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The Effects of Pentazocine and Tripelennamine on Analgesia and Locomotion

James Philip Cleary
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THE EFFECTS OF PENTAZOCINE AND TRIPLENNAMINE ON ANALGESIA AND LOCOMOTION

by

James Philip Cleary

A Dissertation
Submitted to the
Faculty of The Graduate College
in partial fulfillment of the
requirements for the
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Western Michigan University
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THE EFFECTS OF PENTAZOCINE AND TRIPELENNAMINE ON ANALGESIA AND LOCOMOTION

James Philip Cleary, Ph.D.
Western Michigan University, 1982

The effects of pentazocine and tripelennamine, alone and in combination, were assessed on measures of analgesia (hot plate test) and locomotion (open field) in rats and mice. In Experiment 1, the combination of pentazocine and tripelennamine was found to produce analgesia at doses which were not analgesic when the drugs were given alone. This combination also reestablished analgesia in subjects made tolerant to pentazocine's effects. In Experiment 2, development of tolerance to the analgesic effects of pentazocine was delayed by addition of tripelennamine. In Experiment 3, locomotion was decreased by pentazocine at the highest dose. A similar reduction was produced by combining tripelennamine with lower doses of pentazocine. The relation of these data to the rising popularity of pentazocine and tripelennamine abuse is discussed.
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It is impossible to acknowledge every debt incurred across the years of my academic career. In light of this, I hope those deserving people not specifically mentioned below will accept my thanks or my apology.

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James Philip Cleary
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CHAPTER I
INTRODUCTION

Abuse of the analgesic pentazocine in combination with the antihistamine tripelennamine has recently received the concerned attention of many investigators. This combination is known on the illicit drug market as "T's and blues", a slang name derived from the trade name for pentazocine, Talwin (Winthrop Laboratories, New York, NY), and from the light blue color of the tripelennamine tablet. The mixture apparently was first used by addicts as a substitute for more expensive, scarce, or poor quality heroin. Now, however, many addicts apparently prefer T's and blues to street quality narcotics (Showalter, 1980).

At present, the abuse of this drug combination is centered in the metropolitan areas of the midwestern United States (Poklis & Whyatt, 1980; Showalter, 1980; Wadley & Stillie, 1980). Lehmyer and Steingold (1980) studied changes in abuse patterns among veterans living in Chicago. These authors found a sevenfold increase in pentazocine use between 1975 and 1978; over 97% of pentazocine users added tripelennamine to their injection solutions. Similar increases in the use of this combination have been reported in other areas (Poklis & Whyatt, 1980), and the National Institute of Drug Abuse warned local drug clinics in 1979 of increased abuse.

When pentazocine was first marketed as an analgesic in 1967, initial reports indicated that the drug had an extremely low abuse
potential (Kelly, 1977). Most reports claimed that pentazocine's mixed agonist-antagonist nature would prevent its abuse by morphine or heroin addicts (see Chambers, Inciardi, & Stephens, 1971, for a review of early pentazocine use). Indeed, pentazocine may induce symptoms of narcotic withdrawal in morphine-dependent subjects (e.g., Bhargava, 1981).

Two years after the World Health Organization (1966) proclaimed that there was little likelihood of pentazocine abuse, and one year after its introduction onto the market, the first reports of pentazocine dependence were issued by Winthrope Laboratories (1967), pentazocine's manufacturer. Early reports indicated abuse was largely limited to physicians and patients iatrogenically addicted (Chambers, et al., 1971). Documented cases of pentazocine abuse increased throughout the 1970's (Levy, Brown, & Halikas, 1972; Swanson, Weddige, & Morse, 1973).

Tripelennamine, although not known to produce dependence, has shown some abuse potential for several years. O'Driscoll and Lindley (1957) reported tripelennamine abuse by "street addicts" over 20 years ago. Although the antihistamine was sometimes used alone, often the drug was combined with heroin or paregoric in a combination known as "blue velvet" (Wadley & Stillie, 1980). It is of some interest that a brief attempt to use tripelennamine to treat morphine withdrawal during the post World War II years (Kells, 1948) may have introduced tripelennamine to street users. Whatever the original impetus, abuse of tripelennamine alone or in polydrug combinations, was relatively minor until the recent rise in popularity of T's and blues.
The main factor involved in the rise in popularity of T's and blues may be availability. Pentazocine was originally classified as a narcotic antagonist similar to nalorphine. It was not until 1978 that it was reclassified under the Controlled Substances Act, and then placed in the least restrictive category. Illinois has recently reclassified the drug, giving it Schedule II (relatively restricted) status. Whether other states will follow suit is unclear; at present, pentazocine is relatively easy to obtain. Tripelennamine is a common and effective antihistamine obtainable in tablet form by prescription or over-the-counter as a topical ointment.

When used illicitly, both drugs are usually obtained in tablet form. Most commonly, the tablets are in doses of 50 mg pentazocine (Talwin, Winthrop Laboratories) and 50 mg tripelennamine (Pyribenzamine, Geigy Pharmaceuticals, Ardsley, NY). Users dissolve the tablets in water in a ratio of 2 pentazocine tablets to 1 tripelennamine tablet (3:1 or 8:3 ratios are also popular), strain the solution through cotton, and inject it intravenously. The preferred ratio varies among users and is apparently adjusted until the desired euphoric effects are produced. Estimates of the doses used vary from 200 to 600 mg pentazocine and 100 to 250 mg tripelennamine per injection (Poklis & Whyatt, 1980).

