose of 2 mg/kg body weight, i.p. L-Histidine (HIS) was administered simultaneously at a dose of 500 mg/kg, body weight i.p. Pyrilamine (PYR) was administered 30 minutes before administering AMP and HIS at a dose of 10 mg/kg body weight, i.p. Hyperactivity was measured by measuring motor activity horizontal activity (HA), total distance travelled (TD), stereotypy (STR) of animals by Digiscan Animal Activity Monitoring System for 2 hrs after administration of drugs.

**Results:** AMP increased HA, TD and STR by 86.51%, 193.46% and 62.00% in comparison to control respectively, whereas HIS administration attenuated the effect of AMP and produced 12.43%, 51.43% and 4.93% increase in parameters respectively. PYR pretreatment significantly countered the inhibitory effect of HIS, producing 112.98%, 152.11% and 91.36% increase in HA, TD and STR respectively.

**Conclusion:** Inhibitory effect of HIS on hyperactivity induced by AMP was mediated by H<sub>1</sub> receptors.

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**PROPHYLACTIC EFFICACY AND SAFETY OF VARIOUS SUBSTITUTED AMINOALKYLAMINO ETHYL ARYL SULPHIDES AGAINST THE LETHALITY AND TOXICITY OF SULPHUR MUSTARD.**

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**Objective:** Sulphur mustard (SM), chemically bis (2-chloroethyl sulphide), is an alkylating and blistering chemical warfare agent for which till date there is no effective antidote to prevent or limit its toxic effects. DRDE - 07, a s-substituted aminoalkyl amino ethanethiol, developed in our laboratory has shown promising prophylactic activity against SM. In an attempt to develop more effective and safer compound, different analogues of DRDE - 07 were synthesised and evaluated against dermally applied SM.

**Methods:** Female Swiss mice were used for the study. The LD<sub>50</sub> of analogues was determined as per moving averages method. Protective index (PI) of the compounds was determined as a ratio of LD<sub>50</sub> of SM with pretreatment to LD<sub>50</sub> of SM without pretreatment. Percentage DNA fragmentation and hepatic GSH depletion were estimated fluorometrically. Organ to body weight index (OBWI) was determined. Histopathology of liver and spleen was carried out with the help of LEICA - Qwin- 500 IW Image Analyser.

**Results:** Protective index of DRDE-07, DRDE-09 and DRDE-10 was found to be 21.4, 19.1 and 24.1 respectively. SM induced DNA fragmentation and GSH depletion was reduced significantly by pretreatment. OBWI was restored towards normal in the pretreated animals. Histopathological evaluation revealed that there is restoration of normal cell architecture in the animals pretreated with DRDE-07 and its analogues. SM induced body weight loss was also prevented by pretreatment with analogues.

**Conclusion:** All the three analogues evaluated showed significant protection against toxicity induced by dermally applied SM. Methyl substitution at para position of phenyl ring (DRDE-10) of DRDE-07 increased the efficacy as well as reduced the toxicity of parent compound. Variation in the alkyl chain length of DRDE-07 with methyl substitution at para position of phenyl ring (DRDE-09) retained the activity. Phenyl ring of DRDE-07 and substitution at sulphur are important targets for further modification.

**EVALUATION OF CERTAIN CHEMOPROTECTANTS AGAINST CYCLIC PEPTIDE TOXIN, MICROCYSTIN.****Jayaraj R, Nidhi Gupta, Bhaskar ASB, Lakshmana Rao PV.**

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**Introduction:** Toxic cyanobacteria found in eutrophic freshwater, municipal and residential water supplies are increasing environmental hazard in several parts of the world. Cyanotoxins include cyclic peptide hepatotoxins (microcystin, nodularin) and alkaloid neurotoxins (anatoxins, saxitoxins). Acute illnesses and deaths in both humans and animals following exposure to microcystin contaminated water sources have been reported worldwide. Microcystins are powerful tumour promoters and are suspected to be involved in primary liver cancer in humans. The objective of this study is to evaluate certain chemoprotectants against microcystin poisoning.

**Methods:** Swiss albino female mice weighing  $22 \pm 2$  g were used in the study. The agents were administered (i.p.) as 1, 3 and 24 h pretreatment, co-administration and 15 and 30 min post-treatment regimen against lethal dose of microcystin-LR (100  $\mu$ g/kg).

**Results:** Microcystin-LR at 100  $\mu$ g/kg produced consistently 100% mortality and mean time to death was 73 minutes. The osmotic agents viz., mannitol, glucose, dihydroxy acetone; antioxidants NAC, glutathione, Trolox® extended survival time of animals but could not prevent lethality. Among the flavonoids, silymarin (400 mg/kg) completely protected the mice at 3 and 24 h pretreatment. Hepatic activity modulators rifampin (25 mg/kg) and cyclosporin-A (10 mg/kg) protected animals at 1 h pretreatment. Rifampin when administered 15 and 30 min post-treatment could still protect 75% of the mice. Biochemical profile of cyclosporin, silymarin and rifampin protected animals after 24 h showed still elevated serum levels of marker enzymes ALT, LDH and SDH. The increased liver body weight index and elevated serum levels of enzymes in protected animals indicate the persistent toxic effect of microcystin.

**Conclusion:** The microcystin induced acute hepatotoxicity and lethality could not be prevented by osmotic agents, free radical scavengers and antioxidants. Hepatic activity modulators like rifampin, cyclosporin-A and flavonoid silymarin gave complete protection against MC-LR induced lethality.

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**GENETICALLY MODIFIED BHK-21 CELLS PRODUCING GDNF (BHK-GDNF) CO-TRANSPLANTATION WITH VMC AMELIORATES FUNCTIONAL DEFICITS IN RAT MODEL OF PARKINSON'S DISEASE.**

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**Objectives:** To study the effect of genetically modified glial cell line-derived neurotrophic factor (GDNF) producing baby hamster kidney cells (BHK-21) co-transplantation with fetal ventral mesencephalic cells (VMC) on functional restoration in 6-hydroxy dopamine (6-OHDA) lesioned rat model of Parkinson's disease.

**Methods:** Animal model of Parkinson's disease made by giving intrastriatal injection of 6-OHDA. Extent of lesion checked three weeks post lesioning by using d-amphetamine. Transplantation of genetically modified BHK-21 cells capable of constantly producing GDNF, was done in striatal region of 6-OHDA lesioned rats with and without VMC. Functional viability and restoration was assessed using neurobehavioral, neurochemical, immunohistochemical and image analysis parameters at 4 weeks post transplantation.

**Results:** A significant restoration (72% and 77%;  $p < 0.001$ ) in d-amphetamine induced rotations and spontaneous locomotor activity in co-transplanted group was observed as compared to (45% and 42%;  $p < 0.01$ ) VMC alone transplanted group. Levels of dopamine, DOPAC and dopamine D2 receptor binding in the striatum were significantly ( $p < 0.001$ ) restored in co-transplanted group as compared to VMC or BHK-GDNF transplanted animals. The functional viability of transplanted VMC was confirmed by tyrosine hydroxylase (TH) expression and quantification of TH positive cells by image analysis revealed a significant restoration in number of TH-positive cells as well as area of TH expression in co-transplanted animals over VMC transplanted animals.

**Conclusion:** Co-transplantation of BHK-GDNF cells and VMC may be a better approach towards functional restoration in 6-OHDA lesioned rat model of Parkinson's disease.

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### ANTIDOTE FOR SULPHUR MUSTARD : A NOTORIOUS CHEMICAL WARFARE AGENT.

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**Introduction:** Sulphur mustard (SM, 2,2'-dichloro diethyl sulphide) is a potent alkylating and blistering agent. SM reacts in aqueous phase with compounds containing nucleophilic functional groups like amino, sulfhydryl, carboxylic and hydroxyl in proteins and nucleic acids. The toxicity of SM is due to interaction with one or more cell constituents. To combat with the SM toxicity so far no antidote is available.

**Methods:** We have studied the protective effect of quercetin following sulphur SM exposure. SM, was administered to mice through percutaneous route at different concentrations 9.67, 19.33, 38.66 and 77.30 mg/kg. Quercetin was administered three times at the dose of 50, 100, 200 and 400 mg/kg body weight by ip injection, one immediately following SM exposure, then once each day for two days after SM treatment. The effect of quercetin on survival, markers of oxidative damage, WBC counts and purine metabolite was investigated.

**Results:** Survival time increased significantly following quercetin treatment. The reduction in body weight due to SM was significantly protected. Significant decrease in reduced glutathione (GSH) and increase in the level of malondialdehyde (MDA) indicated oxidative damage to hepatic and renal tissues following percutaneous exposure. Quercetin protected hepatic and renal tissues from oxidative damage caused by SM. Alterations due to SM intoxication in WBC counts and end product of purine metabolite were also protected.

**Conclusion:** This study shows that quercetin gives over all protection to the animals. It could enhance survival time, restore decrease in body weight and protect hepatic and renal tissues from oxidative damage following SM intoxication.

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### $\alpha$ - LIPOIC ACID PREVENTS NEUROPATHIC CHANGES IN STZ DIABETIC RATS.

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**Objective:** To evaluate effects of  $\alpha$ -lipoic acid on motor nerve conduction velocity (MNCV), Body wt, blood/urine sugar levels urine volume and nociception in STZ diabetic rat.

**Methods:** In albino rats (250 - 300 g) diabetic neuropathy was produced by injecting STZ (50 mg/kg, iv). MNCV was determined in sciatic posterior tibial conducting system of ether anaesthetised rats by EMG. Body weight, blood/urine sugar levels, urine volume and nociception were studied at 2 week intervals. Animals were divided in to 4 groups of 10 rats each Group - I (control) Group - II (STZ 50 mg/kg, iv) single injection Group - III ( $\alpha$ - Lipoic acid, 100 mg/kg, po, daily) 5 days prior to STZ, and continued for 12 weeks + STZ. Group - IV Insulin (4  $\mu$ /kg, sc, bid) + STZ.

**Results:** The study revealed that  $\alpha$  - lipoic acid was beneficial in preventing diabetic changes including neuropathy in rats. MNCV in diabetic rat was significantly reduced after 6 weeks of STZ. However, in  $\alpha$  - lipoic acid pretreated group MNCV was not significantly differed compared to normal rats.

**Conclusion:**  $\alpha$  - lipoic acid is beneficial in preventing diabetic complications.

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### EFFECT OF PERINOOPRIL IN STREPTOZOTOCINE INDUCED DIABETIC NEUROPATHY IN RATS.

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**Objectives:** To evaluate preventive effect of perindopril on MNCV, blood/urine sugar, urine volume body weight and nociception in STZ diabetic rats.

**Methods:** In albino rats (250 - 300 g) diabetic neuropathy was produced by injecting STZ (50 mg/kg, iv) MNCV was determined in sciatic - posterior tibial conducting system of ether anesthetized animals by EMG. Body weight, blood/urine sugar levels, urine volume and nociception were studied at 2 week intervals. Protocol for preventive study was (n = 10 in each group): Group I - Control, Group II - STZ (50 mg/kg, iv) single injection, Group III - Perindopril (1 mg/kg, po, daily) 5 days prior to STZ and continued for 12 weeks + STZ, Group IV - insulin (4 unit/kg, sc bid) + STZ.

**Results:** Data of the study showed that perindopril was beneficial in preventing diabetic complications including neuropathic changes in rats. MNCV in diabetic rats was significantly reduced after 6 weeks of STZ. MNCV was markedly improved in perindopril pretreated group. Perindopril has no significant effect on body weight, blood urine sugar levels and hyperalgesic responses observed in diabetic rats.

**Conclusion:** Perindopril prevents neuropathic changes associated with STZ diabetes in rats.

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### INFLUENCE OF BLOOD GLUCOSE LEVELS ON NEUROLOGICAL FUNCTIONS.

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Raised blood glucose levels in uncontrolled diabetes cause neuropathy. Insulin substitution suppresses further progression of disease. In the present study, the effect of hypoglycaemia on neurological functions was seen. Adult albino rats of either sex were allocated into 3 groups: STZ-induced hyperglycaemic group (BGL  $\geq 300$  mg/dl), normoglycaemic group (BGL  $\leq 100$  mg/dl) and insulin induced hypoglycaemic group (BGL  $\leq 50$  mg/dl). Neurological functions were assessed using an 18-point scale. The neurological outcome scores in both, hyperglycaemic and hypoglycaemic rats were comparable with each group scoring 9 points which were significantly ( $p < 0.01$ ) high compared to that of normoglycaemic rats. On restoration of normal blood glucose from high with insulin the neurological outcome scores remained same, whereas in hypoglycaemic rats on substitution of 50% glucose to normalise the blood glucose the scores reduced to zero from 9. These findings indicate that blood glucose levels affect neurological functions with long standing hyperglycemia causing irreversible and hypoglycemia causing reversible neurological outcomes.

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### EFFECT OF ESTROGEN ON HYPOGLYCAEMIC STRESS MEDIATED ANXIETY AND TREMULOUSNESS.

