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IV. Drug Toxicity

ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
Defense Atomic Support Agency
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20

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IV. DRUG TOXICITY

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TABLE OF CONTENTS

LIST OF TABLES

FOREWORD
(Nontechnical summary)

An alteration in the response to drugs has been reported in human nuclear accident cases and in studies with irradiated animals. Investigation of this altered drug response is important since it could have a significant influence on the clinical management of radiation-injured individuals.

Larger doses of drugs are likely to be administered to an individual who has a decreased response to medication (a finding in human accident cases). For this reason, information concerning the toxic doses of drugs in irradiated individuals is needed. Drug toxicity studies in animals provide information to estimate the margin of safety (therapeutic ratio) of a given drug dose. Furthermore, toxicity studies permit results to be quantified so that an altered response to drugs in irradiated animals can be measured.

The current study evaluated the acute toxicity (death within 24 hours) of 10 drugs (selected from four drug classes) in groups of irradiated mice at selected times following 500-, 1000-, or 10,000-rad doses of mixed gamma-neutron radiations. Drug evaluation was accomplished by administering one of a graded series of drug doses to subgroups of mice in each radiation dose group. The proportion of mice dying within 24 hours from each drug dose was recorded, and from this information the median lethal dose (LD_{50}) of each drug in irradiated mice was calculated. The drug LD_{50} values in irradiated mice were compared to those obtained in unirradiated controls.

Although the LD_{50} values for several drugs were significantly different in irradiated mice from those of unirradiated controls, no definite pattern of change of drug toxicity with respect to either radiation dose or postirradiation time was identified.

ABSTRACT

The acute toxicity (death within 24 hours) of 10 drugs representing four drug classes (anticonvulsants, hypnotics, hypoglycemics, and psychopharmacologics) was studied in irradiated male CF_1 mice 2 hours, 1 day, or 6 days after 500-, 1000-, and 10,000-rad whole body doses of mixed gamma-neutron radiations. The LD_{50} value for each drug in irradiated mice was calculated and compared to the LD_{50} value obtained in unirradiated controls. Although the LD_{50} values for most drugs studied were altered significantly in some of the dose groups of irradiated mice, no definite pattern of change of drug toxicity with respect to either radiation dose or postirradiation time was identified.

I. INTRODUCTION

The use of medication in the treatment of the symptoms associated with radiation injury has generally been based on the assumption that the responses to the drugs used are unaltered. Evidence from radiation accidents involving humans[6,12] and from animal experiments[1,4,8,9,14] indicates that this assumption may not be valid for all drugs. Further study of drug response in irradiated animals is needed. The current study evaluated one aspect of drug response (drug toxicity) in irradiated mice by determining the acute toxicity of 10 drugs (members of four drug classes) at selected times following 500-, 1000-, and 10,000-rad doses of mixed gamma-neutron radiations. The results of these studies are the subject of this report.

II. PROCEDURE

A total of 6500 male CF_1 mice,* 5 to 6 weeks old and weighing 18 to 28 g, was used. The animals were housed three or four per cage in environment-controlled rooms and were conditioned for a minimum of 1 week. Food and water (pH 2.8, acidified with hydrochloric acid to control the postirradiation septicemia caused by Pseudomonas aeruginosa)[7] were available ad libitum.

Mice were unilaterally exposed to mixed gamma-neutron radiations from the AFRRI-TRIGA reactor. Uniformity of the radiation field in air at the position occupied by the midline of the animals of each exposure group varied less than 4 percent from the mean. Depth-dose measurements made in cylindrical phantoms constructed from Plexiglas rods indicated that the irradiations were Class A.[5] Dose rates were selected so that all exposure times were 10 minutes. Midline tissue doses of 500 rads

* Carworth, Inc., New City, New York

(approximately the LD_{50}), 1000 rads, and 10,000 rads were used. The exposure methods, dosimetric techniques, and reactor characteristics utilized in this investigation have been previously described.[2,10,13]

The following drug classes and drugs were used in this study: anticonvulsants -- diphenylhydantoin*, phenobarbital, and mephenytoin†; hypnotics -- barbital, pentobarbital, and hexobarbital; hypoglycemic -- tolbutamide‡; psychopharmacologics -- chlorpromazine§, triflupromazine**, and chlordiazepoxide††. All drugs were administered by intraperitoneal injection. (Mephenytoin was dissolved in an aqueous solution containing 80 percent propylene glycol by volume; all other drugs were dissolved in sterile water.) Drug doses were selected which would make calculation of the dose response curve possible (LD_1 to LD_{99}). The end point for toxicity was death within 24 hours following drug injection.

