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Effects of Tripelennamine and Pentazocine Alone and in Combination on Schedule-Controlled Performance

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EFFECTS OF TRIPLENNAMINE AND PENTAZOCINE ALONE AND IN COMBINATION ON SCHEDULE-CONTROLLED PERFORMANCE

by

Deborah Lou Grossett

A Dissertation
Submitted to the
Faculty of The Graduate College
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EFFECTS OF TRIPLENNAMINE AND PENTAZOCINE ALONE AND IN COMBINATION ON SCHEDULE-CONTROLLED PERFORMANCE

Deborah Lou Grossett, Ph.D.
Western Michigan University, 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 fixed-ratio 30 and interresponse-time-greater-than-15-second schedules of food delivery. When given alone, tripelennamine and pentazocine produced statistically significant decreases in responding under the fixed-ratio 30 schedule, but did not significantly affect responding under the interresponse-time-greater-than-15-second schedule. Each drug alone significantly decreased the number of reinforcers (food pellets) earned relative to control values under both schedules. The effects of the two drugs in combination were supra-additive. That is, the effects of a given dose of tripelennamine and pentazocine together were identical in direction to, and significantly greater, than the arithmetic summation of the effects of the drugs given alone.
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This work is dedicated to my parents in thanks for their love, encouragement, and understanding.

Deborah Lou Grossett
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INTRODUCTION

An amazing variety of drugs and drug combinations are used illicitly. One rather surprising combination which has recently become popular among midwestern drug abusers is a mixture of tripelennamine and pentazocine. This mixture, used as a heroin substitute, is commonly referred to by the slang name of "T's and Blues", which comes from the trade name of pentazocine (Talwin) and the blue color of tripelennamine (trade name Pyribenzamine) tablets (Showalter, 1980). Although systematic studies of the combination of tripelennamine and pentazocine have only recently begun to appear, the pharmacology of tripelennamine and pentazocine alone, summarized below, are rather well known.

Bovet and Staub were the first investigators to report histamine-blocking activity; they did so in 1937 (Douglas, 1980). Unfortunately, the first few antihistamines developed were too toxic for clinical use. During World War II, the first two therapeutic antihistamines (N-benzyl-N', N'-dimethyl-N-phenylethlenediamine [trade name Antergan], and pyrilamine [trade name Neo-Antergan]) were introduced in France. Two more antihistamines, diphenhydramine (Loew, MacMillan, and Katser, 1946) and tripelennamine (Yonkman, Chess, Mathieson, and Hansen, 1946) were developed in the United States a few years later. Shortly after tripelennamine was introduced in 1946, it was reported to be useful in the treatment of morphine withdrawal (Kells, 1948).
It is speculated that histamine acts as a neurotransmitter in the brain, and it is clear that it is involved in regulating gastric secretion. At present, histamine is thought to act through two separate receptors termed $H_1$ and $H_2$. Tripelennamine is an ethylenediamine antihistaminic which blocks $H_1$ receptors. Drugs that block $H_1$ receptors inhibit the effects of histamine on smooth muscles and limit its ability to affect capillary permeability and the vascular tree, but inconsistently suppress histamine-induced secretions. Tripelennamine and other $H_1$ blockers are used in the treatment of allergies (e.g., pollinois and urticaria), motion sickness, and as a local anesthetic. Low to moderate doses of tripelennamine produce central nervous system excitation; higher doses produce sedation. When antihistamines are combined with alcohol, sedation increases; when combined with caffeine, sedation decreases. "How the various $H_1$-blocking drugs produce their depressant and stimulant effects is not known. Although histaminergic nerves may be present in the brain, there is no obvious correlation between the peripheral histamine-blocking ability of these drugs and their central effects" (Douglas, 1980, p. 625).

