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THE SYNERGISM OF AUTONOMIC DRUGS ON OPIATE OR
OPIOID-INDUCED ANALGESIA: A DISCUSSION OF ITS
POTENTIAL UTILITY AND AN ANNOTATED
BIBLIOGRAPHY

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Report Submitted 29 August 1962

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Psychology Division
US ARMY MEDICAL RESEARCH LABORATORY
Fort Knox, Kentucky

10 October 1962

Pharmacology of the Combat Soldier
Task 04
Internal Medicine
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ABSTRACT

THE SYNERGISM OF AUTONOMIC DRUGS ON OPIATE OR OPIOID-INDUCED ANALGESIA: A DISCUSSION OF ITS POTENTIAL UTILITY AND AN ANNOTATED BIBLIOGRAPHY

OBJECT

The object of this paper is to gather together information pertaining to the potentiation of opiate-induced analgesia by autonomically active drugs to facilitate theoretical explanations of their action and considerations of the practical uses of this type of mixture.

RESULTS

The evidence indicates that combining an opiate with any one of a diverse group of autonomic drugs will result in an increase in the degree of induced analgesia. D-amphetamine was particularly considered since its addition to an opiate increases the analgetic effect by 60 to 100%. At the same time, d-amphetamine helps minimize the undesirable side effects of opiates by reducing the degree of nausea, constipation, sedation and mental depression; and by normalizing blood pressure, oxygen consumption, and respiratory rate.

CONCLUSION

The combination of d-amphetamine with an opiate for the induction of analgesia should offer certain unique advantages for use in civil disasters, combat military medicine, and in other similar situations in which environmental exposure, hemorrhage, and fear contribute to a danger of death due to shock. Its use would also include situations in which sedation is contraindicated due to a need to keep the patient ambulatory and cooperative.

RECOMMENDATION

The possibility of combat military use of this mixture should be given serious consideration. Studies should be conducted to provide an explanation for the potentiation effect and to seek further evidence of its practical applicability.
APPROVED: GEORGE S. HARKER, Ph. D.
Director, Psychology Division

APPROVED: FLOYD A. ODELL, Ph. D.
Technical Director of Research

APPROVED: SVEN A. BACH
Colonel, MC
Commanding
THE SYNERGISM OF AUTONOMIC DRUGS ON OPIATE OR
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I. INTRODUCTION

Two major considerations have tended to restrict the utility of
opiate and opioid alkaloids as analgesic agents: first, their tendency
to produce tolerance and addiction; and second, the problems intro-
duced by their side effects of respiratory depression, reduced blood
pressure, mental depression, constipation, nausea, and sedation.

The problem of tolerance and addiction has not too greatly af-
ected combat military usage since, generally, a trauma case receives
opiates for a comparatively short period of time. However, the side
effects produced by the actions of opiates on the autonomic nervous
system do constitute a problem, especially in those situations in which
shock is present or imminent. Shock is a very common danger when
injury occurs under exposed environmental conditions, and the side ef-
effects of the opiates are such as to intensify shock, or to increase the
likelihood of the appearance of profound shock (1, 2).

Considering these difficulties inherent in the use of opiates, a
method of increasing their analgetic activity while reducing their de-
pressant and shock enhancing effects would be of great use in situations
in which shock, ability to carry out instructions, or the necessity of
maintaining consciousness, contraindicates the use of an opiate alone
as an analgesic.

II. DISCUSSION

A rather diverse group of autonomically active agents have been
shown to potentiate the analgetic activity of opiates. The majority of
the investigations relating to this effect are reported in the accompany-
ing annotated bibliography. Evidence for potentiation has been put forth
for parasympathomimetic agents such as neostigmine (3) and physostig-
mime (4), parasympatholytic drugs such as atropine and scopolamine
(5), sympathomimetic agents such as d-amphetamine (6) and metham-
phetamine (7), sympatholytic drugs like chlorpromazine (8) and di-
benzylone (9), and drugs of the tryptamine and tryptophane type (10).
Furthermore, there is no evidence of a relationship between the par-
ticular physiological changes usually considered in connection with
these drugs and the degree to which they are able to potentiate opiates (11).

At the present time we have no adequate theoretical explanation of this potentiation. Investigators have suggested three theories of action: 1) that an excitation of the central sympathetic nervous system produces analgesia and that the morphine effect is due to a release of adrenaline which facilitates sympathetic action (12), 2) that, since opiates act as cholinesterase inhibitors and morphine is potentiated by cholinesterase inhibitors, the induced analgesia is a "cholinergic" event (13); and 3) that, since all of the agents which potentiate morphine can be structurally related to the hypothesized central adrenergic "alpha" and "beta" receptors, the action of potentiation is through an active competition with morphine for adrenergic sites, thus leaving more opiate available for analgetic action (9). At present, the evidence available discounts the first two theories (5, 11, 14, 10) and not enough evidence exists to support the "adrenergic competition" hypothesis. However, regardless of the present lack of a theoretical explanation of this potentiation, empirical evidence does demonstrate the fact of its existence and its potential usefulness in combat military medicine or situations of civil disaster.

