A STUDY OF THE ANTIDOTAL EFFECT OF NALORPHINE
AND RELATED ANTAGONISTS IN PROPOXYPHENE POISONING

by

Robert E. Fiut

A Thesis Submitted to the Faculty of the
COLLEGE OF PHARMACY
In Partial Fulfillment of the Requirements
For the Degree of
MASTER OF SCIENCE
In the Graduate College
THE UNIVERSITY OF ARIZONA
1966
STATEMENT BY AUTHOR

This thesis has been submitted in partial fulfillment of requirements for an advanced degree at the University of Arizona and is deposited in The University Library to be made available to borrowers under rules of the Library.

Brief quotations from this thesis are allowable without special permission, provided that accurate acknowledgement of source is made. Requests for permission for extended quotation from, or reproduction of, this manuscript in whole or in part may be granted by the head of the Major department or the Dean of the Graduate College when in their judgement the proposed use of the material is in the interests of scholarship. In all other instances, however, permission must be obtained from the author.

Robert E. Fiut

APPROVAL BY THESIS DIRECTORS

This thesis has been approved on the date shown below:

A. L. Picchioni
Professor of Pharmacology

L. Chin
Professor of Pharmacology

May 18, 1966
Date

May 18, 1966
Date
ACKNOWLEDGEMENTS

The writer is deeply grateful to Dr. Albert L. Picchioni and Dr. Lincoln Chin for their unsurpassed guidance, thoughtful suggestions, and perseverant assistance throughout the period of this investigation.

The writer also wishes to express his appreciation to the faculty and staff of the College of Pharmacy for their generous aid during the course of this work.

Propoxyphene hydrochloride (Darvon) used in these investigations was generously supplied by Eli Lilly and Company, Indianapolis, Indiana.

Nalorphine hydrochloride (Nalline) was generously provided by Merck Sharp and Dohme Company, West Point, Pennsylvania as was levallorphan tartrate (Lorfan) by Roche Laboratories, Nutley, New Jersey and naloxone hydrochloride (Naloxone) by Endo Laboratories, Garden City, New York.
The pentobarbital sodium (Nembutal) was similarly provided by Abbott Laboratories, North Chicago, Illinois.

This investigation was supported by a Research Grant from Eli Lilly and Company, Indianapolis, Indiana.
TABLE OF CONTENTS

I. ANTAGONISM OF PROPOXYPHENE POISONING IN MICE . 1

   Introduction .................................................. 1
   Experimental .................................................. 2
   Results ......................................................... 4
   Discussion ..................................................... 5
   SUMMARY .......................................................... 8

II. ANTAGONISM OF CONVULSIVE AND LETHAL EFFECTS
    INDUCED BY PROPOXYPHENE ............................... 13

   Introduction .................................................. 13
   Experimental .................................................. 15
   Results ........................................................ 16
   Discussion ...................................................... 18
   SUMMARY .......................................................... 28
TABLE OF CONTENTS (Cont'd.)

<table>
<thead>
<tr>
<th>III.</th>
<th>ANTAGONISM OF PROPOXYPHENE RESPIRATORY DEPRESSION IN RABBITS</th>
<th>29</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Introduction</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Experimental</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Results</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Discussion</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>SUMMARY</td>
<td>40</td>
</tr>
</tbody>
</table>

| IV.  | SUMMARY AND CONCLUSIONS                                   | 44 |
# LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Effect of Intravenous Nalorphine Hydrochloride on Convulsant and Lethal Effects Induced by Propoxyphene in Mice.</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>Effect of Intravenous Levallophan Tartrate on Convulsant and Lethal Effects Induced by Propoxyphene in Mice.</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>Effect of Intravenous Naloxone Hydrochloride on Convulsant and Lethal Effects Induced by Propoxyphene in Mice.</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>Effect of Intravenous Pentobarbital Sodium Alone and in Combination with Nalorphine Hydrochloride on Convulsant and Lethal Effects Induced by Propoxyphene in Mice.</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>Effect of Narcotic Antagonists on Propoxyphene Dosage at Convulsion Threshold in Mice.</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>Effect of Narcotic Antagonists on Propoxyphene Dosage at Convulsion Threshold in Rats.</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>Effect of Narcotic Antagonists on Propoxyphene Dosage at Mortality Threshold in Mice.</td>
<td>26</td>
</tr>
<tr>
<td>8</td>
<td>Effect of Narcotic Antagonists on Propoxyphene Dosage at Mortality Threshold in Rats.</td>
<td>27</td>
</tr>
<tr>
<td>9</td>
<td>Effect of Narcotic Antagonists on Propoxyphene Depressed Respiratory Rate in Rabbits.</td>
<td>41</td>
</tr>
</tbody>
</table>
# LIST OF TABLES (Cont'd.)

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Effect of Narcotic Antagonists on Propoxyphene Depressed Minute Volume in Rabbits</td>
<td>41</td>
</tr>
<tr>
<td>11</td>
<td>Effect of Narcotic Antagonists on Propoxyphene Depressed Tidal Volume in Rabbits</td>
<td>42</td>
</tr>
<tr>
<td>12</td>
<td>Potency Ratios of Levallophan and Naloxone Compared to the Standard Nalorphine in Rabbits</td>
<td>43</td>
</tr>
</tbody>
</table>
### LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The Mean Convulsive Dose (C. D. 50) of Intraperitoneal Propoxyphene Hydrochloride in Mice...</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>The Effect of Levallorphan Tartrate, Nalorphine Hydrochloride, and Naloxone Hydrochloride on the Convulsion Threshold of Propoxyphene in Mice.</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>The Effect of Levallorphan Tartrate, Nalorphine Hydrochloride, and Naloxone Hydrochloride on the Convulsion Threshold of Propoxyphene in Rats.</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>The Effect of Levallorphan Tartrate, Nalorphine Hydrochloride, Levallorphan Tartrate plus Pentobarbital Sodium, and Pentobarbital Sodium on Mortality Threshold of Propoxyphene in Mice.</td>
<td>23</td>
</tr>
<tr>
<td>5</td>
<td>The Effect of Levallorphan Tartrate, Nalorphine Hydrochloride, Levallorphan Tartrate plus Pentobarbital Sodium, and Pentobarbital Sodium on Mortality Threshold of Propoxyphene in Rats.</td>
<td>24</td>
</tr>
</tbody>
</table>
ABSTRACT