Use of the tablet form of either drug for intravenous injections may produce severe problems. Inflammation, abscesses, and subcutaneous ulcers are frequently reported (Poklis & Whyatt, 1980). A more serious problem stems from the insoluble "talc" (magnesium silicate) used in preparation of the oral form of both drugs. This talc is
seldom completely filtered by the cotton and eventually forms granuloma in the lungs, causing pulmonary occlusions, thrombosis, thrombophlebitis, and pulmonary hypertension (Butch, Yokel, Sigell, Hanenson, & Nelson, 1979; Lahmeyer & Steingold, 1980). Other problems associated with nonsterile injections (e.g., hepatitis) may also occur.

In addition, both drugs produce undesirable side effects. Along with physical dependence, pentazocine may produce nausea, vomiting, and severe headaches. Tripelennamine is known to produce convulsions, loss of consciousness, and seizures at high doses (Poklis & Whyatt, 1980). The most frequent psychological complications reported for pentazocine and tripelennamine abuse involve dysphoria, paranoia, disorientation, hallucinations, and depression (Showalter, 1980).

The severity of the complications associated with abuse of tripelennamine and pentazocine combinations would not be expected from early pharmacological reports of their action. Tripelennamine, (2-[benzyl]2-(dimethylamino)ethyl]-amino)pyridine), is an antihistamine of the ethylenediamine class. Such antihistamines are primary blockers (competitive antagonists) of the effects of histamine on \(H_1\) receptors. Tripelennamine blocks histamine's ability to control smooth muscle, dilate capillaries, constrict bronchial tubes, and increase capillary permeability (Douglas, 1980). The drug may produce both central nervous system sedation (high doses) or excitation (low-moderate doses). The mechanism for these effects is unknown. Although its primary effect at \(H_1\) receptors is only documented in the
periphery, suspected central nervous system effects involve colinergic blocking and gamma aminobutyric acid (GABA) blocking actions (Douglas, 1980).

Pentazocine \([1, 2, 3, 4, 5, 6\text{-hexahydro}-6\text{-dimethyl}-3\text{-}(\text{methyl}-2\text{-buteryl})-2, 6\text{-methano}-3\text{-benzazocine}-8\text{ol}]\), is an analgesic of the benzomorphan series. It is a mixed narcotic agonist-antagonist. As an agonist, it appears to be about 30% as effective as morphine, at least with respect to analgesic actions. The antagonist properties of pentazocine are sufficient to precipitate abstinence symptoms in morphine-dependent subjects (Bhargava, 1981).

Pentazocine has generated modest interest among behavioral pharmacologists. In 1972, Hoffmeister and Schlichting reported that rhesus monkeys would self-administer pentazocine. By this time, some cases of dependence in humans had already been reported (Chambers, et al., 1971). Pentazocine has also been shown to be analgesic in nonhumans (Dykstra & McMillan, 1974), and to serve as a discriminative stimulus (Kuhn, Greenberg, & Appel, 1976). Both of these effects appear only at doses that are two to three times greater than similarly effective doses of morphine.

The behavioral effects of pentazocine and tripelennamine combinations have been little studied in nonhumans. Bhargava (1981) found that the combination blocked some symptoms of narcotic abstinence in mice, while Waller, Katz, and Morris (1980) reported that tripelennamine increased the lethality of pentazocine in this species. The primary purpose of the present studies was to determine how the analgesic actions of pentazocine in rats are affected by the addition
of tripelemamine. Analgesia is an important and readily measured response to pentazocine, and determining how it is affected by the addition of tripelemamine may provide a readily quantifiable measure of how these drugs interact to affect behavior. Analyzing the basic behavioral effects of the drugs is prerequisite to understanding their abuse by humans.
CHAPTER II

EXPERIMENT I

In Experiment I, a hot plate assay of analgesia (Woolfe & Macdonald, 1944) was used to evaluate the effects of superimposing acute tripelennamine injections over a chronic pentazocine regimen. Three doses of pentazocine (10, 20, and 30 mg/kg) were studied in combination with three doses of tripelennamine (0.5, 5.0, and 10.0 mg/kg); the effects of these drugs and doses alone were also determined.

Method

Subjects

Thirty adult male rats of the Sprague-Dawley strain, bred in the Psychology Department colony at Western Michigan University, served as subjects. At the start of the experiment, all rats were approximately 9 months old and weighed 300-350 grams.

Subjects were housed in group cages (5 per cage) with free access to food and water. The colony room, where animals were housed, was constantly illuminated and maintained at 24° centigrade throughout the experiment.

Apparatus

Analgesic tests were performed on a heated plate (Chicago
Surgical & Electrical, Co., Chicago, IL) measuring 17.0 cm by 62.5 cm. The plate was enclosed by wooden walls on three sides and a clear plastic front viewing wall (21.0 cm high). A 0.6 cm thick piece of perforated hardboard, hinged to the back wall, served as a cover for the apparatus. The hot plate was maintained at a temperature of 52° centigrade throughout the experiment.

