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Tripelennamine and Pentazocine Alone and in Combination: Effects on Interresponse-Time-Greater-Than-t Responding of Rats[1]

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GROSSETT, D., S. WALLACE, M. PICKER AND A. POLING. *Tripelennamine and pentazocine alone and in combination: Effects on interresponse-time-greater-than-t responding of rats.* PHARMACOL BIOCHEM BEHAV **20**(5) 697–700, 1984.—The effects of tripelennamine (3, 6, 12, 18, and 24 mg/kg) and pentazocine (5, 10, 20, 30, and 40 mg/kg), given alone and in selected combinations, were determined in rats performing under an interresponse-time-greater-than-15-sec schedule of food delivery. Each drug alone produced statistically insignificant increases in response rates and statistically significant decreases in reinforcement rates. Combinations produced effects identical in direction to, and significantly greater than, those predicted by a simple additive model.

Tripelennamine Pentazocine Drug combinations Operant behavior
Interresponse-time-greater-than-t schedule Rats

ILLICIT use of pentazocine in combination with tripelennamine has recently become widespread and has consequently evoked considerable attention (e.g., [2, 11, 16, 17, 22, 23]). The mixture, which is used by addicts as a heroin substitute, is commonly referred to as "T's and blues" [22].

Pentazocine is a benzomorphan derivative with both narcotic agonist and antagonist characteristics [7,12]. The drug is a potent analgesic and has known addictive potential [10]. Tripelennamine is an ethylenediamine antihistaminic which blocks H_1 receptors. Low to moderate doses produce central nervous system excitation; higher doses produce sedation. Tripelennamine alone has been reported not to have addictive potential [22].

There is emerging interest in the effects of pentazocine and tripelennamine in nonhumans. Recent investigations have demonstrated that the combination: (1) increases lethality in mice relative to either drug alone [19,24]; (2) has morphine-like discriminative properties [21]; and (3) blocks some narcotic abstinence symptoms in mice [1]. Tripelennamine also enhances analgesia in pentazocine-tolerant rats and delays the development of tolerance to the analgesic properties of pentazocine [3].

Nothing has yet been reported concerning the effects of tripelennamine and pentazocine combinations on schedule-controlled behavior, although studies of drug effects on operant performance are well accepted in behavioral pharmacology and have yielded a wealth of information concerning drug-behavior interactions (see [4, 13, 20]). In order to further profile the behavioral actions of tripelennamine and pentazocine in combination, the present study examined the effects of these drugs on the responding of rats maintained under an interresponse-time-greater-than-t (IRT>t) schedule of food delivery. Although the majority of studies of the effects of narcotic agonists and antagonists on schedule-controlled performance have employed fixed-ratio or fixed-interval schedules [6,20], the IRT>t schedule has previously been shown to provide a sensitive baseline for analyzing drug interactions [18]. Thus it was used in the present study.

METHOD

Subjects

Four experimentally naive adult male Sprague-Dawley rats, maintained at 80% of free-feeding weights, served as subjects. They were individually housed with unlimited access to water in a colony area with controlled temperature (23°C) and lighting (12-hr light/dark cycle).

Apparatus

Four plastic and aluminum operant conditioning chambers were used. Each chamber was equipped with two response levers and a feeder which delivered 45 mg Noyes food pellets (P. J. Noyes Co., Inc., Lancaster, NH) when

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desired. The right lever remained inoperative throughout the study. Constant ambient illumination was supplied during experimental sessions by a 7-W white houselight; an exhaust fan provided ventilation and masking noise. Programming of experimental events and recording of data were controlled by a PDP-8/A computer (Digital Equipment Co., Inc., Maynard, MA) equipped with interfacing and software (SUPERSKED) supplied by State Systems Inc. (Kalamazoo, MI).

Behavioral Procedure

The rats were first trained to lever press under a fixed-ratio 1 (FR 1) schedule, where a food pellet followed each lever press. After each rat responded consistently under the FR 1 schedule, it was exposed to an IRT>t schedule. Under the IRT>t schedule, a food pellet followed the first response emitted at least a specified number (t) of seconds after receipt of the preceding pellet; each response emitted before that time reset the interval. Rats were initially exposed to an IRT>1-sec schedule that was lengthened across 15 sessions to an IRT>15-sec. Here, for food to be delivered responses had to be separated in time by at least 15 sec.