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Anxiety and tremulousness are common symptoms of hypoglycaemic stress caused by activation of sympathetic component of autonomic nervous system. Improvement of neurological impairment in stroke with estrogen have been observed in experimental animals. In the present study the effect of estrogen was seen on hypoglycaemic mediated anxiety and tremulousness in rats. Four groups of adult albino female rats were made: group 1 - rats treated with vehicle, group 2 - rats treated with estrogen (100 µg/kg, ip), group 3 - rats treated with insulin (2 u/kg ip) and group 4 - rats treated with estrogen and insulin. Rats of each group were exposed to tests for assessing anxiety and tremulousness at different time intervals. Rats treated with single injection of estradiol benzoate or vehicle did not produce anxiety and tremulousness, whereas insulin treatment produced anxiety and tremulousness in rats due to hypoglycemia. Rats pretreated with estradiol benzoate showed increased anxiety and tremulousness on production of insulin hypoglycemia. Thus it is concluded that estrogen, instead of providing protection against hypoglycaemic stress mediated anxiety and tremulousness, aggravates them.

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### EFFECT OF NEUROLEPTICS ON HEAD DIPPING RESPONSES OF MICE.

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**Introduction:** Several psychopharmacological test paradigm help in evaluation of newer typical and atypical neuroleptic agents. Head dipping response of rodents is a commonly used test system for neuroleptic activity profile for newer chemical/plant product/ marine entities. We have tested two typical neuroleptic (Haloperidol, Centbutindol), one atypical neuroleptic (Clozapine) and one marine product (CDR-229) in mice.

**Methods:** Experiments were done in the CNS lab. Albino mice were first acclimatized in temperature controlled 24 ± 2°C room. Head dipping apparatus was fabricated with hard board box (40 x 40 x 11 cm) having 16 hole of a diameter 1.5 cm. Doses of all the 4 agents were administered i.p. Head dipping responses were measured by an stopwatch in seconds. ED<sub>50</sub> values at different hours were calculated by Probit analysis.

**Results:** Haloperidol ED<sub>50</sub> after 1, 3, 5 hrs of drug administration were similar 0.6 mg/Kg i.p. Centbutindol had similar ED<sub>50</sub> value at first hour while 3<sup>rd</sup> and 5<sup>th</sup> hours it was increased. Clozapine had higher ED<sub>50</sub> of 19 ± 1.4, 20 ± 1.7, 21 ± 1.7 mg/Kg, i.p. at 1, 3, 5 hour respectively. CDR-229 produced much higher ED<sub>50</sub> values of 55 ± 4.1, 58 ± 4.1, 62 ± 4.7 mg/Kg i. p. respectively at different hours.

**Conclusion:** These results suggest that CDR-229 and Centbutindol CDR products have shown atypical and typical neuroleptic profile as compared to Clozapine and Haloperidol in head dipping responses of mice.

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**EFFECT OF NEUROLEPTICS ON DOPAMINE (D2) RECEPTORS ON STREPTONIGRAL AND MESOCORTICAL MEMBRANES OF RAT.**

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**Introduction:** Neuroleptics are known to inhibit various types of dopamine receptors in various regions of central nervous system. In this report effect of two neuroleptics Haloperidol and Centbutindol has been evaluated on streptonigral and mesocortical neurons of Sprague -Dawley rats.

**Methods:** SN and MC neuronal membranes of S-D rats were prepared by ultracentrifugation (35000 rpm, 30 min x 3) in Tris buffer pH 7.7 containing pargyline (10  $\mu$ M) and ketenserine (10  $\mu$ M). [ $^3$ H] Spiroperidol (84 Ci/mmol) was used as radio ligand for saturation kinetics experiments. Haloperidol 1  $\mu$ M or chlorpromazine 10  $\mu$ M was used as cold label for nonspecific binding. Competitive binding experiments were done with haloperidol and centbutindol.

**Results:** Haloperidol and centbutindol blocked the dopamine receptors in SN and MC neurons of S-D rats. IC<sub>50</sub> values of haloperidol were 5.3 and 5.35 nM in SN and MC neurons respectively. Centbutindol IC<sub>50</sub> values were 7.54 and 8.2 nM in SN and MC neurons respectively.

**Conclusion:** It is thus concluded that both the typical neuroleptics block the dopamine receptors in nM concentrations in SN and MC regions. Receptor binding studies will be used for further evaluation of atypical neuroleptics.

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**STUDY OF THE INTERACTION OF  $\beta$ -AMYLOID AND CHOLINESTERASES BY FLUORESCENT POLARIZATION.**

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Fluorescence polarization is a tool to study molecular interactions and binding because it gives a direct and rapid measure of a tracer's bound/free ratio, and does not require physical separation of bound tracer from the large excess of free tracer. Therefore, if viscosity and T are constant, a polarization value is directly related to the rotational relaxation time and the molecular volume, i.e., size. We used this technique to measure the equilibrium dissociation constant of propidium on acetylcholinesterase (AChE) and inhibition constants for decamethonium, edrophonium, tubocurarine, and gallamine in a fluorescent spectrophotometer with a polarization accessory at 25°C in 50 mM phosphate buffer. Results were in good agreement with the literature. Since it was previously demonstrated (Nibaldo et al) that  $\beta$ -amyloid aggregation increased in the presence of AChE and that C1q also enhanced fibril formation (Webster et al), we evaluated fluorescein labelled  $\beta$ -amyloid binding to several proteins including AChE, BChE, electric eel ChE, and C1q. Fluorescent  $\beta$ -amyloid (non-fibrillar) bound to C1q > AChE - BChE > eel ChE.  $\beta$ -amyloid peptide (1-40) aggregation was evaluated by turbidimetric measurements. We observed an increase in the aggregation of the peptide in the presence of Clq > AChE - BChE > eel ChE. When we evaluated fibril formation by thioflavin T fluorescence (which indicates the relative amount of  $\beta$ -sheet found in these fibrils), Clq > AChE > BChE > eel ChE in promoting fibril formation. These results are in agreement with findings that AChE and C1q interact with  $\beta$ -amyloid.



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**DREAM PATTERN IN POST-MYOCARDIAL INFARCTION PATIENTS ON THERAPY.**

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It has been seen that patients who are on cardiovascular drugs complain of problems regarding their sleep and dreams. Therefore, the study was conducted on dream pattern of 100 patients who survived after MI. taking different cardiovascular drugs such as ACE inhibitors, calcium channel blockers, diuretics in their post-myocardial infarction period. Few other drugs such as anti-ulcer tranquillizers etc, were prescribed to these patients which might contribute to alter the sleep pattern and dream of the patients. The dream features were studied with the help of a standardized questionnaires. The dream pattern were compared with a matched group of 100 patients who were not having MI but taking other drugs like analgesics, antihypertensives, antianxiety, etc. which served as control. In control group, 89% were having enjoyable dreams as compared to 72% in post MI. patients. Frightening dreams (47%) and other bad dreams (78%) were observed in control group while the patients of post MI were having less frightening dreams (24%) and other bad dreams (62%). Post MI patients as well as the control group patients (33%) reported the death of ownself or others in the dreams. Dreams regarding past memories or events were 59% in the control while 40% in post MI. patients. Thus the study indicates that the cardiovascular drugs may alter the dream pattern and decrease their frequency.

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**PSYCHOMOTOR PERFORMANCE AND DREAM PATTERN IN PSYCHIATRIC PATIENTS ON PSYCHOACTIVE DRUGS.**

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Psychoactive drugs used for treatment of various psychiatric diseases affect psychomotor and cognitive functions, which were assessed with the help of Six Letter Cancellation Test (SLCT) and Digit Letter Substitution Test (DLST) after obtaining due consent. Prescription audit of 100 patients was also done to study the prescribing pattern in various psychiatric disorders. Dream features as reported by the patients before the onset of illness, during psychiatric illness and after institution of drug therapy were recorded on a dream investigation protocol. Nitrazepam, haloperidol, fluoxetine, lithium and trihexyphenidyl were more frequently prescribed in combination with other psychotherapeutic drugs with an average of 3.8 drugs per patient. Most patients scored significantly lower as compared to normal volunteers who scored more than 30 in SLCT and more than 60 in DLST. The dreams of the patients were less frequently related to present life situations unlike normal volunteers. Frightening and repetitive dreams with visions of snakes were more frequent before and during illness and were suppressed in 78% patients following therapy. Thus, psychomotor performance tests and dream history could serve as important indicators of mental and emotional status during recovery from psychiatric illness. The study was supported by Christian Medical College and Hospital, Ludhiana, India.

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### INFLUENCE OF DDVP (NUVAN) ON HAEMATOBIOCHEMICAL AND HISTOPATHOLOGICAL LESIONS IN FEMALE MICE.

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At present time the organophosphorus insecticides are used extensively in the field of agriculture, veterinary practice and public health. Nuvan (76% w/v dichlorvos) is an organophosphate insecticide and is used increasingly because of its speedy biodegradation, however, it causes hazardous effects on man and the environment. Laboratory acclimatized mice were administered single (9.875 mg/kg body wt) and multiple doses (1.411 mg/kg body wt) of Nuvan subcutaneously for 1, 2, 7 and 14 days. Significant inhibition of Hb% and RBC counts were observed while there was enhancement in WBC counts. There was inhibition of blood cholinesterase and increase in blood glucose level. Histopathological lesions were also induced by Nuvan in the vital organs viz. liver, kidney and lungs. Animals exhibited severe tremors and convulsions at higher doses. The use of insecticides should be reduced, and the public should be cautioned about its ill effects.

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### EVALUATION OF THE EFFECT OF MELATONIN AND ITS POSSIBLE MECHANISM OF ACTION IN MAXIMAL ELECTROSHOCK SEIZURES.

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**Objective:** To study the effect of the pineal hormone melatonin in maximal electroshock seizure and to unravel the underlying receptor mechanism.

**Methods:** Swiss albino male mice (8/group) were used. Seizures were induced electrically by using maximal electroshock with the help of an electroconvulsometer via pinnal clip electrodes. An electric current of 60 mA was applied for 0.2 seconds and duration of hind limb extension was measured to assess the drug effect.

**Results:** Administration of melatonin (25-100 mg/kg, ip) prior to electric shock, dose-dependently decreased the duration of hind limb extension (HLE) the difference being significant with melatonin 50 and 100 mg/kg dose ( $p < 0.05$ ;  $p < 0.01$ ). Administration of diazepam (2.5 mg/kg), lamotrigine (1.3 mg/kg) and carbamazepine (6 mg/kg) along with melatonin significantly enhanced the anticonvulsant effect of melatonin. Mianserin a 5HT<sub>2A</sub> antagonist (2.5 mg/kg) and ondansetron a 5HT<sub>3</sub> antagonist (1-2 mg/kg) enhanced the anticonvulsant effect of melatonin (25 mg/kg) ( $p < 0.02$ ;  $p < 0.001$ ;  $p < 0.02$ ) whereas buspirone, a 5HT<sub>1A</sub> agonist (2.5 mg/kg) failed to do so. There was a reversal of anticonvulsant effect of melatonin with bicuculline, a GABA<sub>A</sub> receptor antagonist ( $p < 0.02$ ). Administration of luzindole a ML<sub>1</sub> antagonist significantly attenuated the anticonvulsant effect of melatonin ( $p < 0.05$ ), while prazosin, a ML<sub>2</sub> antagonist failed to do so.

**Conclusion:** Serotonergic (5HT<sub>2</sub>, 5HT<sub>3</sub>) GABA<sub>A</sub> and ML<sub>1</sub> (melatonin receptor 1) receptors appear to play a role in the anticonvulsant effect of melatonin in MES.

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### CNS EXCITATORY POTENTIAL: COMPARATIVE STUDY OF OLDER AND NEWER FLUOROQUINOLONES.

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**Objective:** Fluoroquinolone (FQ) derivatives are used to treat bacterial infections because of potent antimicrobial activity combined with good tissue penetration. Although these FQs are generally well tolerated, CNS toxicity (importantly convulsions) have been reported with many FQs especially those which have unsubstituted piperazine moiety at the 7 position of their parent nuclei. Newer FQs have been reported to cause less CNS toxicity in humans. In the present work we have assessed the proconvulsive potential of older FQs in comparison with newer FQs.

**Methods:** Comparison of proconvulsive potential was done in mouse using two different approaches. Direct intra-cranial administration of drugs into the mouse brain interaction with Fenbufen. Mice were pretreated orally with fenbuten 15 minutes prior to iv administration of all the FQs and the animals were observed for tonic clonic seizures for an observation period of 3 hours. FQ drugs compared were enoxacin, norfloxacin, ciprofloxacin, pefloxacin - Older FQs sparfloxacin, moxifloxacin, ofloxacin, levofloxacin and gatifloxacin - newer FQs.

**Results:** The order of proconvulsant activity in our intra cranial administration model was norflo> cipro = gati > enoxacin. Spar, moxi, levo and ofloxacin did not induce any convulsions. However, when coadministered with fenbufen the rank order potency was Enox > Nor > Cipro > Peflox.

**Conclusion:** 1. Older FQs are more potent proconvulsive agents as compared to the newer FQs except gatifloxacin. 2. Enoxacin is the most potent proconvulsive FQ as compared to others when coadministered with fenbufen.