Of the various drugs which will potentiate an opiate-induced analgesia, d-amphetamine seems to offer the greatest practical utility because it counteracts the shock-enhancing aspects of morphine action. Also, more evidence exists as to its clinical effects when combined with opiates than for the other agents. The first mention of a true potentiation of an opiate-induced analgesia by d-amphetamine was presented by Ivy and his colleagues in 1944 (6, 15, 16). However, as early as 1941, Abreu and Handley (17) had shown that amphetamine could normalize respiratory depression and oxygen consumption in morphinized rats. Similarly, in 1941, DeVeine Guyot (18) reported that patients with coronary occlusion when treated with 0.5 gr to 0.75 gr of morphine alone would show more vomiting, inhibition of bowel action, respiratory depression, hypotension, and mental depression than when the same dose of morphine was given in combination with 10.0 mg of r-amphetamine. Also, Morrison and Abreu (19) showed that the depression of oxygen uptake in dogs by 10 mg/kg of morphine could be combated by 0.5 mg/kg of l-amphetamine, d-amphetamine, or r-amphetamine. In this study the d-amphetamine raised the depressed oxygen consumption by 22% and was superior to the racemic or levorotary forms.

In 1944, Ivy and his colleagues demonstrated that d-amphetamine could increase an opiate-induced analgesia in dogs (15), in mice (16),
and in man (6). In man, 16 mg of morphine sulfate in combination with 20 mg of d-amphetamine sulfate produced a degree of analgesia 60% greater than with the same dose of morphine alone. At the same time, the mixture overcame the depression of morphine on respiration and blood pressure, reduced nausea and vomiting, and normalized the critical flicker fusion threshold and choice reaction time of the subjects.

Between 1944 and 1950 the potentiation of opiate and analgesia by d-amphetamine was confirmed by Nickerson and Goodman (20) with normal subjects given isonipecaine. Also, Abel and Harris (21) showed the effect with obstetrical patients. During the same period, Handley and his colleagues (22, 23) reconfirmed the normalizing effects of amphetamine on respiration, pulse rate, and blood pressure of morphinized patients. They also showed that d-amphetamine was superior to metrazol, ephedrine, caffeine, and nikethamide in combating opiate side effects. Nickerson (24) in 1950 by testing the reduction of pain induced by immersion of the hand in ice water showed the opiate potentiating effect of d-amphetamine in humans by combining meperidine (100 mg) and d-amphetamine (10 mg).

The first large scale clinical test of an opiate mixed with d-amphetamine was conducted in 1951 (25). Abel and his associates demonstrated with 7,000 obstetrical cases that adding 5 mg of d-amphetamine to 10 mg of morphine would provide good analgesia with the minimum of side effects and also shorten the length of time to the first inspiration by newborn infant as compared to the time of inspiration of the infant for patients given morphine alone.

Since 1951 only a few investigators have shown interest in this problem area. Saxena and Gupta (26), Guseva (27), Matsumura et al (28), Witkin et al (29), and Evans (9, 30), have reconfirmed in laboratory studies the potentiation actions of amphetamine on opiate analgesia and sought theoretical explanations for the effect, but clinical interest seems to have waned.

Perhaps the explanation of the decline of clinical interest lies in the fact that in a modern hospital shock does not present the major problem that it once did. Thus, there is no pressing requirement for a morphine compound with little or no shock enhancing property even if it allows a reduction in the amount of opiate needed to obtain a satisfactory level of analgesia. Similarly, the overcoming of the mental depression and sedation produced by morphine has little advantage in the modern hospital.
On the other hand, the use of morphine in a civil disaster or in the combat military situation may be quite different in terms of the requirements placed upon the drug. The administration of 15 mg morphine from a pre-packaged syringe to a wounded man in a wet, muddy foxhole during a Korean winter presents problems not present in a hospital in the United States. In combat or in situations of civil disaster, every condition is present to maximize the possibility of death due to shock. It is in situations of this nature that the full potential of the mixture of an opiate with d-amphetamine would be realized.

III. CONCLUSION

It has been demonstrated in dogs, rats, mice, healthy humans, and patients that the addition of d-amphetamine to an opiate will increase its analgetic potency from 60 to 100%. At the same time the addition of d-amphetamine helps normalize the opiate side effects of respiratory depression, lowered oxygen consumption, hypotension, mental depression, constipation, and emesis.

