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# Lethality of Pentazocine and Tripelennamine Combinations in Mice Housed Individually and in Groups

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POLING, A., J. KESSELRING, R. G. SEWELL, JR. AND J. CLEARY. *Lethality of pentazocine and tripelennamine combinations in mice housed individually and in groups.* PHARMACOL BIOCHEM BEHAV **18**(1) 103–105, 1983.—Lethality of 80 mg/kg pentazocine alone; 40 mg/kg tripelennamine alone; 20 mg/kg tripelennamine in combination with 40, 60, and 80 mg/kg pentazocine; and 40 mg/kg tripelennamine in combination with 10, 20, and 40 mg/kg pentazocine was determined in mice housed individually and in groups. Results indicate that the lethality of pentazocine and tripelennamine combinations in mice is (1) dose-dependent, (2) potentiated relative to either drug alone, and (3) greater in group-housed than in individually-housed animals.

Pentazocine Tripelennamine Lethality Aggregate toxicity Drug interaction Mice

CONSIDERABLE street abuse of pentazocine, a benzomorphan with mixed narcotic agonist-antagonist properties, in combination with the antihistaminic tripelennamine has been reported recently [10,12]. Clinical surveys suggest the combination is quite dangerous; the Cook County (Illinois) Medical Examiner attributed 39 deaths to it during the last six months of 1977 [13]. Although the factors contributing to drug-related deaths in humans are seldom clear, a recent investigation [13] convincingly demonstrated that the lethality of combinations of pentazocine and tripelennamine was potentiated in mice relative to either drug alone.

In that study, lethality was examined under conditions where mice were housed in groups of 15 after receiving drug injections. It is well established that environmental variables, including the presence of conspecifics, can strongly affect the likelihood of a drug producing death. For example, with *d*-amphetamine (e.g., [1,2]), para-chloroamphetamine [4,8], morphine (e.g., [3,7]), and pentazocine [3], lethality is enhanced by aggregate housing. Whether this is true for combinations of pentazocine and tripelennamine is unknown.

Given that the combination of pentazocine and tripelennamine is frequently associated with death in human users, determining the role of environmental variables in modulating the mixture's toxicity is of some interest. The present study determined the lethality of pentazocine and tripelennamine in mice housed individually and in groups of 16.

## METHOD

### *Subjects*

Two hundred and fifty-six female mice of the CF-1 strain, born and reared in our colony, served as subjects. Prior to the experiment, they were housed in groups of 20 to 30 with unlimited access to food and water in a constantly-illuminated colony room maintained at 24–26°C. Subjects were tested as young adults (17–24 g body weight).

### *Apparatus*

After injection, mice were placed in stainless steel cages 30 cm long, 22 cm wide, and 21 cm high (Unifab, Kalamazoo, MI). Purina rodent chow (Ralston-Purina, St. Louis, MO) and water were freely available in each cage.

### *Procedure*

The lethality of 20 mg/kg tripelennamine in combination with 40, 60, and 80 mg/kg pentazocine, and that of 40 mg/kg tripelennamine in combination with 10, 20, and 40 mg/kg pentazocine was examined under conditions of group and individual housing. The lethality of 40 mg/kg tripelennamine and 80 mg/kg pentazocine, each given alone, was also assessed under these conditions. The range of doses examined was based upon the findings of an earlier study [13].

Two randomly selected groups, each containing 16 mice, were exposed to each of the eight drug regimens of interest (six combination doses plus a single dose of pentazocine alone and a single dose of tripelennamine alone). Under each drug condition, aggregate housing (16 mice per cage) was arranged for members of one group after injection, while members of the other group were individually housed. All testing occurred under conditions of constant illumination and controlled temperature (24–26°C). Tripelennamine hy-