Drugs

The effects of three doses of tripelennamine hydrochloride (0.5, 5.0, and 10.0 mg/kg) and three doses of pentazocine lactate (10.0, 20.0, and 30.0 mg/kg) were evaluated alone and in combination. Doses of tripelennamine (Sigma Chemical Co., St. Louis, MO) refer to the total salt while doses of pentazocine (purchased as Talwin from Winthrop Laboratories) refer to the base. Control injections of isotonic saline (0.9%) were given on all non-drug days. All injections were given intraperitoneally at a volume of 1.0 ml/kg. Drugs were mixed with isotonic saline to obtain the proper concentration for injection.

Procedure

Analgesic sessions were conducted daily. Animals were injected with tripelennamine, pentazocine, a combination of these two drugs, or isotonic saline solution, and then immediately returned to their home cages. Thirty minutes after injection, analgesic testing was begun by placing individual animals in the middle of the heated plate (52° C). The latency from contact with the plate until the
first hind paw lick was recorded for each subject. To minimize tissue damage, subjects were never allowed to be in contact with the plate for more than 30 seconds. If a subject did not lick his paw within 30 seconds, he was immediately removed from the plate and a latency score of 30 seconds was recorded.

Initially, subjects were randomly assigned to one of three groups of 10 animals each. All groups were tested daily on the hot plate under saline control conditions until the mean paw lick latencies were stable over a 3-day period. The stability criterion was defined as a variation of less than 10%, on each given day, from the mean of those 3 days.

When stability was reached, a dose-effect curve was obtained for three doses of tripelemamine (0.5, 5.0, and 10.0 mg/kg). Tripelennamine doses were given in a random order with three control sessions between each tripelemamine dose. Following tripelemamine and with three more placebo sessions intervening, each group began receiving a different daily maintenance dose of pentazocine, either 10.0, 20.0, or 30.0 mg/kg. Daily pentazocine administration and testing were continued until the subjects were tolerant (i.e., paw lick latency returned to predrug control levels). At this time, combinations of tripelemamine and the maintenance dose of pentazocine were administered in a random order with three sessions of pentazocine alone interposed between each combination test. Each group received 0.5, 5.0, and 10.0 mg/kg doses of tripelemamine, in combination with the maintenance dose of pentazocine, on a single occasion.
Combined data from all subjects produced mean paw lick latencies of 5.7, 7.8, and 5.9 seconds at respective doses of 0.5, 5.0, and 10.0 mg/kg tripelennamine. Although the mean latency at 5.0 mg/kg was slightly elevated, none of these means proved significantly different from the saline control mean of 5.8 seconds (repeated measures analysis of variance). Initial pentazocine administration produced mean paw lick latencies of 5.0, 6.8, and 17.1 seconds at doses of 10.0, 20.0, and 30.0 mg/kg, respectively. Only at 30 mg/kg was this mean latency significantly different from that group's saline control latency of 5.2 seconds ($t_{LSD} = 4.85$, df = 45, $p < .001$).

Pentazocine was given to each group for seven consecutive sessions prior to the first combination with tripelennamine. Subjects showed stable response latencies across the final 3 days of this period (within ±10% of 3-day mean). For groups receiving 10.0, 20.0, or 30.0 mg/kg pentazocine, these respective mean latencies were 3.8, 5.3, and 6.1 seconds, compared to respective control mean latency on the 3 saline days just prior to combination tests. Thus paw lick latencies under pentazocine had returned to control levels, demonstrating that the subjects had become tolerant to the pentazocine.

Table 1 summarizes the results of combining tripelennamine with pentazocine for each of the three groups. These results are also presented in Figure 1 as a percentage of the mean paw lick latency over the final 3 days of pentazocine alone. No combination of
## TABLE 1

Summary of the Effects of Combinations of Tripelennamine and Pentazocine on Paw Lick Latencies