It would seem that this combination could be of great use as a combat military analgesic and its potential should be further studied.

IV. REFERENCES


AN ANNOTATED BIBLIOGRAPHY OF THE SYNERGISM OF ANALGESIA OF OPIATES BY AUTONOMIC DRUGS

ABEL, S., ZEIDA B. BALL and S. C. HARRIS

A clinical study of 7,000 cases given 1/6 gr of morphine alone or with 5 mg of d-amphetamine. Also 100 mg of demerol alone and with 1/150 gr of scopolamine. Clinical estimates of morphine-amphetamine on degree of analgesia were favorable. The first inspiration of infant was significantly retarded by morphine alone and normalized by the morphine-amphetamine mixture.

ABEL, S. and S. C. HARRIS

Nine patients were given 1/4 gr of morphine plus 5 mg of benzedrine for labor pain. First inspiration of infants born one to seven hours after drug was 42 sec mean (0-97). Good analgesia during labor was obtained as well as reducing the time to first inspiration by the infant.

ANGIEBAUD, P., L. BUCHEL and J. LEVY

Using mice with a method of thermal and mechanical stimulation, the analgetic action of l-amidone, pethidine and morphine was measured alone and in combination with 2-[(1-piperidyl) ethyl ester hydrochloride of cyclohexylcyclohexanecarboxylic acid. Synergism was shown with l-amidone, but little effect with pethidine and none with morphine.

ABREU, B. E. and C. A. HANDLEY
Six healthy men received 0.3 mg/kg morphine SO₄ orally. They were measured one hour later for: O₂ consumption, respiration, cardiac rate, pain by force of a dull point into hand. Also, O₂ from rats after 20 mg/kg morphine + 10 mg/kg of benzedrine. 0.3 mg/kg benzedrine used in humans.

0.3 mg/kg of morphine did not significantly depress O₂ consumption in humans nor could benzedrine be shown to have any effect to antagonize. In rats, morphine depression and benzedrine antagonism were shown.

BOREUS, L. O. and F. SANDBERG

Chlorpromazine and acepromazine showed some analgesic activity using heat to the thumb nail as a test. Mepazine had no activity. By this test chlorpromazine and acepromazine did not potentiate methadone and mepazine antagonized its analgetic action. Amphenazole had no effect on methadone and a slight activity by itself.

BUCHEL, L., J. LÉVY and O. TANGUY

Serotonin enhances analgetic action of 1-methadone using mechanical stimuli. Reserpine promoted release of serotonin but antagonized methadon.

CHANG TAN-MU, TAH-CHAO FONG and FU-HAN LUE

Using the method of Reinhard et al the alkaloids of Stephania tetranda S. Moore (tetrandrine) and also morphine, pethidine and phenazone were shown to be analgetic alone. Diphenhydramine
significantly potentiated the analgetic action of all of these compounds.

CHEN, J. Y. P.

Used hot plate with mice and found a true potentiation of 7 mg/kg of morphine by: z-134, 20 mg/kg; z-4, 20 mg/kg; chlorpromazine, 2 mg/kg. Similar results with demerol and tail pinching method. Drugs not analgetic at these doses by themselves. z-4 and z-134 were respiratory stimulants in pentobarbitalized dogs. Also, lowered intestinal tone. z-4 and z-134 increased urine output by 500% over saline controls. Both produce a transitory fall in blood pressure. No hypnotic potentiating effects with pentobarbital. Toxic dose of 93 mg in rat produces central excitement and convulsions.

CHRISTENSEN, E. M. and E. G. GROSS
A comparison of the analgesic effects on human subjects of 6 dimethylamino-4-4 diphenyl-3-heptanone (AN148), morphine and meperidine (demerol) and the relative efficiency of AN148 for preoperative and postoperative use. J. A. M. A. 137: 594-599, 1948.

Used Hardy, Wolff, and Goodell method with eleven trained human subjects. Subjects guessed compounds used sometimes. Gave either 0.3 mg of atropine or scopolamine with methadon (2.5 mg), morphine (10 mg) and meperidine (50 mg). In all cases period of analgesia was shortened and reduced threshold increases of analgesic. Neostigmine at a dose of 0.5 mg caused an increase in threshold by itself and also a synergism with opiates.

CHRISTIE, G., S. GERSHON, R. GRAY, F. H. SHAW, L. McCANDE and D. W. BRUCE
Normal humans given 20 mg or 30 mg of morphine alone or with amiphenazone or cyclizine. Both reduced vomiting, nausea or sleepiness of morphine. Amiphenazone at 40-100 mg particularly helpful. No respiratory depression.