The IRT>15-sec schedule was in effect throughout the balance of the study. Each rat was exposed to one 30-min session per day, 6 days per week. Number of responses emitted and number of reinforcers (food pellets) earned per session were recorded.

Pharmacological Procedure

The effects of pentazocine and tripelennamine were evaluated alone and in combination. Drugs were administered only when an individual rat's performance was stable across three consecutive control sessions, in one of which a 1 ml/kg injection of isotonic saline solution was given intraperitoneally (IP) 30 min prior to the experimental session. Responding was assumed to be stable when the mean rate of responding varied by less than 10% across the three sessions. Dose-response curves were determined for 5 doses of pentazocine alone (5, 10, 20, 30, and 40 mg/kg) and 5 doses of tripelennamine alone (3, 6, 12, 18, and 24 mg/kg). Each rat received each dose of pentazocine and tripelennamine on one occasion, in an irregular order. Following testing of the individual drugs, dose-response curves for the two drugs in combination were determined. The effects of 3 doses of pentazocine (5, 10, and 20 mg/kg) and 3 doses of tripelennamine (3, 6, and 12 mg/kg) were evaluated in all possible combinations; the effects of 30 mg/kg pentazocine plus 3 and 6 mg/kg tripelennamine were also determined. Higher combination doses were observed in pilot studies to occasionally produce seizures and death (cf., [19]) and therefore were not evaluated in the present study. Each rat received each of the 11 combined doses once, in an irregular order. Finally, as a test for tolerance or supersensitivity, dose-response curves were redetermined for 3 doses of pentazocine alone (5, 20, and 40 mg/kg) and for 3 doses of tripelennamine alone (3, 12, and 24 mg/kg).

All drug injections were given at a volume of 1 ml/kg. Doses of tripelennamine (Sigma, St. Louis, MO) refer to the total salt, 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 to obtain the proper injection volume. When given alone and in combination, pentazocine and tripelennamine were given IP 30 min prior to the experimental session. Thus, conditions of injection were identical during control, single drug, and multiple drug sessions.

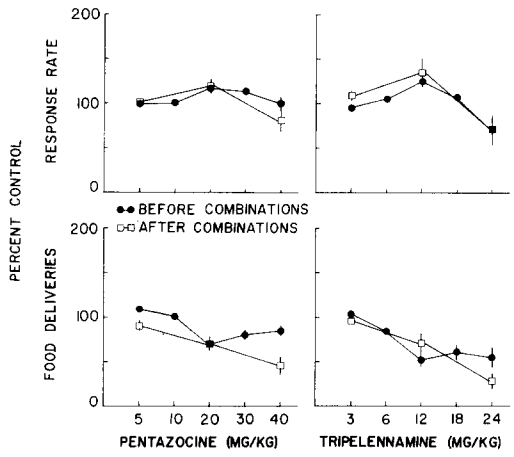

FIG. 1. Effects of pentazocine and tripelennamine alone on the mean group response and reinforcement (number of food pellets delivered per min) rates of rats responding under an IRT>15-sec schedule of food delivery. Response and reinforcement rates during sessions in which drug was given are expressed as a percentage of the rate obtained across the three control sessions preceding drug administration. Circles represent rates for drug administration before combinations were given and squares represent rates after combinations were given. Vertical lines indicate ±1 standard error (SE). The absence of such lines indicates a SE too small to appear on the figure (i.e., within the data point). Reading from left to right across the figure, mean control response rates (and SEs) were 4.1(0.8), 4.8(0.2), 4.4(0.5), 4.5(0.3), 4.3(0.2), 4.2(0.1), 4.8(0.2), 4.3(0.2), 4.5(0.5), and 4.4(0.3) responses per min, and mean control reinforcement rates (and SEs) were 2.0(0.1), 2.1(0.2), 2.2(0.1), 2.2(0.1), 2.2(0.1), 2.1(0.2), 1.8(0.2), 2.0(0.2), 2.0(0.2), and 2.0(0.2) food deliveries per min.

