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BRIEF COMMUNICATION

Lethality of Opioid and Antihistaminic Combinations in Mice

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POLING, A., R. G. SEWELL, JR., J. A. GALLUS AND N. I. NEARCHOU. *Lethality of opioid and antihistaminic combinations in mice.* PHARMACOL BIOCHEM BEHAV 22(2) 333–335, 1985.—The lethality of morphine (37.5, 75, and 150 mg/kg) and tripelennamine (10, 20, 40 and 60 mg/kg), given alone and in combination, was evaluated in mice housed in groups of 16. When given alone, neither drug produced death at any dose. Combining the drugs produced supra-additive effects: some deaths occurred at all combination doses. The lethality of pentazocine (20, 40 and 80 mg/kg) and diphenhydramine (20, 40 and 80 mg/kg), given alone and in combination, also was evaluated. Neither drug alone produced death at any dose. Supra-additive effects were observed when the drugs were combined. These results are similar to earlier findings concerning the lethality of combinations of pentazocine and tripelennamine.

Mice Lethality Drug interaction Pentazocine Morphine Tripelennamine Diphenhydramine

CLINICAL data suggest that street abuse of pentazocine and tripelennamine injected together is quite dangerous (e.g., [7]), and studies with mice have shown that the lethality of pentazocine and tripelennamine combinations is potentiated relative to either drug alone [6,8]. No investigations have assessed whether tripelennamine potentiates the lethality of narcotic analgesics other than pentazocine, or whether antihistaminics other than tripelennamine increase the lethality of pentazocine. The former determination may be of practical as well as theoretical significance, insofar as street abusers at least occasionally combine tripelennamine with pure narcotic agonists such as heroin or morphine [7]. In view of this, the present study assessed in mice the lethality of combinations of (a) morphine and tripelennamine, and (b) diphenhydramine and pentazocine.

METHOD

Subjects

Subjects were 560 young adult (17–24 g body weight) female CF-1 mice. Prior to the study, they were housed in groups of 20–30 with unlimited access to food and water in a constantly-lighted colony area maintained at 24–26 degrees C.

Apparatus

Mice were housed after injection in stainless steel cages 30 cm long, 22 cm wide, and 21 cm high (Unifab, Kalamazoo, MI). Water and Purina rodent chow (Ralston-Purina, St. Louis, MO) were freely available in these cages.

Procedure

Morphine and tripelennamine lethality. The lethality of three doses of morphine (37.5, 75, and 150 mg/kg) and four doses of tripelennamine (10, 20, 40, and 60 mg/kg), given alone and in combination, was determined. Tripelennamine doses were selected on the basis of earlier findings in our laboratory [6]; morphine doses were selected on the basis of pilot data. Each dose of tripelennamine was given in combination with each dose of morphine, thus a total of 19 drug conditions (12 combination doses plus 7 individual doses) were tested. In testing, all mice exposed to a particular drug regimen were housed together after injection. Tripelennamine hydrochloride (Sigma, St. Louis, MO) and a commercially prepared solution of morphine sulfate (Lilly, Indianapolis, IN) were injected intraperitoneally (IP) at a volume of 10 ml/kg. Isotonic saline solution was used as the vehicle for tripelennamine, and was combined with the morphine solution to produce the desired injection volume. All testing occurred between 4:00 and 10:00 p.m. The number of deaths associated with each drug regimen was determined two hours after injection.

Pentazocine and diphenhydramine lethality. The lethality

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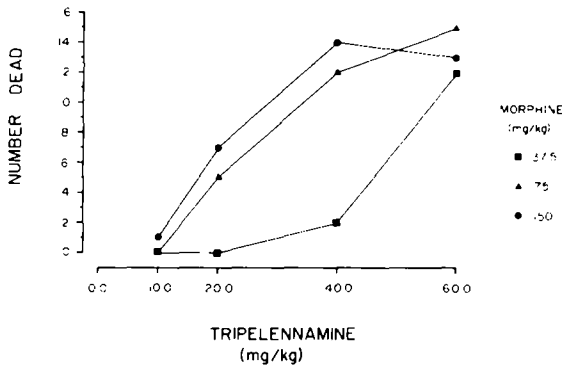

FIG. 1. Number of deaths (per group of 16 mice) produced by IP injections of combinations of morphine and tripelennamine.