A toxicological study was performed to demonstrate the effectiveness of several proposed antidotes against the convulsive and lethal effects of propoxyphene hydrochloride. Intravenous administration with levallorphan tartrate, nalorphine hydrochloride, or naloxone hydrochloride counteracted the convulsive and lethal effects of intraperitoneal propoxyphene hydrochloride in mice. Nalorphine plus pentobarbital also showed protection against convulsions and death induced by the analgesic. Pentobarbital alone prevented convulsions, but showed no protection against the lethal action of propoxyphene. No treatment was effective once the stage of postictal depression was reached.

Intravenous administration of the 3 chemically different narcotic antagonists significantly increased convulsion threshold and mortality threshold of mice and rats infused with propoxyphene hydrochloride. Treatment with levallorphan tartrate plus pentobarbital sodium or pentobarbital sodium alone prevented propoxyphene induced convulsions in a large number 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 sodium alone failed to modify mortality threshold.
Propoxyphene hydrochloride given intravenously to rabbits depressed respiratory rate, minute volume, and tidal volume. A single intravenous administration of levallorphan tartrate, nalorphine hydrochloride, or naloxone hydrochloride reversed the depression of the respiratory parameters caused by the analgesic. After a series of intravenous doses of narcotic antagonists all 3 respiratory parameters were returned to normal. On a basis of mcg/Kg. doses, levallorphan and naloxone were found to be 8 and 19 times more potent, respectively, than nalorphine in elevating depressed minute volume. Any one of the narcotic antagonists, without pentobarbital, is recommended to counteract the toxic symptoms of propoxyphene hydrochloride poisoning.
ANTAGONISM OF PROPOXYPHENE POISONING IN MICE

Introduction

Propoxyphene hydrochloride is structurally similar to methadone, a narcotic analgesic (Wilson and Gisvold, 1962), and has an analgesic activity approximately equal to codeine (Robbins, 1955). The similarity includes the toxic effects which are qualitatively like those of the narcotics (Frasier, 1963).

With a number of properties being similar to the opiates it was not surprising to find that the narcotic antagonist nalorphine hydrochloride was suggested to prevent the toxic signs observed in the first pharmacological study of propoxyphene (Robbins, 1955). In subsequent experiments nalorphine was found to decrease convulsion time (Chapman and Walaszek, 1962) in rats and to stop convulsions in rats (Picchioni, 1963).

However, Harpel and Mann (1965) made the statement that convulsions induced by propoxyphene were diminished slightly by nalorphine in mice but in most cases the animals still suffered
severe clonic convulsions. The same workers cautioned against the use of central nervous system depressants to avoid enhancement of depression produced by propoxyphene. However, no experimental verification was performed and none is available in the literature.

Therefore, in view of the conflicting reports concerning the efficacy of narcotic antagonists on propoxyphene induced seizure, it was considered desirable to determine the effects of 3 narcotic antagonists (Foldes, et al, 1964), a narcotic antagonist plus a barbiturate, and a barbiturate alone against these convulsions. Also it was considered essential to demonstrate the effects of the proposed antidotal treatments against the lethality of propoxyphene in mice.

**Experimental**

A range finding experiment was performed initially to find the dose of propoxyphene hydrochloride to be utilized in this study. Male albino CF#1 mice weighing between 25-30 Gm. were utilized in the range finding experiment and in all subsequent trials. Forty-eight mice were randomly divided into 6 groups of 8 mice each and were given 40, 50, 60, 80, 100, or 120 mg/kg. of propoxyphene hydrochloride by the intraperitoneal route. The animals were then isolated into separate cages for observation. The number of animals to show convulsions in each group was recorded and the results plotted
according to the method of Litchfield and Wilcoxon (1949) as shown in Fig. 1. A dose was chosen which could be expected to produce convulsions in 95% of the animals. This was determined to be 120 mg/kg intraperitoneally in mice and this dose was also found to be 100% fatal in the trial runs.

Ninety-six mice were then randomly divided into 16 groups of 6 mice per group. One group served as a control and was administered intraperitoneal propoxyphene hydrochloride in the chosen dosage. The remaining groups of mice were given the proposed antidotes by tail vein according to the schedule in Tables 1-4 in addition to propoxyphene hydrochloride. Any animal that went beyond 15 minutes without convulsing was considered protected and the ones surviving for longer than 24 hours were considered protected from the lethal effects. In the case of antidotal treatment after reaching the stage of postictal depression the action against convulsions was not determined since the convulsions had stopped. The results were expressed as number of animals convulsing and number of animals surviving. The Chi-Square test (Goldstein, 1964) was used to determine the differences in convulsion and survival numbers between control animals and those given the proposed antidotes. Probabilities
greater than 0.05 were considered non-significant.

Results

The results shown in Tables 1-4 demonstrate that all of the narcotic antagonists offered significant protection when given 2 minutes prior to or following the injection of propoxyphene hydrochloride (P < 0.05). Nalorphine hydrochloride and levallorphan tartrate gave significant protection (P < 0.05) when injected at the onset of propoxyphene induced convulsions but naloxone hydrochloride did not offer the same degree of protection when given at this time. It was shown that protection against convulsions was also significant (P < 0.05) with pentobarbital sodium alone or in combination with nalorphine hydrochloride.