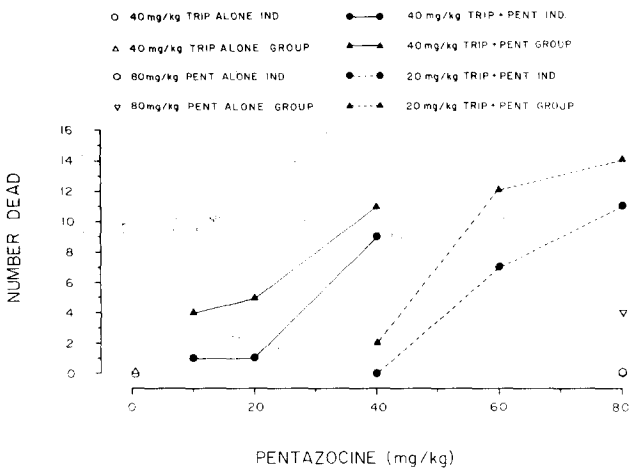


FIG. 1. Number of mice dead per group of 16 two hours after receiving an intraperitoneal injection of the listed drug or drug combination. Data are presented separately for mice housed individually and in groups of 16 after injection.

drochloride (Sigma, St. Louis) and pentazocine lactate (Winthrop, New York) were dissolved in isotonic saline solution and injected intraperitoneally at a volume of 10 ml/kg. All injections occurred between 4:00 and 10:00 p.m. Two hours after injection, the number of dead animals in each group was determined.

## RESULTS

Figure 1 shows the number of mice that died in each of the 16 experimental groups. The most striking aspect of the data is that aggregate housing enhanced the lethality of pentazocine and tripelennamine in combination. Across all combination doses, more group-housed than individually-housed mice died, ($\chi^2=7.1$, $p<.01$). Regardless of housing condition, the lethality of pentazocine and tripelennamine mixtures was dose-dependent. At a given dose of tripelennamine, increasing the dose of pentazocine increased the number of deaths; increasing the dose of tripelennamine given in combination with 40 mg/kg pentazocine did likewise. Tripelennamine alone (40 mg/kg) did not produce death in group-housed or individually-housed mice. Pentazocine alone (80 mg/kg) produced four deaths in aggregated animals, no deaths in isolated subjects. Combination doses at or above 20 mg/kg tripelennamine and 60 mg/kg pentazocine, or 40 mg/kg tripelennamine and 10 mg/kg pentazocine, produced a number of deaths that met or exceeded these values. Thus, the effects of pentazocine and tripelennamine in combination appear to be synergistic.

## DISCUSSION

The present findings are consistent with those of a prior report [13] which indicated that the lethality of combinations of pentazocine and tripelennamine is potentiated in mice relative to either drug alone. In the present study, the likelihood of the mixture producing death was enhanced by aggregate housing. Previous investigations have shown similar effects with *d*-amphetamine (e.g., [1,2]), parachloroamphetamine [4,8], morphine (e.g., [3,7]), and pentazocine [3], although the effects of housing conditions on the toxicity of combinations of narcotics and antihistaminics have not been previously examined.

The manner in which group housing increases drug toxicity is largely speculative. Mohrland and Craigmill [7] note that convulsions and subsequent death in aggregated morphine-treated mice tested at 29°C appear to be induced by stimulation from (i.e., movement by) other mice in the cage. Nonsystematic observations indicated that death was commonly preceded by convulsions in the present study, and it is possible that the movements of other mice precipitated convulsions in group-caged animals.

Crowding induces a wide range of biochemical changes in mice and other species, including catecholaminergic and sympatho-medullary activity [4]. Such effects certainly could influence the pharmacological actions, and resultant toxicity, of pentazocine and tripelennamine in combination. However, since no measures of physiological activity were taken in the present study, speculation as to the biochemical mechanisms whereby aggregate housing enhanced lethality is unwarranted.

Pentazocine and tripelennamine in combination have frequently been associated with death in humans [6, 9, 13]. Some of the toxic effects of the mixture in human abusers appear to result from the intravenous injection of tablets dissolved in water, a preparation that is a local irritant and contains magnesium silicate (talc), which can induce pulmonary occlusion, thrombosis, thrombophlebitis, and pulmonary hypertension [6]. This notwithstanding, the present results and those of an earlier study [13] indicate that, at least in mice, the drugs in combination are lethal apart from the vehicle in which they are administered by street users. In addition, their lethality in combination seems to be greater than predicted on the basis of their individual actions. Finally, the mixture's lethality appears to be enhanced by group housing. Insofar as a variety of stressors (e.g., electric shock, physical restraint) appear to increase drug toxicity much as does group housing [4, 5, 11], this last finding intimates that humans suffering from an overdose of pentazocine and tripelennamine ought not be exposed to highly stimulating (i.e., stressful) environments.

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