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Mean Control Latency (seconds)</th>
<th>Mean Drug Latency (seconds)</th>
<th>Mean % tLSD (df)</th>
<th>p</th>
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<tbody>
<tr>
<td>10 mg/kg pentazocine + .5 mg/kg tripelennamine</td>
<td>3.6</td>
<td>4.4</td>
<td>121%</td>
<td>not significant</td>
</tr>
<tr>
<td>10 mg/kg pentazocine + 5 mg/kg tripelennamine</td>
<td>3.8</td>
<td>4.2</td>
<td>111%</td>
<td>not significant</td>
</tr>
<tr>
<td>10 mg/kg pentazocine + 10 mg/kg tripelennamine</td>
<td>4.0</td>
<td>5.0</td>
<td>125%</td>
<td>not significant</td>
</tr>
<tr>
<td>20 mg/kg pentazocine + .5 mg/kg tripelennamine</td>
<td>5.3</td>
<td>3.9</td>
<td>74%</td>
<td>not significant</td>
</tr>
<tr>
<td>20 mg/kg pentazocine + 5 mg/kg tripelennamine</td>
<td>4.5</td>
<td>5.6</td>
<td>124%</td>
<td>not significant</td>
</tr>
<tr>
<td>20 mg/kg pentazocine + 10 mg/kg tripelennamine</td>
<td>4.7</td>
<td>8.4</td>
<td>178%</td>
<td>3.45(45) 0.0012</td>
</tr>
<tr>
<td>30 mg/kg pentazocine + .5 mg/kg tripelennamine</td>
<td>6.1</td>
<td>6.3</td>
<td>103%</td>
<td>not significant</td>
</tr>
<tr>
<td>30 mg/kg pentazocine + 5 mg/kg tripelennamine</td>
<td>7.2</td>
<td>11.4</td>
<td>159%</td>
<td>1.88(45) 0.066</td>
</tr>
<tr>
<td>30 mg/kg pentazocine + 10 mg/kg tripelennamine</td>
<td>7.0</td>
<td>13.3</td>
<td>191%</td>
<td>2.82(45) 0.0071</td>
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tripelennamine with 10.0 mg/kg pentazocine produced latencies that were significantly different from the latencies associated with that dose of pentazocine alone. Pentazocine at 20.0 mg/kg in combination with 0.5, 5.0, and 10.0 mg/kg tripelennamine produced paw lick latencies of 3.9, 5.6, and 8.4 seconds respectively, with respective control latencies of 5.3, 4.5, and 4.7 seconds \( F = 4.44 \text{ (5.45)}, p < .01 \). At this dose of pentazocine, only the highest dose of tripelennamine produced a mean latency that was significantly different from the control latency \( t_{\text{LSD}} = 3.67 \text{ (5.45)} p < .01 \). Planned comparison tests yielded significance levels of \( p < .10 \), for the 5.0 mg/kg tripelennamine combination with 30.0 mg/kg pentazocine and \( p < .001 \) for the 10.0 mg/kg tripelennamine combined with the same pentazocine dose. At 0.5 mg/kg tripelennamine plus 30.0 mg/kg pentazocine the latencies were not significantly different from pentazocine alone levels.

Paw lick latencies under combination doses are presented in Figure 1 as a percentage of the mean of the final 3 days under pentazocine alone. This figure graphically emphasizes the effect of tripelennamine upon subjects maintained on pentazocine and tolerant to its effects. It may be readily seen in this figure that no dose of tripelennamine much affected latencies under the lowest dose of pentazocine. However, while 5.0 mg/kg tripelennamine only increased latencies under 30.0 mg/kg pentazocine, 10.0 mg/kg tripelennamine substantially increased paw lick latencies under both 20.0 and 30.0 mg/kg pentazocine. At these higher doses of pentazocine, latencies are monotonic across doses of tripelennamine.
Figure 1. Paw lick latencies under combinations of pentazocine and tripelennamine, expressed as a percentage of the mean of the final 3 days of pentazocine maintenance.
Discussion

Tripelennamine, as a member of the ethylenediamine antihista­mine group, is thought to produce weak central nervous system effects. With high doses, central nervous system sedation is apparently the most common side effect (Hays, Johnson, & Perry, 1980). Although such sedation may certainly contribute to a general lessening of respons­iveness, general analgesia has not been reported as a specific effect of this drug. As expected, tripelennamine showed no analgesic properties at the doses tested in the present study.

Pentazocine, promoted for its analgesic effects, increased paw lick latencies at the highest dose tested, but did not produce anal­gesia at the two lower doses. Other authors have reported analgesia at doses comparable to these lower doses, but they employed different, and perhaps more sensitive, procedures (e.g., Goode, Rhodes, & Waterfall, 1979). Under a regimen of chronic daily pentazocine administration in the present study, subjects quickly became tolerant to its analgesic effects (30 mg/kg pentazocine group).

The most interesting finding of this study is the analgesia pro­duced by the combination of the two drugs in subjects already tolerant to pentazocine. In the group receiving 20 mg/kg pentazocine, tripelennamine at 10 mg/kg actually produced significant analgesia when neither drug alone produced analgesia at those doses. Furthermore, paw lick latencies appeared to be a direct monotonic function of the tripelennamine dose under 20 and 30 mg/kg of pentazocine main­tenance. Thus, this drug combination appears to produce an analgesic response similar to that associated with higher doses of pentazocine.

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Since pentazocine taken alone may exacerbate the symptoms of narcotic abstinence, it was assumed for many years that the drug held little potential for abuse among "street" users (Kelly, 1977). Now, however, the abuse of pentazocine in combination with tripelennamine has reached epidemic proportions (Lahmeyer & Steingold, 1980). The ability of this combination to block some of the symptoms of narcotic abstinence has previously been put forward as a rationale for the current popularity of the mixture (Bhargava, 1981). The demonstration, in the present study, that tripelennamine can enhance the major narcotic property of pentazocine (i.e., analgesia) adds a further dimension to this analysis.
CHAPTER III
EXPERIMENT II

Experiment 1 examined the effects of pentazocine and tripelennamine in subjects chronically exposed to pentazocine. Under these conditions, tripelennamine appeared to facilitate the analgesic action of pentazocine. The mechanism of this facilitation is unknown. To clarify the relationship between these two drugs further, Experiment 2 investigated the effects of tripelennamine and pentazocine in non-tolerant subjects.

In this study, drug-naive subjects were exposed to maintenance doses of either pentazocine or a combination of pentazocine and tripelennamine. This procedure allows an assessment of the initial effect of the combination. In addition, under daily maintenance administrations, the course of tolerance development to pentazocine alone and to pentazocine plus tripelennamine can be compared.