All 3 of the narcotic antagonists administered 2 minutes prior to or following the injection of propoxyphene showed significant protection (P < 0.05) against the lethal effects of the analgesic. Again, the only exception in protecting the animals against lethality was naloxone hydrochloride, among the 3 narcotic antagonists given at the onset of convulsions. Also, the ability to protect against death was found to be non-significant with all the proposed antidotes when
administered at the stage of postictal depression. Pentobarbital sodium, in addition, failed to provide any degree of protection against the lethal effects of propoxyphene. The combination of nalorphine and pentobarbital, however, showed significant protection ($P<.05$) against the death produced by propoxyphene.

**Discussion**

The data indicate that nalorphine, levallorphan, and naloxone given intravenously in mice were found to prevent convulsions when given as a pretreatment or 2 minutes after intraperitoneal propoxyphene. When the 3 narcotic antagonists were administered at the onset of convulsions, nalorphine and levallorphan were able to antagonize the established propoxyphene convulsions but naloxone did not. Perhaps this smaller degree of effectiveness is due to a lack of group specificity as suggested by Sadove (1963) for naloxone antagonism of other opiates. This study, therefore, confirms the reports of several investigators (Robbins 1955, Chapman and Walaszek 1962, Picchioni 1963) that nalorphine is capable of preventing and antagonizing the convulsant activity of propoxyphene. In addition it was shown that 2 other narcotic antagonists are generally capable of the same activity as nalorphine. This study contributes data to demonstrate
that nalorphine-pentobarbital and pentobarbital alone render protection against convulsions induced by propoxyphene.

The analgesic, depressant, and lethal effects of the chemically related compound methadone were reported to be antagonized by nalorphine (Smith, 1951). However, in some other experiments, the convulsant activity of morphine was not antagonized in rats (Koppanyi and Karczmar, 1953) and the convulsions produced by other opiates (Winter and Flataker, 1956) were not antagonized by nalorphine. In this study both the convulsant and lethal effects of propoxyphene were counteracted by nalorphine, levallorphan and in most cases naloxone. Thus it appears that these convulsions may be differentiated from those produced by other analgesics, and that they can be effectively antagonized by the narcotic antagonists.

Although pentobarbital completely eliminated convulsions following propoxyphene injection, there is a disturbing lack of protection against the lethal effect of the analgesic. It appears as though the respiratory depression produced by propoxyphene may have been enhanced by pentobarbital and resulted in no survivors. Thus, this study verifies the statement made by Harpel and Mann (1965) that extreme caution must be used when attempting to counteract
propoxyphene-induced convulsions with central depressants.

The combination of nalorphine and pentobarbital in appropriate dosage was found effective in protecting against both the convulsant and lethal effects of propoxyphene. However, on the basis of the results seen with pentobarbital treatment alone, it appears inadvisable to use this combination as an antidote for propoxyphene poisoning. The dosage of barbiturate might be such that the depressant action of propoxyphene on respiration would be synergized and thus prove fatal rather than beneficial. This would occur in spite of the antagonism of respiratory depression by the narcotic antagonists since the depressant effect of the barbiturate is not antagonized by nalorphine (Boyd, 1955).

When the 3 narcotic antagonists were administered intravenously before postictal depression had occurred, there was antagonism of the lethal effect with only one exception. The results are in agreement with other experiments (Harpel and Mann, 1965) done in mice and also demonstrates that naloxone offers similar protection up to a point.
Summary

Three chemically different narcotic antagonists, a barbiturate, and a barbiturate in combination with a narcotic antagonist have been shown to be effective in preventing and eliminating convulsions. It is recommended that a central depressant not be used in conjunction with nalorphine or other narcotic antagonist to counteract the convulsant effects of propoxyphene.

Three narcotic antagonists and the combination were shown to be effective against the lethal effects of propoxyphene. Pentobarbital did not offer any protection against death resulting from propoxyphene intoxication. None of the treatments were effective once the stage of postictal depression was reached. This demonstrates the need for rapid determination of poisoning by propoxyphene and immediate treatment with any one of the narcotic antagonists.
PROPOXYPHENE HYDROCHLORIDE IN MICE

% CONVULSING

MG/KG.

DOSE
### TABLE 1

**EFFECT OF INTRAVENOUS NALORPHINE HYDROCHLORIDE ON CONVULSANT AND LETHAL EFFECTS INDUCED BY PROPOXYPHENE IN MICE**

<table>
<thead>
<tr>
<th>GROUP</th>
<th>NO. OF ANIMALS</th>
<th>ANTIDOTE</th>
<th>NO. CONVULSING</th>
<th>NO. SURVIVING</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>6</td>
<td>None</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>Nalorphine(^a)</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
<td>Nalorphine(^b)</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>IV</td>
<td>6</td>
<td>Nalorphine(^c)</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>V</td>
<td>6</td>
<td>Nalorphine(^d)</td>
<td>-</td>
<td>1*</td>
</tr>
</tbody>
</table>

### TABLE 2

**EFFECT OF INTRAVENOUS LEVALLORPHAN TARTRATE ON CONVULSANT AND LETHAL EFFECTS INDUCED BY PROPOXYPHENE IN MICE**

<table>
<thead>
<tr>
<th>GROUP</th>
<th>NO. OF ANIMALS</th>
<th>ANTIDOTE</th>
<th>NO. CONVULSING</th>
<th>NO. SURVIVING</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>6</td>
<td>Levallorphan(^a)</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>Levallorphan(^b)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
<td>Levallorphan(^c)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>IV</td>
<td>6</td>
<td>Levallorphan(^d)</td>
<td>-</td>
<td>1*</td>
</tr>
</tbody>
</table>
**TABLE 3**

