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BRIEF COMMUNICATION

Tripelennamine Fails to Enhance the Morphine-Like Stimulus Effects of Pentazocine[1]

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OLIVETO, A. H., B. L. SLIFER AND L. A. DYKSTRA. *Tripelennamine fails to enhance the morphine-like stimulus effects of pentazocine.* PHARMACOL BIOCHEM BEHAV **29**(2) 397–401, 1988.—The effects of tripelennamine alone and in combination with morphine or pentazocine were examined in pigeons trained to discriminate between morphine (5.6 mg/kg, IM) and saline under a fixed ratio 30 schedule of food presentation. Tripelennamine (0.3–10.0 mg/kg) produced only saline-appropriate responding and dose-related decreases in response rates. When administered alone, both morphine (0.3–10.0 mg/kg) and pentazocine (1.0–30.0 mg/kg) produced dose-related increases in morphine-appropriate responding and dose-related decreases in response rates. When tripelennamine (0.3, 1.0 mg/kg) was administered in combination with morphine, the morphine dose-effect curve was not altered. Additionally, when tripelennamine (0.3, 1.0, 1.7 mg/kg) was administered in combination with pentazocine, tripelennamine did not alter the extent to which pentazocine produced morphine-appropriate responding. There was some suggestion that tripelennamine attenuated the effects of high doses of pentazocine; however, this effect did not occur in all pigeons. These results suggest that tripelennamine does not enhance the morphine-like discriminative stimulus properties of pentazocine in the pigeon, as it does in the rat.

Drug discrimination Tripelennamine Pentazocine Pigeons Morphine

PENTAZOCINE, a mixed-action opioid agonist-antagonist [9], has a history of abuse in combination with the antihistamine tripelennamine (e.g., [4, 10, 11, 14]). This combination is known as "T's and Blues" [10, 11, 14]. Users of "T's and Blues" report that tripelennamine potentiates pentazocine's euphoric or morphine-like effects and reduces its dysphoric effects [12]. Investigations which examined the interaction of pentazocine and tripelennamine in laboratory animals generally have agreed with these subjective reports. For instance, tripelennamine potentiates the antinociceptive activity of pentazocine [2, 7, 8, 23, 25], and enhances pentazocine's effects on the threshold for self-stimulation behavior in rats [24]. To date, the mechanism by which tripelennamine potentiates the behavioral effects of pentazocine is unclear.

Inasmuch as the discriminative stimulus properties of drugs tend to correlate well with their subjective effects, a few researchers have employed drug discrimination procedures to determine whether tripelennamine might also alter the discriminative stimulus properties of pentazocine. In general, it has been shown that tripelennamine enhances the morphine-like discriminative stimulus effects of pentazocine in rats trained to discriminate between morphine and saline [19,20]. In contrast, we previously reported that tripelennamine did not alter the discriminative stimulus effects of pentazocine in pigeons trained to discriminate pentazocine from saline [22]. Thus, to investigate further the effects of tripelennamine on the discriminative stimulus properties of pentazocine, the present study was conducted to examine the discriminative stimulus properties of tripelennamine alone and in combination with morphine or pentazocine in pigeons trained to discriminate between morphine and saline.

METHOD

Animals

Three adult male White Carneaux pigeons were housed

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individually and maintained at approximately 80% free-feeding weights. Their diet consisted of mixed grain and was supplemented with oyster shells. Water was freely available in the home cage. All pigeons were drug naive at the beginning of the study.

Apparatus

Experimental sessions were conducted with a standard pigeon operant intelligence panel contained inside a ventilated, sound-attenuating chamber which has been described previously [1]. Continuous white noise was presented through a speaker located inside the enclosure. A recessed key, illuminated by a red light, was mounted 25 cm above a grid floor on each side of the front panel of the chamber. When a key was pecked, an audible click was produced and a response was recorded. A food hopper for the presentation of grain was accessible through an opening near the floor in the middle of the front panel. A white houselight was located in the upper right-hand corner of the rear chamber wall and was illuminated during the experimental session. During the 4-sec access to grain, key- and house-lights were extinguished and a white light bulb illuminated the grain. Programming and recording equipment were located in an adjacent room.