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### EFFECT OF ALPHA LIPOIC ACID ON ANTINOCICEPTION AND LOCOMOTOR ACTIVITY IN RATS.

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Alpha lipoic acid (ALA), is a metabolic antioxidant which is known to penetrate the blood brain barrier with ease and has a distinction of affording protection in extracellular and intracellular environment. Recently it was shown to be effective in preventing cognitive impairment and oxidative stress in rat model of Alzheimer's disease. It has also been demonstrated to be effective in ischemia reperfusion model of stroke. Further it also effective in diabetic neuropathy. This suggests the therapeutic potential of ALA in CNS disorders. However, the CNS pharmacological profile of ALA has not been studied. In the present study we evaluated the antinociception and locomotor activity of alpha lipoic acid. For assessment of analgesic activity adult Wistar rats of either sex weighing between 150-200 g were injected ALA 50 and 100 mg/kg i.p. The analgesia was assessed by % maximal possible effect (% MPE). It was observed that ALA at a dose of 100 mg/kg, i.p. caused significant increase in % MPE as compared to vehicle treated. When ALA was combined with submaximal dose of morphine (5 mg/kg, i.p.) significant potentiation in the analgesic effect was observed. The 50 and 100 mg/kg doses of ALA were also tested for locomotor activity by using techno photoactometer. There was no significant change in the activity in one hour. The preliminary findings suggest that the ALA has analgesic effect.

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### **CYP2E1 IN BRAIN: EVIDENCE FOR CONSTITUTIVE AND INDUCIBLE EXPRESSION.**

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Cytochrome P450 2E1 (CYP2E1), the major ethanol inducible isoenzyme in liver, is involved in the metabolism of several drugs and in the metabolic activation of organic solvents and carcinogens. Although CYP2E1 has been shown to be present in rat brain, a debate exists as to the precise levels of its expression in the brain. In the present study attempts were made to study the constitutive and inducible expression of CYP2E1 by investigating mRNA and protein expression and catalytic activity, specific for this isoenzyme in rat brain. RT-PCR, using primers specific for hepatic CYP2E1, and Western blotting with hepatic anti-CYP2E1, indicate significant mRNA and protein expression of CYP2E1 in control rat brain. Ethanol pretreatment was found to significantly increase the mRNA and protein expression for CYP2E1 in rat brain. CYP2E1 in rat brain microsomes was also found to catalyze the activity of N-nitrosodimethylamine demethylase (NDMA-d). Like in the liver, ethanol pretreatment significantly induced the enzyme activity which was associated with an increase in the Vmax and affinity (Km) of the substrate towards the brain enzyme. *In vitro* studies using organic inhibitors, specific for CYP2E1 and anti-CYP2E1 were found to significantly inhibit the constitutive and inducible brain NDMA-d activity indicating that like in liver, CYP2E1 catalyses the activity of NDMA-d in rat brain. Significant differences were also observed in the distribution of NDMA-d activity in the different brain regions, with olfactory lobe exhibiting the maximum enzyme activity. This was further supported by western immunoblotting studies indicating relatively high constitutive expression of CYP2E1 in olfactory lobe. The data demonstrated significant constitutive and inducible mRNA protein expression and have provided biochemical evidence for the expression of the catalytic activity of CYP2E1 in rat brain.

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### **EFFECT OF LINDANE ON BRAIN CYTOCHROME P450s (CYPs) AND INFLUENCE OF CYP MODIFIERS IN THE NEUROTOXICITY OF LINDANE.**

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Lindane ( $\gamma$ -hexachlorocyclohexane), an organochlorine insecticide has been shown to accumulate in the brain. High concentrations of lindane in brain have been related to its neurotoxic effects. Even though much information is available on the interaction of lindane with the hepatic cytochrome P450s (CYPs), involved in its metabolism, not much is known about the in situ metabolism and activation of lindane with the brain. In the present study attempts were made to investigate the effects of lindane on the CYP enzymes and involvement of CYP induction in the neurotoxicity of lindane. Oral administration of lindane was found to produce dose- and time-dependent increase in the activity of CYP - dependent 7-ethoxyresorufin-O-deethylase (EROD), 7-pentoxoresorufin-O-dealkylase (PROD) and N-nitrosodimethylamine demethylase (NDMA-d) in rat brain. The increase in the CYP enzymes was attributed to the significant increase in the mRNA and protein expression of brain CYP1A1, 2B1 and 2E1. Significant region specific differences were also observed in the lindane induced alterations of CYP1A1, CYP2B1 and CYP2E1 expression and the specific enzyme activity. Enzyme induction and inhibition studies using modifiers of CYPs have further shown involvement of CYP2B1/2B2 and CYP2E1 isoenzymes in the neurotoxicity of lindane.

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### CHELATION OF BERYLLIUM WITH TIRON AND VITAMIN E IN FEMALE RATS.

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First discovered in 1798, beryllium is a ubiquitous and lightest bivalent element in the environment. Because of its strength, electrical and thermal conductivity, corrosion resistance and nuclear properties, beryllium products are used in aerospace, automotive, energy, medical and electronics industries. Long term exposure of beryllium causes chronic beryllium disease (CBD) which is a fatal disease of 20th century. The chronic beryllium disease was first associated with occupational exposure to beryllium in 1940s, when a cluster of cases was observed in workers from the fluorescent light industry. It also causes a number of diseases such as bronchitis, pulmonary granulomatosis and hepatomegaly, because the liver is the target organ of beryllium. Its accumulation causes cellular death. In the present study, female albino rats of Sprague Dawley strain weighing  $120 \pm 20$  g were selected. The efficacy of chelating agent, Tiron (4,5-dihydroxy-1,3-benzene disulphonic acid) with and without adjuvant (vitamin E) in the treatment of beryllium induced toxicity was investigated. Beryllium as beryllium nitrate at a dose of 1 mg/kg (ip) for 28 days followed by chelation therapy with Tiron and a combination of Tiron and vitamin E for 5 consecutive days. Administration of beryllium nitrate showed a significant decrease in haemoglobin percentage, blood sugar, serum alkaline phosphatase, serum protein and a significant increase in the activity of serum transaminases. Reduced glutathione was decreased in liver and kidney. It was also found that, level of lipid peroxidation increased after exposure to beryllium nitrate. Besides these, considerable changes observed in histoarchitecture of liver and kidney. Liver showed vacuolation and granulation in cytoplasm of hepatocytes. Hypercellularity was noted in glomeruli of kidney. Exfoliated nuclei were also noted in lumen of tubules. Significant recoument was observed in haematological, biochemical and histological parameters with the combination of Tiron and vitamin E rather than Tiron *per se*.

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### LIPOIC ACID IN COMBINATION WITH 2,3 - DIMERCAPTOSUCCINIC ACID AMELIORATES LEAD INDUCED RENAL CYTOTOXICITY.

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Lead nephropathy has been known to be associated with altered glucose homeostasis and energy metabolism. The beneficial effects of DL- $\alpha$ -lipoic acid (25 mg per kg body weight, i.p.) in combination with meso 2,3- dimercaptosuccinic acid (20 mg per kg body weight i.p.) against lead-induced alterations in glucose homeostasis and energy metabolism of the kidney has been investigated. Rats exposed to lead acetate (Pb - 0.2% in drinking water for five weeks) demonstrated disturbances in the metabolic pathway of renal cells by the inhibition of key glycolytic enzymes (hexokinase, aldolase and phosphoglucosomerase) and enhancement of gluconeogenic enzymes. Activities of the TCA cycle enzymes were lowered in lead poisoned rats along with a marked depletion in the activities of membrane bound ATPases. The importance of co-administering DL- $\alpha$ -lipoic acid along with meso 2,3-dimercaptosuccinic acid in alleviating the lead induced biochemical disturbances with respect to glucose homeostasis and energy metabolism has been the hallmark of this study.

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### EFFECT OF CADMIUM ON ANGIOTENSIN II INDUCED PRESSURE RESPONSES IN RATS.

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**Introduction:** Cadmium ions are known to produce hypertensive response in rats. Role of renin angiotensin system (RAS) is controversial. Angiotensin II produces hypertensive effects in rats. Cadmium induced hypertensive response in rats and its modulation by pressure peptide Angiotensin II has not been evaluated, and therefore we decided to study the cardiovascular interactions with cadmium, an hypertensive agent.

**Methods:** Blood pressure (BP) and heart rate (HR) of anaesthetized (Pentobarbitone 50 mg/kg, ip), S-D rats were recorded on Grass polygraph VII using Statham pressure transducer. Dose response curve of angiotensin II (1, 3.2, 10  $\mu$ g/kg, iv) was produced before and after cadmium (0.32, 1.0 mg/kg, iv) treatment. Statistical analysis was done using one way analysis of variance (ANOVA) followed by Student's t test.

**Results:** Angiotensin II produced dose dependent increase in BP. Cadmium (0.32 mg/kg, iv) treatment produced reduction in angiotensin II response. Highest dose of angiotensin II (10  $\mu$ g/kg, iv) did not produce any significant antagonism. Higher dose of cadmium (1 mg/kg, iv) produced dose dependent reduction in hypertensive response of Angiotensin II. However, different types of blood pressure responses produced by cadmium confirm some complex interactions.

**Conclusion:** Angiotensin II induced hypertensive responses are not dose dependently altered by cadmium treatment of anesthetized S-D rats.

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### CADMIUM INDUCED CHANGES IN NUCLEIC ACID CONTENTS OF NEPHRON SEGMENTS OF RATS.

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**Introduction:** Nephrotoxic and hypertensive effects of cadmium are well established. Effect of Cadmium on various nephron segments in relation with nucleic acid changes has not been reported in literature, therefore we measured deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) contents in different nephron segments of Sprague -Dawley rats.

**Methods:** S-D rats were anesthetized with pentobarbitone (50 mg/kg, ip) and blood pressure and heart rate were recorded on Grass polygraph VII. Rats were treated with normal saline (1ml/kg, iv) and different doses of cadmium (0.1, 0.32 mg/kg, iv). Kidneys were removed and nephron segments (proximal, distal tubules, glomerulus) were separated by percoll gradient ultracentrifugation technique. DNA and RNA contents of the tubules were measured by standard techniques.

**Results:** Cadmium produced hypertensive response in rats. Distal nephron segment RNA levels were dose dependently decreased by cadmium treatment in rats. Cadmium (0.1, 0.32 mg/kg, iv) DNA levels were increased by 112 % and 228% respectively. DNA levels were increased dose dependently in proximal tubules and glomerulus.

**Conclusion:** Finding of the present investigation reveal that Cadmium treatment of rats produced decreased RNA activity while DNA activity was increased in different nephron segments of rats.

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**HISTOPATHOLOGICAL CHANGES IN REPRODUCTIVE ORGANS INDUCED BY ETHANOLIC EXTRACT OF *CROTALARIA JUNCEA* IN FEMALE RATS.**

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*Crotalaria juncea* popularly known as Brown Hemp has been reported for number of medicinal properties in Ayurvedic literature. Ethanolic extract of its seeds is also known to induce antifertility effect in female rats, however, its administration has been reported toxic. Its LD<sub>50</sub> through oral route has been reported to be 0.768 gm/kg body weight. Being an antifertility plant, its toxic effect on low and high doses has not yet been observed on reproductive organs. Present paper deals with histopathological alterations in ovary and uterus of rats treated with various doses of ethanolic extract of seeds of *C. juncea*. Three different doses viz. 1/5, 1/10 and 1/50th, of LD<sub>50</sub> of *C. juncea* were administered to intact cyclic rats for 1, 2, and 4 weeks. Ovary and uterus were studied for histopathological changes. Studies revealed that the administration of extract increased vascularity and degeneration of the Graafian follicles in ovary. Remarkable utrotrophic changes were observed in the uterus which included the fibrosis, hyperplasia, leucocytic infiltration and enlargement of luminal epithelium. The alterations were dose and duration dependent. 1/5th of LD<sub>50</sub> dose was found more potent. Findings will be discussed in relation to the reproductive toxicity of *C. juncea*.

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**PROTECTIVE ROLE OF VITAMIN E ON BIOCHEMICAL CHANGES IN UROGENITAL TUBERCULOSIS PATIENTS ASSOCIATED WITH UROLITHIASIS.**

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The incidence of renal calculi was evaluated to be 25% in urogenital tuberculosis patients. The stone could be caused due to the host, the pathogenic organism, or possibly the treatment. The first group comprised of 24 normal volunteers. The second group comprised of 24 renal tuberculosis patients treated with regular anti tuberculosis drug regimen (Pyrazinamide 35 mg/kg, Isoniazid 7.5 mg/kg, and Rifampin 10 mg/kg daily) for sixty days. The third group comprised of 21 renal tuberculosis patients treated with anti-tuberculosis drug regimen along with supplementation of antioxidant vitamin E (400 mg/day) for sixty days.

