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Effects of the Combination of Tripelennamine and Pentazocine at the Behavioral and Molecular Levels

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SHANNON, H. E. AND T.-P. SU. *Effects of the combination of tripelennamine and pentazocine at the behavioral and molecular levels*. PHARMAC. BIOCHEM. BEHAV. 17(4)789–795, 1982.—The purpsoe of the present experiments was to determine if the antihistamine tripelennamine potentiates the morphine-like effects of the narcotic-antagonist analgesic pentazocine at the behavioral level or the molecular level or both. At the behavioral level, the effects of pentazocine were determined alone and in combination with tripelennamine in rats trained to discriminate between saline and either morphine or the psychotomimetic narcotic derivative SKF 10,047. The interaction between pentazocine and tripelennamine were also evaluated in the guinea-pig ileum preparation and in the [^{3}H]-naloxone opiate receptor binding assay. Tripelennamine significantly enhanced the morphine-like discriminative stimulus effects of pentazocine and markedly reduced the SKF 10,047-like stimulus effects of pentazocine. Naloxone antagonized the morphine-like effects of pentazocine plus tripelennamine. Pentazocine significantly constricted pupils in the rat, an effect which was additive with the mydriatic effects of tripelennamine. Inhibition of the twitch-height of the electrically stimulated guinea-pig ileum by pentazocine was not affected by tripelennamine. Further, tripelennamine did not modify the K_e for naloxone in antagonizing pentazocine. Inhibition of specific [^{3}H]-naloxone binding by pentazocine was also not affected by tripelennamine. These results are consistent with the hypothesis that the potentiation of the morphine-like effects of pentazocine by tripelennamine which was observed behaviorally was not due to molecular interactions at the morphine receptor. At least a part of this interaction may be attributable to tripelennamine decreasing the psychotomimetic actions of pentazocine.

Drug discrimination Pentazocine Tripelennamine Morphine Naloxone
N-Allyl normetazocine (SKF 10,047)

CONCOMITANT abuse of the antihistamine tripelennamine with the narcotic antagonist pentazocine has recently become recognized [3, 25, 32, 33]. Under the street name of "T's and Blues," this drug combination is reportedly preferred by some users over pentazocine alone and may be taken by some users as a substitute for heroin when the latter drug is available only in poor quality. The combination of tripelennamine and pentazocine reportedly gives the user a more heroin-like effect than is experienced with pentazocine alone. Pentazocine, while a narcotic antagonist, produces predominantly morphine- or heroin-like subjective effects at lower doses in man, whereas higher doses produce prominent psychotomimetic effects which postaddict subjects report to be unpleasant or dysphoric [11]. As an antihistamine, there are no known mechanisms whereby tripelennamine might enhance the morphine- or heroin-like effects of pentazocine. Further, no such interactions have been reported under controlled conditions.

The purpose of the present investigation was to determine if tripelennamine potentiates the morphine-like effects of pentazocine at either the behavioral level or the molecular level or both. The discriminative stimuli produced by narcotics and narcotic antagonists in the rat have been demonstrated to be a valid animal model for the subjective effects produced by these drugs in man [17, 29, 30]. Thus, the effects of pentazocine alone and in combination with tripelennamine were evaluated in rats trained to discriminate between morphine and saline. The effectiveness of naloxone in antagonizing the effects of the drug combination was also evaluated. To test the possibility that tripelennamine might act by reducing the dysphoric psychotomimetic component of action of pentazocine, pentazocine was also tested alone and in combination with tripelennamine in rats trained to discriminate between saline and the prototypic psychotomimetic narcotic derivative SKF 10,047 [21]. In order to determine if the interactions observed behaviorally occurred at the receptor or molecular level, the interactions between tripelennamine and pentazocine were also evaluated in the guinea-pig ileum and in the [^{3}H]-naloxone opiate receptor binding assay.

METHOD

Subjects

Male CDF rats (Charles River Breeding Laboratories, Wilmington, MA) weighing 325 to 375 g and housed three per

cage in a large colony room were used as subjects. Food and water were continuously available. Lights in the colony room were turned off between 6:00 p.m. and 6:00 a.m.