Method

Subjects

Thirty experimentally naive male rats of the Sprague-Dawley strain, obtained from the Psychology Department colony at Western Michigan University, served as subjects. At the start of the experiment, the rats were approximately 9 months old and weighed 300-350 grams. Subjects were housed in group cages with free access to food and water, in a constantly illuminated room maintained at 24° centigrade.
Apparatus

Analgesic tests were performed on the hot plate apparatus described in Experiment 1.

Drugs

The effects of 30.0 mg/kg pentazocine, alone and in combination with 5.0 and 10.0 mg/kg tripelennamine, were evaluated. These drugs were prepared as in Experiment 1. All injections were intraperitoneal and isotonic saline (0.9%) again served as the vehicle control.

Procedure

Analgesic sessions were conducted as described as in Experiment 1. Briefly, subjects were placed on the hot plate 30 minutes after injection and the latency to lick the hind paw was recorded. A maximum latency of 30 seconds was allowed for any subjects on any given day.

Subjects were divided into 3 groups of 10 rats per group. Each group was first exposed to 10 sessions of analgesic testing under control conditions, where injections of isotonic saline solution were given. Immediately following these sessions, one group was exposed to 18 consecutive daily sessions in which 30.0 mg/kg pentazocine was given. The other two groups were treated identically, but tripelennamine at either 5.0 or 10.0 mg/kg was added to the 30.0 mg/kg of pentazocine. This dose of pentazocine alone, and these combinations of pentazocine and tripelennamine produced significant analgesia in Experiment 1.
Results

Mean paw lick latencies for the first drug session were 16.5, 13.4, and 18.5 seconds for the groups that received 30.0 mg/kg pentazocine, 30.0 mg/kg pentazocine plus 5.0 mg/kg tripelennamine, and 30.0 mg/kg pentazocine plus 10.0 mg/kg tripelennamine, respectively. None of these means were significantly different from each other. Mean control latencies for these groups, averaged across the final 3 days of saline administration, were 6.3 (SEM = 0.49), 5.9 (SEM = 0.62), and 5.7 (SEM = 0.43) seconds, respectively. Comparisons between drug and control means indicated that pentazocine alone, and together with both doses of tripelennamine, produced latencies on the first drug day that were significantly different from their control values. Obtained $t_{LSD}$ values were $t_{LSD} = 3.90$ (df = 45) $p < .001$ for the group that received 30.0 mg/kg pentazocine, $t_{LSD} = 2.85$ (df = 45) $p < .01$ for the group that received 30.0 mg/kg pentazocine plus 5.0 mg/kg tripelennamine, and $t_{LSD} = 4.92$ (df = 45) $p < .001$ for the group that received 30.0 mg/kg pentazocine plus 10.0 mg/kg tripelennamine.

Figure 2 shows the paw lick latencies for all three groups during the 18 days of drug administration. All groups showed tolerance to the drug administrations by eventually returning to their saline control levels. The most interesting results presented in Figure 2 occurred during the first 10 days. From Days 4 through 9, both groups receiving tripelennamine showed considerably less tolerance than the group receiving pentazocine alone. By the 10th day, latencies for all 3 groups converged.
Figure 2. Paw lick latencies under 30 mg/kg pentazocine, alone and in combination with 5 and 10 mg/kg tripelennamine, across 18 consecutive daily sessions. Means and SEM (brackets) for the final 3 days under saline control conditions are presented in the left panel.
Subjecting the data from the first 10 days of drug administration to analysis of covariance (ANCOVA) resulted in an F of 2.52 (df = 2, 26) with p < .05. Basically this may be interpreted as a significant difference between the adjusted means of the 3 groups. Since, in this case, the groups started out with essentially equivalent mean latencies, the adjusted means are the same as the simple means; they were 9.9, 10.7, and 13.3 seconds, under 30.0 mg/kg pentazocine, 30.0 mg/kg pentazocine plus 5.0 mg/kg tripelennamine, and 30.0 mg/kg pentazocine plus 10.0 mg/kg tripelennamine, respectively.

Discussion

As was the case in the first experiment, Experiment 2 showed that 30 mg/kg pentazocine produced significant analgesia. From the enhanced analgesia produced in pentazocine tolerant subjects in Experiment 1, it might be expected that tripelennamine would also enhance the effects of pentazocine in drug-naive subjects. This was not the case however, as there was no significant difference between the degree of analgesia produced by pentazocine alone and that produced by pentazocine plus either dose of tripelennamine.

Despite tripelennamine's inability to enhance analgesia when combined with initial pentazocine injections, the antihistamine did affect the subsequent development of tolerance. By Day 4, the mean paw lick latency for the pentazocine alone group was clearly lower than that of the two groups receiving the combination. Not until Day 10 does it appear that data for all three groups are again
equivalent. Just how tripelennamine interferes with tolerance develop-
opment, or enhances analgesia in rats already tolerant to pentazocine, is not addressed by these data. It is clear, however, that the former effect is not permanent but is itself subject to tolerance.
CHAPTER IV

EXPERIMENT III

One potential problem with interpretation of the preceding two experiments involves the validity of the hot plate test as a measure of analgesia. The paw lick, though a common measure of analgesia (see Fraser & Harris, 1967, for a review), is a complex motor movement and several variables may affect an organism's propensity to emit this response. For example, reduced activity due to ataxia or sedation could increase paw lick latencies. Babbini, Gaiardi, and Bartoletti (1981) have reported that pentazocine (30 mg/kg) suppresses motility in drug-naive rats during the first post-injection hour, while Bhargava (1981) reported increased ataxia due to the combined effects of pentazocine and tripelennamine in mice already addicted to morphine. Thus it is possible that the apparent analgesia evidenced in Experiments 1 and 2 is at least in part the result of gross motor deficits. Such a nonspecific drug effect is certainly less interesting than a specific analgesic action.