COOK, L., GERALDINE NAVIS and E. J. FELLOWS

The investigators used tail flick method in rats and found a true potentiation at 100 mg/kg of SKF 525A of morphine; 2 mg of 4.6x, meperidine, 10 mg of 2.2x; also of demerol, 3 mg, methorphinan 0.3 mg and codeine 60 mg. Did not effect morphine induced depression of respiration. SKF 525A enhances analgetic response of morphine tolerant rats.

COURVOISIER, S., J. FOURNEL, R. DUCROT, M. KOLSKY and P. KOETSCHET

The investigators used the hot plate method with mice and found that chlorpromazine produced marked increases in analgetic potency and time of action of morphine, meperidine, aspirin, salicylamide, aminopyrine and phenacetin.

DE JONGH, D. K.

Using radiant heat stimulus in guinea pigs (method of Winder), tested morphine (4 mg/kg), salicylamide (50 mg/kg), prostigmine (0.025 mg/kg), atropine (1.0 mg/kg) alone and in combination. Each drug by itself raised the threshold. Morphine plus prostigmine was not even additive while atropine plus morphine was additive. Prostigmine and atropine were antagonistic. The results do not suggest that morphine acts through a cholinergic mechanism.
DE VOINE GUYOT, J.

Human patients with coronary occlusion treated with 1/2 to 3/4 gr morphine plus 10 mg of benzedrine orally. Vomiting was controlled, bowel action inhibited far less, the blood pressure fall of 50 to 75 mm with morphine alone was reduced to 20 mm by combination. Mental depression was minimized.

EVANS, W. O.

Using the jump-flinch method in rats codeine SO₄ was found at a dose of 30 mg/kg to be potentiated by about 65% by d-amphetamine (2.5 mg/kg) and antagonism by about 40% by caffeine citrate (12 mg/kg). Iproniazid (40 mg/kg), β-phenylisobutylhydrazine (5.0 mg/kg) and β-phenylisopropylhydrazine (5 mg/kg) were found to have no effect.

EVANS, W. O.

Using the jump-flinch method in rats 16 mg/kg of morphine SO₄ was found to be potentiated by 100% by both d-amphetamine (5 mg/kg) and methamphetamine (5 mg/kg). Morphine analgesia was also potentiated by about 60% by trimethylamine HCl (30 mg/kg), 3,4-dihydroxybenzaldehyde (20 mg/kg) and 3,4-dichlorobenzaldehyde (20 mg/kg). Isopropylamine (2 mg/kg), n-propylamine (2 mg/kg) and sec-butylamine (5 mg/kg) were found to antagonize morphine by about 50%. Pre-treatment with 30 mg/kg of phenoxybenzamine was found to potentiate morphine analgesia. The results suggest a relationship to alpha and beta adrenergic receptors, perhaps a competition of adrenergic agents and morphine.
FLODMARK, S. and T. WRAMNER

Using 19 human subjects with radiant heat method to compare 15 mg of morphine with 3 mg of morphine plus 0.5 mg of prostigmine. Mixture was 40% more analgetic. Prostigmine at 1 mg and also essérine at 1 mg produced slight rises in threshold of pain.

GERSHON, S., D. W. BRUCE, N. ORCHARD and F. H. SHAW

500 cases treated with morphine and amiphcrazole (2-4, diamino-5-phenylthiazole) (in doses up to 200 mg t.i.d.). Morphine may be given in large doses without risk. No sedation found, addiction to morphine doesn't develop with months of treatment. No euphoria is present with mixture. No withdrawal symptoms.

GOETZL, F. R., D. Y. BURRILL and A. C. IVY

Using mice with tail pinching method given 20 mg/kg of morphine SO₂ and 35 mg/kg of d-amphetamine. Mixture produced an increase in threshold to squeal of about 50% and eliminated the usual morphine induced Straub reaction. Action developed within 60 min to max and lasted six hours to base line return.

GOETZL, F. R., D. Y. BURRILL and A. C. IVY

Using voltage to metal tooth filling in dogs and man. Used first twitch or first pain report. Found d-amphetamine enhanced analgesia. Results confirmed with tail pressure to squeal in mice.
GRIMMETT, M. R., K. D. NEAME and F. N. FASTIER

W45 has some analgetic potency of its own and also enhances that of morphine using pricking of a rat's ear as the method in doses 20-40 mg/kg of morphine and 2.0 to 6.0 of W45. Its own analgetic effects are not antagonized by nalorphine. Its own effect was increased by a pre-treatment with phendiamine but not effected by reserpine or amphetamine.

GRODEN, B. M.