Training Procedure

Pigeons were trained to discriminate between saline and morphine under a fixed ratio (FR) 30 schedule of food presentation. On each training day, pigeons were administered either morphine or saline according to a double alternation schedule (DD, SS, D . . .). Following morphine administration, the completion of 30 responses on one of the two keys was followed by 4-sec access to grain; after saline administration, the completion of 30 responses on the other key was followed by 4-sec access to grain. If the pigeon switched keys before the ratio was completed, the ratio requirement was reset. Sessions were conducted 5 days a week and were 20 min in duration.

At the beginning of the study, 10.0 mg/kg of morphine was selected as the training dose. Initially, this dose greatly reduced rates of responding in 2 pigeons, and eliminated responding in a third. Tolerance to these rate-decreasing effects did not develop in all pigeons. Thus, after 30–40 training sessions at 10 mg/kg of morphine, the training dose was decreased to 5.6 mg/kg. Training continued until the following 2 criteria were met for 10 consecutive sessions: the number of responses made before the first reinforcer was not greater than 59, and the percentage of responses emitted on the appropriate key for the entire session was not less than 85%. During dose-effect curve determinations, training continued 3 times a week and test sessions were conducted on Tuesdays and Fridays, provided that the performance met criteria on the previous day. During test sessions, responses on either key were reinforced; otherwise, test sessions and training sessions were the same in all respects.

Dose-Effect Curve Determinations

Once a pigeon met the criteria, dose-effect curves for the following drugs were determined: morphine (0.3–10.0 mg/kg) alone, tripelennamine (0.3–10.0 mg/kg) alone, and morphine in combination with tripelennamine (0.3, 1.0 mg/kg). Subsequently, the dose-effects curves for morphine and tripelennamine alone were redetermined. Then the dose-response curves for pentazocine (1.0–30.0 mg/kg) alone and for pentazocine in combination with tripelennamine (0.3, 1.0, 1.7 mg/kg) were determined.

TABLE 1

THE EFFECTS OF TRIPELENNAMINE ON PERCENT MORPHINE-KEY RESPONDING (%MKR) AND ON PERCENT SALINE RESPONSE RATE (%SRR)

Dose (mg/kg)	%MKR*	%SRR*
S	0.0 (0.00)	107.3 (2.58)
0.3	0.0 (0.00)	109.8 (1.46)
1.0	0.0 (0.00)	87.9 (18.45)
3.0	0.0 (0.00)	38.9 (22.37)
10.0	0.0†	12.8 (12.75)

*Data represent the mean (±S.E.) performance of three pigeons, except at †, where data represent the performance of one pigeon.

Morphine sulfate (N.I.D.A., Rockville, MD) and tripelennamine hydrochloride (Geigy Pharmaceuticals, CIBA-GEIGY Corp., Summit, NJ) were dissolved in saline. Pentazocine base (Sterling-Winthrop Research Institute, Rensselaer, NY) was dissolved in a saline solution, to which a few drops of lactic acid were added. All doses of morphine and tripelennamine were expressed in terms of the salt. Doses of pentazocine were expressed in terms of the base. Injections were administered intramuscularly into the breast muscle in a 0.5 ml/kg volume 15 min before the experimental session. Within each series of drug tests, doses were administered in an ascending and descending order, with two determinations of each dose and of vehicle in every pigeon.

Data Analysis

The data are expressed as the percentage of overall responses emitted on the drug-appropriate key. Rates of responding are expressed as percent of saline response rate. Saline response rates represent the mean of rates of responding on saline training days during the 10-day period in which the training criteria were met.

RESULTS

All pigeons learned to discriminate between morphine (5.6 mg/kg) and saline. The number of sessions required for each pigeon to meet the training criteria ranged from 20–32. Mean saline control rates of responding in individual pigeons ranged from 88.13 to 132.09 responses per min, and generally were consistent throughout the study.