Experiment 3 attempted to determine the contribution of gross motor incapacities to the apparent analgesia evident in Experiments 1 and 2. In this study, an "open field" test was used to quantify the effects of pentazocine and tripelennamine on locomotion in the absence of exogenous aversive stimulation.
Method

Subjects

One hundred sixty adult male CF-1 mice, bred in the Psychology Department colony at Western Michigan University, served as subjects. Subjects were housed in large cages, with 20-30 mice per cage, and with free access to food and water. The colony room was maintained at 24° centigrade under constant illumination.

Apparatus

The open field was made of opaque plastic with a floor area of 60 cm by 45 cm. Plastic walls (32 cm high) entirely enclosed the field area. The floor was divided, by white lines, into a grid consisting of 30 squares. Each square was 9.4 cm on a side.

Electromechanical equipment was used to time observation periods and record data.

Drugs

Each group of subjects received either saline (0.9%), tripelennamine (5.0, 10.0, or 20.0 mg/kg), pentazocine (5.0, 10.0, or 20.0 mg/kg), or one of nine possible combinations of these drugs and doses. All injections were intraperitoneal. Injection volumes were held constant at 10.0 ml/kg by adjusting the concentrations with isotonic saline solution.

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Procedure

On the day of testing, one-half of a group was injected with the appropriate drug(s) and placed in a holding cage. Twenty minutes later, the second half of the group was injected. This staggered injection procedure insured that all subjects were tested at approximately the same post-injection times.

Thirty minutes after injection, single subjects were removed from the holding cage and placed in the center of the open field. For the next three minutes one or two observers, blind in regard to the experimental conditions, recorded the number of squares the subject entered. At the end of the 3-minute period the subject was removed, the floor cleaned of feces, and another subject tested. This procedure was repeated until all mice were tested.

On 9 of the 16 test days, two observers were used. Interobserver agreement was calculated by correlating the scores of the two observers on each of these days. Pearson product-moment correlations ranged from $r = .97$ to $r = .99$, indicating a high degree of interobserver agreement. One observer was always the primary data collector and her scoring was used as the dependent measure.

Results

Table 2 provides a summary of the results for all 16 groups tested on the open field. One-way analysis of variance produced an overall significant F-value among all groups [$F = 2.57(df = 15, 144)$, $p < .01$]. Under saline control conditions, mice entered an average of 137 squares during the 3-minute observation period. Mean squares
### TABLE 2

Summary of Results from the Open Field Test Under Saline, Pentazocine, Tripelennamine, and All Combinations of the Two Drugs

<table>
<thead>
<tr>
<th></th>
<th>Mean Squares Entered (SEM)</th>
<th>Percent Saline Control</th>
<th>t_{LSD} (df = 144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9% saline</td>
<td>137 (13.4)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5.0 mg/kg tripelennamine</td>
<td>132 (15.9)</td>
<td>95.7%</td>
<td>not significant</td>
</tr>
<tr>
<td>10.0 mg/kg tripelennamine</td>
<td>143 (11.4)</td>
<td>103.8%</td>
<td>not significant</td>
</tr>
<tr>
<td>20.0 mg/kg tripelennamine</td>
<td>142 (20.3)</td>
<td>103.3%</td>
<td>not significant</td>
</tr>
<tr>
<td>5.0 mg/kg pentazocine</td>
<td>127 (13.9)</td>
<td>91.3%</td>
<td>not significant</td>
</tr>
<tr>
<td>10.0 mg/kg pentazocine</td>
<td>154 (10.5)</td>
<td>111.9%</td>
<td>not significant</td>
</tr>
<tr>
<td>20.0 mg/kg pentazocine</td>
<td>91 (11.8)</td>
<td>65.9%</td>
<td>t_{LSD} = 1.99 p &lt; .05</td>
</tr>
<tr>
<td>5.0 mg/kg pentazocine +</td>
<td>128 (20.3)</td>
<td>93.3%</td>
<td>not significant</td>
</tr>
<tr>
<td>5.0 mg/kg tripelennamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.0 mg/kg pentazocine +</td>
<td>96 (16.8)</td>
<td>70.2%</td>
<td>not significant</td>
</tr>
<tr>
<td>10.0 mg/kg tripelennamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.0 mg/kg pentazocine +</td>
<td>115 (15.4)</td>
<td>83.3%</td>
<td>not significant</td>
</tr>
<tr>
<td>20.0 mg/kg tripelennamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.0 mg/kg pentazocine +</td>
<td>103 (16.4)</td>
<td>75.1%</td>
<td>not significant</td>
</tr>
<tr>
<td>5.0 mg/kg tripelennamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.0 mg/kg pentazocine +</td>
<td>135 (18.4)</td>
<td>98.4%</td>
<td>not significant</td>
</tr>
<tr>
<td>10.0 mg/kg tripelennamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10.0 mg/kg pentazocine +</td>
<td>76 (13.9)</td>
<td>55.1%</td>
<td>t_{LSD} = 2.63 p &lt; .01</td>
</tr>
<tr>
<td>20.0 mg/kg tripelennamine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Mean Squares Entered (SEM)</th>
<th>Percent Saline Control</th>
<th>( t_{LSD} ) (df = 144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.0 mg/kg pentazocine + 5.0 mg/kg tripelennamine</td>
<td>124 (25.8)</td>
<td>90.0% not significant</td>
</tr>
<tr>
<td>20.0 mg/kg pentazocine + 10.0 mg/kg tripelennamine</td>
<td>72 (17.7)</td>
<td>52.6% ( t_{LSD} = 3.36 ) ( p &lt; .01 )</td>
</tr>
<tr>
<td>20.0 mg/kg pentazocine + 20.0 mg/kg tripelennamine</td>
<td>78 (14.5)</td>
<td>57.3% ( t_{LSD} = 2.78 ) ( p &lt; .05 )</td>
</tr>
</tbody>
</table>

