Pharmacology Biochemistry & Behavior, Vol. 19, pp. 911–915, 1983.

Effects of Pentazocine and Tripelennamine on Analgesia[1]

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Received 22 March 1983

CLEARY, J., S. WALLACE, D. GROSSETT, M. PICKER AND A. POLING. *Effects of pentazocine and tripelennamine on analgesia.* PHARMACOL BIOCHEM BEHAV **19**(6) 911–915, 1983.—The analgesic effects of pentazocine and tripelennamine, alone and in combination, were assessed in rats with a hot plate apparatus. In Experiment 1, the combination of tripelennamine with chronic pentazocine produced 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. These data may contribute to a rationale for the current popularity of combined pentazocine and tripelennamine abuse.

Pentazocine Tripelennamine Analgesia Drug Interaction Rats

EXPERIMENT 1

Abuse of the analgesic pentazocine in combination with the antihistamine tripelennamine has received increasing attention. 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. This mixture has been used by addicts as a substitute for heroin, although some addicts now apparently prefer the pentazocine-tripelennamine combination to street quality narcotics [12].

Pentazocine is an analgesic of the benzomorphan series with mixed narcotic agonist-antagonist properties. Low doses produce heroin-like effects while high doses are psychotomimetic [6]. These latter properties have apparently prevented its widespread use by drug abusers (see [2] for a review of early pentazocine use). Tripelennamine is a common and effective antihistamine of the ethylenediamine class. It is a primary competitive antagonist of histamine at H_1 receptor sites. Tripelennamine may produce both central nervous system sedation (high doses) or excitation (low-moderate doses). Suspected central nervous system effects involve cholinergic blocking, gamma aminobutyric acid blocking [3], and potentiation of the effects of norepinephrine [5,8]. Abuse of tripelennamine, alone or in polydrug combinations, has been relatively minor until its recent combination with pentazocine.

Recent studies investigating the effects of pentazocine-tripelennamine combinations have provided evidence of a potent interaction. Bhargava [1] found the combination blocked some symptoms of narcotic abstinence in mice, while other reports showed tripelennamine increased the lethality of pentazocine in this species [10,13]. Shannon and Su [11] demonstrated that tripelennamine may increase pentazocine's ability to produce morphine-appropriate responding in a 2 lever morphine-saline discrimination. The primary purpose of the present studies was to determine how the analgesic properties of pentazocine were affected by the addition of tripelennamine.

METHOD

Subjects

Thirty adult male rats of the Sprague-Dawley strain, from 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 (43.2×25.4×17.8 cm), five per cage, with unlimited access to food and water. The colony room was constantly illuminated and maintained at 23–25° centigrade.

Apparatus

Analgesic tests were performed on a heated plate (Chicago Surgical and 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° (±1°) centigrade throughout the experiment.

[1]The reported studies were supported by a Faculty Research Grant and Fellowship awarded to Alan Poling by Western Michigan University.

Procedure

Analgesic testing 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 [14]. The latency from contact with the plate until the first hind paw lick was recorded by the experimenter with the aid of an electronic timer. 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 its paw within 30 seconds it 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 response latencies were stable, a dose-effect curve was obtained for three doses of tripelennamine (0.5, 5.0, and 10.0 mg/kg). Tripelennamine doses were individually randomized and given to all animals in all groups with three control sessions between each tripelennamine dose. Following tripelennamine injections, 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 was continued for seven days, at the end of which mean paw lick latencies returned to predrug control levels. At this time, combinations of tripelennamine and the maintenance dose of pentazocine were administered in a random order with three sessions of pentazocine alone interposed between each combination injection. Animals in each group received 0.5, 5.0, and 10.0 mg/kg doses of tripelennamine, in combination with the maintenance dose of pentazocine, on a single occasion.

Throughout the study, all injections were given intraperitoneally (IP) at a volume of 1.0 ml/kg. Doses of tripelennamine (Sigma, St. Louis, MO) refer to the total salt, while doses of pentazocine (purchased as Talwin from Winthrop Laboratories, New York, NY) refer to the total base. Both drugs were mixed with isotonic saline solution so as to obtain the proper injection volume.

RESULTS

Combined mean paw lick latencies for all subjects were 5.7, 7.8, and 5.9 seconds at respective tripelennamine doses of 0.5, 5.0, and 10.0 mg/kg. 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 the mean group latency significantly different from the saline control latency of 5.2 seconds, $t_{LSD}(45)=4.85$, $p<0.001$. While systematic data were not collected on pentazocine's effect on gross locomotion, animals did not appear to be impaired during the hot plate test.

Pentazocine was administered 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 (each day's mean was within 10% of the 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 with respective control (saline) mean latencies of 4.8, 4.9, and 5.2 seconds. Thus paw lick latencies under 30 mg/kg pentazocine had returned to control levels, demonstrating that tolerance had developed to the drug's analgesic effects.