The effects of tripelennamine alone on morphine-appropriate responding and on rates of responding are shown in Table 1. It can be seen that all doses of tripelennamine produced saline-appropriate responding, while decreasing rates of responding in a dose-related manner. At the highest dose (10.0 mg/kg), tripelennamine eliminated responding in 2 of the 3 pigeons.

Figure 1 shows dose-effect curves for morphine alone and in combination with tripelennamine. It can be seen that morphine produced dose-related increases in responding on the morphine-appropriate key, as well as dose-related decreases in rates of responding. Complete morphine-appropriate responding was first produced by 5.6 mg/kg of morphine, a dose which decreased response rates to approximately 65% of control. When morphine was administered in combination with either 0.3 or 1.0 mg/kg of tripelennamine, rates of responding and percent morphine-appropriate responding did

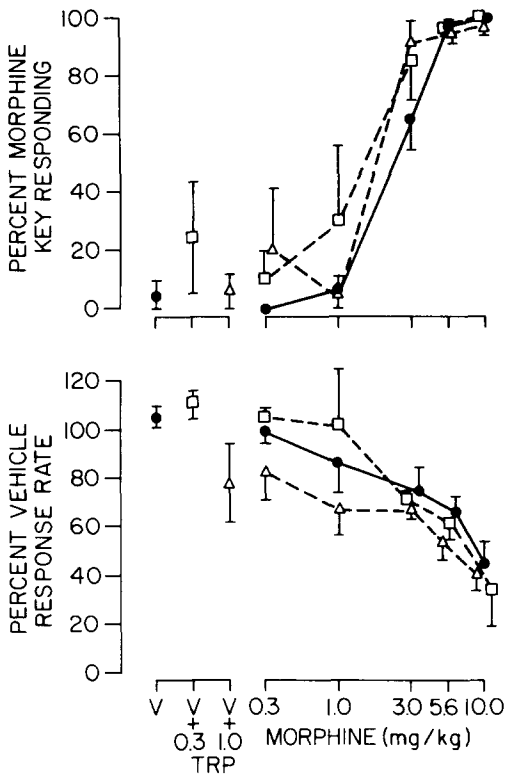

FIG. 1. Dose-effect determinations for morphine alone (●) and in combination with 0.3 (□) or 1.0 (△) mg/kg of tripelennamine in pigeons trained to discriminate between 5.6 mg/kg morphine and saline. The top panel shows the percent of morphine-appropriate responding over the entire session as a function of the dose of morphine. The bottom panel shows the effects of morphine alone and in combination with tripelennamine on rate of responding, expressed as the percent of responding during saline training sessions. Points above "V" represent percent morphine-appropriate responding (top panel) or percent saline rate of responding (bottom panel) during test sessions in which saline alone or in combination with tripelennamine was administered. Brackets represent standard errors. Each dose was determined twice in each pigeon; all points represent the group mean of individual averages.

