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## Effect of N-Allylnormorphine Upon Massive Doses of Narcotic Drugs. (22694)

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Although N-allylnormorphine (nalorphine) is an effective antagonist against a wide spectrum of pharmacological actions of opiates (1,2), and has proven to be clinically useful in cases of narcotic overdosage(3-6), Koppanyi and Karczmar(7) did not succeed in saving mice from lethal doses of morphine by single injections of nalorphine. On the other hand, Unna(8) reported that nalorphine in divided doses reduced mortality in mice receiving 800 mg/kg of norphine, and Gruber (9) showed that even a single dose of the antagonist was protective against morphine sulfate up to 800 mg/kg if the ratio of the two drugs was properly chosen.

The present experiments demonstrate a difference in the protective effect of nalorphine against lethal doses of various opiates and a species difference in the responses.

*Experimental.* Preliminary experiments were performed in rabbits receiving meperidine hydrochloride by slow intravenous injection. The dose of meperidine used was 25 mg/kg, except in two rabbits in which severe convulsions forced discontinuance of the injection at 15 and 20 mg kg, respectively. The results (Groups I-III, Table I) show that nalorphine, administered subcutaneously 30 minutes before the opiate, was in no case successful in preventing convulsions. In each case where death occurred, respirations ceased at about the same time convulsions set in. Respirations were maintained, however, in the meperidine-injected rabbits pre-treated with 10 mg/kg of nalorphine (Group III). In these, the convulsant action of the opiate persisted for 4 to 10 minutes, and the animals then recovered. Two animals (Group IV) receiving the anticonvulsant agent, phenobarbital, in addition to nalorphine exhibited neither convulsions nor grossly visible respiratory depression when 25 mg/kg of meperidine was injected.

These preliminary observations in rabbits suggested that nalorphine antagonized the respiratory depressant effect of the opiate without markedly influencing the convulsant activity. In Group III, sufficient nalorphine was administered so that respiration did not stop and the animals survived, but the convulsions were as severe as in the previous groups. It appeared, then, that convulsant activity might be one effect of opiates that nalorphine would not antagonize. In order to test this further, experiments were conducted in mice and rats.

For these experiments, male IS32 mice of about 20 g body weight and male Holtzman rats of about 130 g were employed. Table II

TABLE I. Effect of N-Allylnormorphine upon Convulsant and Lethal Effects of Intravenous Meperidine in Rabbits.

| Group | Antidote | No. of animals | No. convulsing | No. surviving |
|---|---|---|---|---|
| I | None | 2 | 2 | 0 |
| II | Nalorphine, 1 mg/kg | 2 | 2 | 0 |
| III | Nalorphine, 10 mg/kg | 4 | 4 | 4 |
| IV | Nalorphine, 10 mg /kg + phenobarbital, 100 mg/kg | 2 | 0 | 2 |

TABLE II. Protection of Mice by Nalorphine Hydrochloride against Lethal Doses of Morphine or Methadone.

| Morphine sulfate | | | Methadone hydrochloride | | |
|---|---|---|---|---|---|
| | No. dead/total | | | No. dead/total | |
| Dose, mg/kg | Without nalorphine | With nalorphine* | Dose, mg/kg | Without nalorphine | With nalorphine† |
| 350 | 6/10 | 0/10 | 25 | 3/10 | 0/10 |
| 440 | 7/10 | 2/10 | 29.5 | 7/10 | 0/10 |
| 555 | 7/10 | 1/10 | 35 | 8/10 | 0/10 |
| 700 | 10/10 | 5/10 | 41 | 8/10 | 0/10 |
| | | | 50 | 9/10 | 0/10 |
| | | | 70 | 10/10 | 2/10 |

* Nalorphine HCl dose: 25 mg/kg, repeated at ½- to 1-hr intervals until total of 225 mg/kg had been given.

† Nalorphine HCl dose: 10 mg/kg 15 min. before methadone, repeated 1 hr and 6 hr after methadone.

demonstrates that, contrary to the findings of Koppanyi and Karczmar (*loc. cit.*), adequate doses of nalorphine offer considerable protection to mice receiving lethal doses of morphine. It is evident, however, that nalorphine is more effective against methadone than against morphine in mice. One difference was observed between the mice receiving morphine and those receiving methadone: These high doses of morphine produced convulsions in the animals, while methadone did not. The results are therefore consistent with the finding in rabbits that nalorphine is less effective against convulsions than against respiratory depression.