RESULTS

Across all control sessions (the three sessions immediately prior to each drug administration), the mean group response rate was 4.4 responses per min; mean rates during individual control sessions ranged from 3.5 to 5.7 responses per min. Control rates prior to each drug administration are presented in the figure legends.

Figure 1 depicts the effects of pentazocine and tripelennamine alone on group response and reinforcement (number of food pellets delivered per min) rates. In all figures, response and reinforcement rates during sessions in which drug was given are expressed as a percentage of the rate obtained across the three control sessions immediately preceding drug administration. Repeated measures analyses of variance [9] indicated that neither pentazocine ($F=1.7$, $p>0.05$) nor tripelennamine ($F=2.0$, $p>0.05$) alone significantly affected response rates relative to control values during pre-combination dose-response determinations, although both drugs were associated with slight increases in response rates. Across all doses, pentazocine ($F=3.7$, $p<0.01$) and tripelennamine ($F=3.8$, $p<0.01$) alone significantly lowered reinforcement rates relative to control values. The magnitude of this effect was generally dose-dependent for each drug. Planned comparisons tests (Fisher's protected least significant difference [t_{LSD}] tests, see [9]) were used to com-

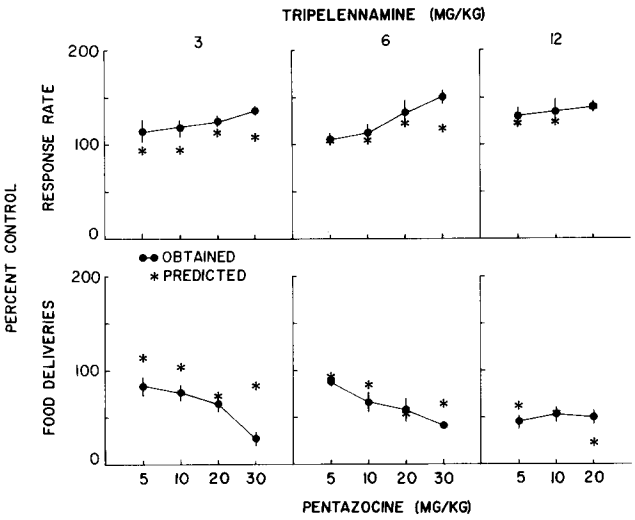

FIG. 2. Effects of pentazocine and tripelennamine combinations on the mean group response and reinforcement (number of food pellets delivered per min) rates of rats responding under an IRT>15-sec schedule of food delivery. Response and reinforcement rates during sessions in which drug was given are expressed as a percentage of the rate obtained across the three control sessions preceding drug administration. Vertical lines indicate ±1 standard error (SE). The absence of such lines indicates a SE too small to appear on the figure (i.e., within the data point). Asterisks represent values predicted by an additive model, where the effects of individual drugs are summated to predict their combined effects. Reading from left to right across the figure, mean control response rates (and SEs) were 4.3(0.3), 4.1(0.2), 4.6(0.4), 4.2(0.2), 4.4(0.3), 3.9(0.1), 4.3(0.1), 4.5(0.3), 4.3(0.2), 4.5(0.4), and 4.1(0.4) responses per min, and mean reinforcement rates (and SEs) were 2.4(0.1), 2.3(0.1), 2.3(0.1), 2.5(0.1), 2.4(0.1), 2.4(0.1), 2.5(0.1), 2.3(0.1), 2.4(0.1), 2.4(0.1), and 2.5(0.1) food deliveries per min.

pare response rates and reinforcement rates at each drug dose to control values. Results of these tests indicated that reinforcement rates were significantly ($p<0.05$) lowered at the 20 and 30 mg/kg doses of pentazocine, and at the 12, 18, and 24 mg/kg doses of tripelennamine. Post-combination dose-response determinations provided no evidence of tolerance or supersensitivity; post-combination dose-response curves closely approximately pre-combination curves.