A review of the literature on the combination of amiphenazole and morphine. Concludes the combination is clinically useful.

GUSEVA, E. N.

Morphine and morphine like drugs were combined with amphetamine (30 mg/kg), caffeine (0.3 mg/kg) or 5 (2-bromoallyl)-5-isopropylbarbituric acid (30 mg/kg). Mice were used to test analgetic potency. All potentiated morphine. Larger doses of caffeine or amphetamine antagonized morphine.

HANDLEY, C. A.

Same material as in Anesthesiology, 6: 561-564, 1945.

HANDLEY, C. A. and D. L. ENSBERG
A comparison of amphetamine sulfate with other stimulants of the central nervous system in morphine respiration depression. Anesthesiology, 6: 561-564, 1945.
Fourteen humans took 0.5 mg/kg s. c. of morphine SO₄. Five studied with each drug.

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<td>Caffeine and Na Benzoate</td>
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<td>Ephedrine SO₄</td>
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<td>30</td>
</tr>
<tr>
<td>Metrazol</td>
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<tr>
<td>Nikethamide</td>
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Amphetamine and ephedrine also raised morphine depressed pulse and blood pressure. None of the others did this.

HANDLEY, C. A., D. ENSBERG and H. M. SWEENEY

Eight human subjects given 0.5 mg/kg of morphine SO₄ produced consistent respiratory depression which was maximal after one hour. Stimulants were given one hour after morphine. 0.1 - 0.4 mg/kg of amphetamine (s. c.) increased respiration back to normal. Metrazol and caffeine produced a weak stimulation but not as effective as amphetamine.

HARRIS, S. C. and F. J. FRIEND

Using tail pinching method in rats after 5 mg/kg of morphine SO₄ (s. c.). In rats with bilateral adrenalectomy, but with cortices autotransplanted to the anterior chamber of the eye, the effect of morphine was reduced by 40%.

HERZ, A.
The cataleptic-narcotic action of morphine is enhanced by scopolamine, benactyzine, trihexyphenyldyl, caramiphen and beperiden. Muscle tone is greatly reduced. The analgetic actions of morphine are enhanced some by scopolamine. A large enhancement of analgesia occurs with phenylbutazone and beperiden. The active drugs are considered to be acting in a similar fashion to chlorpromazine. Beperiden is 2-(Bicyclo [2:2:1] Hept-5-EN-2YL) phenyl-1-piperidinopropanol (it lowers Ach content of brain: see Haas, H. et al, Arch. Int. Pharmacodyn. 128: 204-252, 1960).

HURST, E. W. and O. L. DAVIS

Using the reaction of rats to thermal stimuli the effect of a number of substances on morphine analgesia were studied by changes in mean reaction time. Of theocin, sodium lactate, hexamine, glycerol, adrenalin (0.002 mg/100 g) + pituitrin and histamine (17.5 mg/100 g) only histamine and pituitrin + adrenalin changed morphine (0.2 mg/100 g) actions by potentiating analgesia. Also using various dyes it was found that neutral-red chloride (1 cc/100 g of 1%) given i.p. for four successive days prior to morphine produced a potentiation. No explanation was presented.

IVY, A. C., F. R. GOETZL and D. Y. BURRILL

21 healthy humans were given s. c. 16 mg of morphine SO₄ and 20 mg dextroamphetamine. Recorded pain threshold by stimulating metal filling of tooth, critical flicker fusion, blood pressure, pulse rate and choice reaction time. D-amphetamine raised pain threshold of morphine about 60%. Mixture also raised CFF threshold above morphine, blood pressure, pulse rate were normalized and speeded choice RT. There was less nausea and vomiting following the mixture than with morphine alone. Drowsiness was much less with the mixture.
IVY, A. C., F. R. GOETZL, S. C. HARRIS and D. Y. BURRILL
The analgesic effect of intracarotid and intravenous injections of epinephrine in dogs and subcutaneous injections in man.

Using tooth pulp stimulation method in dogs they found that epinephrine, ephedrine and amphetamine all produced a potentiation of morphine analgesia. These drugs also had some analgesic action of their own. Similar studies on man confirmed the results.

KNOLL, J. and E. KOMLOS

Used mice on hot plate method and found that at a dose of between 50-100 µg/kg atropine significantly potentiated the analgesic action of morphine at doses of 1-5 mg/kg. Similarly at a dose of 5 mg/kg scopolamine synergized the analgetic effects of morphine. Giving atropine plus prostigmine (0.1 mg/kg) plus morphine produced a degree of analgesia greater than any one or any combination of two of them.