Drug Discrimination

Standard two-lever rat chambers (Model 1101-L, Grason-Stadler Co., Bolton, MA) were modified by adding a single lever midway along the wall opposite the original levers. The two original levers were designated the "choice" response levers, and the single lever the "starting" response lever. Midway between the two choice levers, a 5-cm wide clear Plexiglas partition was mounted perpendicular to the wall and extended from the ceiling to 1 cm above the grid floor. A scrambled electric shock was delivered to the grid floor by a constant current shock generator (Model 700, Grason-Stadler). The animal chamber was housed in a light and sound attenuating enclosure. Schedule contingencies were programmed and data recorded by a SCAT 3002/PDP8 system (BKP Scientific, Berlin, MA).

Rats were trained to discriminate between saline and 3.0 mg/kg of morphine or 3.0 mg/kg of SKF 10,047 in a discrete-trial shock avoidance procedure [28] to respond, on each trial, first on the starting response lever and then on one of the two choice response levers to avoid or escape shock delivery. During each training session, responses on only one choice lever terminated a trial (the "appropriate" lever) and responses on the other choice lever (the "inappropriate" lever) had no programmed consequences. A trial during training sessions was defined as being correct if the first choice lever response emitted by the animal following a starting response was to the appropriate choice lever. However, during test sessions, a response on either choice lever following a starting response terminated a trial (i.e., nondifferential reinforcement of choice responding). Training sessions and test sessions were identical in all other respects.

During both training and test sessions, the beginning of a trial was signalled by the simultaneous onset of the houselight and white noise. The first starting response of each trial terminated the white noise; the houselight remained on until the appropriate choice response was emitted, which immediately terminated the trial. Beginning 5.0 sec after the onset of a trial, a scrambled 1.0 mA electric shock was intermittently presented as 1.0 sec pulses with 2.0 sec between pulses for the duration of the trial. A trial was immediately terminated by the completion of the two-response chain, or the end of the session. The interval between trials was held constant at 45 sec during which the chamber was dimly illuminated with red light. Sessions ended after 20 trials or 30 min, whichever occurred first.

The rats were trained as described previously [28] until they completed at least 90 percent (i.e., 18 of 20) of the trials on the appropriate choice lever for four consecutive training sessions (two morphine or SKF 10,047 and two saline sessions) followed by two consecutive test sessions (one morphine or SKF 10,047 and one saline). During subsequent drug substitution testing, experimental sessions were conducted 6 days a week with the first and second sessions serving as a training pair and the fourth and fifth sessions as another training pair. Morphine (or SKF 10,047) or saline was administered prior to a session in random order within each pair of training sessions. If choice responding was at least 90 percent correct for both sessions of a training pair, a drug test session was conducted the following session (the third or sixth session of a week).

Morphine sulfate, tripelennamine HCl, naloxone HCl and SKF 10,047 HCl (N-allyl normetazocine) were dissolved in 0.9 percent saline. Pentazocine base was dissolved in 8.5 percent lactic acid plus 1.0 N NaOH in a ratio of 3:2. All doses refer to the free base. All drugs and drug vehicles were administered SC 30 min prior to the start of a session. Within each series of drug tests, doses were administered in a different random sequence for each animal. Data were analyzed using standard bioassay statistics [5].

Pupil diameter was measured photographically as described previously [27] with a Polaroid CU5 close-up camera [20] giving a threefold magnification. The horizontal diameter was obtained using a pair of dividers; measurements were made on a scale photographed with the pupils. Pupils were photographed immediately before the rats were injected (control) and again immediately before the start of the test session 30 min later. Ambient illumination was 25 footcandles.

