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Interactions Between Pentazocine and Tripelennamine on Autonomic and Nociceptive Measures in the Dog[1]

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VAUPEL, D. B. *Interactions between pentazocine and tripelennamine on autonomic and nociceptive measures in the dog.* PHARMACOL BIOCHEM BEHAV **33**(1) 245–251, 1989.—Pentazocine and tripelennamine, which have been abused in combination by humans, were evaluated for pharmacologic interactions on autonomic, behavioral, and antinociceptive measures in chronic spinal dogs. Pentazocine (0.31–5 mg/kg, IV) produced miosis, hypothermia and antinociception which was mediated by spinal and supraspinal reflexes; these effects were antagonized by naltrexone. Tripelennamine (0.63–2.5 mg/kg, IV) elicited mydriasis, hyperthermia and antinociception; these effects were not blocked by naltrexone. Tripelennamine produced antinociception only on the supraspinally-mediated skin twitch reflex. Interactions between pentazocine and tripelennamine varied depending on the response measured. Effects of both drugs on pupils were additive. Temperature effects were infra-additive, with the hyperthermic effects of tripelennamine predominating over the pentazocine hypothermia, resulting in a complete physiologic antagonism of pentazocine hypothermia. Antinociception, measured by flexor reflex depression, represented only the effect of pentazocine, whereas skin twitch reflex antinociception reflected either infra-additive or additive properties. The coadministration of nonconvulsive doses of pentazocine and tripelennamine produced seizures indicating a potentiated adverse interaction. In summary, the patterns of the pentazocine-tripelennamine interactions were complex and the effects of tripelennamine could not be attributed to opioid activity.

Pentazocine Tripelennamine T's and Blues Pharmacological interactions Opioid Antihistamine Autonomic, antinociceptive and behavioral responses

THE epidemic in the abuse of pentazocine and tripelennamine, a combination commonly referred to as "T"s and Blues," began in 1977, peaked in the years 1980–1982 and began declining in 1984 (13). Contributing to the abuse of this drug combination as a substitute for heroin was the poor quality of street heroin and the low cost and ready availability of both pentazocine, a mixed opioid agonist-antagonist, and tripelennamine, a type 1 histamine antagonist (12). Another factor was a pharmacologic interaction, reputed to render the pentazocine-tripelennamine combination as euphorigenic as heroin (12,19). When administered alone, pentazocine has been considered to have a low abuse liability (7,8); and tripelennamine was regarded to have little or no dependence liability despite a history of being abused with paregoric (26). Therefore, it was of interest to determine how tripelennamine modifies the pharmacology of pentazocine to make the combination a desirable substitute for heroin.

Most recent investigations on the interaction of pentazocine and tripelennamine have been conducted with rodents. As measured by the hot plate method, acute doses of tripelennamine (10–20 mg/kg) produced antinociception in rats, which was not antagonized by the opioid antagonist naloxone and was less efficacious than pentazocine (27). In mice, however, the antinociceptive effects of tripelennamine (1.5–15 mg/kg) as measured by the tail clip and hot plate methods were partially blocked by naloxone implicating the involvement of an opioid mechanism (6,22). Tripelennamine has been reported to interact with the antinociceptive actions of pentazocine either by addition or potentiation in naive (6,22) and morphine-tolerant mice (22). Acute toxicity studies also have shown that tripelennamine potentiates pentazocine lethality in mice (21,25). Together, these rodent studies have described additive or potentiating effects of tripelennamine on the acute antinociceptive effects of pentazocine in drug-naive animals, but the ability of tripelennamine to affect opioid antinociceptive mechanisms was not consistent and may be species-dependent.

The present studies were conducted in the chronic spinal dog preparation in order to evaluate the acute interaction of tripelennamine with pentazocine and the opioid antagonist naltrexone on nociceptive reflexes as well as autonomic nervous system responses and behavior. The major question was whether the interactions of pentazocine and tripelennamine adhered to a simple additive model or whether their combined actions were supra-

[1]A preliminary report of these results was presented at the April, 1984 meeting of the Federation of American Societies for Experimental Biology. Fed. Proc. 43:746; 1984.