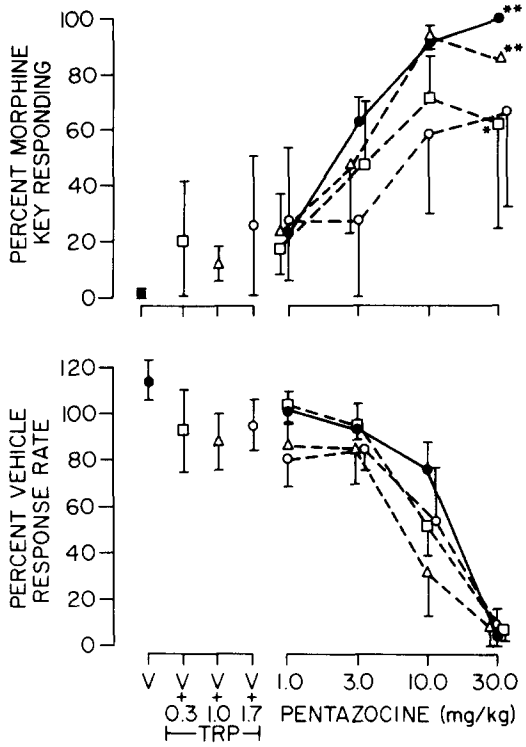

FIG. 2. Dose-effect determinations for pentazocine alone (●) and in combination with 0.3 (□), 1.0 (△) or 1.7 (○) mg/kg of tripelennamine in pigeons trained to discriminate between 5.6 mg/kg morphine and saline. The top panel shows the percent of morphine-appropriate responding over the entire session as a function of the dose of pentazocine. The bottom panel shows the effects of pentazocine alone and in combination with tripelennamine on rate of responding, expressed as the percent of responding during saline training sessions. Points above "V" represent percent morphine-appropriate responding (top panel) or percent saline rate of responding (bottom panel) during test sessions in which pentazocine vehicle alone or in combination with tripelennamine was administered. The number of asterisks (*) above each data point represents the number of pigeons whose rate of responding was too low (i.e., completed less than 1 ratio/session for both dose determinations) to include the data for morphine-appropriate responding. Other details are as described in Fig. 1.

not differ from those produced by morphine alone.

The dose-effect curves for morphine alone and tripelennamine alone were redetermined prior to the administration of pentazocine (data not shown). Each dose-effect curve was similar to the initial determination, in terms of both the degree of morphine-appropriate responding as well as the rate of responding produced at each dose.

The dose-response curves for pentazocine alone and in combination with tripelennamine (0.3, 1.0, 1.7 mg/kg) are shown in Fig. 2. It can be seen that pentazocine produced dose-related increases in responding on the morphine-appropriate key and dose-related decreases in response rates. Morphine-appropriate responding was produced at 10.0 mg/kg of pentazocine and response rates were decreased to 80% of control. When a fixed dose of tripelennamine was administered in combination with pentazocine, rates of responding did not differ from those produced by pentazocine alone. In addition, the percentage of responses on the morphine-appropriate key was not greater when tripelennamine was combined with pentazocine. Indeed, there was some suggestion that tripelennamine (0.3, 1.7 mg/kg) attenuated the morphine-like discriminative stimulus effects of higher doses of pentazocine. For instance, the highest dose (1.7 mg/kg) of tripelennamine examined in combination with 10.0 mg/kg of pentazocine decreased the percentage of morphine-appropriate responding from 92% to 58%; however, the attenuation of pentazocine's morphine-like effects did not occur in all pigeons.

DISCUSSION

In the present study, the discriminative stimulus effects of morphine did not generalize to the antihistamine tripelennamine, which is in agreement with previous reports about tripelennamine's discriminative stimulus properties in rats [19,20]. In contrast, the morphine discriminative stimulus generalized completely to pentazocine. This is also in keeping with a number of studies which have reported either complete [17,18] or partial generalization to pentazocine in morphine-trained rats, monkeys and pigeons [5, 13, 16, 19,

20]. The fact that pentazocine does not always produce complete generalization with morphine may be related to the dose of morphine employed as a discriminative stimulus. For example, Herling *et al.* [5] have found that morphine's discriminative stimulus properties do not generalize completely to pentazocine in pigeons trained to discriminate 10.0 mg/kg of morphine from saline; however, in the present study in which complete generalization occurred between morphine and pentazocine, pigeons were trained to discriminate 5.6 mg/kg morphine from saline. Indeed, other studies have reported that training dose is an important determinant of generalization between mu agonists and mixed-action opioid agonist/antagonists, such as cyclazocine [3,18] and nalbuphine [18]. Overall, such a variety of results serves to illustrate the complexity of pentazocine's discriminative stimulus properties.