Opiate Receptor Binding Assay

Synaptic membranes from guinea-pig brains were prepared as previously described [37,41]. The binding of [^{3}H]-naloxone (6.4×10^{-9} M) to opiate receptors in the membrane preparation (1 g tissue wet weight per 100 ml Tris HCl buffer, 0.1 M, pH 7.4) was measured by filtration assay [24]. The nonspecific binding in the presence of levallorphan (1 μM) was subtracted from the total binding to yield specific binding. Concentration-displacement curves for pentazocine alone and in the presence of 100 nM of tripelennamine were determined.

Guinea-Pig Ileum Assay

The myenteric plexus-longitudinal muscle strip from the guinea-pig ileum was prepared as described previously [14]. Contractions were induced by field stimulation (Grass S88 stimulator, 80 V, 0.1 Hz, pulse duration 0.25 msec) at the resting tension of 1 g. The isometric twitches were recorded by means of a force displacement transducer (Grass FT 03C) and Grass polygraph. Initially, the IC_{50} of pentazocine was determined for each ileum. After thoroughly washing out the pentazocine, the ileum was incubated for 5 to 10 min with 500 nM tripelennamine, and the effect of tripelennamine on the IC_{50} of pentazocine was determined. In addition, the effect of tripelennamine (500 nM) on the effectiveness of naloxone to antagonize the action of pentazocine (i.e., the K_e value of naloxone) was also determined. In six ileal strips, the K_e for naloxone was first determined with pentazocine alone and then with pentazocine and tripelennamine; the order of testing was reversed in eight additional strips.

RESULTS

Drug Discrimination

Pentazocine produced a dose-related increase in the percentage of trials completed on the morphine-appropriate lever when tested over a nearly sixtyfold dose-range (Fig. 1A). The highest dose of pentazocine (17.5 mg/kg), however, produced only approximately 70 percent morphine-appropriate responding. Higher doses could not be tested because they disrupted bar-pressing behavior and produced convulsions in some animals in the presence of repeated shock delivery. Pentazocine also significantly constricted pupils relative to saline control values (Fig. 1B).