Hyperuricosuria and hypercalciuria were observed after 60 days in group 11 patients, along with increased excretion of stone promoters such as oxalate, protein and creatinine and decreased concentration of inhibitors such as citrate and GAGs. There was increased leakage of lactate dehydrogenase, alkaline phosphatase and  $\gamma$ - glutamyl transferase in the urine of renal tuberculosis patients at day 0 and day 60. Plasma calcium, phosphorus and uric acid levels were also found to be significantly elevated in these patients. There was a decrease in the levels of  $\alpha$ -tocopherol in the plasma of group II patients along with an increased plasma lipid and lipid peroxidation. Vitamin E supplemented group III patients were found to have lipid and lipid peroxidative products appreciable to that of normal and urinary enzyme levels were also found to be decreased. The results conclude that there is membrane injury as dictated by the high levels of lipid peroxidation and urinary marker enzymes, which in turn leads to cellular damage which is a pre-requisite for crystal retention. Antioxidant therapy prevents renal stone formation by preventing membrane injury.

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**EFFECT OF DL- $\alpha$ -LIPOIC ACID ON ADRIAMYCIN INDUCED CARDIO AND HEPATO TOXICITY IN RATS.**

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The protective role of DL  $\alpha$ -Lipoic acid (LA) on Adriamycin (ADR) induced acute cardiac and hepatic oxidative toxicity was evaluated in rats. ADR toxicity, induced by single intravenous injection (7.5 mg/kg, bw), was determined by an elevation in the activities of serum SGOT, SGPT, CPK and LDH. There was significant rise in MDA, with decrease in the level of GSH and lowered activities of SOD and GPx in heart and liver tissues. Catalase activity was lowered in heart, whereas there was a significant increase in hepatic tissue. Pre-treatment with DL  $\alpha$ -Lipoic acid (70 mg/kg, bw, ip) showed significant reduction in the MDA level and ameliorated the activities of antioxidant enzymes in the cardiac and hepatic tissues. In addition, LA treated rats showed significant decrease in the activities of serum SGOT, SGPT, CPK and LDH when compared with ADR treated rats. These results suggested the efficacy of LA in mitigating the toxicity produced by ADR.

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**PROTECTIVE EFFECTS OF ZINC AND ASCORBIC ACID EITHER INDIVIDUALLY OR IN COMBINATION AGAINST ALUMINUM INTOXICATION IN RATS.**

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The study describes their preventive values of zinc and ascorbic acid (25 mg/kg, orally once daily) either individually or in combination against the appearance of signs and symptoms of sub-chronically aluminum intoxicated (0.2% aluminum in drinking water for 4 weeks) male rats. The results suggest beneficial effect of zinc and ascorbic acid supplementation in preventing the appearance of signs of aluminum toxicity based on few haematological ( $\delta$ -aminolevulinic acid dehydratase, zinc protoporphyrin), liver and kidneys biochemical variables (oxidized and reduced glutathione, thiobarbituric acid reactive substances, transaminases, etc) and aluminum concentration in blood and soft tissues. Best results however, were obtained when these chemicals were given concomitantly with aluminum consecutively for 4 weeks. The present results indicate that combined administration of zinc and ascorbic acid could be a more effective preventive measure against aluminum intoxication than individual supplementation of zinc or ascorbic acid. The results also suggest further exploration in this direction particularly their role (zinc and ascorbic acid) post-aluminum exposure therapy.



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**ALUMINUM INDUCED OXIDATIVE STRESS IN RAT BRAIN AND ITS RESPONSE TO COMBINED ADMINISTRATION OF CITRIC ACID AND HEDTA.**

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The study describes the therapeutic efficacy of combined administration of citric acid and a amino chelator, N-(2-hydroxyethyl) ethylenediaminetriacetic acid (HEDTA) in decreasing blood and brain aluminum concentration and biochemical parameters indicative of haematological disorders and brain oxidative stress. Adult male Wistar rats were exposed to drinking water containing 0.2% aluminum nitrate for 8 months and treated for once daily for 5 consecutive days with citric acid (50 mg/kg, orally) or HEDTA (50 mg/kg, intraperitoneally) either individually or in combination. The results suggest significant alterations in blood  $\delta$ -aminolevulinic acid dehydratase (ALAD) and zinc protoporphyrin indicating altered heme synthesis. Significant changes in glutathione S-transferase (GST), thiobarbituric acid reactive substance (TBARS) level, and glutathione were also observed on aluminum exposure. Most of the above biochemical changes responded moderately favourable to the individual treatment with citric acid and HEDTA but significantly reduced blood and brain aluminum burden. However, more pronounced beneficial effects were observed when citric acid and HEDTA was administered concomitantly. It can thus be concluded that in order to achieve optimum effect of chelation, combined administration of citric acid and HEDTA might be preferred. However, further work in this direction is recommended before a final recommendation could be made.

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**AGED F344 RATS ARE RESILIENT TO CHLORDECONE POTENTIATED  $CCl_4$  HEPATOTOXICITY AND LETHALITY.**

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**Objective:** To investigate the effects of Chlordecone (CD) +  $CCl_4$  in young adult (3 months) and aged (14 months) male F344 rats.

**Methods:** After pretreatment with either dietary CD (10 ppm) or normal diet, rats were challenged with a single non-toxic dose of  $CCl_4$  (100  $\mu$ l/kg, ip, 1:4 solution in corn oil) or corn oil (500  $\mu$ l/kg) on day 16. Liver injury was assessed via plasma ALT and AST and histopathology during a time course of 0 to 96 h. Tissue repair was assessed by  $^3H$ -T incorporation into heptonuclear DNA..

**Results:** No mortality occurred in either age group exposed to  $CCl_4$  alone. Exposure to CD +  $CCl_4$  resulted 100% mortality in young adults by 96 h whereas there was no mortality in aged rats. CD +  $CCl_4$  caused identical elevation of ALT and AST in young adult and aged rats up to 36 h. Thereafter, liver injury escalated in young adults while declining in aged rats. Compensatory liver regeneration was robust in aged rats as compared to young adults.

**Conclusion:** Aged rats are resilient to CD +  $CCl_4$ -induced hepatotoxicity by virtue of prompt and robust tissue repair whereas young adults succumb to death due to failed tissue repair (Supported by NIH/AG19058).

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### PROTECTIVE VALUE OF THIAMIN OR METHIONINE AGAINST CADMIUM INTOXICATION IN RATS.

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**Objective:** The protective effects of simultaneous supplementation of thiamin, methionine on cadmium induced nephrotoxicity and hepatotoxicity, hepatic and renal levels of cadmium, copper and zinc was determined in male rats.

**Methods:** Male rats were administered 1 mg/kg cadmium as cadmium chloride, subcutaneously once daily for 8 days either alone or in combination with 25 mg/kg thiamin or methionine, given orally 5 minutes after cadmium administration. Half of the animals were sacrificed on day 9 and remaining half on day 16 after the start of the experiment.

**Results:** Exposure to cadmium produced a significant inhibition of hepatic alanine (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP), subsequent increase in the serum levels of these enzymes, gamma glutamate transpeptidase ( $\gamma$ -GT) and creatinine levels together with protein urea and high hepatic and renal burden indicate dysfunction of these organs. Thiamin and methionine were moderately and equally effective in preventing the accumulation of cadmium in soft organs and alteration in the selected biochemical indices during concomitant administration. Adequate intake of sulfur amino acid following methionine supplementation might be increasing the bio-availability of glutathione facilitating the prevention of binding of cadmium to different compartment and consequently reversing cadmium induced biochemical disorders. In case of thiamin, possibility of formation of readily excretable complex between cadmium and thiamin or increase in body's resistance to cadmium might be the beneficial factors.

**Conclusion:** Simultaneous supplementation of thiamin and methionine during cadmium exposure have only limited protective value but could be tried as an complimentary agents during chelation with a strong chelator.

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### COMPARATIVE TOXICITY AND CARDIORESPIRATORY EFFECTS OF 2-DEOXY-D-GLUCOSE IN RATS.

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2-deoxy-D-glucose (2-DG) is a glucose analogue, which has been extensively used as a tool to study glucose transport and regulation of glucose metabolism in a variety of cellular systems and intact organisms including primates and humans. Earlier studies have shown that the glucose analogue and glycolytic inhibitor 2-DG when co-administered with radiation, selectively inhibits the post irradiation repair processes in cancer cells, thereby enhancing radiation induced cytotoxicity *in vitro* and *in vivo*. Therefore, it has been shown that 2-DG offers a unique property to improve the radiotherapy of tumours. Multi centric trials are planned in cerebral glioma patients, which need large quantities of 2-DG. Therefore, indigenous production of 2-DG was undertaken in our establishment to reduce the overall cost of treatment and affordability.

The aim of the present investigation is to compare the toxicity and effect on various physiological parameters following administration of two sources of 2-DG - one procured from Sigma and other indigenously synthesised in our establishment. The physiological variables were recorded in urethane anaesthetized rats using Grass polygraph. The carotid artery was cannulated to record blood pressure (BP) using pressure transducer through a low level DC preamplifier. The respiratory rate (RR) was recorded using pneumotachograph and the twitch response of gastrochemius muscle using force transducer. The results indicate that the toxicity was more or less same in rats and mice following administration of Sigma 2-DG as well as DRDE 2-DG. The results also indicate that intravenous administration of sigma 2-DG and DRDE 2-DG produced similar effects on mean arterial pressure (MAP), heart rate (HR), respiratory rate (RR), neuromuscular transmission (NMT) and rectal temperature in urethane anaesthetized rats. In summary, the combined treatment using 2-DG prepared by DRDE, Gwalior would be cost effective and useful in therapy of cancer.

**PP - 77****HAEMATOLOGICAL VARIABLES IN COMMONLY USED LABORATORY ANIMALS.****Sugendran K, Jatav PC\*, Malhotra PR\*, Vijayaraghavan R.**

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Defence Research and Development Establishment Gwalior, is maintaining laboratory animals for research purpose for the last three decades. The laboratory animals, viz., Mice - Swiss (*Mus musculus*), Rats - Wistar (*Rattus norvegicus*), Guinea pigs - English (*Cavia porcellus*) and Rabbits - New Zealand (*Oryctolagus cuniculus*), are being used for pharmacological, toxicological, micro-biological and related disciplines. Haematological parameters of the laboratory animals form an essential component of the guidelines laid by CPCSEA. During the last two years (Jan 2000 to Jun. 2002), in all, 455 blood samples were randomly collected and analysed. The haematological determinations include erythrocytes, leukocytes, haemoglobin concentration, cell volume, polymorphs, lymphocytes and eosinophils. The haematological variables of the laboratory animals were statistically analysed using one way analysis of variance (ANOVA). The results show their close similarity with the data provided by CPCSEA. The range of normal values indicate that the animals are healthy, being bred in a clean atmosphere, pathogen / ectoparasite free and suitable for experimentation.

**PP- 78****SIMULTANEOUS ADMINISTRATION OF ZINC AND MONOISOAMYL DMSA IN THE PREVENTION AND TREATMENT OF ACUTE ARSENIC POISONING IN RATS.****Modi M, Kannan GM, Flora SJS.**

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**Objective:** Administration of zinc either alone or in combination with monoisoamyl dimercaptosuccinic acid (MiADMSA) during arsenic exposure and post-arsenic exposure was investigated in rats.

**Methods:** Male rats were administered 5 mg/kg arsenic as sodium arsenite, intraperitoneally once daily for 3 days either alone or in combination with 25 mg/kg zinc (as zinc acetate) given orally (p.o.), 2 hrs after arsenic administration. Another groups of arsenic treated animals were given both zinc and MiADMSA (50 mg/kg, p.o.). Animals were sacrificed 24 hr after the last dose. Half of the arsenic pre-exposed rats were also given saline, zinc, MiADMSA or zinc plus MiADMSA for another 3 days and sacrificed thereafter.

**Results:** Exposure to arsenic led to a significant inhibition of d-aminolevulinic acid dehydratase (ALAD), a marginal elevation of blood zinc protoporphyrin (ZPP) and glutathione (GSH) levels. Hepatic alanine and aspartate aminotransferase (ALT and AST) activities too decreased marginally suggesting hepatotoxicity. Concomitant administration of MiADMSA had limited effects on the above biochemical variables but zinc supplementation provided significant protection. Combined administration of zinc and MiADMSA also had no additional beneficial effects. Interestingly, post-arsenic exposure treatment with MiADMSA provided significant protection to ALAD activity and the best results were obtained when zinc and MiADMSA were administered together post arsenic exposure. The results suggest that concomitant administration of zinc and MiADMSA during arsenic exposure had limited value but administration of zinc and MiADMSA post arsenic exposure provided the best turnover in the altered biochemical variables.

**Conclusion:** Concomitant administration of zinc and MiADMSA could be a better treatment for arsenic poisoning compared to mono-therapy with MiADMSA. However, more detailed studies are required particularly after chronic arsenic exposure.

PP-79

### RAPID DETECTION OF RICIN BY SENSITIZING CARBOXYLATED LATEX PARTICLES BY RICIN ANTIBODIES.

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**Introduction:** Ricin is a highly toxic glycoprotein of *Ricinus communis* seeds. Ricin inhibits protein synthesis by inactivating ribosome, leading to cell death. No antidote is available to counter measure the toxicity of ricin. Detection is important to avoid ill effects of ricin.