Tripelennamine is readily absorbed from the gastrointestinal tract. After 15 to 30 minutes following oral administration to humans, noticeable effects develop; they peak in one to two hours. On the average, these effects last for approximately four to six hours. Once absorbed, tripelennamine is distributed throughout the body. Within 24 hours the majority of tripelennamine is metabolized.
and inactivated via the liver; however, a small portion is excreted unchanged in urine (Douglas, 1980). Tripelennamine has anticholinergic properties and induces atropine-like effects, such as drowsiness, dry mouth, and blurred vision. When large doses are administered, seizures, hallucinations, urinary retention, and tachycardia are reported (Lahmeyer and Steingold, 1980). Common side effects of therapeutic doses of tripelennamine are somnolence and gastrointestinal problems (Douglas, 1980). Despite the wide safety margin of $H_1$-blocking drugs, they are frequently the cause of acute poisoning.

Tripelennamine alone has been reported not to have addictive potential; however, it is abused by "street users" and is referred to as "blue velvet" when combined with heroin, morphine, or paregoric (Wadley and Stillie, 1980). Widespread abuse of tripelennamine combined with pentazocine has created an epidemic-like pattern and has resulted in human fatalities (Bhargava, 1981).

Pentazocine was introduced in 1967 as an analgesic without abuse potential. It is a benzomorphan derivative with both opioid agonist and antagonist characteristics. As an opioid agonist, the effects of pentazocine include analgesia, sedation, and respiratory depression. With respect to analgesic effects in humans, pentazocine appears to be approximately 30% as potent as morphine. As an antagonist, high doses of pentazocine produce nalorphine-like dysphoric and psychotomimetic effects and also can induce withdrawal symptoms in morphine-dependent subjects (Bhargava, 1981).
Pentazocine is readily absorbed in the gastrointestinal tract and at intramuscular and subcutaneous sites. After an intramuscular injection, peak values are obtained within 15 to 60 minutes. The half-life of pentazocine is approximately two to three hours in humans. The majority of pentazocine is metabolized and inactivated in the liver; however, some is excreted unchanged in urine. Common side effects of pentazocine include nausea, vomiting, dizziness, sweating, and sedation. Large doses are associated with respiratory depression, increases in blood pressure, and tachycardia. Extensive use via injections can result in fibrosis of muscular and subcutaneous tissue (Jaffe and Martin, 1980). Tolerance has been reported to develop to pentazocine's analgesic effects.

Although pentazocine was initially marketed as "a nonaddicting drug that could be safely included in emergency medical kits in such accessible places as fallout shelters and lifeboats without danger of theft by drug addicts" (Chambers, Inciardi, and Stephens, 1971, p. 627), illicit use of pentazocine by physicians and others was soon reported (Chambers et al., 1971). Although early reports of the abuse of pentazocine were concerned with only that drug, subsequent articles emphasized that pentazocine was frequently combined with tripelennamine (Butch, Yokel, Sigell, Hanenson, and Nelson, 1979; Lahmeyer and Steingold, 1980; Poklis, 1978; Poklis and Whyatt, 1980; Showalter, 1980; Wadley and Stillie, 1980). This mixture is reported to produce heroin-like subjective effects, and is by virtue of lower cost and greater availability frequently used as a heroin substitute.
When self-administered together, pentazocine and tripelennamine are usually procured in 50-mg tablets. The user crushes the two tablets, dissolves them in water, drains the solution through cotton, and injects the mixture intravenously. The reported effect is an immediate "rush" similar to that associated with heroin (Showalter, 1980). There are no set rules concerning the pentazocine to tripelennamine tablet ratio: Generally the user varies the ratio until the desired effects are obtained. Several pentazocine to tripelennamine ratios have been used, including 1:1, 2:1, 3:1, and 8:3. The latter three appear to be the most popular as seizures occur more frequently when the pentazocine to tripelennamine ratio is 1:1. Although there is wide variation across users, usual doses vary from 200 - 600 mg pentazocine and 100 - 250 mg tripelennamine (Poklis and Whyatt, 1980).

The most commonly reported adverse reactions to the combination of pentazocine and tripelennamine are nausea, vomiting, and headache which are typical effects of large doses of pentazocine. Other undesired effects include convulsions, loss of consciousness, dysphoria, paranoia, disorientation, and loss of short-term memory (Poklis and Whyatt, 1980).

