Antagonism of Convulsive and Lethal Effects Induced by Propoxyphene

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A toxicological study was performed to demonstrate the effectiveness of several proposed antidotes against the convulsant and lethal effects of propoxyphene hydrochloride. Intravenous administration of levallorphan tartrate, nalorphine hydrochloride, or naloxone hydrochloride at a dose of 1 mg./Kg. significantly increased convulsion threshold and mortality threshold of mice and rats infused with propoxyphene hydrochloride. Treatment with levallorphan tartrate, 1 mg./Kg., plus sodium pentobarbital, 10 mg./Kg., or sodium pentobarbital alone, 10 mg./Kg., prevented propoxyphene-induced convulsions in a large percentage of mice and rats. The combination treatment was effective in elevating mortality threshold in both species, but was no more effective in this respect than a narcotic antagonist alone. Pentobarbital failed to modify mortality threshold. It is recommended that any one of the narcotic antagonists, without pentobarbital, be used to counteract the toxic symptoms of propoxyphene hydrochloride poisoning.

PROPOXYPHENE HYDROCHLORIDE is a widely used analgesic which has been involved in a number of accidental poisonings. The symptoms of massive overdose are referable to the central nervous system and have been reported to include severe depression, hyperactive reflexes, convulsions, respiratory depression, apnea, cyanosis, coma, and death (1–10).

Results of animal studies suggest that the narcotic antagonists are potentially useful for the treatment of propoxyphene toxicito (11–14). In recent years, narcotic antagonists have been used in the treatment of a number of clinical cases of propoxyphene intoxication and appear to be useful in antagonizing the respiratory depression caused by the analgesic (2, 6–8, 10). However, the value of narcotic antagonists against propoxyphene-induced convulsions has been inadequately documented and is controversial. For example, Parker believes that nalorphine may precipitate convulsions when it is used to counteract propoxyphene and cautions against its use as an antidote (5). McCarthy and Keenan (6) reported that nalorphine had no appreciable effect against convulsions in a lethal case of propoxyphene poisoning. On the other hand, in another fatal case, Frasier and coworkers (2) found that the antagonist *N*-allylmorphinan counteracted convulsions caused by the analgesic. Furthermore, a case report by Hara (3) suggests that nalorphine was of value in stopping convulsions displayed by another victim of propoxyphene overdose.

Since there is some uncertainty with respect to the use of narcotic antagonists in propoxyphene poisoning, further investigations to evaluate their effectiveness as specific antidotes are essential. Also, since some investigators have used (2, 8) or suggested the use (1) of central nervous system depressants, *e.g.*, barbiturates, to control convulsions produced by propoxyphene, studies are needed to determine the possible role of depressants in the treatment of poisoning by the analgesic.

The purpose of the present investigation is to determine the relative capacity of three chemically different narcotic antagonists, a barbiturate, and a barbiturate in combination with a narcotic antagonist to control the convulsive and lethal effects induced by propoxyphene in mice and rats. The results obtained constitute the basis of this report.

EXPERIMENTAL

Male CF No. 1 mice, weighing between 25 and 30 Gm., and male Sprague-Dawley rats weighing between 200 and 250 Gm., were randomized according to species into groups of 10. One group from each species was used to test each of the following intravenous treatments: nalorphine hydrochloride, levallorphan tartrate, or naloxone hydrochloride, 1 mg./Kg.; sodium pentobarbital, 10 mg./Kg.; a combination of levallorphan tartrate, 1 mg./Kg.; and sodium pentobarbital, 10 mg./Kg.; or normal saline, 2 ml./Kg. (control group). Three minutes later, propoxyphene hydrochloride, 1.0% for mice and 0.5% for rats, was infused into the animals according to the intravenous infusion technique described by McQuarrie and Fingl (15). The propoxyphene solutions were infused at the rate of 0.005 ml./sec. by means of a constant-infusion apparatus (16) until 2 end points were observed. The first

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end point consisted of 3 sec. of persistent clonus, and the second end point consisted of death. Relative effectiveness of the drug treatments was determined by comparing the time required for the onset of convulsions or death in the test group of animals with that of the control groups of animals. The data obtained were evaluated by analysis of covariance (17) and the results expressed as threshold ratios (*i.e.*, test value/control value).