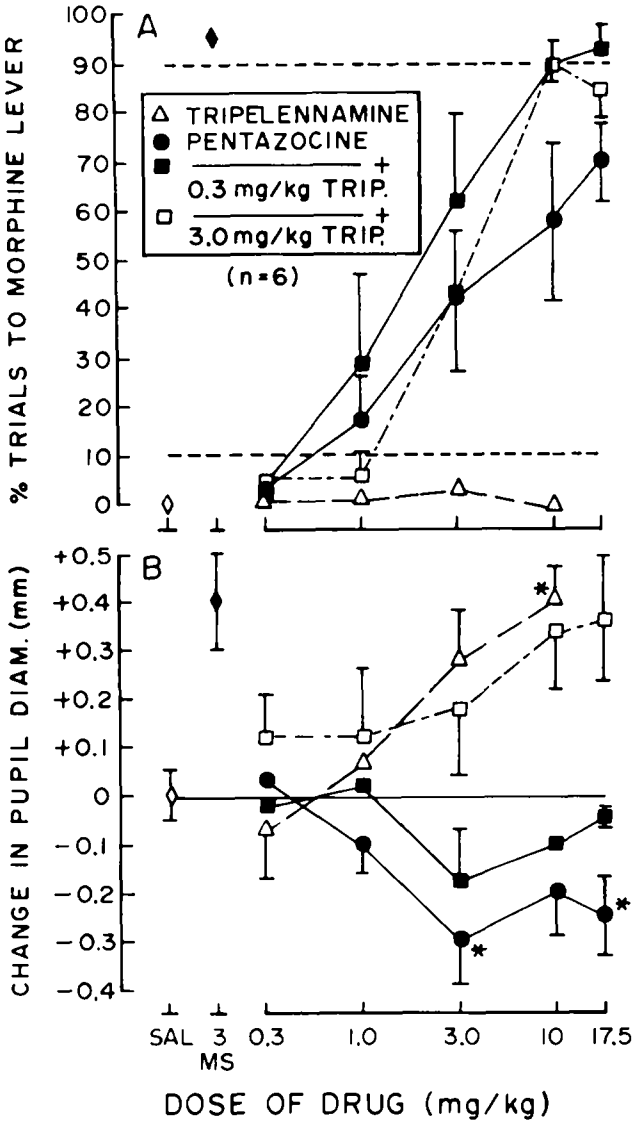

FIG. 1. Dose-effect curves for pentazocine administered alone or concomitantly with tripelennamine. (A) Percent morphine-appropriate responding in rats trained to discriminate between saline and 3.0 mg/kg of morphine. (B) Change in pupil diameter relative to preinjection control values when measured just before starting the test session (30 min after drug administration) in the same rats. Each point represents the mean of one observation in each of six rats. The points at SAL and 3MS represent the effects of saline alone and 3.0 mg/kg of morphine, respectively. The vertical lines represent ±1 S.E.M. and are shown on only one side of some of the points for greater clarity. Where vertical lines are absent, the S.E.M. is less than the size of the point. *Significantly different from saline, $p<0.05$.

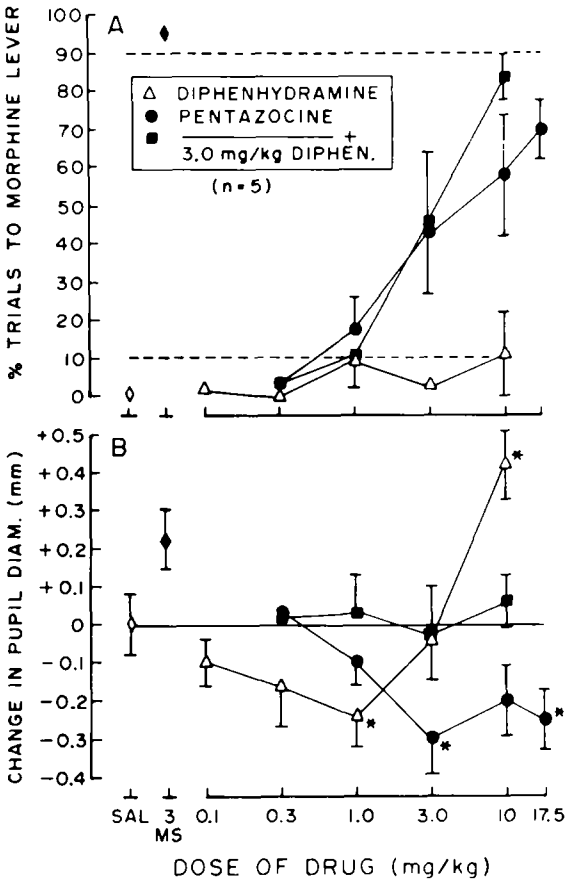

FIG. 2. Dose-effect curves for pentazocine administered alone or concomitantly with diphenhydramine. (A) Percent morphine-appropriate responding in rats trained to discriminate between saline and 3.0 mg/kg of morphine. (B) Change in pupil diameter relative to preinjection control values when measured just before starting the test session (30 min after drug administration) in the same rats. Each point represents the mean of one observation in each of five rats. The points at SAL and 3MS represent the effects of saline alone and 3.0 mg/kg of morphine, respectively. The vertical lines represent ±1 S.E.M. and are shown on only one side of some of the points for greater clarity. Where vertical lines are absent, the S.E.M. is less than the size of the point. *Significantly different from saline, $p<0.05$.

Tripelennamine alone (0.3 to 10 mg/kg) failed to produce any morphine-appropriate responding (Fig. 1A) but did produce significant dose-related increases in pupil diameter (Fig. 1B). Pentazocine administered concomitantly with 0.3 mg/kg of tripelennamine was significantly more potent than when administered alone (relative potency=2.95 (1.42–7.04)) and also produced greater than 90 percent morphine-appropriate responding at doses of 10 and 17.5 mg/kg (Fig. 1). Pentazocine administered concomitantly with 3.0 mg/kg of tripelennamine was not altered in potency, but did produce greater than 90 percent morphine-appropriate responding at a dose of 10 mg/kg. The magnitude of the morphine-like discriminative stimulus effects of pentazocine administered alone was significantly less than when administered concomitantly with either 0.3 or 3.0 mg/kg of tripelennamine as indicated by significant preparations differences in the bioassays, $F(1,45)=9.37$, $p<0.01$, and $F(1,45)=4.30$, $p<0.05$, respectively. The effects of the combined administration of pentazocine and tripelennamine (0.3 or 3.0 mg/kg) on pupil diameter were additive (Fig. 1B).