**Methods:** Ricin toxin was purified and antisera was raised against ricin in rabbit. Polyclonal antibodies were covalently coupled through a water-soluble carbodiimide to carboxylated latex particles in various concentrations, and latex agglutination assay was developed.

**Result:** Polyclonal antibodies were covalently coupled through a water-soluble carbodiimide to carboxylated latex particles in various concentrations (800 to 3200 µg protein/0.5ml latex particles). Maximum antibodies binding was obtained at 2400 to 3200 µg protein/0.5ml of 2 % (wt/vol) latex particles with a sensitivity of 200 ng toxin per test. The sensitivity of latex agglutination (LA) test increased as amount of protein bound to the latex particles increased. The optimum sensitivity of test was recorded when latex particles were sensitized with 2800 µg protein/0.5 ml of latex particles. The reagents were stable for one year without loss of its sensitivity.

**Conclusion:** Developed latex agglutination test is rapid, sensitive, does not require trained personnel and costly equipments to perform the test.

PP-80

### AMINOALKYLAMINO ETHANETHIOL DERIVATIVES AS POTENT ANTIDOTES AGAINST SULFUR MUSTARD INTOXICATION.

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Defence Research and Development Establishment, Gwalior - 474002.

**Introduction:** Bis(2-chloroethyl) sulfide, commonly known as sulfur mustard (SM), is a highly toxic chemical warfare agent, having strong blistering properties. A really effective antidote against SM is not available so far in spite of several decades of research. In search for an effective antidote, a series of aminoalkylamino ethanethiol derivatives were synthesized and evaluated for their protective efficacy against SM intoxication.

**Methods:** Chemicals were purchased from Aldrich/Fluka/Lancaster. The compounds were prepared by the condensation of aminoalkylamino ethyl bromide with desired thiols in the presence of a base under varying reaction conditions. The purity of the compounds was checked by TLC and these were characterized by IR, NMR and Mass spectrometry. The evaluation of the compounds was done in female Swiss mice by determination of protective index.

**Results:** Sulfur mustard is a bifunctional alkylating agent and has great affinity towards a number of biomolecules containing thiol, amino, carboxylic and heterocyclic nitrogen and sulfur moieties. In view of this fact, a series of novel aminoalkylamino ethanethiol derivatives were designed, synthesized and evaluated against SM as potential antidotes. Some of the compounds showed promising protective efficacy. Amongst these, DRDE-02, 07, 10, 21 and 30 were found to provide significant protection against dermally applied SM.

**Conclusion:** Novel compounds having potential prophylactic efficacy against sulfur mustard intoxication have been identified. The compounds need to be further explored for developing effective drugs against SM intoxication

**PP-81****INSECTICIDAL EFFICACY OF TWO SYNTHETIC PYRETHROIDS AGAINST STABLE FLY AND TABANIDS ON DERMAL APPLICATION ON MARES.**

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Studies on the insecticidal efficacy of two synthetic pyrethroids, fenvalerate and deltamethrin against stable fly, *Stomoxys calcitrans*. Linn. (Diptera: Muscidae) and tabanids by dermal application on mares were carried out in a field trial. Fenvalerate resulted in 63.7% and 84.6% control of stable flies at 0.01% and 0.02% concentrations for 3 days while at 0.03%, 0.04% and 0.05%, hundred percent control of stable flies was observed for 3, 6 and 9 days respectively. On the other hand, fenvalerate was ineffective at 0.01% and 0.02% concentrations against tabanids while at 0.03% and 0.04% concentrations, it resulted in 90.7% and 91.4% control of tabanids for 3 days and at 0.05%, it provided 100% control for 6 days. Deltamethrin concentrations of 0.001% and 0.002% resulted in 100% control of stable flies for 3 and 9 days respectively while 0.003% and 0.004% concentrations provided 100% control for 12 days. At 0.005% concentration, deltamethrin provided 100% control for 18 days. In the case of tabanids, deltamethrin provided 76.6% and 90.7% control for 3 days at 0.001% and 0.002% concentrations respectively and 94.4% control at 0.003% for 6 days. Hundred percent tabanid control was observed at 0.004% and 0.005% concentrations for 9 and 15 days respectively. These studies indicate that deltamethrin is more effective than fenvalerate against stable flies and tabanids when applied dermally on mares.

**PP- 82****SYNTHESIS AND CHARACTERISATION OF SULFINES: A POTENTIAL LACHRYMATORS.**Vivek Polshettiwar, Manisha Nivsarkar, Acharya J, Pandey KS, Kaushik MP.  
Process Technology Development Division, Defence Research and Development Establishment, Gwalior - 474002.

The lachrymatory action of onion (*Allium cepa*) has been widely recognised and appreciated more than 6000 years ago. The unique ability of the onion to bring tears to the eyes of those that would cut it must surely have been noticed. The first suggestion that sulfur compounds might be responsible for the odour and lachrymatory factor of the onion appears to have been made in 1892. In the intervening years the application of increasingly sophisticated methods of analysis such as microwave spectroscopy, NMR, led ultimately to the characterization of so called lachrymatory factor (LF) of onion as the sulfine, an organosulfur compound known as propanethial S-oxide. Sulfines may considered to be an alternative source of sensory irritant. These compounds also account for medicinal properties keeping in view of the lachrymatory property of sulfine as well as their unique history of their use in folk medicine, we have synthesized five different analogue of sulfines by chlorination followed by dehydrochlorination of organic disulfides and characterised by IR and GCMS technique.

PP- 83

**COMPARATIVE BIOEFFICACY OF CHLORPYRIFOS AND CYPERMETHRIN AGAINST HOUSEHOLD PESTS.**

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Chemical control is the best weapon in the armory of vector control. The present study has been undertaken to evaluate bioefficacy of chlorpyrifos (2%), cypermethrin (0.5%) and mixture of both insecticides against insects of public health importance namely *Aedes aegypti*, *Musca nebulo* and *Periplaneta americana* adults at different period of intervals. The insecticide was applied on glass, wood, cement and mud surfaces. Mixture of chlorpyrifos and cypermethrin was found to be most effective against all the three species of insects tested. The  $LC_{50}$  and  $LC_{90}$  determination indicated that *Aedes aegypti* is most susceptible followed by *Musca nebulo* and *Periplaneta americana*. The efficacy of insecticide was found to be influenced by structure and type of surfaces used in the study.

PP- 84

**ELECTROPHYSIOLOGICAL RESPONSES OF Aedes aegypti ANTENNAL SENSILLA TO CERTAIN HUMAN SPECIFIC SKIN EMANATIONS.**

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Mosquito's attraction and repulsion to host involves antennal responses of female mosquitoes to host chemical emanations. The present study has been undertaken to record the electro physiological responses of *Aedes aegypti* antennae to various carboxylic acids such as propanoic acid, pentanoic acid, hexanoic acid, heptanoic acid, octanoic acid, nonanoic acid, decanoic acid, undecanoic acid, dodecanoic acid, tridecanoic acid, tetradecanoic acid, pentadecanoic acid, hexadecanoic acid, heptadecanoic acid and octadecanoic acid at different concentrations ranging from  $10^{-6}$  to  $10^{-8}$ g dose. *Aedes aegypti* antennae indicated 2-5 folds response to most of the carboxylic acids except heptanoic acid at  $10^{-6}$ g dose. Further, propanoic acid, heptanoic acid to tridecanoic acid and octadecanoic acid did not show appreciable response at  $10^{-8}$ g dose. Contrary to this, hexanoic acid, tetradecanoic acid to heptadecanoic acid indicated higher amplitude at the same dose level. Interestingly, hexanoic acid showed 5 folds increase at  $10^{-6}$ g dose. In addition, the electro physiological response of the antennae of *Aedes aegypti* was recorded to synthetic mixture of 14 carboxylic acids at different concentrations ranging from  $10^{-5}$ - $10^{-8}$ g dose. The antennae have shown concentration dependent electro physiological activity to the mixture. These studies have shown that the antennae of *Aedes aegypti* exhibited varied electrophysiological response to various carboxylic acids found in human skin emanations.

**PP- 85****SYNTHESIS OF 1-(N,N-DIETHYLAMINO), 3-(N'-PHTHALIMIDO)PROPAN-2-ONE-OXIME; A KEY INTERMEDIATE FOR THE SYNTHESIS OF ANATOXIN-a(s).****Acharya J, Manisha Nivsarkar, Kaushik MP.**

Process Technology Development Division, Defence Research and Development Establishment, Gwalior - 474002.

Anatoxin-a(s), a potent cyanobacterial neurotoxin produced by *Anabaena flosquae*. Among all the known neurotoxins, it is one of the most toxic compound having LD<sub>50</sub> (i.p.) 20-40 µg/kg in mice. Death occurs most probably due to respiratory arrest within minutes or hours depending upon the exposure. Structurally anatoxin-a(s) is a unique a N-hydroxy guanidine methyl phosphate ester. 1-(N,N diehtylamino), 3-(N'-phthalimido) propan-2-one-oxime is a key intermediate in the multi step synthesis for anatoxin-a(s). The synthesis starts from glycine with protection of the amino group by phthalyl moiety followed by conversion to acid chloride. Reaction with diazomethane and HBr gave a Bromo-propanone derivative. The Bromine functionality was replaced with diethylamine to give the 1-(N,N-Diethylamino),3-(N'-Phthalimido) propanone. Finally the ketone was converted to oxime by the action of hydroxylamine hydrochloride in presence of pyridine to afford 1-(N,N-diethylamino),3-(N'-phthalimido)propan-2-one-oxime and characterized by spectral data.

**PP- 86****BIOLOGICAL EVALUATION OF PHOSPHORUS CONTAINING SYNTHETIC NATURAL TOXIN AND ITS ANALOGUES.****Gupta AK, Dubey DK, Parashar BD, Gupta GP, Kaushik MP.**

Defence Research and Development Establishment, Gwalior - 474002.

Toxins are poisonous substances produced by large variety of living organisms such as algae, fungi and bacteria, etc. They have military interest because of extremely high degree of toxicity. A survey of open literature reveals a dramatic increase of interest in the studies related to toxins, mainly because of the fact that many toxins are much more toxic than most toxic chemical warfare agents known till date, and easy of their large scale production. To date, a total of eight toxins have been isolated and purified from *Ptychodiscus brevis*. These toxins are called breve toxins. About two decades ago, isolation and x-ray crystal structure of ichthyotoxic metabolite of *G. brevis* was reported. Its structure was established as O,O-dipropyl(E)-2-(1-methyl-2-oxopropylidene)phosphorohydrazidothioate-(E)-oxime (TG-1). This toxic metabolite was proved to be a fish toxin. It has two stereochemical centres and at each both E & Z configurations are possible. Since the biological activity of several compounds is profoundly influenced by stereochemical disposition of various groups. In general very little information is available on the toxicity of toxin TG-1 against fresh water fish *Rasbora doniconius*. Therefore in order to investigate the influence of various substituent on the biological activity of this compound various analogues bearing basic structure with different substituents were synthesised and evaluated against fresh water fish *Rasbora doniconius*. Further it is known that molecules bearing P=O functionality are more toxic than P=S moiety. Therefore P=O analogues of natural toxins TG-1 were also synthesised and evaluated. Total 19 compounds including natural toxin TG-1 were evaluated against fresh water fish *Rasbora doniconius*. The LC<sub>50</sub> value of parent toxin TG-1 has been found to be 3.25 ppm. Out of 19 compounds toxicity of 4i, 4c and 4h was found to be more or less similar (3.0 - 3.32pm). The toxicity of seven analogues of synthetic toxin TG-1 has been observed to vary from 6.49 to 9.95 ppm. While rest of the compounds showed LC<sub>50</sub> values ranging from 13.12 to 95.99 ppm.

PP- 87

### STUDIES OF SENSORY IRRITATION POTENTIAL AND ACUTE TOXICITY OF SYNTHESIZED NATURAL CAPSAICINOIDS.

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**Objective:** Synthesis, characterization and evaluation of selected naturally occurring capsaicinoids to assess their efficacy as non-lethal incapacitating agent.

**Methods:** Capsaicin (8-methyl-N-vanillyl-6-nonenamide; (E)-isomer), dihydrocapsaicin (DHC) and their three analogues were synthesized and characterized by elemental analysis, IR, <sup>1</sup>H NMR and mass spectral analysis (purity of the compounds were >99% by GC analysis). Solutions of the compounds were prepared in propylene glycol and were fed to 3-4 hours fasted male albino mice (25-31 g), and LD<sub>50</sub> was calculated by method of moving average. An all glass static inhalation exposure assembly (6 L) was used for determination of sensory irritation potential through inhalation. The respiration of male mice were sensed, amplified, recorded and analysed using a polygraph coupled with computer. Mean of percent respiratory rate during the exposure was calculated considering the pre-exposure rate as 100%. Fifty percent depression of the respiratory rate (RD<sub>50</sub>) was determined by obtaining the linear curve fitting equation and putting the value of 'Y' = 50.