Intravenous injections of the combination have been associated with a burning sensation and irritation at the site of injection, abscesses, inflammation, and subcutaneous ulcers (Poklis and Whyatt,
Two major problems with administration are nonsterile injection techniques, which can lead to the development of local and systemic infections and the transmission of diseases (e.g., hepatitis, septicemia, endocarditis, and venereal disease) and intravenous injections of insoluble tablet particles which can result in thrombosis, pulmonary hypertension, and granulomas (Butch et al., 1979; Lahmeyer and Steingold, 1980; Poklis and Whyatt, 1980; Showalter, 1980).

With the exception of self-reports, nothing has appeared concerning the behavioral effects of pentazocine and tripelennamine in humans. However, a number of studies have examined the effects of the mixture in nonhumans. Recent investigations have demonstrated that the combination in nonhumans: 1) increases lethality in mice relative to either drug alone (Poling, Kesselring, Sewell, and Cleary, 1983; Waller, Katz, and Morris, 1980); 2) has morphine-like discriminative properties in rats (Shannon and Su, 1982); and 3) blocks some opiate abstinence symptoms in mice (Bhargava, 1981). Tripelennamine also enhances analgesia in pentazocine-tolerant rats and delays the development of tolerance to the analgesic effects of pentazocine (Cleary, Wallace, Grossett, Picker, and Poling, 1983).

The effects of pentazocine when given alone have been studied in nonhumans responding under schedules of operant reinforcement (Downs and Woods, 1976; McMillan and Harris, 1972; McMillan and Morse, 1967), but nothing has yet been reported concerning the
effects of tripelemamine and pentazocine combinations on schedule-controlled behavior. Studies of drug effects on operant performance are well accepted in behavior pharmacology and have yielded a wealth of information concerning drug-behavior interactions:

The relevance of schedules of reinforcement to behavioral research is inestimable. The use of schedules has also had substantial influence on the developing course of behavioral pharmacology. Traditional assumptions about the effects of drugs on behavior have been modified considerably, and entirely new viewpoints have emerged. Although the benefits from schedule concepts that have accrued to the field of behavioral pharmacology have been substantial, analysis of the effects of drugs on behavior likewise has had considerable impact on experimental psychology. Many cherished psychological concepts have been radically revised or discarded as a result of findings in behavioral pharmacology, and schedules of reinforcement have been of critical importance in this development. (McKearney and Barrett, 1978, p.3).

The present study evaluated how pentazocine and tripelemamine given alone and in combination influence responding of rats maintained at widely different rates under fixed-ratio and inter-response-time-greater-than-t (also referred to as differential-reinforcement-of-low-rates, or DRL) schedules of food delivery.
EXPERIMENT I

This experiment examined the effects of pentazocine and tripelennamine alone and in combination on the responding of rats maintained under an interresponse-time-greater-than-t (IRT>t) schedule of food delivery. The IRT>t schedule has previously been shown to provide a sensitive baseline for analyzing drug interactions (Poling, Cleary, Jackson, and Wallace, 1981). Thus it was used in the present experiment.

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 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., 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 seconds.

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., Poling, Kesselring, Sewell, and Cleary, 1983) 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.

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 (Huitema, 1980) 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 [Huitema, 1980]) were used to compare 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 approximated 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...
Figure 1. Effects of pentazocine and tripelennamine alone on the mean group response and reinforcement rates of rats responding under an IRT>15-sec schedule of food delivery.

Response and reinforcement (number of food pellets delivered per min) 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 they 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 minute.
Figure 1

Effects of pentazocine and tripelennamine alone on mean group response and reinforcement rates of rats responding under an IRT > 15-sec schedule of food delivery.
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 figure
2. In all instances, pentazocine plus tripelennamine produced larger
increases in response rates than predicted by an additive model. A
chi-square analysis (Hopkins and Glass, 1978) indicated that the
effects of the two drugs on response rate were significantly greater
(p<0.01) than predicted by simple additivity. Decreases in rein­
forcement rates were greater than predicted by simple additivity in
8 of 11 instances (5 mg/kg pentazocine plus 3, 6, and 12 mg/kg
tripelennamine, 10 mg/kg pentazocine plus 3 and 6 mg/kg
tripelennamine, 20 mg/kg pentazocine plus 3 mg/kg tripelennamine, and
30 mg/kg pentazocine plus 3 and 6 mg/kg tripelennamine). A
chi-square analysis indicated that the overall departure from
additivity was statistically significant (p<0.01).
Figure 2. Effects of pentazocine and tripelennamine combinations on the mean group response and reinforcement rates of rats responding under an IRT>15-sec schedule of food delivery.