In order to determine whether or not the interaction between tripelennamine and pentazocine was general for other antihistamines, pentazocine was also tested with diphenhydramine. Diphenhydramine administered alone produced only saline-appropriate choice responding (Fig. 2A) while produc-

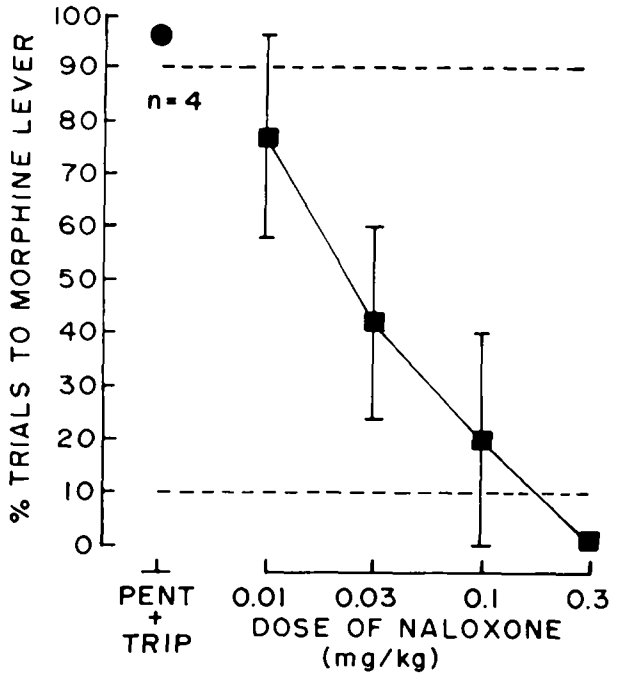

FIG. 3. Antagonism of the morphine-like discriminative effects of pentazocine (10 mg/kg) and tripelennamine (0.3 mg/kg) administered concomitantly in rats trained to discriminate between saline and 3.0 mg/kg of morphine. Each point represents the mean of one observation in each of four rats. The point at PENT + TRIP represents the percentage of morphine-appropriate responding after 10 mg/kg of pentazocine plus 0.3 mg/kg tripelennamine plus saline. The vertical lines represent ±1 S.E.M. and are absent when the S.E.M. is less than the size of the point.