The mice used in each drug study were divided into seven groups and tested as follows: unirradiated controls; 500-rad groups on day 0 (drug administered 2-3 hours

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postirradiation), day 1, or day 6; 1000-rad groups on day 0 or day 1; 10,000-rad group on day 0. Each of the groups contained a minimum of 80 mice which were further divided into six drug-dose subgroups. Each subgroup received one of a graded series of drug doses. A given mouse was used only once in the study. In addition to the mice used for toxicity studies, a group of mice was simultaneously exposed to each radiation dose and then injected with saline. The latter mice totaled 360 and served as controls to characterize radiation-induced deaths.

Toxicity of the drugs was analyzed using a digital computer. The regression line of log dose on the probit of the proportion of animals dying at a given drug dose was calculated. Each regression line was fitted by the maximum likelihood method.[3] The median lethal dose (LD_{50}) and its 95 percent confidence limits were calculated for each fitted regression line. The toxicity data on each drug yielded seven regression lines which were tested for parallelism. If the lines were parallel, the LD_{50} values of the drug were compared by the methods of Finney.[3] Relative potency values were calculated by dividing the LD_{50} for each irradiated group by the LD_{50} for unirradiated controls. When the regression lines for a given drug were parallel, the relative potency represented the ratio for all equally toxic doses. (A relative potency of less than 1.0 indicates a more toxic drug.) When the 95 percent confidence limits of the relative potency value did not include 1.0, the toxicity was different from the unirradiated controls at the 0.05 probability level.

The data for phenobarbital and chlordiazepoxide did not yield parallel regression lines. The LD_{50} values for the seven regression lines for each of these two drugs were compared by Scheffé's method of testing contrasts of means.[11] Since these lines were not parallel, only the LD_{50} values of the regression lines were compared.

III. RESULTS

The LD_{50} and relative potency values and their 95 percent confidence limits for the anticonvulsant, hypnotic, hypoglycemic, and psychopharmacologic agents are summarized in Tables I, II, III, and IV, respectively. While toxicity was found to have increased at some of the times tested for all three anticonvulsants, the toxicity of phenobarbital decreased on day 1 following 500 rads. Hexobarbital was the only hypnotic that had a change in toxicity in irradiated mice (more toxic on day 6 following

Table I. Acute Toxicity of Anticonvulsants in Irradiated Mice

Midline tissue dose (rads)	Post-irradiation day tested	Diphenylhydantoin		Phenobarbital	Mephenytoin	
		LD_{50}† mg/kg	Relative potency‡	LD_{50} mg/kg	LD_{50} mg/kg	Relative potency
0		264 (240-294)		223 (212-235)	258 (243-275)	
500	0	191* (167-217)	0.7 (0.6-0.9)	214 (204-224)	225* (213-237)	0.9 (0.8-0.9)
500	1	212* (191-236)	0.8 (0.7-0.9)	248* (238-261)	256 (240-274)	1.0 (0.9-1.1)
500	6	232 (197-274)	0.9 (0.7-1.1)	180* (169-195)	215* (200-229)	0.8 (0.8-0.9)
1,000	0	212* (190-237)	0.8 (0.7-0.9)	184* (176-189)	284 (265-307)	1.1 (1.0-1.2)
1,000	1	241 (217-268)	0.9 (0.8-1.1)	211 (202-223)	264 (248-282)	1.0 (0.9-1.1)
10,000	0	150* (130-169)	0.6 (0.5-0.7)	166* (150-178)	272 (250-298)	1.1 (0.9-1.2)

* $P < .05$

† 95 percent confidence limits in parentheses

‡ Ratio of equally effective doses of the irradiated group to the controls (95 percent confidence limits in parentheses)

500 rads than in unirradiated controls). Tolbutamide was more toxic in the mice receiving 10,000 rads than in controls. In the group of psychopharmacologic agents, chlorpromazine was more toxic in irradiated mice on day 6 following 500 rads and less toxic on day 1 after both 500 and 1000 rads; the toxicity of trifluprομazine increased in the mice receiving 10,000 rads. Chlordiazepoxide was less toxic in irradiated mice on days 0 and 1 following both 500 and 1000 rads than in control mice.