**EFFECT OF INTRAVENOUS NALOXONE HYDROCHLORIDE ON CONVULSANT AND LETHAL EFFECTS INDUCED BY PROPOXYPHENE IN MICE**

<table>
<thead>
<tr>
<th>GROUP</th>
<th>NO. OF ANIMALS</th>
<th>ANTIDOTE</th>
<th>NO. CONVULSING</th>
<th>NO. SURVIVING</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>6</td>
<td>Naloxone\textsuperscript{a}</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>Naloxone\textsuperscript{b}</td>
<td>3*</td>
<td>3*</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
<td>Naloxone\textsuperscript{c}</td>
<td>4*</td>
<td>2*</td>
</tr>
<tr>
<td>IV</td>
<td>6</td>
<td>Naloxone\textsuperscript{d}</td>
<td>-</td>
<td>1*</td>
</tr>
</tbody>
</table>

\textsuperscript{a} - 1 mg/kg 2 min. before administration of propoxyphene  
\textsuperscript{b} - 1 mg/kg 2 min. after administration of propoxyphene  
\textsuperscript{c} - 1 mg/kg at onset of propoxyphene induced convulsions  
\textsuperscript{d} - 1 mg/kg at onset of postictal depression  

* - Not significant (P > .05)
**TABLE 4**

EFFECT OF INTRAVENOUS PENTOBARBITAL ALONE AND IN COMBINATION WITH NALORPHINE HYDROCHLORIDE ON CONVULSANT AND LETHAL EFFECTS INDUCED BY PROPOXYPHENE IN MICE

<table>
<thead>
<tr>
<th>GROUP</th>
<th>NO. ANIMALS</th>
<th>ANTIDOTE</th>
<th>NO. CONVULSING</th>
<th>NO. SURVIVING</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>6</td>
<td>Pentobarbital$^e$</td>
<td>0</td>
<td>0*</td>
</tr>
<tr>
<td>II</td>
<td>6</td>
<td>Nalorphine-pentobarbital$^f$</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
<td>Nalorphine-pentobarbital$^g$</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

$e$ - 10 mg/kg at onset of propoxyphene induced convulsions

$f$ - 1 mg/kg and 10 mg/kg respectively 2 min. before administration of propoxyphene

$g$ - 1 mg/kg and 10 mg/kg respectively at onset of propoxyphene induced convulsions

* Not significant (P>.05)
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 (Cann and Verhulst 1960, Frasier 1963, Hara 1964, Hyatt 1962, Jacobziner 1963, McCarthy 1964, Nitzke 1960, Qureshi 1964, Storts 1963, Swarts 1964).

Results of animal studies suggest that the narcotic antagonists are potentially useful for the treatment of propoxyphene toxicity (Robbins 1955, Chapman and Walaszek 1962, Picchioni 1963, Harpel and Mann 1965).

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 (Frasier 1963, McCarthy and Keenan 1964, Qureshi 1964, Swarts 1964). 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 (Jacobziner, 1963). McCarthy and Keenan, (1964) 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 co-workers, (1963) found that the antagonist N-allylmorphinan counteracted convulsions caused by the analgesic. Further, a case report by Hara (1964) 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 (Frasier 1963, Qureshi 1964) or suggested the use (Cann and Verhulst, 1960) of central nervous system depressants, such as 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 3 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#1 mice, weighing between 25-30 Gm., and male Sprague-Dawley rats weighing between 200-250 Gm., were randomized according to species into groups of 10 animals. 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.; pentobarbital sodium, 10 mg./Kg.; a combination of levallorphan tartrate, 1 mg./Kg. and pentobarbital sodium, 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,
(1958). The propoxyphene solutions were infused at the rate of 0.005 ml./sec. by means of a constant infusion apparatus (Gabardi and Esplin, 1957) until 2 end points were observed. The first 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 was evaluated by analysis of covariance (Finney, 1952) and the results expressed as threshold ratios (i.e. test value/control value).

RESULTS

Antagonism of convulsions caused by Propoxyphene--The capacity of the 3 narcotic antagonists to elevate convulsion threshold in mice and rats is shown in Figs. 2 and 3, 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 50%, 41%, and 23% (p.<05), and in rats it was increased 50%, 57%, and 60% (p.<05) by levallorphan, nalorphine, and naloxone, respectively. There was no significant difference among the 3 narcotic antagonists with regard to their relative capacity to elevate
convulsion threshold in either mice or rats. (See Tables 5 and 6).

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.