**Results:** Acute toxicity (LD<sub>50</sub>, mg.kg<sup>-1</sup>) of the compounds was in the following sequence: nordihydrocapsaicin (100) = homodihydrocapsaicin (100) > nor-norcapsaicin (178) > dihydrocapsaicin (200) = (E)-capsaicin (200). The concentration of capsaicin and dihydrocapsaicin in air which induced respiratory depression by 50% (RD<sub>50</sub>) were as follows: (E)-capsaicin, 15.52 µg.L<sup>-1</sup> (1.242 ppm) and dihydrocapsaicin, 10.3 µg.L<sup>-1</sup> (0.819 ppm).

**Conclusion:** The results suggest that E-capsaicin and dihydrocapsaicin are less toxic compared to their analogues, and dihydrocapsaicin was found to be > 1.5 times more potent sensory irritant compared to that of (E)-capsaicin.

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### WOUND HEALING PROFILES OF *DATURA ALBA*.

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**Objectives:** 1. To assess the effects of *Datura alba* on collagenation phase of healing, 2. Wound contraction rate, 3. Epithelization period of wound healing.

**Methods:** Incision wound, excision wound and dead space wound models were made and the aqueous extract of *Datura alba* at a dose of 800 mg/kg orally were administered for 10, 22 and 10 days respectively. 8 animals of 200 gm each were used in each group. In incision wound model skin breaking strength was estimated; in dead space wound model granulation tissue breaking strength, dry granuloma weight, and hydroxy proline content in mg/gm was estimated; in excision wound model rate of wound contraction and period of epithelization were noted and compared with that of control.

**Results:** The aqueous extract of *Datura alba* showed significant reduction in dry granuloma weight, increase in hydroxy proline content and reduction in period of epithelization but less significant effect on skin breaking strength and granulation tissue breaking strength.

**Conclusion:** *Datura alba* possesses wound healing property.



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### MECHANISM OF ANTI-INFLAMMATORY ACTIVITY OF TEA ROOT EXTRACT.

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**Objective:** To get an insight into the mechanism of anti-inflammatory effect of tea root extract (TRE).

**Methods:** The models of inflammation used are: carrageenan-induced oedema, cotton pellet-induced granuloma, Freund's adjuvant-induced polyarthritis and arachidonic acid-induced paw oedema in rat and croton oil-induced ear inflammation in mice. The effect of TRE was compared with reference anti-inflammatory agents.

**Results:** At a dose of 10 mg/kg, ip TRE produced anti-inflammatory effect comparable to acetyl salicylic acid in the carrageenan-induced paw oedema, cotton pellet-induced granuloma, croton oil-induced ear inflammation and Freund's adjuvant-induced polyarthritis models. TRE and the dual blocker BW755C significantly inhibited the arachidonic acid-induced paw oedema model while indomethacin failed to produce any inhibition in this model.

**Conclusion:** The study reveals that TRE possesses significant anti-inflammatory activity and that this effect is probably mediated via dual blockade of the lipooxygenase and cyclooxygenase pathways of arachidonic acid metabolism.

PP - 90

### MOLECULAR MECHANISM OF CARDIOPROTECTION PRODUCED BY *WITHANIA SOMNIFERA* AND *OCIMUM SANCTUM*.

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Present study evaluated the cardioprotective potential of hydroalcoholic extract of *Withania somnifera* (Ws) and *Ocimum sanctum* (Os) against isoproterenol (ISO) induced myocardial infarction in rats. Rats were administered different doses viz, Ws (50, 100 and 200 mg/kg) and Os (25, 50, 75, 100, 200 and 400 mg/kg) orally using intragastric tube for two weeks. ISO-200 was administered to produce oxidative stress reflected in significant ( $p < 0.05$ ) GSH and LDH depletion from the myocardial tissue. Myocardial necrosis was determined directly by staining with triphenyl tetrazolium chloride (TTC) and by histopathological examination, which depicted clear focal myonecrosis with myophagocytosis and lymphocytic infiltration (myocarditis) and presence of marked inflammatory cells. Further biochemical studies also confirmed the presence of myocardial necrosis. Ws and Os both positively modulated the antioxidant parameters (GSH rise, SOD rise), lipid peroxidation marker (TBARS fall) and myocardial enzyme (LDH restoration) significantly ( $p < 0.05$ ) under oxidative stress. On histopathological examination Os (25, 50, 75 and 100 mg/kg) has also shown the visible reversal of changes observed on administration of ISO. However, Os at (200 and 400 mg/kg) doses did not modulate LDH, GSH, SOD and TBARS significantly and hence were found to be ineffective. Histological examination revealed that Ws (50, 100 and 200 mg/kg) doses significantly reversed myocardial damage and also modulated biochemical parameters. Inhibition of oxidative stress as reflected biochemically both by Ws and Os confirms the antioxidant activity of both herbs. Therefore, cardioprotection demonstrated histopathologically, biochemically and morphologically in the present study can thus be partly attributed to their antioxidant properties.

**PP - 91****WITHANIA SOMNIFERA MODULATES HEMODYNAMICS AND AUGMENTS ENDOGENOUS ANTIOXIDANTS IN THE EXPERIMENTAL MODEL OF ISOPROTERENOL INDUCED MYOCARDIAL NECROSIS.****Mohanty I, Arya DS, Joshi S, Bansal P, Saxena A, Gupta SK.**

Dept. of Pharmacology, All India Institute of Medical Sciences, New Delhi - 110029.

The present study was designed to evaluate cardioprotective potential of hydroalcoholic extract of *Withania somnifera* (Ws) on haemodynamic, histopathological and biochemical parameters against isoproterenol (ISP) induced myocardial necrosis in rats. Wistar albino rats (150-200 g) were divided into four main groups: sham, ISP control, drug control and drug treatment groups. Ws was administered at doses of 25, 50 and 100 mg/kg orally for 4 weeks. On day 29<sup>th</sup> and 30<sup>th</sup> the rats of control and drug treatment group were administered ISP (85 mg/kg), subcutaneously at an interval of 24 h. On the 31<sup>st</sup> day hemodynamic parameters, viz., systolic, diastolic and mean arterial pressure (SAP, DAP, MAP), heart rate (HR), left ventricular end diastolic pressure (LVEDP), left ventricular peak (+) dP/dt and (-) dP/dt were recorded. Heart was removed and processed for histopathological and biochemical studies: myocardial enzymes, creatine phosphokinase (CPK) and lactate dehydrogenase (LDH), antioxidant parameters: malondialdehyde (MDA), glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX) were estimated. A significant decrease in GSH ( $p < 0.05$ ), activities of SOD, CAT, LDH and CPK ( $p < 0.01$ ) as well as increase in MDA level ( $p < 0.01$ ) was observed in the control group rats as compared to sham group. The changes in levels of protein and GPX was however, not significant. A slight decrease in the hemodynamic parameters was also recorded in the control group. Histopathological evaluation also confirmed myocardial damage. Ws (25,50,100 mg/kg) doses significantly reversed myonecrosis, augmented endogenous antioxidants and restored haemodynamic parameters though not significantly. Ws 50 mg/kg dose was found to be the most effective dose.

**PP - 92****EFFECT OF CENTELLA ASIATICA ON PENTYLENETETRAZOLE INDUCED KINDLING, COGNITION AND OXIDATIVE STRESS IN RATS.****Gupta YK, Veerendra Kumar MH.**

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**Objective:** Cognitive impairment in epileptics may be a consequence of the epileptogenic process as well as antiepileptic medication. Thus there is a need for drugs, which can suppress epileptogenesis as well as prevent cognitive impairment. In the present study the effect of aqueous extract of *Centella asiatica* (CA) (100 and 300 mg/kg) an Indian medicinal plant known to possess antiepileptic, cognitive enhancing and antioxidant property was evaluated on the course of kindling development, kindling induced learning deficit and oxidative stress markers in pentylenetetrazole (PTZ) kindled rats.

**Methods:** Male Wistar rats (200-250 g) were injected PTZ (30 mg/kg, i.p.) once every alternate day ( $48 \pm 2$  h) till the development of the kindling. Passive avoidance test and spontaneous locomotor activity were carried out 24 and 48 h after the last administration of PTZ, while the oxidative stress parameters (malondialdehyde and glutathione) were carried out in the whole brain upon completion of the behavioural assessment.

**Results:** The administration of CA 300 mg/kg orally decreased the PTZ kindled seizures and showed improvement in the learning deficit induced by PTZ kindling as evidenced by decreased seizure score and increased latencies in passive avoidance behaviour. However low dose of the CA 100 mg/kg showed improvement only in the learning deficit due to the kindling and failed to improve the seizure score.

**Conclusion:** The findings suggest the potential of aqueous extract of CA as adjuvant to antiepileptic drugs with an added advantage of preventing cognitive impairment.

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**A PRELIMINARY REPORT OF THE CNS EFFECTS OF PLANT, CDRI CODE NO. 4570.**

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**Introduction:** Development of drugs from plant is an age old tested strategy. Our Institute has embarked this path since its inception and has developed certain useful drugs like a standardised extract for memory enhancement, anti-hyperlipaemic, hepatoprotective etc. We report here the results of our preliminary investigation on a plant bearing the CDRI Code No.4570.

**Methods:** The alcoholic extract of the plant was subjected to a battery of tests to elucidate its CNS effects on gross observation, antidepressant, potentiation of pentobarbital sleeping time, feeding behaviour and anxiolytic effects.

**Results:** The plant extract in a dose of 100 mg/kg i.p produced an increase in SMA, respiration and reactivity to sound and touch. It also showed piloerection and exophthalmous. A counteraction of reserpine (2.5 mg/kg i.p.) induced syndromes in terms of ptosis, sedation and crouching was produced indicating a mild anti depressant effect. The plant also produced dose dependent appetite suppressant effect and no fall in rotarod test. However, no significant prolongation of pentobarbitone induced sleeping time was observed. The plant also showed an anxiolytic profile of action.

**Conclusion:** The plant has promising effect as anxiolytic. Further investigations are in progress to make activity guided extraction to localize the activity.

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**CRITICAL EVALUATION OF ANTIMICROBIAL AGENTS (AMA) UTILIZATION IN HOSPITAL DELIVERIES.**

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**Objective:** To critically evaluate the rationality of AMA utilization in hospital deliveries.

**Method:** 400 hospital delivery cases containing AMA were analysed of which 200 from Lady Goshen hospital and 100 each from two private nursing homes. The rationality of AMA use were analysed by using Kunin's and INRUD (Indicators of Rationale Use of Drugs) criteria.

**Results:** In our study 26.25% prescriptions were rational (Kunin's criteria grade I & II) which was less than Duke University Study (36%). There was also a significant difference in rationality ( $P < 0.001$ ) among hospitals in prescribing AMA. The average number of AMA used per prescription should be less than 2 according to INRUD Criteria, which was 1.63 / case in our study. Percentage of prescribed drugs containing AMA should be less than 30% which was 31.90%. in our study with variation among hospitals. The percentage of injectable AMA used should be  $< 20\%$ . In our study it was found to be 39.45% which was significant ( $P < 0.05$ ).

**Conclusion:** From our study it was concluded that duration of prophylaxis should be reduced to 24-36 hrs and time of administration should be modified.

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**A PRELIMINARY EVALUATION OF SAUROPUS ANDROGYNUS OINTMENT ON THE RATE OF WOUND CONTRACTION IN WISTAR RATS.**

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**Introduction:** *Sauropus androgynus* popularly known as vitamin green is used traditionally as wound applicant, for weight control and also in worm infestation. The leaves and fruits of this plant is rich in many active principles that include carotenoids, vitamin B and C. The present study is undertaken to validate the traditional claim that *Sauropus androgynus* acts as a pro-healer. The objective of the study is to unravel the action of *Sauropus androgynus* on excision wound healing.

**Methods:** Wistar rats of either sex BW 150-250 grams were grouped (n=6) into four, at random. A full thickness dermal excision wound (500 mm<sup>2</sup>) was inflicted on the dorsal interscapular region under pentobarbitone anaesthesia (30 mg/kg, i.p). The tracing of the raw wound area were taken on a transparent sheet and transferred to a millimetre graph paper to monitor rate of wound contraction from 3rd day up to the period of complete wound healing. *Sauropus androgynus* ointment and its base were applied twice a day: a fixed quantity 0.25 and 0.5 cm of uniform length; from wounding day to the period of wound closure. Results were analysed by unpaired Student's 't' test.

**Results:** *Sauropus androgynus* ointment produced dose dependent 'prohealing' action and accelerated wound closure very significantly. (P< 0.001). 0.25 cm ointment/base = 39.57 ± 2.5 / 101 ± 15.4 and 0.5 cm ointment/base = 25 ± 3.8 / 69 ± 6.8

**Conclusion:** Vitamin green ointment promoted excision wound healing. The ointment base did modify the rate of wound contraction evincing that base is not inert.

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**VITAMIN GREEN- SAUROPUS ANDROGYNUS PROMOTES RE-EPITHELIZATION.**

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Department of Pharmacology; Kasturba Medical College, Mangalore - 575001.