Table 1 summarizes the results of combining tripelennamine with pentazocine for each of the three groups. These results are also presented in Fig. 1 as a percentage of the mean paw lick latency over the final 3 days of pentazocine alone. No combination of 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, $F(5,45)=4.44$, $p<0.01$. At this dose of pentazocine, only 10.0 mg/kg of tripelennamine produced a mean latency that was significantly different from the control latency, $t_{LSD}(45)=3.67$, $p<0.01$. Planned comparison tests yielded significance levels of $p<0.10$, for the 5.0 mg/kg tripelennamine combination with 30.0 mg/kg pentazocine and $p<0.001$ 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 ($p=0.066$) from pentazocine alone levels.

Figure 1 shows the effect of tripelennamine on paw lick latencies of subjects receiving daily pentazocine, and, in the case of the 30 mg/kg group, tolerant to its effects. No dose of tripelennamine appreciably 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 increased monotonically across doses of tripelennamine.

DISCUSSION

Tripelennamine is thought to produce weak central nervous system effects; sedation is the most common side effect of the drug at high doses [4]. Although such sedation may 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, significantly increased paw lick latencies at the highest dose tested, but did not produce analgesia at the two lower doses. Other authors (e.g., [9]) have reported analgesia at doses comparable to these lower doses, but they employed different, and perhaps more sensitive, procedures. Under a regimen of chronic daily pentazocine administration in the present study, tolerance quickly developed to its analgesic effects (30 mg/kg pentazocine group).

Interestingly, analgesia was also produced by the combination of the two drugs in subjects already tolerant to that dose of pentazocine alone (30 mg/kg group). In the group receiving 20 mg/kg pentazocine, 10 mg/kg tripelennamine produced significant analgesia under conditions where acute administration of either drug alone did not produce

TABLE 1

SUMMARY OF EFFECTS OF COMBINATIONS OF TRIPELENNAMINE AND PENTAZOCINE ON PAW LICK LATENCIES

	Mean Pentazocine Control Latency* (Seconds)	Mean Drug Cmbination Latency (Seconds)	Mean % Control	t_{LSD}
10 mg/kg pentazocine + 0.5 mg/kg tripelennamine	3.6 SEM=0.26	4.4	121%	
10 mg/kg pentazocine + 5 mg/kg tripelennamine	3.8 SEM=0.34	4.2	111%	
10 mg/kg pentazocine + 10 mg/kg tripelennamine	4.0 SEM=0.31	5.0	125%	
20 mg/kg pentazocine + 0.5 mg/kg tripelennamine	5.3 SEM=0.47	3.9	74%	
20 mg/kg pentazocine + 5 mg/kg tripelennamine	4.5 SEM=0.32	5.6	124%	
20 mg/kg pentazocine + 10 mg/kg tripelennamine	4.7 SEM=0.51	8.4	178%	$p=0.001$
30 mg/kg pentazocine + 0.5 mg/kg tripelennamine	6.1 SEM=0.78	6.3	103%	
30 mg/kg pentazocine + 5 mg/kg tripelennamine	7.2 SEM=0.93	11.4	159%	$p=0.066$
30 mg/kg pentazocine + 10 mg/kg tripelennamine	7.0 SEM=1.4	13.3	191%	$p=0.007$

*Control latencies represent the mean of three (pentazocine alone) sessions just prior to testing drug combinations.

analgesia. Furthermore, paw lick latencies were a direct monotonic function of the tripelennamine dose under 20 and 30 mg/kg of pentazocine maintenance. Thus, in pentazocine-tolerant rats and rats chronically exposed to a previously ineffective dose, the drug combination produced an analgesic response similar to that which would be expected with doses of pentazocine greater than the maintenance dose.

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 [7]. However, when mixed with tripelennamine, the combination blocks some narcotic abstinence symptoms [1]. This ability was put forward by Bhargava as a rationale for the current popularity of the mixture. That tripelennamine can enhance the analgesic properties of pentazocine adds a further dimension to this analysis.

EXPERIMENT 2

In this study, drug-naive subjects were exposed daily to 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 administration, the course of tolerance development to pentazocine alone and to pentazocine plus tripelennamine can be compared.

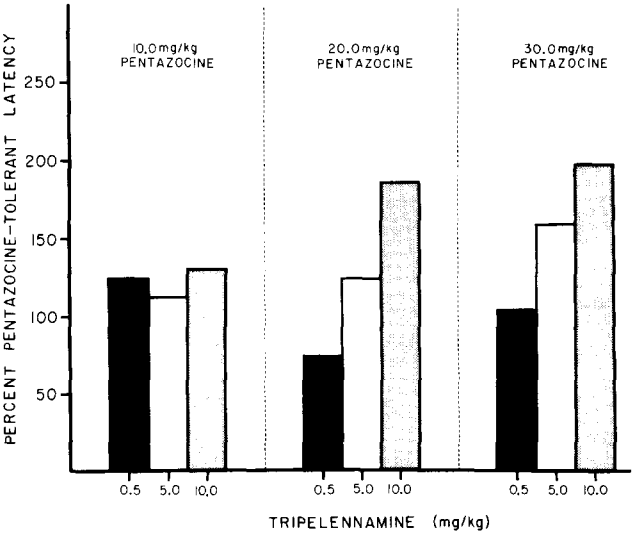

FIG. 1. Paw lick latencies under combinations of pentazocine and tripelennamine, expressed as a percentage of the mean of the final 3 days of pentazocine maintenance.