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. 4 and 5, respectively. The mean infusion time for death following intravenous infusion of propoxyphene was 74 seconds in control mice and 372 sec. in control rats. The mortality threshold in mice was increased 60%, 50%, 59%, and 34% (p < .05) and in rats it was increased 114%, 127%, 132%, and 98% (p < .05) by levallorphan, nalorphine, naloxone, and the drug combination levallorphan-pentobarbital, respectively. There was no significant difference among these 4 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
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, such as nalorphine, arrests convulsions in rats initiated by the analgesic (Picchioni, 1963). That the narcotic antagonists can counteract established propoxyphene convulsions was also demonstrated by Chapman and Walaszek, (1962) who administered nalorphine subcutaneously to rats at the onset of the first convolution and observed a reduction in the duration of convolution. Even more dramatically, it can be demonstrated in rats that administration of nalorphine after onset of propoxyphene-induced convolution prevents further episodes of seizure within 90 seconds following intravenous injection of the narcotic antagonist (Picchioni 1963).
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, (1962) reported that pretreatment of rats with nalorphine increased the LD50 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, (1965) 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 pretreated with levallorphan, nalorphine, or naloxone. Indeed, no increase in mortality threshold occurred in mice and rats administered pentobarbital alone, a pretreatment procedure which also 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. In fact, since a barbiturate possesses depressant action of its own, this effect could add to the respiratory toxicity caused by propoxyphene. 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 (Boyd 1955, Jaffe 1965), 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 (Frasier 1963, McCarthy and Keenan 1964, Nitzke 1960, Qureshi 1964, Swarts 1964), 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.
Figure 2. The effect of levallorphan tartrate, nalorphine hydrochloride, and naloxone hydrochloride on the convulsion threshold of propoxyphene in mice.
Figure 3. The effect of levallorphan tartrate, nalorphine hydrochloride, and naloxone hydrochloride on the convulsion threshold of propoxyphene in rats.
Figure 4. The effect of levallorphan tartrate, nalorphine hydrochloride, naloxone hydrochloride, levallorphan tartrate plus pentobarbital sodium, and pentobarbital sodium on mortality threshold of propoxyphene hydrochloride in mice.
Figure 5. The effect of levallorphan tartrate, nalorphine hydrochloride, naloxone hydrochloride, levallorphan tartrate plus pentobarbital sodium, and pentobarbital sodium on mortality threshold of propoxyphene hydrochloride in rats.
### TABLE 5

**EFFECT OF NARCOTIC ANTAGONISTS ON PROPOXYPHENE DOSAGE AT CONVULSION THRESHOLD IN MICE**

<table>
<thead>
<tr>
<th>No. Mice</th>
<th>Treatment</th>
<th>Convulsion Threshold Dose (mg/Kg.)</th>
<th>Ratio Test/Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Saline</td>
<td>9.8</td>
<td>1.00</td>
</tr>
<tr>
<td>10</td>
<td>Levalloorphan tartrate</td>
<td>15.2</td>
<td>1.60 (1.33 - 1.92)*</td>
</tr>
<tr>
<td>10</td>
<td>Nalorphine hydrochloride</td>
<td>13.4</td>
<td>1.41 (1.18 - 1.69)</td>
</tr>
<tr>
<td>10</td>
<td>Naloxone hydrochloride</td>
<td>11.9</td>
<td>1.23 (1.03 - 1.48)</td>
</tr>
</tbody>
</table>

*Represents 95% confidence limits.

### TABLE 6

**EFFECT OF NARCOTIC ANTAGONISTS ON PROPOXYPHENE DOSAGE AT CONVULSION THRESHOLD IN RATS**

<table>
<thead>
<tr>
<th>No. Rats</th>
<th>Treatment</th>
<th>Convulsion Threshold Dose (mg/Kg.)</th>
<th>Ratio Test/Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Saline</td>
<td>1.8</td>
<td>1.00</td>
</tr>
<tr>
<td>10</td>
<td>Levalloorphan tartrate</td>
<td>2.7</td>
<td>1.50 (1.46 - 1.55)*</td>
</tr>
<tr>
<td>10</td>
<td>Nalorphine hydrochloride</td>
<td>2.5</td>
<td>1.57 (1.51 - 1.62)</td>
</tr>
<tr>
<td>10</td>
<td>Naloxone</td>
<td>2.5</td>
<td>1.60 (1.56 - 1.65)</td>
</tr>
</tbody>
</table>

*Represents 95% confidence limits.
### TABLE 7

**EFFECT OF NARCOTIC ANTAGONISTS ON PROPOXYPHENE DOSAGE AT MORTALITY THRESHOLD IN MICE**

<table>
<thead>
<tr>
<th>No. Mice</th>
<th>Treatment</th>
<th>Mortality Threshold Dose (mg/Kg.)</th>
<th>Ratio Test/Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Saline</td>
<td>13.2</td>
<td>1.00</td>
</tr>
<tr>
<td>10</td>
<td>Levallorphan tartrate</td>
<td>21.1</td>
<td>1.60 (1.33 - 1.92)*</td>
</tr>
<tr>
<td>10</td>
<td>Nalorphine hydrochloride</td>
<td>19.1</td>
<td>1.50 (1.25 - 1.81)</td>
</tr>
<tr>
<td>10</td>
<td>Naloxone hydrochloride</td>
<td>21.0</td>
<td>1.59 (1.35 - 1.96)</td>
</tr>
<tr>
<td>10</td>
<td>Pentobarbital</td>
<td>11.5</td>
<td>0.91 (0.76 - 1.09)</td>
</tr>
</tbody>
</table>
### TABLE 8

**EFFECT OF NARCOTIC ANTAGONISTS ON PROPOXYPHENE DOSAGE AT MORTALITY THRESHOLD IN RATS**

<table>
<thead>
<tr>
<th>No. Mice</th>
<th>Treatment</th>
<th>Mortality Threshold Dose (mg/Kg.)</th>
<th>Ratio Test/Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Saline</td>
<td>36.1</td>
<td>1.00</td>
</tr>
<tr>
<td>10</td>
<td>Levallophorphan tartrate</td>
<td>79.8</td>
<td>2.14 (1.79 - 2.57)*</td>
</tr>
<tr>
<td>10</td>
<td>Nalorphine hydrochloride</td>
<td>80.6</td>
<td>2.27 (1.89 - 2.72)</td>
</tr>
<tr>
<td>10</td>
<td>Naloxone hydrochloride</td>
<td>83.6</td>
<td>2.32 (1.94 - 2.79)</td>
</tr>
<tr>
<td>10</td>
<td>Levallophorphan + pentobarbital</td>
<td>75.7</td>
<td>1.98 (1.52 - 2.58)</td>
</tr>
<tr>
<td>10</td>
<td>Pentobarbital</td>
<td>39.5</td>
<td>1.00 (0.70 - 1.30)</td>
</tr>
</tbody>
</table>