KNOLL, J., E. KOMLOS and J. PORSZASZ

Used the mice on hot plate method to measure analgetic activity and cholinesterase activity of morphine, methadone, prostigmine, amidazophene, pethiadine and atropine. No relationship was found between ChE activity and analgesia. A synergism of analgetic activity was found between morphine and prostigmine. Used 5 mg/kg of morphine and 0.1 mg/kg of prostigmine.

KOMLOS, E., J. PORSZASZ and J. KNOLL

Used hot plate method in mice and found prostigmine to potentiate morphine at doses 0.8 - 5.0 of morphine and 0.1 of prostigmine.
There was also a potentiation of toxicity. Atropine (320 mg/kg) reduced the synergism of toxicity.

KULSRESHTHA, J. K. and P. N. SAXENA

No significant changes in the AD50 of morphine in rats was produced in combination with 150-300 µg/kg or scopolamine HBr at 150 µg/kg at 300 µg/kg in rats scopolamine reduced analgesia.

MATSUMURA, M., S. TAKAORI and R. INOKI

Cats under hexobarbital or spinal chord cut. Drugs given i.v. The effective dose of morphine was 6 mg/kg. Both morphine and methamphetamine suppressed cortical and intraspinal potentials of splanchnic afferent stimulation. Morphine was more potent at suppressing augmenting responses following repetitive stimulation of the medial leminicus. Definite synergism was shown for the drugs on this augmenting response. Methamphetamine more strongly suppressed recruiting responses following repetitive stimulation of nucleus central median. Possibly some synergism here. Morphine inhibited cortical responses but methamphetamine did not. No synergism shown in the cortex.

McKENZIE, J. S.

Used hot plate method in mice and found amiphenazone to potentiate morphine analgesia by i.p., s.c., oral routes. Effects on codeine were mild and variable. Suggest use in clinic to reduce necessary amount of narcotic.

MERCIER, F. and PAULETTE ETZENSPERGER
Used the D'Amour and Smith method with the rat. Both temperature and time to reaction were measured. Sparteine (10 mg/kg) was given with:

- morphine 1.5 mg/kg
- morphine 2.5 mg/kg
- dihydromorphine 0.5 mg/kg
- codeine 20.0 mg/kg
- dihydromorphone 10.0 mg/kg
- dihydrocodeine 10.0 mg/kg
- dihydrocodeinone 10.0 mg/kg
- dihydrocodeine ethylene 10.0 mg/kg
- dihydrocodeinone ethylene 10.0 mg/kg
- dihydrocodeine 1.0 mg/kg
- piritosal 5.0 mg/kg
- antipyrine 100.0 mg/kg
- pyramiden 100.0 mg/kg
- aspirine 60.0 mg/kg
- benzoazolone 100.0 mg/kg

Potentiating agents:
- potentiate
- 
- 
- 
- antagonize
- no effect

MERCIER, F. and PAULETTE MARINACCE

Using hot plate method of Woolfe and Macdonald animals received either morphine (2.5 - 5.0 mg/kg), dihydron (2.0 mg/kg) or pethidine (10 mg/kg) alone or in combination with 25 mg/kg of an ester of diethylaminoéthanol (anisylhydro-cinnamol), an antispasmodic agent. The degree of enhancement of analgesia was the same as if the dose of morphine had been increased by 100%.

MERCIER, F., J. MERCIER, PAULETTE ETZENSPERGER and D. ROUILLON

Used rats with the method of Lespagnol and Mercier in which the intensity of hot plate heat to reaction is measured. 1.5 mg/kg of morphine was enhanced by Sparteine (10 mg/kg), pendimotide (2.5 mg/kg), penthonium (2.5 mg/kg), hexamethonium (2.5 mg/kg) and tetraethylammonium (2.5 mg/kg). Enhancement up to 100% for Sparteine and down to 3% for tetraethylammonium. The analgetic activity was not prolonged.
MILOSEVIC, M. P.
Contact heat in mice showed weak action of adrenalin which is blocked by adrenergic blockers. Adrenergic blockers potentiated methadone. Nalorphine did not block epinephrine effect. Amphetamine and methamphetamine potentiated opiate. Adrenaline does not potentiate opiate.

MORRISON, J. L. and B. E. ABREU
O2 consumption in dogs given 10 mg/kg morphine SO4 plus 0.5 mg/kg of r-amphetamine, d-amphetamine, or l-amphetamine. R-amphetamine raised O2 consumption 13% above basal morphine level, d-amphetamine 22% and l-amphetamine 15%.

NICKERSON, M.
Used human subjects with ice water immersion method and dolorimeter with meperidine (100 mg oral) N2O (33% by mask) with d-amphetamine (10-20 mg). Amphetamine potentiated the analgesia of meperidine, but not of N2O. Very little change under any condition with dolorimeter but good results with ice water method.