RESULTS

Antagonism of Convulsions Caused by Propoxyphene.—The capacity of the three narcotic antagonists to elevate convulsion threshold in mice and rats is shown in Figs. 1 and 2, respectively. The mean infusion time of propoxyphene for clonus was 55 sec. in control mice and 181 sec. in control rats. The convulsion threshold in mice was increased 60, 41, and 23% ($p < 0.05$), and in rats it was increased 50, 57, and 60% ($p < 0.05$) by levallorphan, nalorphine, and naloxone, respectively. There was no significant difference among the three narcotic antagonists with regard to their relative capacity to elevate convulsion threshold in either mice or rats.

In the case of the pentobarbital-treated animals, 50% of the mice and 70% of the rats displayed no clonus even when propoxyphene was infused to the end point of death. Similarly, when the animals were pretreated with the drug combination levallorphan–pentobarbital, 50% of the mice and 60% of the rats displayed no convulsion.

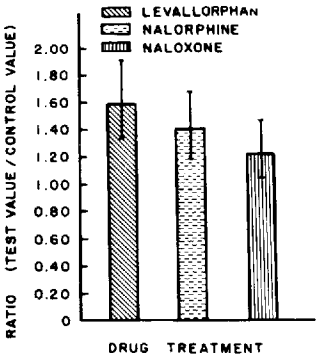

Fig. 1.—The effect of levallorphan tartrate, nalorphine hydrochloride, and naloxone hydrochloride on the convulsion threshold of propoxyphene in mice.

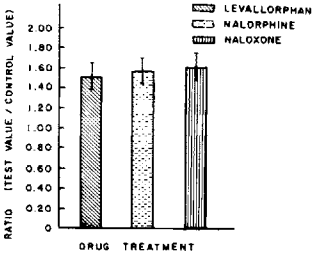

Fig. 2.—The effect of levallorphan tartrate, nalorphine hydrochloride, and naloxone hydrochloride on the convulsion threshold of propoxyphene in rats.

Antagonism of Lethal Effects of Propoxyphene.—The capacity of the various drug treatments to protect mice and rats from the lethal effects of propoxyphene is shown in Figs. 3 and 4, respectively. The mean infusion time for death following intravenous infusion of propoxyphene was 74 sec. in control mice and 372 sec. in control rats. The mortality threshold in mice was increased 60, 50, 59, and 34% ($p < 0.05$), and in rats it was increased 114, 127, 132, and 98% ($p < 0.05$) by levallorphan, nalorphine, naloxone, and the drug combination levallorphan–pentobarbital, respectively. There was no significant difference among these four drug treatments with regard to their relative capacity to elevate mortality threshold in either mice or rats. In contrast to the other drug treatments, pentobarbital, given alone, failed to produce a significant increase in mortality threshold in either animal species.

DISCUSSION

The results of this study show that pretreatment of mice and rats with the narcotic antagonists, nalorphine, levallorphan, or naloxone, markedly increases the amount of propoxyphene required to induce convulsions in these animals, as indicated by an increase in infusion time of the analgesic. Although the experimental design in this investigation required that the antagonists be administered prior to propoxyphene, previous studies in this laboratory have demonstrated that a narcotic antagonist, *e.g.*, nalorphine, arrests convulsions initiated by the analgesic in rats (13). That the narcotic antagonists can counteract established propoxyphene convulsions was also demonstrated by Chapman and Walaszek (12) who administered nalorphine subcutaneously to rats at the onset of the first convulsion and observed a reduction in the duration of convulsion. Even more dramatically, it can be demonstrated in rats that *intravenous* administration of nalorphine after onset of propoxyphene-induced convulsion prevents further episodes of seizure within 90 sec. following injection of the narcotic antagonist (13).