METHOD

Subjects

Thirty experimentally naive male rats of the Sprague-Dawley strain, obtained and maintained as in Experiment 1, served as subjects.

Apparatus

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

Procedure

Analgesic sessions were conducted and drugs prepared and injected as described 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 subject 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 administered. The other two groups were treated identically, but tripelennamine (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, 13.5, and 18.5 seconds for the groups receiving 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. These mean latencies did not differ significantly 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 of drug and control means indicated pentazocine, alone and with both doses of tripelennamine, was associated with latencies on the first drug day that were significantly different from control values. Planned comparison values were $t_{LSD}(45)=3.90$, $p<0.001$, for the group that received 30.0 mg/kg pentazocine; $t_{LSD}(45)=2.85$, $p<0.01$, for the group that received 30.0 mg/kg pentazocine plus 5.0 mg/kg tripelennamine; and $t_{LSD}(45)=4.92$, $p<0.001$, for the group that received 30.0 mg/kg pentazocine plus 10.0 mg/kg tripelennamine.

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 $p<0.05$. This indicates there was a significant difference between the adjusted means of the three groups. Since the groups began with essentially equivalent mean latencies, the adjusted means are the same as the simple means; they were 9.9, 10.7, 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.

Figure 2 shows the paw lick latencies for all three groups during the 18 days of drug administration. All groups developed tolerance to the effects of drug administrations, with latencies eventually returning to saline control levels. 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 near their previous saline levels.

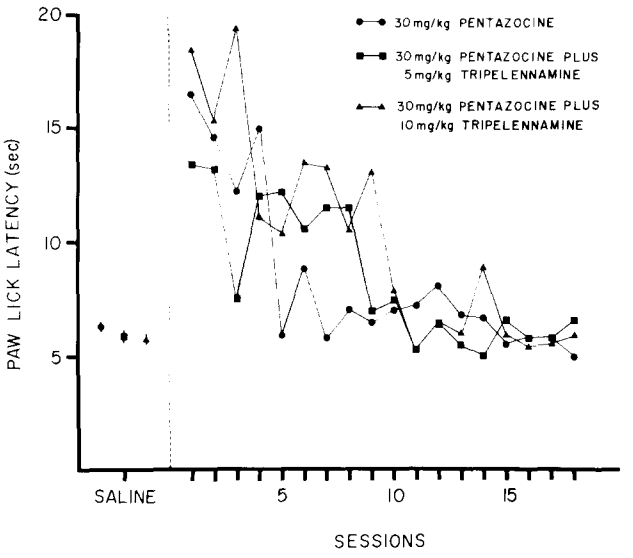

FIG. 2. Paw lick latencies under 30 mg/kg pentazocine, alone and in combination with 5 and 10 mg/kg tripelennamine, across 18 consecutive daily sessions. Means and standard errors (brackets) for the final 3 days under saline control conditions are presented in the left panel.

DISCUSSION

As 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 failure to enhance analgesia when initially combined with pentazocine, the antihistamine did affect the subsequent development of tolerance. On day 4, the mean paw lick latency for the pentazocine-alone group reached the saline level and was clearly lower than that of the two groups receiving the combination. Not until day 10 were the data for all three groups again equivalent. Just how tripelennamine interferes with tolerance development, or enhances analgesia in rats already tolerant to pentazocine, is not addressed by these data. It is clear, however, that the former effect is temporary and is subject to tolerance.

GENERAL DISCUSSION

Bhargava [1] found that both pentazocine and tripelennamine, when given alone, induced narcotic abstinence symptoms 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 suggested that one possible explanation for the combined use of pentazocine and tripelennamine is their ability to inhibit some of the centrally mediated responses precipitated by narcotic withdrawal.

The enhanced analgesia produced by adding tripelennamine to pentazocine in tolerant subjects in Experiment 1 suggests a different rationale for the popularity of this combination. The combination: (1) produced analgesia at drug doses which were incapable of producing analgesia when given alone, and (2) reestablished analgesia in subjects tolerant to pentazocine. Experiment 2 revealed tripelennamine significantly slowed the development of tolerance to the analgesic properties of pentazocine. Thus, tripelennamine appears to either enhance the narcotic agonist properties of pentazocine or reduce its antagonistic properties. The net effect is a more potent, or perhaps a less aversive, narcotic.

Since the animals in the present experiment were housed in group cages, it is possible that this aggregation enhanced the effects of the drugs. Indeed, Poling *et al.* found that group housing increased the lethality of pentazocine-tripelennamine combinations in mice [10]. In that study, however, the doses used were relatively high and the group size large. Whatever contribution aggregate housing may have made to results of the present studies, if any, is unknown.

ACKNOWLEDGEMENTS

The helpful comments of Dr. Fred Gault and Dr. Travis Thompson on an earlier version of this manuscript are gratefully acknowledged.

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