**Introduction:** *Sauropus androgynus* popularly known as vitamin green is used as wound medicament for weight control and as anti-worm agent. The leaves and fruits of this plant is rich in active principles which include carotenoids, vitamin B and C. The current study aims at providing a basis for traditional use of *Sauropus androgynus* for wound management. The objective of the study is to evaluate the effect of *Sauropus androgynus* ointment on re-epithelization of rodent dermal wound.

**Methods:** Four randomly grouped (n=6) Wistar rats of either sex (BW 150-250 gms) were employed for the study. A circular piece (500 mm<sup>2</sup>) of full thickness skin was excised (Morton and Malone) from the dorsal interscapular region under pentobarbitone anaesthesia (ie., 30 mg/kg, i.p). The fall off wound scab was taken as the measure of complete epithelization. A fixed quantity of *Sauropus androgynus* ointment and its base 0.25 and 0.5 cm of uniform length applied twice a day; from wounding day up to the period of re-epithelization. Results were analysed by unpaired Student's 't' test.

**Results:** *Sauropus androgynus* accelerated the period of re-epithelization in a dose dependent manner (P<0.001). 0.25 cm ointment/base 14.4 ± 0.36 / 13.6 ± 1.2 and 0.5 cm ointment/base 12.33 ± 0.4/15.5 ± 0.37.

**Conclusion:** Present findings suggest that *Sauropus androgynus* accelerates re-epithelization.

PP - 97

### WOUND HEALING EFFECT OF *TILWADI GHRITA*

Langde AS, Charde MS, Fulzele SV, Satturwar PM, Dorle AK.

Department of Pharmaceutical Sciences, Nagpur University Campus, Nagpur - 440010.

**Objective:** To evaluate the wound healing activity of *Tilwadi ghrita*, a herbal formulation.

**Methods:** *Tilwadi ghrita* is a herbal formulation containing *Glycyrrhiza glabra*, *Seasamum indicum* and Ghee as the active constituents. *Tilwadi ghrita* was studied for its topical healing effect on incision (tensile strength) and excision wounds (wound contraction) in rats. The results were compared with those with Framyccetin sulphate cream (FSC 1% w/w) and untreated control rats. Sections of the healed tissue were observed histopathologically for keratinization, epithelization, fibrosis and collagenation as healing markers. The results were compared statistically ( $P < 0.05$ ) using ANOVA followed by Turkey Kramer Multiple Comparisons test.

**Results:** The test formulation significantly promoted the healing of incision wounds as evidenced by the tensile strength measurements. These results are supported by the histopathological observations which reveal that *Tilwadi ghrita* promotes collagenation, keratinization, fibrosis and epithelization. The test formulation also showed positive healing effect on excision wounds as revealed by complete healing around day 24 as compared to day 30 with untreated control.

**Conclusion:** The study demonstrates wound healing potential of *Tilwadi ghrita* in rats.

PP - 98

### ANTICANCER ACTIVITY OF *ALOE VERA* A PRELIMINARY SCREENING.

Shalini Adiga, Vasanth Kumar A, Namitha Rao, Uma Devi P\*.

Department of Pharmacology and Radiobiology\*, Kasturba Medical college, Manipal - 576119.

**Objective:** To evaluate the possible anticancer activity of *Aloe vera* against a solid tumour model in Swiss albino mice.

**Methods:** The solid tumour fibro sarcoma was obtained by intradermal inoculation of  $5 \times 10^5$  viable tumour cells on the dorsal side of mice. Effect of two different doses (1.2 ml and 1.6 ml /100 g) of aloe juice was studied by administering the drug orally for 10 days after the tumour size reached  $100 \pm 10 \text{ mm}^3$ . Tumour response was evaluated by tumour volume measurement, assay of volume doubling time and growth delay.

**Results:** *Aloe vera* showed a significant delay to reach a tumour volume of  $500 \text{ mm}^3$  ( $p \leq 0.05$ ). A significant increase ( $p \leq 0.05$ ) in volume doubling time and growth delay was observed. Animals treated with a high dose showed better response than lower dose. No spontaneous regression of the tumour was seen during the observation period.

**Conclusion:** *Aloe vera* shows antitumour effect against transplantable fibro sarcoma tumour model.

PP - 99

### ANTI-ULCER EFFECT OF DRIED FRUITS OF *CARICA PAPAYA* LINN IN RATS.

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Dept. of Pharmacology, Vinayaka Mission's College of Pharmacy, Salem - 636008, Tamil Nadu. <sup>1</sup>Institute of Pharmacology, Madurai Medical College, Madurai - 625002.

**Objective:** To evaluate the ulcer protective effect of alcoholic extract of dried fruits of *Carica papaya* Linn in rats.

**Methods:** The Anti-ulcer activity of alcoholic extract of *C. papaya* was evaluated against gastric ulcer induced by pyloric ligation and aspirin induced ulcer model in rats. The stomach was incised along with greater curvature and examined for ulcer. Effect of alcoholic extract of *C. papaya* on volume of gastric secretion, total, free acidity and ulcer index in pyloric ligated and aspirin induced ulcer rat was determined. Each group consisted of six animals.

**Results:** Oral administration of alcoholic extract of *C. papaya* decreased the volume of gastric secretions, total acidity and ulcer index with respect to control.

**Conclusion:** The alcoholic extract of *C. papaya* possesses significant ulcer protective activity.

PP- 100

### INVESTIGATION OF WOUND HEALING ACTIVITY OF *DARVHI GHIRTA*, A HERBAL FORMULATION.

Charde MS, Fulzele SV, Satturwar PM, Dorle AK.

Department of Pharmaceutical Sciences, Nagpur University Campus, Nagpur - 440010.

**Objective:** *Darvhi ghrita* (DG) a ghee based herbal formulation is claimed to promote wound healing in traditional practices. However no systematic studies are reported in modern literature with regard to the verification of medicinal claims of DG. The present study aims to verify the wound healing activity of DG in experimental animals.

**Methods:** Incision and excision wound models were employed for the present investigation. Wounds were inflicted under light ether anaesthesia in male Wistar rats (150-250 g). Tensile strength and wound contraction were taken as measure of incision and excision wounds respectively. Healing markers like keratinization, epithelization, fibrosis, neovascularization and collagenation were monitored histopathologically by microscopic examination of the sections of healed tissues. Treatment with Framycetin sulphate cream (FSC 1 % w/w) was taken as positive control, while the results were compared with untreated healing response. Turkeys multiple range criterion calculated from one way ANOVA ( $p=0.05$ ) was considered for statistical significance.

**Results:** In the present study, it was observed that the test formulation promotes wound healing in incision wounds and it is confirmed by tensile strength measurement. These results are clarified by histopathological observation which reveal that *Darvhi ghrita* promotes collagenation, epithelization, keratinization and fibrosis. In excision wound study it was observed that DG promotes wound contraction as revealed by complete healing around day 21 as compared to day 30 with untreated control.

**Conclusion:** *Darvhi ghrita*, a herbal formulation is proved to exhibit potent wound healing activity comparable to FSC 1% w/w.

PP -101

**EFFECT OF GARLIC ON ETHANOL INDUCED GASTRIC ULCERS IN RATS.**

**Khosla P, Karan RS, Bhargava VK.**

Deptt. of Pharmacology, GMC & H, Chandigarh, Deptt. of Pharmacology, PGIMER, Chandigarh.

**Objective:** To evaluate the gastroprotective activity of garlic oil against ethanol induced ulcers in rats.

**Methods:** Study was conducted using Wistar rats. Effect of pretreatment with garlic oil in doses of 0.125, 0.25, 0.5 mg/kg thirty minutes before administration of ethanol (1ml of 100%) was determined on ulcer index, lipid peroxidation and antioxidant enzyme activity (GPx, catalase and SOD).

**Results:** Pretreatment with garlic oil caused decrease in ulcer index and lipid peroxidation and ameliorated decrease in antioxidant levels caused by ethanol.

**Conclusion:** Garlic oil possesses antioxidant properties and provided protection against ethanol induced injury in rats.

PP - 102

**HEPAOPROTECTIVE EFFECT OF PLANTS AND THEIR ACTIVE PRINCIPLE AGAINST CCl<sub>4</sub> INDUCED HEPATOTOXICITY.**

**Anjana Jadon J. Sangeeta Shukla**

School of Studies in Zoology, Jiwaji University, Gwalior - 474011.

A large section of world's population relies on traditional remedies to treat a plethora of disease. Medicinal herbs are an indispensable part of the world due to low cost, easy access and ancestral experience. In Ayurveda, various herbal and herbomineral preparation are extensively used for the treatment of various liver disorders. In the present study, the hepatoprotective activity of *Terminalia belerica* and its active principle Gallic Acid (3,4,5-trihydroxy benzoic acid, GA) were tested against carbon tetrachloride (CCl<sub>4</sub>) induced toxicity. The degree of protection was measured by using the different doses of ethanolic extract of the fruit of *Terminalia belerica* and with its active principle. Female albino rats weighing 130 ±10 g were divided into five groups of five animals each. First group served as normal control. Groups 2-6 were administered 1.5 ml/kg of CCl<sub>4</sub> (i.p.) and group 2 was treated as experimental control. The animals of group 3 and 4 were treated with ethanolic extract of *Terminalia belerica* at a dose of 200 mg/kg and 400 mg/kg, p.o., respectively and group 5 was administered with aqueous suspension of GA (200 mg/kg, po) after 24 hours of toxicant administration. Administration of CCl<sub>4</sub> to normal rats caused significant decrease in the activity of serum alkaline phosphatase, Hb% and blood sugar level. Marked increase was observed in the level of transaminases (SGOT and SGPT) in the serum protein was also observed. Significant elevation in hepatic lipid peroxidation and sharp depletion in reduced glutathione level were also seen. Ethanolic extract of *Terminalia belerica* was evaluated for its hepatoprotective activity against CCl<sub>4</sub> induced haematological and biochemical alterations in the liver. Trihydroxy benzoic acid provided significant protection against CCl<sub>4</sub> induced toxicity.

**PP -103****HEPATOPROTECTIVE ACTION OF PROPOLIS EXTRACT AGAINST CCl<sub>4</sub> INTOXICATION.****Monika Bhaduria, Sangeeta Shukla.**

School of Studies in Zoology, Jiwaji University, Gwalior - 474011.

Uncontrolled environmental pollution, poor sanitary conditions, increasing recourse to drug abuse and expanding therapy with potent drug predispose liver, which is the key organ of metabolism and excretion, to vast array of disorders. In the present investigation, an attempt has been made to validate the hepatoprotective activity of ethanolic extract of propolis against experimentally induced liver injury. Propolis is the "glue" that bees use to seal up the hive. It is mainly composed of a sticky resin that originally comes from the buds and bark of trees such as poplar and horse chestnut. The bees gather it and use it to cement the hive together. The main chemical classes present in propolis are flavonoids, phenolics and various aromatic compounds. Female albino rats weighing 130±20 g. were divided into six groups of five animals each. Group 1 served as normal control, groups 2-6 were administered with 1.5 ml/kg of CCl<sub>4</sub> (i.p.). Group 2 was treated as experimental control. Groups 3 and 4 were treated with ethanolic extract of propolis of 100 and 200 mg/kg (p.o.) dose respectively prior to 24 hours of toxicant administration. Groups 5 and 6 were administered with propolis at 100 and 200 mg/kg (p.o.) dose respectively 24 hours after toxicant administration. The substantially elevated serum enzymatic activities of alanine/aspartate amino transferase and serum protein level due to CCl<sub>4</sub> treatment were restored towards normalization. Significant decrease in serum alkaline phosphatase and blood sugar was observed after toxicant treatment, which were recouped by propolis extract. In addition propolis also significantly prevented the elevation of hepatic malondialdehyde formation and depletion of reduced glutathione content in the liver of intoxicated rats in a dose dependent fashion. Liver study histopathologically confirmed the biochemical results. The results of this study clearly indicate that propolis extract given after toxicant has a dose dependent hepatoprotective action.

**PP - 104****OCIMUM SANCTUM LEAF EXTRACT REVERSES THE STRESS INDUCED DENDRITIC DEFICIENCY IN SUBSTANTIA NIGRAL NEURONS.****Rodrigues V\*, Rao MS\*\*, Rao GM.\*\*\***

Department of Anatomy\* and Pharmacology\*\*\* International Centre for Health Sciences, Manipal; Department of Anatomy\*\*, Kasturba Medical College, Manipal - 576119.

**Introduction:** Chronic exposure to stress has been shown to cause neuronal cell loss and atrophy of dendrites of substantia nigral neurons. Many ayurvedic plants were known to possess antistress activity and *Ocimum sanctum* is one among these antistress plants. Study was conducted to evaluate the antistress effect of crude leaf extract of *Ocimum sanctum* on stress induced dendritic atrophy of substantia nigral neurons.

**Methods:** The adult rats of 2½ months old were stressed for 6 weeks by giving electric foot shock at 5 minutes interval, 3 hours/day. The stressed rats were divided into 3 groups. First group of rats (n=6) received saline orally (2 ml/kg/day) for a period of six weeks. Second and third groups (n=6 in each group) received crude leaf extract of *Ocimum sanctum* plant orally at a dosage of 2 ml and 4 ml/kg/day respectively. The rats of the same age without stress or any treatment served as normal control. All the rats were then sacrificed and suprarenal glands were removed and weighed. Brain was dissected and substantia nigral neurons were stained by Golgi staining procedure.