*Represents 95% Confidence Limits.*
SUMMARY

Intravenous Administration of levallorphan tartrate, nalorphine hydrochloride, or naloxone hydrochloride significantly increased convulsion threshold and mortality threshold of mice and rats infused with propoxyphene hydrochloride. Treatment with the combination of levallorphan-pentobarbital or pentobarbital alone 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.
ANTAGONISM OF PROPOXYPHENE RESPIRATORY DEPRESSION IN RABBITS

Introduction

The synthetic analgesic, propoxyphene hydrochloride, has been reported to produce respiratory depression as one of its toxic symptoms in animals (Chapman and Walaszek 1962, Picchioni 1963) and in man (Frasier 1963, Hara 1964, Hyatt 1962, McCarthy and Keenan 1963, Nitzke 1960, Qureshi 1964, Storts 1963, Swarts 1964). Indeed, death was due to respiratory arrest from overdose of propoxyphene in dogs (Robbins, 1955) as well as in a human case (Frasier 1962).

Nalorphine hydrochloride was suggested as an agent to prevent the toxic manifestations of propoxyphene in rats, however, respiratory depression was not mentioned (Robbins 1955). Levallorphan tartrate and nalorphine hydrochloride were of value in antagonizing the lethal effects of propoxyphene in mice, but specific antagonism of respiratory depression was not considered (Harpel...
and Mann 1965). In one study an increase of respiratory rate was observed after nalorphine was administered to propoxyphene depressed rats (Picchioni 1963). However, the extent of propoxyphene induced respiratory depression has not been determined nor have quantitative data been presented to demonstrate the antidotal effect of the narcotic antagonists against this depression.

The purpose of this present investigation is to ascertain the nature and amount of depressant action of propoxyphene hydrochloride on respiratory rate, tidal volume, and minute volume in rabbits. In addition it was considered necessary to determine the antidotal effect of levallorphan tartrate, nalorphine hydrochloride and naloxone hydrochloride in counteracting the depression of these respiratory parameters. Finally, a determination of the relative efficacy of the 3 narcotic antagonists in elevating depressed minute volume was carried out to conclude the study.

**Experimental**

Fifteen albino rabbits of both sexes, weighing between 2.5 - 3.5 Kg., were randomly divided into 3 groups of 5 animals per group. Each animal was anesthetized with urethane hydrochloride,
1 Gm./Kg., and respiratory activity was measured with an Anderson Inspirometer, Metro Scientific Company ME-5531, attached to a tracheal cannula. The instrument was previously calibrated and adjusted so that respiration could be recorded on kymograph paper. Calibration permitted direct, quantitative measurement of the respiratory tracings after the investigation was completed. One additional rabbit was utilized to demonstrate the duration and depth of propoxyphene depression on respiratory rate, tidal volume, and minute volume.

Propoxyphene hydrochloride was administered by marginal ear vein in a dose of 3 mg/Kg. to all animals. One minute was allowed to attain a steady state of depression. Each of the 3 groups of animals then received one of the following intravenous treatments: Levallophan tartrate, nalorphine hydrochloride or naloxone hydrochloride according to the dosage schedule in Tables 9 - 12. Thereafter, at one minute intervals, another dose of narcotic antagonist was given until a series of 5 injections was completed. Each dose was considered as the cumulative total of all injections of narcotic antagonist up to, and including, a particular injection.
The results are reported for the effects of propoxyphene on the respiratory parameters as a percentage of the normal value compiled from 5 animals. Each rabbit served as its own control so that the effects of the narcotic antagonists could be compiled as a percent of normal as well. Finally, the results of the comparative potency study are reported as cumulative doses of levallorphan tartrate, nalorphine hydrochloride, and naloxone hydrochloride, calculated as mcg/Kg. of base, required to produce an elevation in respiratory minute volume over the depressed state induced by propoxyphene. The relative capacity of the narcotic antagonists to elevate minute volume was determined by a parallel line bioassay procedure (Finney 1952) using nalorphine as the standard agent for elevating respiratory activity.

Results

The effect of intravenous propoxyphene hydrochloride on the 3 respiratory parameters measured in this investigation is shown in Tables 9 - 11. Respiratory rate was decreased by a mean value for the 3 groups of 66.6% of normal. Administration of levallorphan tartrate and nalorphine hydrochloride prevented further drop in respiratory rate; the rate remained at 56 and 51% of normal, respective-
ly. Naloxone hydrochloride treatment reversed the fall in respiration rate and effected an immediate rise to 83% of normal. At the end of the series of 5 doses both nalorphine and naloxone had returned the rate to 112% of normal, but levallorphan had produced a gradual rise in the rate to 73% of normal.

Minute volume was depressed to a mean value of 49.6% of normal for the 3 groups of animals. All 3 of the narcotic antagonists elevated the depressed minute volume with the first dose as follows: Levallorphan to 73%, nalorphine to 55%, and naloxone 79% of normal. The final dose of narcotic antagonist elevated the minute volume above normal in all 3 cases.