Response and reinforcement (number of food pellets delivered per min) 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), and 2.5(0.1) food deliveries per minute.
Figure 2

Effects of pentazocine and tripelennamine combinations on the mean group response and reinforcement rates of rats responding under an IRT>15-sec schedule of food delivery.
Discussion

Previous studies have shown that under some conditions low doses of pentazocine increase low-rate operant responding, whereas high doses nonselectively suppress behavior (Downs and Woods, 1976; McMillan and Harris, 1972; McMillan and Morse, 1967). 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 (Showalter, 1980), 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 (Poling et al., 1983; Waller et al., 1980). At lower doses, tripelennamine enhances the morphine-like
discriminative stimulus properties of pentazocine in rats tested under a two-response drug discrimination procedure (Shannon and Su, 1982). Tripelennamine also delays the development of tolerance to the analgesic effects of pentazocine in rats tested in a hot-plate assay and increases analgesia in pentazocine-tolerant rats tested in this apparatus (Cleary et al., 1983). Thus the supra-additive effects evidenced in the present experiment are consistent with the results of earlier experiments in which dissimilar dependent measures were utilized.
EXPERIMENT II

In order to further profile the behavioral actions of tripeledennamine and pentazocine in combination, this experiment investigated the effects of these drugs on high-rate operant responding maintained under a fixed-ratio schedule of food delivery. The fixed-ratio schedule is widely used in studies evaluating the effects of opioid agonists and antagonists on schedule-controlled performance (Goldberg, Spealman, and Shannon, 1982; Seiden and Dykstra, 1977); thus it was used in the present experiment.

Method

Subjects

Four experimentally naive adult male Sprague-Dawley rats, maintained as in Experiment I, served as subjects.

Apparatus

Same as in Experiment I.

Behavioral Procedure

The rats were first trained to lever press under a fixed-ratio 1 (FR 1) schedule, in which a 45-mg Noyes (Lancaster, NH) food pellet followed each lever press. After each rat responded consistently under the FR 1, the ratio value was gradually lengthened across sessions until an FR 30 schedule was in effect. Each rat was exposed
to one 30-min session per day, 6 days per week. The number of responses emitted and food pellets delivered each session were recorded.

Pharmacological Procedures

All pharmacological procedures were identical to those described in Experiment I with two minor exceptions. First, fewer combined doses of pentazocine and tripelennamine were administered to all subjects. The effects of three doses of pentazocine (5, 10, and 20 mg/kg) and three doses of tripelennamine (3, 6, and 12 mg/kg) were evaluated in all possible combinations. Each rat received each of the nine combined doses once, in an irregular order. The doses of 30 mg/kg pentazocine plus 3 and 6 mg/kg tripelennamine were not administered to all subjects as they were observed to produce convulsions. Second, a test for tolerance was not completely determined. In the previous experiment, post-combination dose-response determinations provided no evidence of tolerance or supersensitivity.

Results

Figure 3 shows the effects of pentazocine and tripelennamine alone on group response rates. Repeated measures analyses of variance (Huitema, 1980) indicated that pentazocine ($F=6.8$, $p<0.01$) and tripelennamine ($F=16.1$, $p<0.01$) alone significantly lowered response rates relative to control values. The magnitude of this
effect was generally dose-dependent for each drug. Planned comparison tests ($t_{LSD}$) indicated that response rates were significantly ($p<0.05$) lowered at the 30 and 40 mg/kg doses of pentazocine, and at the 12, 18, and 24 mg/kg doses of tripelennamine.

Figure 4 depicts the effects of pentazocine and tripelennamine in combination on group response rates. Overall, combined doses significantly decreased group response rates relative to control values (repeated measures analysis of variance, $F=10.44$, $p<0.01$). Planned comparison tests ($t_{LSD}$) indicated that response rates were significantly ($p<0.05$) decreased relative to control values at seven combination doses. These were 5 mg/kg pentazocine plus 6 and 12 mg/kg tripelennamine, 10 mg/kg pentazocine plus 6 and 12 mg/kg tripelennamine, and 20 mg/kg pentazocine plus 3, 6, and 12 mg/kg tripelennamine.