**Results:** Results of the dendritic quantification of nigral neurons showed that there was a significant decrease in the dendritic intersections and dendritic branching points in the rats stressed and treated with saline when compared to normal rats. Whereas such a change was not observed in the rats stressed and treated with *Ocimum sanctum* when compared to normal rats. In addition to this the saline treated rats also had increased suprarenal gland weight when compared to normal and *Ocimum sanctum* treated rats.

**Conclusion:** These results reveal the antistress activity of *Ocimum sanctum* in preventing the stress-induced dendritic atrophy of substantia nigral neurons.



PP - 105

**EFFECT OF *CENTELLA ASIATICA* ON THE DENDRITIC MORPHOLOGY OF AMYGDALOID NEURONS IN ADULT RATS.**

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Department of Anatomy\*, Pharmacology\*\* ICHS, Manipal and Department of Anatomy\*\*\*, KMC Manipal - 576119.

**Introduction:** *Centella asiatica* (CeA) is reported to improve the learning and memory in animals and humans. But there is no report on its effect on regions of the brain like amygdala and hippocampus, which are known to play a role in learning and memory. The aim of the present study is to find out the effects of different doses of CeA on amygdaloid neurons.

**Methods:** Adult Wistar rat pups were divided into 3 groups. Normal control (n=6), ii. Saline control (n=8), iii. CeA treated groups. The CeA treatment groups received orally CeA leaf extracts 4 ml (n=8) and 6 ml/kg/day (n=6) for 6 weeks. After 6 weeks the rats were sacrificed for dendritic morphological analysis of amygdaloid neurons.

**Results:** CeA 4 ml group did not show any change in dendritic intersections and branching points compared to control groups. Whereas, CeA 6 ml group showed significant increase in both dendritic intersections and branching points.

**Conclusion:** These morphological changes may be the neuronal basis for improved learning and memory reported earlier.

PP - 106

**THE PROTECTIVE EFFECT OF *CLEOME GYNANDRA* LEAF EXTRACT ON ADJUVANT INDUCED ARTHRITIS IN RATS.**

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<sup>1</sup>Department of Inorganic Chemistry, University of Madras, Guindy Campus, Chennai - 600025; <sup>2</sup>Department of Biochemistry, Kongunadu Arts and Science College, Coimbatore - 641029.

Rheumatoid arthritis is a systemic auto immune and inflammatory disorder expressed most commonly in the joints. Causing pain, swelling and restricted movements in the joints. Due to side effects and ever increasing prices of the drugs especially in developing countries, need to search for cheap drugs from natural sources become imperative. In folk medicine various indigenous drugs are used in single and / or combined forms for treating different types of inflammatory and arthritic conditions. *Cleome gynandra* is a common weed, which occurs throughout the greater parts of India. This plant has long been used in India as a household remedy. The anti-inflammatory property of the leaf extract of *Cleome gynandra* was studied. The drug was administered at a dose level of 150 mg/kg body weight for 14 days to arthritic animals after the adjuvant injection. Significantly increased levels of urea, uric acid and creatinine as observed in arthritic condition was reduced in drug treated animals and the doses of aqueous suspensions of the leaf powder were effective to significant levels of the haematological parameters against the inflammatory response. The extract exhibited strong topical anti-inflammatory effects shown as inhibition of adjuvant induced arthritis model in rats.

PP - 107

### EFFECT OF *BACOPA MONNIERI* LINN ON ACTIVE ANAPHYLAXIS IN MICE.

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Department of Pharmacology, Research and Development Centre, Natural Remedies Pvt. Ltd., Plot No. 5B, Veerasandra Indl. Area, Hosur Road, Bangalore - 561229.

**Objective:** To evaluate the anti-anaphylactic activity of methanolic extract of *Bacopa monnieri*.

**Method:** Fifty Albino mice of either sex were grouped into 5 (n = 10/group). The 1<sup>st</sup> group of mice received 0.5% CMC orally, the 2<sup>nd</sup> group was treated with Prednisolone (14 mg/kg) while group 3, 4 and 5 were treated with methanolic extract of *B. monnieri* at 50, 100 and 200 mg/kg orally for 30 days. All the groups of mice were sensitized by subcutaneous injection of egg albumin (0.25 mcg). The hind paw edema due to antigen antibody reaction was measured 15 minutes after the rechallenge with egg albumin (10 mcg) on 12th day of sensitization. One way analysis of variance followed by Scheffe's test was applied to test significance.

**Results:** *Bacopa monnieri* (methanolic extract) produced 32%, 46% and 48.5% inhibition of edema due to antigen at 50, 100 and 200 mg/kg respectively. The effect was statistically significant at 100 and 200 mg/kg.

**Conclusion:** The methanolic extract of *B. monnieri* possesses significant anti-anaphylactic activity in mice at 100 and 200 mg/kg.

PP-108

### CHEMICAL STUDY OF MEDICINAL PLANTS.

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Process Technology Development Division, and \*Microbiology Division, Defence Research & Development Establishment, Gwalior - 474002; \*\*Defence Research Laboratory, Tezpur - 784001.

In our country, which is rich in flora, the importance of plants materials for medicinal purposes has been realized since earlier times. Both in Ayurvedic and Unani systems of medicine, the plant materials are used in the crude form for the treatment of various ailments with considerable success. However, in recent times attempts have been made to isolate the components actually responsible for the remedial action and put them into pharmaceutical use. However, there is still scope and need to screen the numerous plant materials of medicinal value and to study them in detail wherever necessary. With this objective in view, in the present study chemical investigation of plant materials having medicinal value have been undertaken. For the isolation and separation of the constituents, solvent extraction and chromatographic technique will be employed. To elucidate the structure of the components, both spectroscopic and chemical methods have been used. Related synthetic studies of the new components will also be undertaken to verify the structure of the new components.

PP-109

**PRELIMINARY PHARMACOLOGICAL STUDIES ON THE TOXIC PRINCIPLE OF INDIAN MARINE SNAIL *TELESCOPIUM TELESCOPIUM*.**

**Mukherjee S**, Singh AK, Samanta S, Sen T, Nag Chaudhuri AK.

Division of Pharmacology, Department of Pharmaceutical Technology, Jadavpur University, Kolkata - 700032.

The toxic principles obtained from *Telescopium telescopium* were evaluated for pharmacological effects. Preliminary results revealed significant effects on Central Nervous System e.g., behavioural changes, phenobarbitone-induced sleeping time, pentylenetetrazole-induced convulsions, exploratory behaviour and muscle relaxant activity. The detailed findings and their significance would be presented and discussed.

PP-110

**EVALUATION OF TANNINS OF *ACORUS CALAMUS* LINN. FOR HYPOLIPIDEMIC ACTIVITY**

Snehlatha P, Dhanalakshmi K, Pandita N, **Mengi, S.**

Department of Pharmacology, CU Shah College of Pharmacy, SNDT Women's University, Sanatcruz (W), Mumbai - 400049.

**Objective:** The hydroalcoholic extracts of the roots and rhizomes of the plant *Acorus calamus* indicated in ancient Ayurvedic texts for medo roga, demonstrated hypolipidemic activity in atherogenic rats. Phytochemical investigations revealed the presence of saponins, tannins and alkaloids in these two parts of the plant. The present investigation deals with evaluation of the tannins separated from hydroalcoholic extracts for hypolipidemic activity in atherogenic rats.

**Methodology:** Atherogenesis was induced by feeding 1% cholesterol and 0.8% cholic acid for a period of two weeks in rats and was continued until the end of the study. Tannins; 20 mg/kg and 40 mg/kg were administered orally for a period of fifteen days in , atherogenic rats and monitored for serum cholesterol, triglycerides and HDL cholesterol. The activity has been compared with two reference drugs - Gemfibrozil; 30 mg/kg and Simvastatin; 5 mg/kg.

**Results:** Tannins decreased the serum cholesterol and triglyceride levels back to the baseline value. Gemfibrozil reduced the cholesterol and triglyceride levels and the HDL cholesterol levels were raised significantly ( $p < 0.01$ ) as compared to control. Simvastatin demonstrated the lipid profile analogous to that of tannins whereby the cholesterol and triglyceride level were brought back to the baseline value but with respect to serum HDL cholesterol the baseline value was not obtained.

**Conclusion:** The findings indicate the contribution of tannins of the plant towards hypolipidemic activity and lipid profile analogous to the reference drug Simvastatin paves way for unravelling the mechanism of action.

PP-111

**STUDIES ON THE ANTIOXIDANT ACTIVITY OF *PLUCHEA INDICA* ROOT EXTRACT.**

**Singh AK, Gurain B, Sen T, Nag Chaudhuri AK.**

Division of Pharmacology, Department of Pharmaceutical Technology, Jadavpur, University, Kolkata - 700032.

Studies were undertaken to evaluate the free radical scavenging activity of the methanolic fraction of *Pluchea indica* root extract. The studies showed that the extract significantly inhibited hydroxyl radical and superoxide generation. The extract significantly decreased lipid peroxidation induced with  $\text{CCl}_4$  and  $\text{FeCl}_3/\text{ADP/NADPH}$ . The detailed results and their implications would be presented and discussed.

PP-112

**COMPARATIVE STUDY OF DICLOFENAC PLUS ACETAMINOPHEN WITH DICLOFENAC ALONE IN POST OPERATIVE PAIN.**

**Khosla P. P, Singh S and Malhotra A.**

Govt. Medical College and Rajendra Hospital Patiala.

**Objectives:** To compare the effect of i.m. diclofenac (75mg) plus acetaminophen(500mg) with diclofenac (75mg) alone in postoperative pain.

**Methods:** A prospective, randomised, double blind, controlled, parallel group, add-on "pragmatic" study was conducted on 60 patients undergoing surgery. Patients were verified for fulfilling inclusion criteria and ruled out for any exclusion criteria. Informed written consent was obtained and the Institute Review Board cleared the protocol. Similar anesthesia, premeditation and adjuvant were used. Patients were allocated to i.m. diclofenac plus acetaminophen or to i.m. diclofenac plus placebo by block randomization (n=30 in both groups) The first dose was given when the patient complained of pain after the post anesthetic sleep. The base line pain intensity (PI) was recorded. Pain relief (PAR) and PI were recorded on a five-point scale at 0 hours, 30 minutes, 1,2,3,4,5, and 6 hours after the trial medication. Rescue analgesia was permitted and recorded.

**Results:** The two groups were comparable on account of patient characteristics, disease particulars and base line parameters of pain ( $p \geq 0.05$ ). In both the groups, there was significant pain relief after 1 hour ( $p \leq 0.05$ ) and maintained throughout the 6-hour follow up. The PI, PI D, PAR, time to onset of PAR Peak PAR, Area under pain relief time curve, rescue analgesic consumption and spontaneously reported side effects were similar in two groups ( $p \geq 0.05$ ).

**Conclusions:** There is no additional benefit in postoperative pain with addition of i.m. acetaminophen 500mg to i.m. diclofenac 500 mg.

PP-113

## PHARMACEUTICAL PROPERTIES OF HONEY: AN UPDATE

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Honey is often used as natural sweetener, energy food, tonic and medicine. In ayurveda, it is widely employed as medicine or as vehicle of other herbal medicines. A large number of honey formulations have been recommended for the treatment of various diseases such as cough, cold, sore throat, tonsils, fevers, ulcers of tongue, mouth and alimentary canal, indigestion, malnutrition, fatigue, anaemia, eye problems, cuts, wounds, burns, skin infections, skin sores and cosmetics. It is considered to be a good laxative and blood purifier and good health is maintained by its regular consumption. In spite of its sweet taste, it is acceptable to diabetics also. It is supposed to have antioxidant properties and helps to delay ageing effects. In recent past several scientific studies, including animal models, in vitro investigations and controlled clinical trials, have been carried out to demonstrate antimicrobial and healing properties of honey. In some cases it was proved to be effective where conventional modern treatments have failed and it was found to be effective against antibiotic resistant strains of bacteria. Further, the use of honey is rather safe and free from any harmful side effects. But in the present era of pharmaceuticals, honey is not considered to be an established medicine. In reality, honey deserves much more attention than given to it. The present communication is an attempt to provide an up-to-date information, to enhance our understanding and to draw the attention of the medical professionals.

## **PANEL DISCUSSION**

### **PHARMACEUTICAL INDUSTRY AND ACADEMIA INTERACTION**

**Date** : 29 -11-2002  
**Time** : 1100 – 1300  
**Venue** : Hall- A

**Panel list** : Prof. S.K. Gupta  
Prof. Y.K. Gupta  
Prof. S.K. Kulkarni  
Prof. A. Ray  
Dr. Rama Mukherjee  
Dr. A. Sankaranaryanan  
Dr. J. Bhaduri

**Co-ordinator** : Dr. Amarjit Singh

**SPONSOR** : **PANECEA BIOTEC LTD,  
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