Table II. Acute Toxicity of Hypnotics in Irradiated Mice

Midline tissue dose (rads)	Post-irradiation day tested	Barbital		Pentobarbital		Hexobarbital	
		LD_{50}† mg/kg	Relative potency‡	LD_{50} mg/kg	Relative potency	LD_{50} mg/kg	Relative potency
0		498 (478-519)		117 (96-138)		254 (236-273)	
500	0	501 (466-539)	1.0 (0.9-1.1)	114 (108-119)	0.9 (0.9-1.0)	256 (237-276)	1.0 (0.9-1.1)
500	1	540 (507-579)	1.1 (1.0-1.2)	136 (117-159)	1.2 (0.9-1.5)	234 (216-253)	0.9 (0.8-1.0)
500	6	441 (413-468)	0.9 (0.8-1.0)	90 (73-107)	0.8 (0.6-1.0)	197* (183-210)	0.8 (0.7-0.8)
1,000	0	485 (456-516)	1.0 (0.9-1.0)	111 (95-129)	0.9 (0.8-1.2)	252 (234-272)	1.0 (0.9-1.1)
1,000	1	515 (484-551)	1.0 (1.0-1.1)	116 (99-134)	1.0 (0.8-1.3)	232 (216-249)	0.9 (0.8-1.0)
10,000	0	457 (424-489)	0.9 (0.8-1.0)	128 (110-148)	1.1 (0.9-1.4)	263 (244-285)	1.0 (0.9-1.1)

* $P < .05$

† 95 percent confidence limits in parentheses

‡ Ratio of equally effective doses of the irradiated group to the controls (95 percent confidence limits in parentheses)

Table III. Acute Toxicity of the Hypoglycemic, Tolbutamide, in Irradiated Mice

Midline tissue dose (rads)	Post-irradiation day tested	Tolbutamide	
		LD_{50}† mg/kg	Relative potency‡
0		1138 (1096-1181)	
500	0	1106 (1057-1156)	1.0 (0.9-1.0)
500	1	1185 (1132-1240)	1.0 (1.0-1.1)
500	6	1039 (988-1088)	0.9 (0.9-1.0)
1,000	0	1213 (1173-1256)	1.1 (1.0-1.1)
1,000	1	1040 (1006-1075)	0.9 (0.9-1.0)
10,000	0	995* (963-1027)	0.9 (0.8-0.9)

* $P < .05$

† 95 percent confidence limits in parentheses

‡ Ratio of equally effective doses of the irradiated group to the controls (95 percent confidence limits in parentheses)

Table IV. Acute Toxicity of Psychopharmacologics in Irradiated Mice

Midline tissue dose (rads)	Post-irradiation day tested	Chlorpromazine		Trifluprom azine		Chlordi-azepoxide
		LD_{50}† mg/kg	Relative potency‡	LD_{50} mg/kg	Relative potency	LD_{50}† mg/kg
0		188 (171-206)		213 (190-241)		230 (223-238)
500	0	219 (201-240)	1.2 (1.0-1.3)	219 (197-244)	1.0 (0.9-1.2)	275* (258-302)
500	1	229* (210-251)	1.2 (1.1-1.4)	215 (194-241)	1.0 (0.9-1.2)	299* (282-327)
500	6	134* (119-150)	0.7 (0.6-0.8)	183 (164-203)	0.9 (0.7-1.0)	204 (178-236)
1,000	0	217 (199-238)	1.2 (1.0-1.3)	193 (173-215)	0.9 (0.8-1.1)	257* (233-282)
1,000	1	259* (235-286)	1.4 (1.2-1.6)	243 (218-272)	1.1 (1.0-1.3)	286* (263-323)
10,000	0	168 (153-184)	0.9 (0.8-1.0)	169* (148-189)	0.8 (0.7-0.9)	235 (211-254)

* $P < .05$

† 95 percent confidence limits in parentheses

‡ Ratio of equally effective doses of the irradiated group to the controls (95 percent confidence limits in parentheses)

There were no radiation-induced deaths in the 360 saline injected mice during the time after irradiation in which the toxicity studies were conducted.