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entered, by groups that received 5, 10, and 20 mg/kg tripelennamine, were 132, 143, and 142, respectively. None of these means were significantly different from the saline control mean. Under pentazocine, means were 127, 154, and 91 squares entered at respective doses of 5, 10, and 20 mg/kg. Planned comparison tests revealed that only the mean at the highest dose of pentazocine was significantly different from the saline control mean \( t_{LSD} = 1.99 (144), p < .05 \).

Pentazocine at 5 mg/kg combined with 5, 10, and 20 mg/kg tripelennamine was associated with respective means of 128, 96, and 115 squares entered. None of these means were significantly different from the saline control mean, nor were they significantly different from the pentazocine-alone mean.

At 10 mg/kg pentazocine, in combination with 5, 10, and 20 mg/kg tripelennamine, mean number of squares entered was 103, 135, and 76, respectively. This final mean value was significantly different from the saline control mean \( t_{LSD} = 2.63 (144), p < .01 \). Interestingly, this dose of pentazocine increased the number of squares entered when it was given alone. However, when combined with 5 and 20 mg/kg of tripelennamine, the mean number of squares was substantially reduced. In fact, these two dose combinations proved significantly different from the 10 mg/kg pentazocine alone mean of 154 \( t_{LSD} = 2.18 (144), p < .05 \) and \( t_{LSD} = 3.36 (144), p < .01 \).

Finally, 20 mg/kg pentazocine combined with 5, 10, and 20 mg/kg tripelennamine was associated with respective means of 124, 72, and 78 squares entered. Both of the latter means were significantly different from the saline control mean, with respective planned
None of the combinations of tripelennamine and 20 mg/kg pentazocine proved significantly different from the pentazocine alone mean of 90 squares entered.

Figure 3 presents the results of the combination of tripelennamine and pentazocine as a percentage of the saline control mean. Numerical percentages are given in Table 2. Again, mean entry values significantly different from saline control level (100%) were found at the highest dose of pentazocine (20 mg/kg) combined with the two highest doses of tripelennamine (10 and 20 mg/kg) and the medium dose of pentazocine (10 mg/kg) combined with the highest dose of tripelennamine (20 mg/kg). It may be seen from Figure 3 that no combination doses increased the number of squares entered over saline levels. When compared with pentazocine alone levels, tripelennamine further reduced the mean number of squares entered under 7 out of 9 combination doses. However, the highest dose of pentazocine (20 mg/kg) combined with the lowest dose of tripelennamine (5 mg/kg) did substantially increase locomotion over the pentazocine alone mean.

Discussion

Pentazocine has previously been reported to both increase (Holtzman & Jewett, 1972) and decrease (Babbini et al., 1981) mobility in rodents. In the present study, pentazocine produced a decrease at the highest dose but had no effect on locomotion at lower doses. In general, when the drugs were combined, tripelennamine enhanced the locomotion decreasing effect of pentazocine. Only when the highest pentazocine dose was combined with the lowest tripelennamine dose did the antihistamine appear to reverse the
Figure 3. Number of squares entered under combinations of pentazocine and tripeleennamine, expressed as a percentage of the saline control mean.
locomotion decrement produced by pentazocine. As in Experiment 1, the combination of pentazocine and tripelennamine produced a significant effect at doses where neither drug was effective alone.

In general, the results of the open field test paralleled those of Experiment 1. This suggests that the decrease in locomotion under combinations of tripelennamine and pentazocine could indeed have contributed to the increased paw lick latencies found in the first study. However, even at the highest combination doses, the mice showed considerable mobility in the absence of programmed aversive stimulation. Thus, these motor deficits may well have been minimally disruptive. In addition, the results of the present study may only be relevant to a subject's first exposure to the combination and are not necessarily applicable to the effect of tripelennamine in subjects already tolerant to pentazocine.