The mean depression of tidal volume for the 3 groups was 76% of normal following intravenous propoxyphene. Reflex increase in the tidal volume is noted in the untreated animal, but reaches a steady level at 80% of normal. In the groups of rabbits treated with narcotic antagonists the tidal volume immediately rose to 130, 109, and 94% of normal following intravenous levallorphan, nalorphine and naloxone, respectively. After the last dose of narcotic antagonist, the tidal volume was elevated 159, 111, and 97% of normal by levallorphan, nalorphine, and naloxone, respectively.
In the comparison of relative efficacy of the narcotic antagonists, on the basis of mcg/Kg. of base required, using nalorphine as 1 (unit), to elevate propoxyphene depressed minute volume, levallorphan had a mean potency ratio of 8.85 times that of nalorphine and naloxone had a value of 19.19 times that of the standard. Although the mean value for naloxone shows a tendency for greater potency than levallorphan, there was no significant difference between the 2 narcotic antagonists. Probabilities greater than 0.05 were insignificant. (See Table 12).

Discussion

The data indicate that propoxyphene hydrochloride is capable of decreasing all 3 parameters of respiratory activity measured in this investigation. A comparison of the percent of normal figures in rabbits demonstrates that the depressed values after propoxyphene are effectively reversed by intravenous treatment with levallorphan tartrate, nalorphine hydrochloride, and naloxone hydrochloride.

Depressant activity of the respiration has been known to occur with the more potent analgesics (Murphree 1965). For example, larger than therapeutic doses of the narcotic analgesics produces increasingly severe depression of the respiratory rate (Swerdlow 1955)
and frequently causes apnea. This investigation has shown this to be true for propoxyphene overdose as well, since respiratory rate was depressed and apnea observed in two cases. The decrease in rate is more marked after intravenous, than after intramuscular, administration of the narcotic analgesics (Dripps 1947). The administration of 0.03 mg/Kg. of levallorphan 30 minutes after intravenous meperidine corrects the respiratory depression produced by the narcotic (Foldes, 1957). In the present investigation levallorphan as well as nalorphine and naloxone correct the respiratory depression produced by a non-narcotic analgesic, namely propoxyphene. Thus, the usefulness of these narcotic antagonists has been extended to include propoxyphene intoxication which was not originally considered to be antagonized.

Tidal volume is also depressed by the narcotic analgesics (Orkin 1955). The depression of the tidal volume is usually less marked and of shorter duration than that of the respiratory rate (Foldes 1957). The less marked effect of narcotic analgesics on the depth of respiration is probably due to the fact that the elevation of the alveolar pCO₂ caused by the decreased respiratory rate has a more marked effect on the depth than on the rate of respiration.
(Dripps 1947). This also explains the compensatory increase in the tidal volume observed after narcotic induced depression of the respiratory rate (Swerdlow, 1955). Although no direct measurements have been made of alveolar pCO$_2$ concentration after propoxyphene depression, there was a compensatory increase in tidal volume observed in the untreated animal. Thus, it is tempting to speculate that overdose of propoxyphene might produce a depression in tidal volume by a mechanism similar in nature to that of the narcotic analgesics.

Minute volume is at first depressed by narcotic analgesics more than the rate or the depth of respiration (Foldes, et al, 1964). After the development of the compensatory increase in the tidal volume, however, the depression of the minute volume of respiration is usually less than that of the respiratory rate (Foldes 1957). Propoxyphene also initially depressed the minute volume to a greater degree than the other parameters, but the effect remains and the duration appears to be as long as the depression of the rate even after development of the compensatory increase in tidal volume.

It is of interest to note the similarity of propoxyphene induced respiratory depression to that produced by the opiates.
Since propoxyphene is related in structure to methadone (Murphree 1965), a narcotic analgesic, some of the toxic symptoms might be expected to be similar. Propoxyphene does produce some opiate-like effects in large doses (Fraser and Isbell, 1955) and this study provides evidence that it is capable of inducing a profound respiratory depression similar in many respects to that of methadone and other narcotics. However, propoxyphene has shown very little addiction liability and, in therapeutic doses, respiratory depression appears to be minimal (Burget and Greene, 1962). Moderately toxic doses usually produce central nervous system and respiratory depression (Jaffe 1965). However, only one case of physical dependence and withdrawal symptoms has been reported (Elson and Domino 1963).

In the present evaluation of comparative efficacy of the narcotic antagonists it is apparent that levallorphan and naloxone are more potent than nalorphine in elevating propoxyphene depressed minute volume. Thus, in cases of propoxyphene intoxication it would appear that levallorphan is to be preferred over nalorphine, since these are the only 2 narcotic antagonists currently available to clinicians.
This is not to imply that nalorphine is ineffective. On the contrary, it was shown to be quite capable of elevating all parameters of respiratory depression in the present study and against the depression induced by its parent compound, methadone, in previous studies (Huggins 1950, Isbell 1953, Lynch and Meyers 1958). However, unlike a study where nalorphine potency was not differentiated from other narcotic antagonists (Eckenhoff and Funderburg, 1954) this investigation did demonstrate the greater potency of levallorphan and naloxone. This corresponds with other observations where the potency of naloxone was demonstrated to be greater than either levallorphan or nalorphine (Blumberg 1951, Foldes, 1963) against opiate depression. But, in this investigation, both levallorphan and naloxone must be considered more potent than nalorphine and not being significantly different from each other. Therefore, it would appear that levallorphan or naloxone might be considered as first choice in treating overdose of propoxyphene, and all 3 narcotic antagonists as specific antidotes to counteract the respiratory depression from poisoning with propoxyphene.

However, further studies are indicated to determine the therapeutic index of the narcotic antagonists when used to antagonize
propoxyphene toxicity before one of them can be recommended as the antidote of first choice.
SUMMARY

Levallorphan and naloxone were found to be 8 times and
19 times more effective, respectively, than nalorphine in elevating
propoxyphene induced depression of minute volume in rabbits.
However, they do not differ significantly from each other. This
study confirms reports of greater potency of levallorphan and
naloxone but in this case the agonist being antidoted was a non-
narcotic analgesic, propoxyphene hydrochloride.