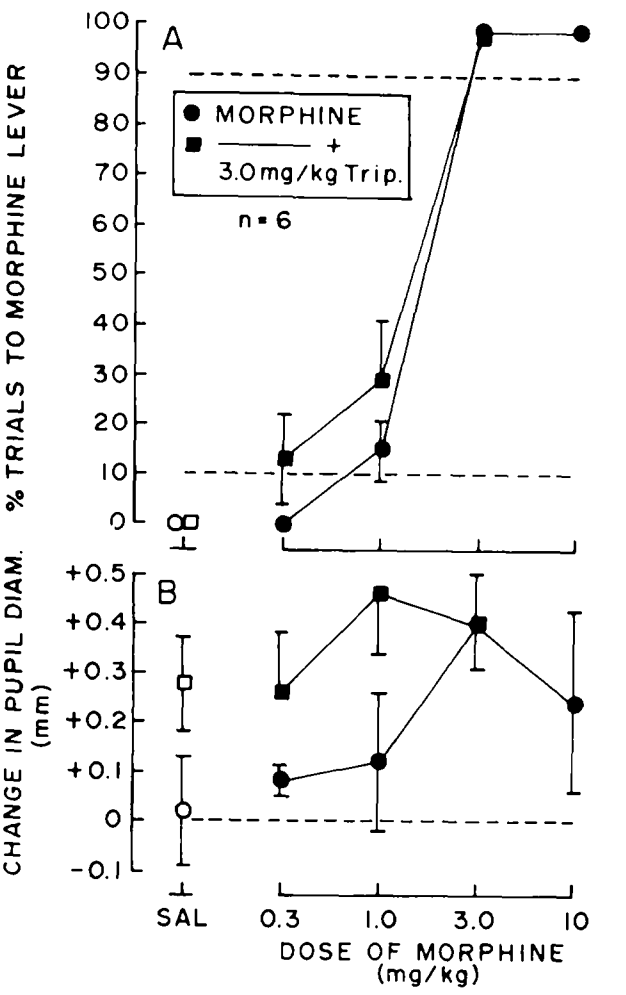

FIG. 4. Dose-effect curves for morphine administered alone or concomitantly with tripelennamine. (A) Percent morphine-appropriate responding in rats trained to discriminate between saline and 3.0 mg/kg of morphine. (B) Change in pupil diameter relative to preinjection control values when measured just before starting the test session (30 min after drug administration) in the same rats. Each point represents the mean of one observation in each of six rats. The points at SAL represent the effects of saline alone or saline plus 3.0 mg/kg of tripelennamine. The vertical lines represent +1 S.E.M. and are shown on only one side of some of the points for greater clarity. Where vertical lines are absent, the S.E.M. is less than the size of the point.

ing significant biphasic changes in pupil diameter (Fig. 2B). The pentazocine dose-effect curve for choice responding was not significantly altered by the concomitant administration of diphenhydramine (3.0 mg/kg; Fig. 2A), and the effects on pupil diameter were additive (Fig. 2B).

To assess whether the morphine-like discriminative stimulus effects of the combined administration of pentazocine and tripelennamine were blocked by a specific narcotic antagonist, graded doses of naloxone were administered concomitantly with constant doses of 10 mg/kg of pentazocine plus 0.3 mg/kg of tripelennamine. Naloxone alone (0.01–1.0 mg/kg) occasioned only saline-appropriate responding (data not presented). However, naloxone (0.01 to 0.3 mg/kg) produced dose-related decreases in the percentage of morphine-appropriate responding occasioned by the concomitant administration of pentazocine and tripelennamine (Fig. 3). A dose of 0.3 mg/kg of naloxone was required in order to antagonize completely the morphine-like effects of pentazocine plus tripelennamine.

For purposes of comparison, dose-effect curves were also determined for morphine administered alone and concomitantly with 3.0 mg/kg of tripelennamine. Morphine alone produced dose-related increases in the percentage of morphine-appropriate responding (Fig. 4A). Tripelennamine (3.0 mg/kg) had virtually no effect on the morphine dose-effect curve. In contrast to pentazocine, morphine significantly increased pupil diameter (Fig. 4B). The mydriatic effect of 3.0 mg/kg of tripelennamine was additive with the effects of 0.3 and 1.0 mg/kg of morphine but not with the effects of 3.0 mg/kg of morphine.

The psychotomimetic component of action of pentazocine was evaluated by testing this drug in rats trained to discriminate between saline and the prototypic psychotomimetic narcotic derivative SKF 10,047. Pentazocine alone produced dose-related increases in SKF-appropriate responding, and a dose of 17.5 mg/kg of pentazocine produced greater than 90 percent SKF-appropriate responding (Fig. 5). In the presence of tripelennamine (0.3 mg/kg), the pentazocine dose-effect curve was flattened. These changes in the pentazocine dose-effect curve were due to tripelennamine antagonizing completely the SKF-like effects of 10 and 17.5 mg/kg of pentazocine in two of the five rats while