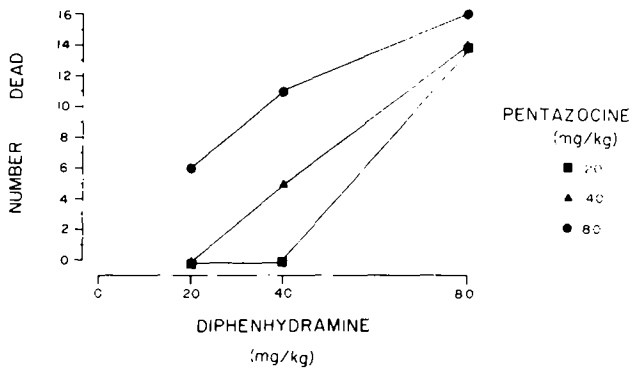

FIG. 2. Number of deaths (per group of 16 mice) produced by IP injections of combinations of pentazocine and diphenhydramine.

of three doses of pentazocine (20, 40, and 80 mg/kg) and three doses of diphenhydramine (20, 40, and 80 mg/kg), given alone and in combination, was determined. Each dose of pentazocine was given in combination with each dose of diphenhydramine, thus a total of 15 drug conditions (9 combination doses plus 6 individual doses) were evaluated. Sixteen mice were tested under each of these conditions. In testing, all mice exposed to a particular drug regimen were housed together after injection. Diphenhydramine hydrochloride (Sigma, St. Louis) and pentazocine lactate (Winthrop, New York) were dissolved in isotonic saline solution and injected IP at a volume of 10 ml/kg. All testing occurred between 10:00 a.m. and 2:00 p.m., and number of deaths was determined two hours after injection.

RESULTS

No dose of morphine or tripelennamine alone produced death, thus data for the single drugs are not presented. Figure 1 shows that, with the exception of 37.5 mg/kg morphine in combination with 10 or 20 mg/kg tripelennamine, each of the combination doses was lethal in some number of subjects. Thus, the toxic effects of the two drugs in combination were supra-additive. At a given dose of either morphine or tripelennamine, increasing the dose of the other drug typically increased the number of deaths; all or nearly all of the mice exposed to high combination doses died. A chi-square analysis [3] indicated that, across all doses, morphine plus tripelennamine produced significantly more deaths than predicted on the basis of an arithmetic summation of the effects of the individual drugs ($\chi^2=6.5$, $p<0.05$).

No dose of pentazocine or tripelennamine alone produced death, thus data for individual drugs are not presented. Figure 2 shows that, with the exception of 20 mg/kg pentazocine in combination with 20 or 40 mg/kg diphenhydramine and 40 mg/kg pentazocine combined with 20 mg/kg diphenhydramine, each of the combination doses was lethal in some number of subjects. Thus, the toxic effects of the two drugs in combination were supra-additive. At a given dose of pentazocine or diphenhydramine, increasing the dose of the other drug typically increased the number of deaths; most of the mice exposed to high combination doses died. A chi-square analysis [3] indicated that, across all doses, pentazocine plus diphenhydramine produced significantly more deaths than predicted on the basis of an arithmetic summation of the effects of the individual drugs ($\chi^2=11.7$, $p<0.01$).

DISCUSSION

Like tripelennamine [6,8], diphenhydramine markedly enhanced the lethality of pentazocine in mice. This finding, coupled with demonstration that tripelennamine markedly increased the lethality of morphine, indicates that the supra-additive lethal effects of opioid and antihistaminic combinations are not limited to pentazocine and tripelennamine.

The mechanism responsible for the supra-additive lethality of the drugs tested in the present studies is speculative. Morphine alone can produce death via respiratory depression, which appears to be responsible for most deaths in human abusers [2]. It is possible that tripelennamine and morphine together usually produce death in mice via respiratory depression, but this appears unlikely for two reasons. First, H_1 blockers such as tripelennamine do not directly compromise respiration to an appreciable degree; when lethal, these drugs typically induce tonic-clonic seizures followed by cardiorespiratory collapse and death [1]. Second, many mice which died when exposed to the combination of morphine and tripelennamine were observed to convulse prior to expiring. This suggests that death was not due to depression of the respiratory center, but rather involved seizure-induced cardiorespiratory collapse.

It has been reported that morphine given to mice tested at 29 degrees C regularly produced convulsions and death, probably due to asphyxia from tetanic fixation of the respiratory muscles [5]. This finding, coupled with the known ability of morphine to lower the convulsive threshold of mice as measured by pentylenetetrazol-induced seizures [4], supports the hypothesis that seizure-induced cardiorespiratory collapse, and not simple respiratory depression, was responsible for the striking lethality of morphine and tripelennamine combinations. A similar mechanism also appears to account for the supre-additive lethality of pentazocine and diphenhydramine combinations, since mice given these drugs were regularly observed to seizure before expiring.

ACKNOWLEDGEMENTS

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