NICKERSON, M. and L. S. GOODMAN
Investigated human subjects with cold water immersion, amperage applied to metal tooth filling and dolorimeter. 100 mg isonipecaine + 10 mg amphetamine orally affected as a potentiation only on the "deep pain" of ice water technique. Considered a factor of more "subjective factor" of deep pain.
PORSZASZ, J., J. KNOLL and E. KOMLOS
Wirkung der parasympathomimetika auf die analgesia. Acta

Used a modified hot plate method with mice. Found a synergism
of morphine, methadone, amidazophen, dolantin and hexalgon by:
prostigmine, 0.1 mg/kg; physostigmine, 0.1 mg/kg; carbachol,
0.25 mg/kg. Of these carbachol gave greatest degree of effect.
Tetraethylpyrophosphate at dose of 0.5 mg/kg gave no synergism.
Concluded that effect is not due to parasympathomimetic action.

SADOVE, M. S., M. J. LEVIN, R. F. ROSE, L. SCHWARTZ and
F. W. WITT
Chloropromazine and narcotics in the management of pain of

Chloropromazine in dose of 25 mg orally b. i. d. was given to 30
patients while reducing their narcotic dose by 50%. All patients
maintained a satisfactory degree of analgesia and some were
better on the mixture than previously on narcotics alone.
Similarly nausea and vomiting were reduced.

SAXENA, P. N.
Mechanism of cholinergic potentiation of morphine analgesia.

The experimenter used albino rats with bulldog clamp on tail as
analgesic measurement technique. Drugs given alone and in com-
1bination with morphine. Pilocarpine, DFP, prostigmine and
atropine tested at doses from 50 to 200 μg/kg.

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<tr>
<th>Drug</th>
<th>AD₅₀ in mg/kg</th>
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<tbody>
<tr>
<td>morphine</td>
<td>3.36</td>
</tr>
<tr>
<td>morphine + pilocarpine</td>
<td>2.13* (significant)</td>
</tr>
<tr>
<td>morphine + 100 DFP</td>
<td>3.45</td>
</tr>
<tr>
<td>morphine + 100 prostigmine + 200 μg atropine</td>
<td>2.58</td>
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</table>

Thus atropine does not antagonize prostigmine potentiation of
morphine. Also, DFP does not potentiate although it is a very
strong anti ChE compound.
SAXENA, P. N. and G. P. GUPTA
Analgesia potentiating effects of ephedrine and methamphetamine.
J. Indian Med. Prof. 4: 1553-1554 and 1599, 1957.

Analgetic level determined in rats by hot wire to tail method.

<table>
<thead>
<tr>
<th>Drug</th>
<th>AD50 of morphine (mg/kg)</th>
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<tr>
<td>morphine</td>
<td>4.29</td>
</tr>
<tr>
<td>phenylbutazone</td>
<td>lethal at these doses</td>
</tr>
<tr>
<td>morphine + ephedrine (6.25 mg/kg)</td>
<td>2.94</td>
</tr>
<tr>
<td>morphine + ephedrine (12.50 mg/kg)</td>
<td>2.17</td>
</tr>
<tr>
<td>morphine + methamphetamine (1.2 mg/kg)</td>
<td>3.58</td>
</tr>
<tr>
<td>morphine + methamphetamine (2.5 mg/kg)</td>
<td>3.12</td>
</tr>
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</table>

SCHAUMANN, W.

Using the Haffner method in mice it was found that morphine analgesia was potentiated by neostigmine and physostigmine. ChE inhibition by morphine previously found in vitro could not be confirmed in vivo. Irreversible peripheral inhibition of ChE had no effect on morphine analgesia. Morphine potentiated the toxicity of neostigmine, but not of physostigmine in mice. A cholinergic mechanism of morphine seems unlikely.

SCHNEIDER, J. A.

Using tail flick method in mice given 10.0 mg/kg of morphine SO4 alone and with either reserpine (10.0 mg/kg) or chloropromazine (10 mg/kg). Reserpine antagonized analgesia while chloropromazine slightly enhanced it and considerably prolonged it.
SCHNEIDER, J. A. and MARIE McARTHUR

Ibogaine, an indole alkaloid from Tabernanthe iboga, which has central stimulant properties was measured with the mouse tail flick method alone and in combination with 3 mg/kg morphine for analgesia. Alone, Ibogaine (6 - 24 mg/kg) had no effect but it significantly potentiated morphine analgesia by about 30 to 50%. It also increased LD₅₀ dose of morphine and Ibogaine LD₅₀ by five fold. It acted in a similar manner on codeine, methadone and ketobemidone. Aminopyrine was not potentiated.