The proportion of tripelennamine to pentazocine that is used in a preparation has been reported to be a major factor in the desirability of this combination among drug abusers (Poklis & Whyatt, 1980). The dose proportion also appears to be crucial to predicting the combination's effect on locomotion. None of the combinations of tripelennamine with a given dose of pentazocine showed a monotonic dose-effect relationship. Even the direction of tripelennamine's effect, whether enhancement or reduction of mobility already reduced by pentazocine, may not easily be predicted from the data in Table 2. Tripelennamine and pentazocine combinations produced significant differences over the pentazocine-alone mean only at 10 mg/kg pentazocine. At both the higher and lower doses of pentazocine, tripelennamine did not significantly change the locomotion decrement produced by pentazocine alone.
CHAPTER V

GENERAL DISCUSSION

Dramatic increases in the abuse of pentazocine in combination with tripelennamine have been well documented (Lahmeyer & Steingold, 1980; Poklis & Whyatt, 1980; Showalter, 1980; Wadley & Stillie, 1980). This abuse pattern is somewhat surprising since neither drug has much abuse potential when used alone (Kelly, 1977; Showalter, 1980). In interviews with drug abusers, Lahmeyer and Steingold (1980) found that many addicts turned to this drug combination to compensate for poor quality heroin. Other addicts said that cost and consistency were major advantages to the use of T's and blues. Those with whom the drug combination was popular reported that it is an effective substitute for heroin and many addicts actually prefer the combination (Wadley & Stillie, 1980).

Bhargava (1981) offered the only empirically based rationale for the popularity of T's and blues. He found that both drugs, when given alone, actually induced narcotic abstinence in mice. The abstinence was qualitatively similar to that produced by the narcotic antagonist naloxone. The two drugs in combination enhanced some aspects of the abstinence syndrome (ataxia, loss of coordination, falls), but other abstinence measures were reduced (stereotyped jumping). Bhargava concluded that one possible explanation for the use of T's and blues is their ability to inhibit some of the centrally mediated responses precipitated by narcotic withdrawal.
The enhanced analgesia produced by adding tripelemamine to pentazocine in already tolerant subjects in Experiment 1, suggests a different rationale for the popularity of T's and blues. This study found that the drug combination: (1) produced analgesia at doses where neither drug was analgesic alone, and (2) reestablished analgesic levels of response in subjects tolerant to pentazocine. This enhancement of one of pentazocine's major narcotic properties implies that perhaps other of the drug's narcotic properties, including euphoria, may also be enhanced by tripelemamine. Experiment 2 supported the findings of the first experiment by demonstrating that tripelemamine significantly slowed the development of tolerance to the analgesic properties of pentazocine.

Just what mechanism might be responsible for these effects is unclear. Other authors have reported potent interactions between narcotics and antihistamines. Waller et al. (1980) reported that the lethal dose of pentazocine could be potentiated ($LD_{50}$ lowered) by tripelemamine and vice versa. Williams, Maickel, and Spratto (1978) reported that, in morphine-dependent rodents, antihistamines were more toxic than in morphine-naive animals. The authors of both of these studies emphasized the central nervous system stimulating properties of antihistamines in an attempt to account for their findings.

One explanation that would account for the data presented in Experiments 1 and 2 involves pentazocine's mixed agonist-antagonist nature. If tripelemamine blocked or interfered with the antagonistic properties of pentazocine, then one would expect the resultant effects to be similar to those of a higher dose of pentazocine. Such
effects were seen in the first two experiments. However, no simple opiate receptor model can easily accommodate such a direct antihis­tamine interaction.

Decreased motility, as seen in Experiment 3, may have confounded the increased paw lick latencies of Experiment 1. However, such locomotion deficits do not easily account for the delayed tolerance demonstrated in Experiment 2 when tripelennamine and pentazocine were given in combination. In addition, the aversive stimulus of the hot plate would be expected to somewhat counteract any sedating effects. Holtzman (1974) reported that, under a continuous avoidance schedule where shock was the aversive stimulus, pentazocine actually increased responding at doses comparable to those used in the present study. Another analgesic test that does not depend so heavily on gross motor function (e.g., tail-flick) might determine the generality of the results obtained on the hot plate.

Results of the present study suggest three potential lines of laboratory research. In one, the similarity of the drug combination to pure narcotics, such as morphine or heroin, would be studied using procedures previously applied to the investigation of the discriminative stimulus properties of drugs. In such a procedure a subject would be trained to make one response after injection of a drug, for example morphine, and another response after saline injections. Once this behavior is well established, periodic test doses of tripelennamine, pentazocine, and their combination, would be administered. Proportions of morphine-appropriate responses under the various test doses would reveal tripelennamine's ability to make pentazocine more
morphine-like and identify the dose proportions that most closely produce morphine-like responses.

A second interesting line of research would involve testing the hypothesis that central nervous system stimulation, due to tripelennamine's ability to block reuptake of norepinephrine, is responsible for the potent interactive effects of the combination. Central nervous system stimulation may be blocked by pharmacological means (e.g., anesthetics), and the effects of tripelennamine and pentazocine combinations in the presence of such a blockade could be compared to their effects in its absence. The contribution of central nervous arousal to the action of the drugs could thus be assessed.

Finally, self-administration procedures could be used to determine the most reinforcing ratio of pentazocine to tripelennamine. This procedure could compare the reinforcing efficacy of various tripelennamine plus pentazocine combinations with that of morphine or heroin. Such information may provide a further understanding of the factors responsible for the dramatic increase in the abuse of tripelennamine and pentazocine combinations. An understanding of this abuse pattern may help predict other drug combinations that have a high abuse potential when taken together but appear relatively safe alone.