Figure 2 shows the effects of pentazocine and tripelennamine in combination. All combined doses increased group response rates and reduced reinforcement rates relative to control values. Across all doses, these effects were statistically significant (repeated measures analysis of variance $F=2.3$, $p<0.01$ for response rate, $F=5.2$, $p<0.01$ for reinforcement rate). Planned comparisons tests (t_{LSD}) indicated that response rates were significantly ($p<0.05$) increased relative to control values at 5 combination doses. These were 5 mg/kg pentazocine plus 12 mg/kg tripelennamine, 20 mg/kg pentazocine plus 6 and 12 mg/kg tripelennamine, and 30 mg/kg pentazocine plus 3 and 6 mg/kg tripelennamine. Seven combination doses (5 mg/kg pentazocine plus 12 mg/kg tripelennamine, 10 mg/kg pentazocine plus 12 mg/kg tripelennamine, 20 mg/kg pentazocine plus 3, 6, and 12 mg/kg tripelennamine, and 30 mg/kg pentazocine plus 3 and 6 mg/kg tripelennamine) significantly reduced reinforcement rates relative to control values. The magnitude of the increases in response rates and decreases in reinforcement rates was generally dose-dependent.

The effects of pentazocine and tripelennamine combinations were similar to, although in most cases greater than, those predicted by a simple additive model. Effects predicted by arithmetic summation of the effects of individual drugs are indicated by asterisks in Fig. 2. In all instances, pentazocine plus tripelennamine produced larger increases in response rates than predicted by an additive model. A chi-square analysis [8] indicated that the effects of the two drugs on response rate were significantly greater ($p<0.01$) than predicted by simple additivity. Decreases in reinforcement rates were greater than predicted by simple additivity in 8 of 11 instances. A chi-square analysis indicated that the overall departure from additivity was statistically significant ($p<0.01$).

DISCUSSION

Previous studies have shown that under some conditions low doses of pentazocine increase low-rate operant responding, whereas high doses nonselectively suppress behavior [5, 14, 15]. To our knowledge, no reports have appeared concerning the effects of tripelennamine on schedule-controlled behavior. Neither pentazocine nor tripelennamine alone significantly affected response rates in the present study, although at certain doses each drug significantly decreased reinforcement rates relative to control values. When given together, the effects of the two drugs on the performance of rats exposed to an IRT>15-sec schedule of food delivery were supra-additive, i.e., identical in direction to, but significantly greater in magnitude than, those predicted on the basis of a simple arithmetic summation of the actions of the individual agents.

Pentazocine and tripelennamine together are used on the street as a substitute for heroin [22], thus there is considerable interest in the effects of the combination. Although the biochemical mechanism responsible for their interaction is unclear, previous investigations have shown that relatively high doses of pentazocine and tripelennamine produce strongly supra-additive effects in mouse assays of lethality [19,24]. At lower doses, tripelennamine enhances the morphine-like discriminative stimulus properties of pentazocine in rats tested under a two-response drug discrimination procedure [21]. Tripelennamine also delays the development of tolerance to the analygesic effects of pentazocine in rats tested in a hot-plate assay and increases analgesia in pentazocine-tolerant rats tested in this apparatus [3]. Thus the supra-additive effects evidenced in the present study are consistent with the results of earlier experiments in which dissimilar dependent measures were utilized.

REFERENCES

1. Bhargava, H. N. Mechanism of toxicity and rationale for use of the combination of pentazocine and pyribenzamine in morphine-dependent subjects. *Clin Toxic* **18:** 175–188, 1981.

2. Butch, A. J., R. A. Yokel, L. T. Sigell, I. B. Hanenson and E. D. Nelson. Abuse and pulmonary complications of injecting pentazocine and tripelennamine tablets. *Clin Toxic* **14:** 301–306, 1979.