Codeine phosphate and prisilidene hydrochloride are convulsant drugs at toxic dose levels in mice, but not in rats. In the latter species, hypnosis, catalepsy and respiratory depression are the prominent effects of toxic doses of these drugs, and convulsions do not develop except terminally (probably asphyxial in origin). In Table III, it is shown that rats, but not mice, are easily protected by nalorphine against lethal doses of these drugs.

Another experiment therefore was performed in which an anticonvulsant drug was included. Forty mice were divided into 4

TABLE III. Species Difference in Response of Rats and Mice to Nalorphine Hydrochloride when Given Lethal Doses of Codeine or Prisilidene.

| Mice | | | Rats | | |
|---|---|---|---|---|---|
| | No. dead/total | | | No. dead/total | |
| Dose, mg/kg | Without nalorphine | With nalorphine* | Dose, mg/kg | Without nalorphine | With nalorphine† |
| | | A. Codeine phosphate | | | |
| 300 | 3/10 | 3/10 | 500 | 7/10 | 0/10 |
| 330 | 3/10 | 4/10 | 700 | 5/ 5 | 0/ 5 |
| 363 | 2/10 | 9/10 | 1000 | 5/ 5 | 0/ 5 |
| 400 | 9/10 | 10/10 | | | |

* Nalorphine HCl dose: 25 mg/kg immediately before codeine, repeated ½ hr later. Death occurred before a third dose could be given.

† Nalorphine HCl dose: 25 mg/kg ½ hr before codeine, repeated 1 hr and 4 hr after codeine.

B. Prisilidene hydrochloride

| Mice | | | Rats | | |
|---|---|---|---|---|---|
| 50 | 0/10 | 0/10* | 40 | 5/5 | 0/5† |
| 72 | 1/10 | 2/10 | 60 | 4/5 | 0/5 |
| 104 | 7/10 | 5/10 | 80 | 5/5 | 0/5 |
| 150 | 9/10 | 10/10 | | | |

* Nalorphine HCl dose: 25 mg/kg repeated at ½-hr intervals to a total of 200 mg/kg.

† Nalorphine HCl dose: 25 mg/kg—no repetition.

TABLE IV. Effect of Combination of Anticonvulsant Drug and Nalorphine in Mice Receiving Lethal Dose of Codeine.

| Group | No. of animals | Pretreatment | Effect of codeine $PO_4$ (450 mg/kg) No. animals Convulsing | Dead |
|---|---|---|---|---|
| I | 10 | Phenobarbital Na, 50 mg/kg | 2 | 9 |
| II | 10 | Nalorphine HCl, 50 mg/kg | 10 | 8 |
| III | 10 | Combination | 1 | 1 |
| IV | 10 | None | 10 | 10 |

groups, with drugs injected subcutaneously as follows: *I.* Phenobarbital sodium 50 mg kg. *II.* Nalorphine hydrochloride 50 mg kg. *III.* Both phenobarbital and nalorphine, each 50 mg kg. *IV.* Uninjected controls. One-half hour later, the animals received codeine phosphate 450 mg kg, a dose slightly above the $LD_{100}$ according to the data in Table III. The results of this experiment are shown in Table IV. It is apparent that phenobarbital alone controlled the convulsions in most of the mice, but did not prevent death. Nalorphine alone failed to control the convulsions, and saved the life of only 2 of 10 mice. When both nalorphine and phenobarbital were given, convulsions and death were prevented in 9 of 10 animals.

*Discussion.* It appears from these experiments that not all of the effects of opiates are equally well inhibited by nalorphine. One effect in particular seems to be poorly antagonized, and that is the convulsant action. The tendency of narcotic analgesic drugs to produce convulsions varies among drugs and among species. For example, large doses of morphine are convulsant in some species, but convulsions are rare in man(10). Our results indicate that codeine and prisilidene are highly convulsant for mice, but not for rats. If one assumes that nalorphine competes with morphine-like drugs at their sites of action, it is possible that it has less affinity for sites responsible for convulsions than do the convulsant opiates.

*Summary.* Nalorphine is an effective antidote for doses of opiates which would otherwise be lethal, in those instances where signs of depression are the dominant toxic manifestations. It is relatively ineffective, however, in those instances where convulsions are a prominent feature. In rabbits and mice receiving convulsant doses of meperidine, codeine or prisilidene, nalorphine alone was seldom life-saving, but administration of both phenobarbital and nalorphine adequately protected the animals. Codeine and prisilidene did not produce convulsions in rats; nalorphine alone was an effective antidote in these instances.

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