The results of the present study also show that pretreatment with any one of the narcotic antagonists tested markedly increases the amount of propoxyphene required to cause death in mice and rats. In this regard, Chapman and Walaszek (12) reported that pretreatment of rats with nalorphine increased the LD_{50} of the analgesic from 68 to 105 mg./Kg. In addition, these workers showed that the administration of nalorphine, after a toxic dose of propoxyphene which causes 50% mortality in rats, completely abolishes death. Harpel and Mann (14) also reported that nalorphine or levallorphan pretreatment increased the survival rate of mice injected with a lethal dose of propoxyphene.

It is of interest to note that despite the capacity of the drug combination, levallorphan–pentobarbital, to prevent convulsions caused by lethal doses of propoxyphene in a high percentage of mice and rats, the mortality thresholds of these animals were not significantly different from those of animals

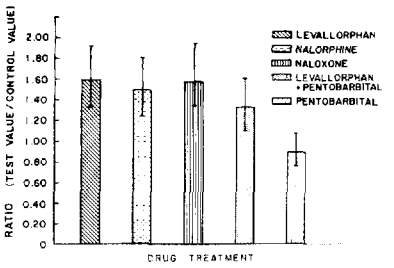

Fig. 3.—The effect of levallorphan tartrate, nalorphine hydrochloride, naloxone hydrochloride, levallorphan tartrate plus sodium pentobarbital, and sodium pentobarbital on mortality threshold of propoxyphene hydrochloride in mice.

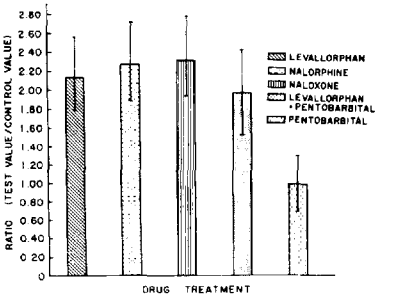

Fig. 4.—The effect of levallorphan tartrate, nalorphine hydrochloride, naloxone hydrochloride, levallorphan tartrate plus sodium pentobarbital, and sodium pentobarbital on mortality threshold of propoxyphene hydrochloride in rats.

pretreated with levallorphan, nalorphine, or naloxone. Indeed, *no* increase in mortality threshold occurred in mice and rats administered pentobarbital alone, a pretreatment procedure which prevented convulsions in a high percentage of the animals given lethal doses of propoxyphene. In view of these findings, it is tempting to speculate that convulsion *per se* may not contribute as much to the lethal effect of propoxyphene as do other factors, such as respiratory depression induced by this drug. If this be the case, then a barbiturate would not reduce mortality, because it does not antagonize the respiratory depression. On the other hand, the results of the present study do not rule out the possibility that convulsion *per se* may contribute to the lethal effect of propoxyphene; the dose of pentobarbital employed could have reduced the convulsive component of toxicity but simultaneously increased the respiratory component such that no significant alteration in propoxyphene-induced lethality was apparent. It is conceivable that there may be an optimal dose of barbiturate which produces an anticonvulsive effect against propoxyphene without causing respiratory depression. However, clinically speaking, it would be difficult as well as potentially hazardous to determine such an optimal dose because of differences in degree of toxicity displayed by victims of propoxyphene poisoning and because respiratory depression resulting from overtitration with a barbiturate would add to postconvulsive and propoxyphene-induced respiratory depression. When a barbiturate is used in conjunction with one of the narcotic antagonists, it is also possible that the respiratory depressant action of the barbiturate, which is not antagonized by these antidotes (18, 19), could reduce the salutary effect of a narcotic antagonist against the lethal action of propoxyphene. Hence, it would appear inadvisable to use a barbiturate alone or in combination with a narcotic antagonist, in the treatment of intoxication caused by propoxyphene. On the other hand, since the narcotic antagonists are known to antagonize the respiratory depressant action of propoxyphene (2, 6–8, 10), and since the present investigation confirms the effectiveness of these drugs in counteracting convulsions and in counteracting the lethal action caused by propoxyphene, it is recommended that one of the narcotic antagonists alone be employed in the treatment of propoxyphene poisoning.

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