In general, tripelennamine did not enhance morphine's discriminative stimulus properties as had been reported previously in rats [19]. Similarly, tripelennamine did not enhance the morphine-like discriminative stimulus properties of pentazocine. Indeed, there was some suggestion that tripelennamine attenuated the morphine-like discriminative stimulus properties of higher doses of pentazocine. This is in contrast to previous studies that have shown that pentazocine's morphine-like discriminative stimulus properties can be enhanced by tripelennamine [19,20]. The reason for this discrepancy is unclear. One possibility concerns differences in the degree to which pentazocine alone produced morphine-appropriate responding. For example, those studies which report an enhancement of pentazocine's morphine-like discriminative stimulus effects following tripelennamine also report incomplete generalization between pentazocine and morphine [19,20]. Thus, the degree to which pentazocine alone produces morphine-like responding may be an important determinant of the effects of pentazocine in combination with tripelennamine.

Species differences may also account for the fact that tripelennamine did not enhance pentazocine's discriminative stimulus properties in morphine-trained pigeons, whereas it has been reported to enhance the discriminative stimulus properties of pentazocine in morphine-trained rats [19,20]. In this context, it is interesting to note that the discriminative stimulus effects of other opioids also differ between pigeons and rats. For example, pigeons differ from rats in their ability to discriminate ethylketocyclazocine from morphine [6]. Moreover, when tripelennamine/pentazocine combinations have been examined in rats and pigeons trained to discriminate between a sigma/PCP-like agonist such as N-allylnormetazocine or phencyclidine and saline, tripelennamine has been shown to attenuate the N-allynormetazocine-like discriminative stimulus properties of pentazocine in rats [19], whereas it did not alter the discriminative stimulus effects of phencyclidine in phencyclidine-trained pigeons (unpublished observations) or pentazocine in pentazocine-trained pigeons [22]. As a whole, these previous results and those of the present study suggest that the mechanism of action of these compounds may be different in the pigeon than in the rat. At the very least, these results confirm the importance of cross-species comparisons when drawing conclusions about the discriminative stimulus properties of pharmacological compounds.

One point which has been reported in previous studies of pentazocine-tripelennamine interactions concerns the enhancement of pentazocine's effects following the administration of various dose combinations of tripelennamine and pentazocine. For instance, Shook and colleagues [20] report that combinations of pentazocine and tripelennamine in dose ratios of 10:1 and 3:1 potentiated pentazocine's effects on morphine-appropriate responding in morphine-trained rats. Moreover, in experienced drug users the pentazocine-tripelennamine dose ratio of 80:50 produced greater morphine-like effects than either drug alone or other dose ratio combinations (40:50, 40:100, 80:100) administered [12]. These dose ratios are similar to those preferred by street users [12, 15, 21]. In contrast, in the present study none of the pentazocine-tripelennamine dose ratios administered enhanced pentazocine's morphine-like discriminative stimulus properties, including ratios of 3:1 and 10:1. Thus, the lack of effect observed here cannot be explained by the use of inappropriate dose ratios. More research is needed to elucidate the conditions under which tripelennamine might enhance the morphine-like stimulus properties of pentazocine.