The effects of pentazocine and tripelennamine combinations were similar to, although in 6 of 9 instances slightly 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 figure 4. A chi-square analysis (Hopkins and Glass, 1978) indicated that the effects of the two drugs on response rate were significantly greater ($p<0.01$) than predicted by simple additivity.
Figure 3. Effects of pentazocine and tripelennamine alone on mean group response rates of rats responding under an FR 30 schedule of food delivery.

Response rates during sessions in which a drug was given are expressed as percentages of the rates 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 in the figure (i.e., within the data point). Reading from left to right across the figure, mean control response rates (and SEs) were 136.5(25.7), 137.8(24.5), 132.8(25.4), 139.9(25.6), 138.8(24.4), 126.7(15.5), 124.1(12.0), 130.0(25.3), 126.9(22.3), and 132.7(17.3) responses per minute.
Figure 3

Effects of pentazocine and tripelennamine alone on mean group response rates of rats responding under an FR 30 schedule of food delivery.
Figure 4. Effects of pentazocine and tripelennamine combinations on mean group response rates of rats responding under an FR 30 schedule of food delivery.

Response rates during sessions in which a drug was given are expressed as percentages of the rates 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, in which 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) for each drug administration were 143.8(32.0), 144.1(35.2), 142.8(29.0), 129.0 (30.9), 153.5(27.4), 148.3(27.7), 143.9(30.2), 134.8(27.6), and 141.6(25.5) responses per minute.
Figure 4

Effects of pentazocine and tripelennamine combinations on mean group response rates of rats responding under an FR 30 schedule of food delivery.
Discussion

Previous investigations have shown that pentazocine decreases high-rate operant behavior (McMillan and Harris, 1972; McMillan and Morse, 1967). In the previous experiment, tripelennamine alone appeared to have little effect on low-rate operant responding. However, no reports of the effects of tripelennamine on high-rate operant responding have appeared. In the present experiment, both pentazocine and tripelennamine alone significantly decreased high-rate operant behavior maintained under a FR 30 schedule of food delivery.

When given together, the effects of the two drugs on high-rate operant behavior were identical in direction to, but occasionally greater in magnitude than, those predicted on the basis of a simple arithmetic summation of the actions of the individual agents. Previous studies have shown that pentazocine and tripelennamine in combination produce strongly supra-additive effects in a mouse assay of lethality (Poling et al., 1983; Waller et al., 1980). The previous experiment showed that the drugs in combination produced weak supra-additive increases in the low-rate operant responding of rats maintained under an interresponse-time-greater-than-t schedule of food delivery. This finding is similar to that of the present experiment, in which the effects of the two drugs in combination sometimes were slightly greater in magnitude than would be predicted.
by a simple additive model. When considered together, the results of the two experiments provide a clear demonstration that the behavioral effects of a drug combination are powerfully determined by control (i.e., nondrug) response rates, as are those of individual agents.
GENERAL DISCUSSION

In the present study, tripelennamine decreased high-rate operant behavior, but did not significantly affect low-rate performance. Although no previous reports of the effects of tripelennamine on schedule-controlled responding have appeared, Goldberg (1980) has shown that another H₁ blocker, diphenhydramine, reduced high-rate operant responding in squirrel monkeys.

The finding that pentazocine decreased high-rate operant behavior in the present study is generally consistent with results of previous investigations (McMillan and Harris, 1972; McMillan and Morse, 1967). These studies (McMillan and Harris, 1972; McMillan and Morse, 1967) reported that low doses (1 and 3 mg/kg) of pentazocine slightly increased the low-rate responding of pigeons maintained under FR and fixed-interval (FI) schedules, but higher doses (10, 17.5, and 30 mg/kg) decreased responding in a dose-dependent fashion. However, data were not statistically analyzed in these investigations, and it appears doubtful that the slight rate increases observed at low doses were statistically significant, for mean response rates at these doses fell within the non-drug control range. Downs and Woods (1976) also reported that a low dose (0.032 mg/kg) of pentazocine resulted in a small (10% or less) increase in FI rates in monkeys but not in pigeons; larger doses reduced FR and FI rates of pigeons and monkeys. No inferential statistics were employed, but it seems unlikely that the rate increases attributed
to pentazocine were statistically significant.