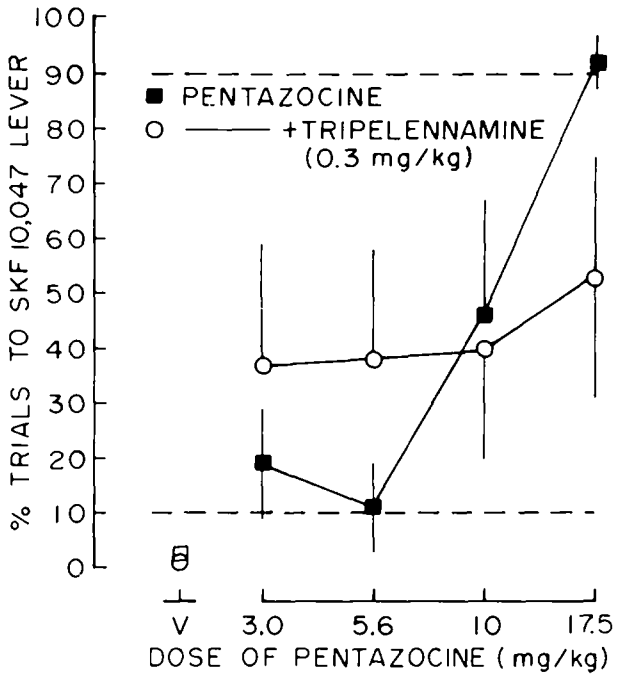

FIG. 5. Dose-effect curves for pentazocine administered alone or concomitantly with tripelennamine in rats trained to discriminate between saline and 3.0 mg/kg of SKF 10,047. The points at V represent the effects of vehicle alone or vehicle plus 0.3 mg/kg of tripelennamine. Each point represents the mean of one observation in each of five rats. The vertical lines represent ±1 S.E.M. and are shown on only one side of some of the points for greater clarity, or are absent when the S.E.M. is less than the size of the point.

also enhancing the SKF-like effects of 3.0 and 5.6 mg/kg of pentazocine in two other rats.

Opiate Receptor Binding Assay

Pentazocine alone produced a concentration-dependent inhibition of specific [^{3}H]-naloxone binding in the guinea-pig brain synaptosomal preparation. In the absence of tripelennamine, the IC_{50} for pentazocine was 14.4 (95 percent C.L., 12.7–16.4) nM. Tripelennamine (100 nM) had no significant effect on the inhibition of naloxone binding by pentazocine in that the IC50 for pentazocine in the presence of tripelennamine (12.7 (95 percent C.L., 10.2–13.4) nM) was not significantly different from that obtained in the absence of tripelennamine. Tripelennamine alone had no effect on [^{3}H]-naloxone binding.

Guinea-Pig Ileum Assay

The concentration of pentazocine required to reduce by 50 percent (i.e., the IC_{50}) the twitch-height of the electrically stimulated guinea-pig ileum was determined in each of three ileal strips. When the ileal strips were preincubated with 500 nM of tripelennamine, the previously determined IC_{50} dose of pentazocine still reduced the twitch-height by 45 to 50 percent (data not presented).

The K_e for naloxone in antagonizing the effects of pentazocine on the twitch-height of the stimulated ileum was determined in fourteen ileal strips and had a mean value of 22.63±3.76 nM. In the presence of 500 nM of tripelennamine, the K_e for naloxone in antagonizing the effects of pentazocine was virtually identical (22.06±4.37 nM).

DISCUSSION

The concomitant administration of the antihistamine tripelennamine, but not another antihistamine diphenhydramine, with the narcotic antagonist analgesic pentazocine enhanced the morphine-like discriminative stimulus effects of pentazocine. Similar interactions were not observed on the pupil since the effects on pupil diameter of tripelennamine and pentazocine were essentially additive. On the other hand, tripelennamine antagonized the SKF 10,047-like discriminative effects of pentazocine in some, but not all, animals. No interactions were observed between tripelennamine and pentazocine at the molecular level in the opiate receptor binding assay or guinea-pig ileum assay. These results suggest that the preference of some drug users for the combination of tripelennamine and pentazocine over pentazocine alone is due to interactions which occur primarily at the behavioral level rather than at a common opiate receptor site and may involve in part a reduction in the psychotomimetic component of action of pentazocine in these persons.