IV. DISCUSSION

Evaluation of drug response requires the selection of tests in which results can be quantified. Although toxicity studies use drug doses higher than those of clinical interest, the results of these studies are quantifiable. Dividing the LD_{50} of a drug by the therapeutic dose results in a value known as the therapeutic ratio, which is an index of drug safety. A different LD_{50} value is indicative of a new therapeutic

ratio (and altered drug safety) only if the therapeutic dose does not change to the same degree as the LD_{50}. Thus, while LD_{50} values may be different in irradiated animals than in unirradiated controls, the effect of such a change on drug safety can only be fully evaluated by determining the therapeutic dose of the drug in irradiated animals. Since the therapeutic ratio is commonly 5 to 10, the less than twofold change of toxicity of the drugs investigated in the current study is not likely to significantly alter the safety of these drugs in clinical situations.

Although it might be speculated that drug toxicity would generally be greater in irradiated animals than in unirradiated ones, this was not supported by the results. Toxicity did increase in some cases; however, in most instances toxicity either did not change or decreased in irradiated mice. The reasons for this altered toxicity in irradiated mice are not known. Radiation-induced changes in excretion rates, drug metabolism, drug distribution in the body, and sensitivity to the drug may be responsible for the altered toxicity.

Frik[4] reported on the toxicity of four of these drugs in irradiated mice on day 4 following 500 rads of x radiation. The results of the current study and those of Frik for hexobarbital, phenobarbital, chlorpromazine, and chlordiazepoxide are consistent.

V. SUMMARY

The acute toxicity of 10 drugs was determined in groups of irradiated male CF_1 mice receiving 500-, 1000-, or 10,000-rad whole body doses of mixed gamma-neutron radiations. While the toxic doses for several drugs in irradiated mice were significantly different from those in unirradiated mice, no definite pattern of change of drug toxicity with respect to either radiation dose or postirradiation time was found.

REFERENCES

1. Doull, J. Pharmacological responses in irradiated animals. Radiation Res. 30: 333-341, 1967.

2. Dowling, J. H. Experimental determination of dose for the monkey in a reactor pulse environment. Bethesda, Maryland, Armed Forces Radiobiology Research Institute Scientific Report SR66-3, 1966.

3. Finney, D. J. Probit Analysis, 2nd ed. Cambridge, England, Cambridge University Press, 1952.

4. Frik, W., Strubelt, O. and Wittmann, K. The acute toxicity of drugs based on total body irradiation. Strahlentherapie 127:245-252, 1965.

5. International Commission on Radiological Units and Measurements (ICRU) Report 10e, 1962. Radiobiological dosimetry. National Bureau of Standards Handbook No. 88. Washington, D. C., U. S. Government Printing Office, 1963.

6. Karas, J. S. and Stanbury, J. B. Fatal radiation syndrome from an accidental nuclear excursion. New Eng. J. Med. 272:755-761, 1965.

7. McPherson, C. W. Reduction of Pseudomonas aeruginosa and coliform bacteria in mouse drinking water following treatment with hydrochloric acid or chlorine. Lab. Anim. Care 13:737-744, 1963.

8. Nair, V. Modification of pharmacological activity following X-irradiation. Radiation Res. 30:359-373, 1967.

9. Nair, V., Finer, S. and Shah, D. Interactive effects of X-irradiation and barbiturates. Proc. Soc. Exp. Biol. Med. 120:246-252, 1965.

10. Sayeg, J. A., compiler. Neutron and gamma dosimetry measurements at the AFRRI-DASA TRIGA Reactor. Bethesda, Maryland, Armed Forces Radiobiology Research Institute Contract Report CR65-6, 1965 (originally issued as Edgerton, Germeshausen and Grier, Inc. Report S-260-R, Santa Barbara, California, 1964).

11. Scheffé, H. A method for judging all contrasts in the analysis of variance. Biometrika 40:87-104, 1953.

12. Shipman, T. L. A radiation fatality resulting from massive overexposure to neutrons and gamma rays. In: Diagnosis and Treatment of Acute Radiation Injury (Proceedings of a Scientific Meeting sponsored by the International Atomic Energy Agency and the World Health Organization, Geneva, October 17-21, 1960), pp. 113-133. Geneva, World Health Organization, 1961.

13. Strike, T. A., Seigneur, L. J. and Stanley, R. E. Acute mortality of mice and rats exposed to mixed gamma-neutron radiations or to x rays. Bethesda, Maryland, Armed Forces Radiobiology Research Institute Scientific Report SR68-6, 1968 (in press).

14. Zauder, H. L. and Orkin, L. R. The response of radiated animals to anesthetics. Anesthesiology 21:119, 1960.

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13 ABSTRACT

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