Given the absence of statistical tests and the small magnitude of alleged pentazocine-induced increases in low-rate responding, it is not clear whether the drug actually increases low-rate operant behavior at small doses. Surely no such effect was observed in the present study. However, previous investigations which have reported pentazocine-induced increases in low-rate behavior differed from the present study in that 1) different schedules of reinforcement were employed; 2) different doses and routes of administration were utilized; and 3) different species were evaluated. Any or all of these factors, as well as the willingness of prior investigators to accept very small changes in behavior as indicative of a drug effect, may have contributed to the fact that pentazocine-induced rate increases were observed in earlier studies, but not in the present investigation.

In addition to the effects on schedule-controlled behavior previously described, pentazocine alone has been shown to have discriminative stimulus properties (Kuhn, Greenberg, and Appel, 1976), reinforcing properties (Hoffmeister and Schlichting, 1972), analgesic properties (Dykstra and McMillan, 1974; Goode, Rhodes, and Waterfall, 1979), and to interfere with avoidance behavior (Holtzman, 1974; Holtzman and Jewett, 1972). When combined with tripelennamine, the drugs have been reported to produce supra-additive, morphine-like effects. For example, tripelennamine enhances the discriminative stimulus properties of pentazocine in rats (Shannon and Su, 1982),
delays the development of tolerance to the analgesic effects of pentazocine and enhances analgesia in pentazocine-tolerant rats (Cleary et al., 1983), and increases lethality in mice relative to either drug alone (Poling et al., 1983; Waller et al., 1980). The findings of the present study that when combined pentazocine and tripelennamine acted in a supra-additive manner are consistent with the previous investigations. However, it is unclear whether tripelennamine increased the morphine-like properties of pentazocine on schedule-controlled behavior, for the effects of morphine on schedule-controlled behavior are imperfectly understood. For example, Seiden and Dykstra (1977) pointed out that morphine typically decreases both low- and high-rate behaviors in pigeons, rhesus monkeys, and squirrel monkeys; however, low doses of morphine have occasionally been reported to increase low-rate responding of pigeons, rhesus monkeys, and rats, and even to increase high-rate responding of rats. Although results obtained are occasionally inconsistent; it is still important to study the effects of opioids and other drugs on schedule-controlled behavior:

It is now known that the temporal and sequential relations between behavior and its consequences (i.e., the schedule) can be fundamental in determining whether opioids and opioid antagonists increase or decrease rates of responding. Similarly, the schedule under which these drugs are administered can be critical in determining whether they maintain responding that leads to their injection or maintain responding that terminates their injection. Such findings represent an important initial step in understanding how environmental conditions alter the behavioral effects of opioids and opioid antagonists. Since opioid antagonists can block opiate receptors, which mediate the actions of endorphins, the behavioral effects of these drugs might reveal functional characteristics of the endorphin system. Although opioid
antagonists typically have few effects on schedule-controlled behavior at low doses that block opiate receptors, higher doses can markedly alter responding. Moreover, under suitable conditions, the behavioral effects of these drugs can become more pronounced or can occur at relatively low doses in animals that have previously received morphine or opioid antagonists. Clearly, further research is required to elucidate the role of drug-environment interactions in modulating the functions of the endorphin system (Goldberg, Spealman, and Shannon, 1982, pp. 294-295).

Evaluating drug effects on operant behavior maintained under various schedules of reinforcement can help not only in understanding how environmental conditions can influence drug effects but can also contribute to understanding the deleterious behavior effects of abused drugs. If Skinner (1969) is correct in stating that, "It is only when we have analyzed behavior under known contingencies of reinforcement that we can begin to see what is happening in daily life" (p. 10), studying the effects of pentazocine and tripelennamine alone and in combination under controlled contingencies in the laboratory may facilitate understanding how these drugs affect the behavior of street users. Hopefully, the findings of the present study will contribute viable information to the ever growing body of literature concerning the interactions of drug and environmental variables.
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