In humans, the subjective effects of pentazocine are complex in that lower doses are predominantly morphine-like whereas higher doses produce a syndrome which resembles that of cyclazocine- or nalorphine-like drugs and is characterized by tiredness, drunkenness and psychotomimetic phenomena [10]. The discriminative stimulus effects of pentazocine in laboratory animals are also complex. In rats trained to discriminate between vehicle and pentazocine, morphine has been reported both to produce [16] and not to produce [8,23] pentazocine-like stimulus control; nalorphine and cyclazocine also failed to produce pentazocine-like stimulus control [8,23]. The prominent morphine-like component of action of pentazocine is further evidenced by the findings that in animals trained to discriminate between saline and morphine, pentazocine has been reported both to produce [4, 7, 29, 31, 42] and not to produce [9, 23, 27, 42] morphine-like stimulus control; these differences are dependent upon both species [27,29] and strain ([29] and this report) of animals used. On the other hand, the cyclazocine-like component of action of higher doses of pentazocine is evidenced by the findings that in animals trained to discriminate between saline and cyclazocine, pentazocine produced either cyclazocine-like stimulus control or an appreciable percentage of cyclazocine-appropriate responding [8, 26, 36]. The present results further demonstrate that pentazocine has at least two components of action, one which is morphine-like and one which is like psychotomimetic narcotic derivatives such as SKF 10,047 or cyclazocine.

Prominent interactions between tripelennamine and pentazocine have also been reported by previous investigators. Waller *et al.* [39] demonstrated that tripelennamine potentiated the lethal effects of pentazocine in mice in that tripelennamine (20 to 40 mg/kg) decreased the LD_{50} of pentazocine from 116 mg/kg to as low as 8 mg/kg. In anesthetized rats, doses of these two drugs which produced no mortality when administered alone produced cardiorespiratory paralysis and death when administered concomitantly [38]. Bhargava [1] has reported that when administered alone both pentazocine and tripelennamine worsen the symptoms of abstinence in morphine-withdrawn mice. However, when pentazocine and tripelennamine were administered concomitantly, jumping

was decreased in these mice, but other signs such as falls, loss of coordination and ataxia were enhanced and convulsions and prolonged hypothermia were also observed. These observations led Bhargava [1] to conclude that humans may abuse the combination of pentazocine and tripelennamine because certain centrally mediated responses are inhibited although fatalities may result from inappropriate dose combinations.

Pentazocine produced significant dose-related decreases in pupil diameter in the present study, whereas morphine increased pupil diameter. Morphine has long been known to produce mydriasis in the rat although it produces miosis in humans [15]. The magnitude of the mydriatic effects of morphine observed here is in close agreement with the findings of Klemfuss *et al.* [13] and also replicates previous findings from our laboratories [28]. That pentazocine produces changes in pupil diameter opposite in reaction from those of morphine in the rat distinguishes this species from both the dog [6] and humans [11] where both drugs produce miosis, although the effects of pentazocine appear to plateau in dog and man. The miotic effect of pentazocine in the rat is apparently due to its SKF 10,047-like activity since both SKF 10,047 [28] and cyclazocine (unpublished observations) constrict pupils in the rat. These results demonstrate that pupil diameter changes in the rat are useful in refining further the pharmacologic profile of drug activity.

The concomitant abuse of tripelennamine with a narcotic derivative is not restricted to pentazocine. Abuse of the combination of tripelennamine and paregoric ("blue velvet") has also been reported [2, 35, 40]. Tripelennamine has also been tried as an adjunct therapy in withdrawal from morphine [12]. Also, O'Driscoll and Lindley [22] have reported the abuse of tripelennamine alone by narcotic addicts. This latter report suggests the possibility that tripelennamine may have primary reinforcing properties and that the concomitant abuse of tripelennamine and narcotics such as pentazocine and paregoric may also be attributable to the summation of their primary reinforcing properties. Thus, the concomitant abuse of tripelennamine and pentazocine may be due to a multiplicity of factors.

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