SIGG, E. B., G. CAPRIO and J. A. SCHNEIDER

Used tail flick in mice with s. c. doses: 5 mg/kg morphine SO₄ synergized
1. 5-hydroxytryptamine (5-10 mg/kg) Antagonized by
2. tryptamine (100 mg/kg) reserpine at 2.5
3. 5-hydroxytryptophane (30-400 mg/kg) mg/kg but not by
4. amphetamine (3-5 mg/kg) isoreserpine, iproniazid
5. mescaline (10-50 mg/kg) niazid (or iproniazid
6. epinephrine (2-5 mg/kg) + reserpine).

Iproniazid, tryptophane or 5-hydroxyindoleacetic acid had no effect. Reserpine antagonism believed to be due to catalchol amine depletion, but this has no effect on synergisms. Suggest retardation of demethylation as possible mechanism of synergism.

SLAUGHTER, D. H.

Used Wolff, Hardy and Goodell method on untrained subjects (6) with a double blind. Repeated measurements on same subjects used. Results in units of threshold over 150 min are by integration of difference from control: morphine SO₄ (16 mg), 150; morphine SO₄ (6 mg) + neostigmine methyl SO₄ (0.5 mg), 181; pantophon (20 mg), 91; pantophon (10 mg), 31; pantophon (10 mg) + neostigmine (0.5 mg), 57; dilaudid (6 mg), 327; dilaudid (3 mg), 23
156; dilaudid (3 mg) + neostigmine (0.5 mg), codeine PO₄ (64 mg), codeine (32 mg), codeine (32 mg) + neostigmine (0.5 mg), neostigmine alone at 0.5 mg. Neostigmine is said to reduce side effects of the opiates. Drugs were given LM.

SLAUGHTER, D. H. and D. W. MUNSELL

The investigators used responses of cats having their tail clamped (Eddy method). Drugs given s. c. atropine (0.085 mg/kg) and prostigmine (0.04 mg/kg) were given alone, in combination with morphine (1.0 mg/kg), and all three together. Prostigmine had no effect of itself but potentiated morphine about 100%. Atropine did not potentiate and reduced the effect of prostigmine potentiation.

SZERB, J. C. and D. H. McCURDY

Determining if neostigmine potentiates by increasing the passage of morphine into the brain by measuring brain morphine with and without neostigmine treatment. Rats were made tolerant by 37.5 mg/kg of morphine per day for seven days, 75.0 mg/kg for the next ten and 150 mg/kg for the last ten. Neostigmine by i. v. 0.2 mg/kg 20 min prior to morphine. Spontaneous activity and blood and brain morphine measured in tolerant and non-tolerant animals. Free morphine of blood and brain of tolerant rats was lower than non-tolerant. Neostigmine did not change the free or bound morphine in blood or brain, but did reduce tolerance to morphine and potentiate its action.

TORDOS, L. and Z. JOBBAGYI

Using a modified Woolfe-Macdonald method (hot plate) in rats reserpine (0.5 - 1.0 mg/kg) given 60 min prior, potentiated
morphine, pethidine and aminopyrine. Using tail flick method this potentiation was not found.

WIRTH, W.

Used rats and guinea pigs with a mechanical stimulation method. Found that the addition of chlorpromazine reduced threshold doses of morphine, meperidine and dormoran to one half to one third. Lethal dose of opiates was not changed.

WITKIN, L. B., C. F. HEUBNER, F. GALDI, E. O'KEEFE, P. SPITALETTA and A. J. PLUMMER

Used tail flick method in mice and hot plate method with SU-8629 at 5 mg/kg and morphine at 2 mg/kg. Also used writhing from acetic acid, spontaneous motor activity, blood sugar, EST and gastric motility. Orally, SU-8629 is same potency as morphine but s.c. it is 1/5 as potent. SU-8629 is mild central stimulant similar to amphetamine but 1/4 as potent. SU-8629 not antagonized by nalorphine. Both SU-8629 and amphetamine potentiated morphine analgesia at same dose of 5 mg/kg but amphetamine was more potent.

WITKIN, L. B., M. MAGGIO and W. E. BARRETT

The experimenters used tail flick in mice and found methylphenidate at 5 mg/kg to potentiate morphine analgesia by about 300%. Reserpine, syrosingopine and methyl-18-0 (dimethylamino benzoyl) reserpate (SU-5171) all antagonized morphine to about the same degree yet all three are not equipotent at sedation.
WITKIN, L. B., M. MAGGIO, E. O'KEEFE and F. GALDI

The investigators used tail flick to heat in mice. Morphine analgesia was potentiated by methylphenidate and also by d-amphetamine. Metrazol was found to have no effect and reserpine antagonized analgetic action.
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