3. Cleary, J., S. Wallace, D. Grossett, M. Picker and A. Poling. Effects of pentazocine and tripelennamine on analgesia. *Pharmacol Biochem Behav* **19:** 911–916, 1983.
4. Dews, P. B. and J. DeWeese. Schedules of reinforcement. In: *Handbook of Psychopharmacology*, vol 7, edited by L. L. Iversen, S. D. Iversen and S. H. Snyder. New York: Plenum Press, 1977, pp. 107–150.
5. Downs, D. A. and J. H. Woods. Morphine, pentazocine and naloxone effects on responding under a multiple schedule of reinforcement in rhesus monkeys and pigeons. *J Pharmacol Exp Ther* **196:** 298–306, 1976.
6. Goldberg, S. R., R. D. Spealman and H. E. Shannon. Psychotropic effects of opioids and opioid antagonists. In: *Handbook of Experimental Pharmacology*, vol 55, edited by F. Hoffmeister and G. Stille. New York: Springer-Verlag, 1982, pp. 269–304.
7. Harris, L. S. and A. K. Pierson. Some narcotic antagonists in the benzomorphan series. *J Pharmacol Exp Ther* **143:** 141–148, 1964.
8. Hopkins, K. D. and G. V. Glass. *Basic Statistics for the Behavioral Sciences*. Englewood Cliffs, NJ: Prentice-Hall, Inc., 1978.
9. Huitema, B. *The Analysis of Covariance and Alternatives*. New York: Wiley, 1980.
10. Jasinski, D. R., W. R. Martin and R. D. Hoeldtke. Effects of short- and long-term administration of pentazocine in man. *Clin Pharmacol Ther* **11:** 385–493, 1970.
11. Lahmeyer, H. W. and R. G. Steingold. Pentazocine and tripelennamine: A drug abuse epidemic. *Int J Addict* **15:** 1219–1232, 1980.
12. Martin, W. R. Opioid antagonists. *Pharmacol Rev* **19:** 463–521, 1967.
13. McKearney, J. W. and J. E. Barrett. Schedule-controlled behavior and the effects of drugs. In: *Contemporary Research in Behavioral Pharmacology*, edited by D. E. Blackman and D. J. Sanger. New York: Plenum Press, 1978, pp. 1–64.
14. McMillan, D. E. and L. S. Harris. Behavioral and morphine-antagonist effects of the optical isomers of pentazocine and cyclazocine. *J Pharmacol Exp Ther* **180:** 569–579, 1972.
15. McMillan, D. E. and W. H. Morse. Some effects of morphine and morphine antagonists on schedule-controlled behavior. *J Pharmacol Exp Ther* **157:** 175–184, 1967.
16. Poklis, A. "T's and blues." *J Am Med Assoc* **240:** 108, 1978.
17. 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.
18. Poling, A., J. Cleary, K. Jackson and S. Wallace. d-Amphetamine and phencyclidine alone and in combination: Effects on fixed-ratio and interresponse-time-greater-than-t responding of rats. *Pharmacol Biochem Behav* **15:** 357–361, 1981.
19. Poling, A., J. Kesselring, R. G. Sewell, Jr. and J. Cleary. Lethality of pentazocine and tripelennamine combinations in mice housed individually and in groups. *Pharmacol Biochem Behav* **18:** 103–105, 1983.
20. Seiden, L. S. and L. A. Dykstra. *Psychopharmacology: A Biochemical and Behavioral Approach*. New York: Van Nostrand Reinhold, 1977.
21. Shannon, H. E. and T. Su. Effects of the combination of tripelennamine and pentazocine at the behavioral and molecular levels. *Pharmacol Biochem Behav* **17:** 789–795, 1982.
22. Showalter, C. V. T's and blues: Abuse of pentazocine and tripelennamine. *J Am Med Assoc* **244:** 1224–1225, 1980.
23. Wadley, C. and G. D. Stillie. Pentazocine (Talwin®) and tripelennamine (Pyribenzamine®): A new drug abuse combination or just a revival. *Int J Addict* **15:** 1285–1290, 1980.
24. Waller, D. P., N. L. Katz and R. W. Morris. Potentiation of lethality in mice by combinations of pentazocine and tripelennamine. *Clin Toxicol* **16:** 17–23, 1980.