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REFERENCES

1. Carter, R. B. and J. D. Leander. Discriminative stimulus properties of naloxone. *Psychopharmacology (Berlin)* **77:** 305–308, 1982.
2. Cleary, J., S. Wallace, D. Grossett, M. Picker and A. Poling. Effects of pentazocine and tripelennamine on analgesia. *Pharmacol Biochem Behav* **19:** 911–915, 1983.
3. Colpaert, F. C., C. J. E. Niemegeers and P. A. J. Janssen. Factors regulating drug cue sensitivity: The effect of training dose in fentanyl-saline discrimination. *Psychopharmacology (Berlin)* **19:** 705–713, 1980.
4. Garey, R. E., G. C. Daul, M. S. Samuels and R. R. Egan. Medical and sociological aspects of T's and Blues abuse in New Orleans. *Am J Drug Alcohol Abuse* **9:** 171–182, 1982–83.
5. Herling, S., H. Coale, R. J. Valentino, D. W. Hein and J. H. Woods. Narcotic discrimination in pigeons. *J Pharmacol Exp Ther* **214:** 139–146, 1980.
6. Herling, S. and J. H. Woods. Mini-symposium IV. Discriminative stimulus effects of narcotics: Evidence for multiple receptor-mediated actions. *Life Sci* **28:** 1571–1584, 1981.
7. Hui, F. W., C.-L. J. Sun and J. P. Hanig. Opiate mixed agonist-antagonist interactions with histamine antagonists vs. morphine. *Neurobehav Toxicol Teratol* **7:** 443–447, 1985.
8. Hui, F. W., C. J. Sun, E. C. Tocus and J. P. Hanig. The effect of tripelennamine alone and in combination with opiates to produce antinociception in mice. *Life Sci* **32:** 1531–1538, 1983.
9. Jaffe, J. H. and W. R. Martin. Opioid analgesics and antagonists. In: *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, edited by A. G. Gilman, L. S. Goodman, T. W. Rall and F. Murad. New York: Macmillan Publishing Co., 1985.
10. Lahmeyer, H. W. and R. G. Steingold. Medical and psychiatric complications of pentazocine and tripelennamine abuse. *J Clin Psychiatry* **41:** 275–278, 1980.
11. Lahmeyer, H. W. and R. G. Steingold. Pentazocine and tripelennamine: A drug abuse epidemic? *Int J Addict* **15:** 1219–1232, 1980.
12. Lange, W. R. and D. R. Jasinski. The clinical pharmacology of pentazocine and tripelennamine (T's and Blues). *Adv Alcohol Subst Abuse* **5:** 71–83, 1986.

13. Overton, D. A. and S. K. Batta. Investigation of narcotics and antitussives using drug discrimination techniques. *J Pharmacol Exp Ther* **211:** 401–408, 1979.
14. Poklis, A. Pentazocine/tripelennamine (T's and Blues) abuse: A five year survey of St. Louis, Missouri. *Drug Alcohol Depend* **10:** 257–267, 1982.
15. Poklis, A. and P. L. Whyatt. Current trends in the abuse of pentazocine and tripelennamine: The metropolitan St. Louis experience. *J Forensic Sci* **25:** 72–78, 1980.
16. Schaefer, G. J. and S. G. Holtzman. Morphine-like stimulus effects in the monkey: Opioids with antagonist properties. *Pharmacol Biochem Behav* **14:** 241–245, 1981.
17. Shannon, H. E. and S. G. Holtzman. Evaluation of the discriminative effects of morphine in the rat. *J Pharmacol Exp Ther* **198:** 54–65, 1976.
18. Shannon, H. E. and S. G. Holtzman. Morphine training dose: A determinant of stimulus generalization to narcotic antagonists in the rat. *Psychopharmacology (Berlin)* **61:** 239–244, 1979.
19. Shannon, H. E. and T.-P. Su. Effects of the combination of tripelennamine and pentazocine at the behavioral and molecular levels. *Pharmacol Biochem Behav* **17:** 789–795, 1982.
20. Shook, J. E., M. J. Kallman, B. R. Martin and W. L. Dewey. Characterization of the interaction of pentazocine and tripelennamine: Drug discrimination and mu-receptor binding assay. *Pharmacol Biochem Behav* **21:** 877–881, 1984.
21. Showalter, C. V. T's and blues: Abuse of pentazocine and tripelennamine. *J Am Med Assoc* **244:** 1224–1225, 1980.
22. Slifer, B. L., L. A. Dykstra and A. H. Oliveto. Discriminative stimulus effects of pentazocine alone and in combination with tripelennamine in pentazocine-trained pigeons. *Fed Proc* **43:** 746, 1984.
23. Tagashira, E., J. F. Kachur, W. H. Carter and W. L. Dewey. Potentiation of narcotic-induced antinociception by tripelennamine in morphine-tolerant and drug-naive mice. *J Pharmacol Exp Ther* **229:** 214–217, 1984.
24. Unterwald, E. M. and C. Kornetsky. Effects of concomitant pentazocine and tripelennamine on brain-stimulation reward. *Pharmacol Biochem Behav* **21:** 961–964, 1984.
25. Yeh, S. Y. Potentiation of pentazocine antinociception by tripelennamine in the rat. *J Pharmacol Exp Ther* **235:** 683–689, 1985.