All 3 narcotic antagonists were capable of reversing
propoxyphene depressed respiratory rate, minute volume, and
tidal volume.
TABLE 9

EFFECT OF NARCOTIC ANTAGONISTS ON PROPOXYPHENE DEPRESSED RESPIRATORY RATE IN RABBITS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Normal</th>
<th>Propoxyphene (1)</th>
<th>(2)</th>
<th>(3)</th>
<th>(4)</th>
<th>(5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lev</td>
<td>100</td>
<td>62</td>
<td>56</td>
<td>56</td>
<td>61</td>
<td>67</td>
</tr>
<tr>
<td>Nal</td>
<td>100</td>
<td>72</td>
<td>51</td>
<td>63</td>
<td>77</td>
<td>90</td>
</tr>
<tr>
<td>Nalox</td>
<td>100</td>
<td>64</td>
<td>83</td>
<td>92</td>
<td>97</td>
<td>109</td>
</tr>
</tbody>
</table>

TABLE 10

EFFECT OF NARCOTIC ANTAGONISTS ON PROPOXYPHENE DEPRESSED MINUTE VOLUME IN RABBITS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Normal</th>
<th>Propoxyphene (1)</th>
<th>(2)</th>
<th>(3)</th>
<th>(4)</th>
<th>(5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lev</td>
<td>100</td>
<td>60</td>
<td>73</td>
<td>83</td>
<td>91</td>
<td>103</td>
</tr>
<tr>
<td>Nal</td>
<td>100</td>
<td>37</td>
<td>55</td>
<td>76</td>
<td>87</td>
<td>99</td>
</tr>
<tr>
<td>Nalox</td>
<td>100</td>
<td>52</td>
<td>79</td>
<td>91</td>
<td>99</td>
<td>104</td>
</tr>
</tbody>
</table>
### TABLE 11

EFFECT OF NARCOTIC ANTAGONISTS ON PROPOXYPHENE DEPRESSED TIDAL VOLUME IN RABBITS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Normal</th>
<th>Propoxyphene</th>
<th>Doses&lt;sup&gt;h&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(1)</td>
<td>(2)</td>
</tr>
<tr>
<td>Lev</td>
<td>100</td>
<td>95</td>
<td>130</td>
</tr>
<tr>
<td>Nal</td>
<td>100</td>
<td>52</td>
<td>109</td>
</tr>
<tr>
<td>Nalox</td>
<td>100</td>
<td>82</td>
<td>94</td>
</tr>
</tbody>
</table>

<sup>h</sup> - Levalorphan tartrate (Lev) and Naloxone hydrochloride (Nalox) were administered at doses of 1.6, 3.2, 6.4, 12.8, and 25.6 mcg/Kg. respectively. Nalorphine hydrochloride (Nal) was administered at doses of 15.0, 30.0, 60.0, 120.0, and 240.0 mcg/Kg. respectively.
**TABLE 12**

POTENCY RATIOS OF LEVALLORPHAN AND NALOXONE COMPARRED TO THE STANDARD NALORPHINE IN RABBITS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Elevation of Minute Volume (Liters/Minute at 2 doses)</th>
<th>Potency Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nal</td>
<td>0.220 (1) 1.038 (5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Lev</td>
<td>0.167 0.855</td>
<td>8.85 (3.67 - 19.25)</td>
</tr>
<tr>
<td>Nalox</td>
<td>0.413 0.904</td>
<td>19.19 (8.77 - 42.96)</td>
</tr>
</tbody>
</table>

1 - Dosage schedule the same as in Tables 9 - 11, but calculated as mcg/Kg. of base for comparative purposes.
SUMMARY AND CONCLUSIONS

The present study was initiated to determine whether nalorphine hydrochloride or other proposed antidotes might be used as specific antidotes for propoxyphene poisoning.

The following summarizes the result of this work:

1. Intravenous treatment with levallorphan tartrate, nalorphine hydrochloride, or naloxone hydrochloride, 1 mg/Kg., prevented and reversed the convulsive and lethal effects of intraperitoneal propoxyphene hydrochloride, 120 mg/Kg. The combination of nalorphine hydrochloride, 1 mg/Kg., and pentobarbital sodium, 10 mg/Kg., also showed protection against convulsions and death from overdose of the analgesic. Pentobarbital sodium alone, 10 mg/Kg., prevented convulsions but showed no protection against the lethal action of propoxyphene. No treatment was effective after the stage of postictal depression was reached.

2. 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 pentobarbital sodium, 10 mg/Kg., or pentobarbital sodium 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 sodium alone failed to modify mortality threshold.

3. Propoxyphene hydrochloride, 3 mg/Kg. intravenously, depressed respiratory rate, minute volume, and tidal volume in rabbits. A single intravenous dose of levallorphan tartrate, naloxone hydrochloride, 1 mcg/Kg., or nalorphine hydrochloride, 15 mcg/Kg., reversed the depression caused by the analgesic. After a series of intravenous treatments with the narcotic antagonists, all 3 respiratory parameters were returned to normal. On a comparison of mcg/Kg. doses of narcotic antagonist base, levallorphan and naloxone were found to be more potent than nalorphine in elevating depressed minute volume.
Conclusions of this work are as follows:

The toxic symptoms of propoxyphene poisoning, especially convulsions and respiratory depression, are counteracted by levallorphan tartrate, nalorphine hydrochloride, or naloxone hydrochloride. Although pentobarbital was found to prevent convulsions, it is recommended that any one of the narcotic antagonists without the barbiturate be used as a specific antidote for the toxic effects of propoxyphene hydrochloride poisoning.
REFERENCES


15. Ibid., p. 51.


29. Ibid., p. 279.