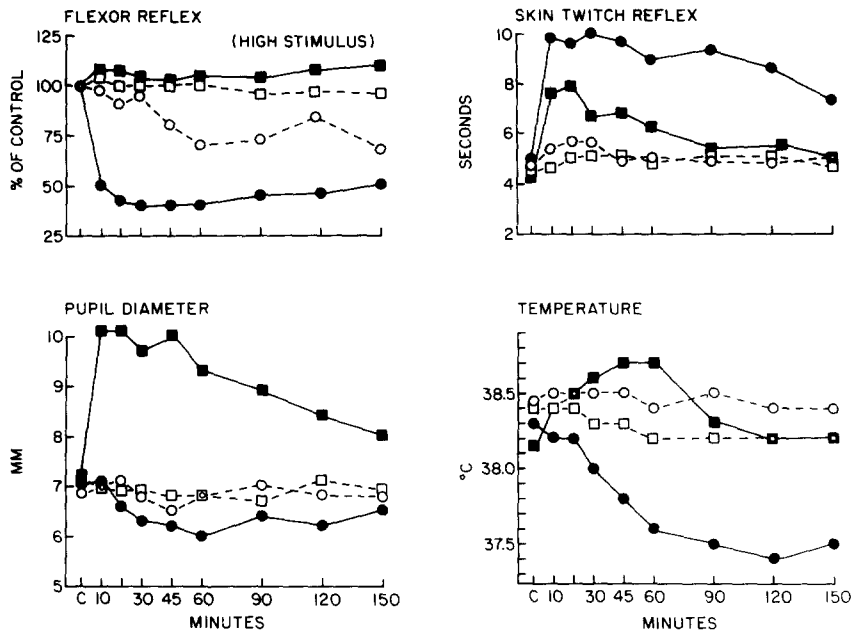

FIG. 1. Time course comparison of 5 mg/kg of pentazocine (●), its lactic acid/NaOH vehicle (○), 2.5 mg/kg of tripelennamine HCl (■) and its saline vehicle (□). C represents the average of the three control responses. Drugs were administered over 3 to 4 min immediately after the final control measurement; postdrug observations began 10 min after the drugs had been administered. Each point represents the mean of 6 dogs.

additive or infra-additive (3) on the opioid systems affected by pentazocine. Insofar as the spinal cord has been transected in the preparation used, the effects of these drugs on two nociceptive reflexes, the skin twitch and flexor reflexes, were obtained. The skin twitch reflex uses high spinal and supraspinal pathways, and the flexor reflex is physiologically characterized as a spinal reflex.

Previous studies have characterized the dose-response relationships of pentazocine in the chronic spinal dog (5). In the present experiments the dose-response and time course effects of tripelennamine in the dog were first characterized and compared to those of pentazocine. Pentazocine-tripelennamine interactions were then assessed including the respective dose ratios of 1:1, 2:1 and 4:1 which have been cited in clinical reports of T's and Blues abuse (2,19). As previous reports had suggested a species difference in the sensitivity of tripelennamine-induced antinociception to reversal by narcotic antagonists (6, 22, 27), single doses of pentazocine and tripelennamine were tested for antagonism by naltrexone. The results obtained demonstrated that tripelennamine and pentazocine interacted additively and infra-additively depending on the response measured, and that in the dog, the antinociceptive and autonomic effects of tripelennamine are mediated by other than opioid mechanisms.

METHOD

Subjects

Six female dogs, 4 pure-bred beagles and 2 mixed beagles, weighing between 7 and 11 kg, were used for these studies. The dogs had their spinal cords transected at the T-10 level according to published methods (11) at least two years before this study. The health of the dogs was monitored using periodic complete blood cell counts, blood chemistry analyses and urinalyses.

Measurements

Physiological and behavioral responses in chronic spinal dogs placed in a laterally recumbent position on their right sides were obtained using both objective and subjective techniques, which have been described previously in detail (19, 23, 24). The flexor reflex of the left hindlimb was evoked continuously at 1-min intervals using a pneumatically driven, mechanically programmed toe pincher capable of delivering one of three stimulus strengths (low, 4.5 psi, medium, 9.0 psi, and high, 18 psi) to the third toe. The resulting flexions were recorded isotonically on a kymograph, peak heights were measured with a digitizer, and the data were normalized by expressing each response as a percentage of the mean control value. The skin twitch reflex was produced by directing a radiant heat lamp onto an India ink-darkened, shaved area of the left shoulder. Control latencies ranged from 3 to 5 sec and a 10-sec cut-off was used. Changes in autonomic nervous system activity were determined by measuring respiratory rate, heart rate, pupil diameter, nictitating membrane width and rectal temperature.

General behavior activity (unresponsive, sleeping, quiet, restless, or struggling) and secretory activity were scored by a trained observer according to operational definitions (4,10) or modifications of them. Vocalizations (primarily whining and howling), nystagmus, rapid and random eye movements, staring, stereotypic head movements, attending to auditory or visual stimuli, opisthotonic posturing and the medial and lateral canthal reflexes plus other signs were scored as present or not.

Experimental Design and Analysis

Three types of experiments were conducted using complete crossover designs and the same protocol. The single drug and two drug interaction experiments consisted of a 30-min control period during which three sets of baseline observations were obtained at 10-min intervals, followed by the consecutive IV administration of either a drug and vehicle, two vehicles or two drugs over 4 min. Separate syringes were used for administering each drug or

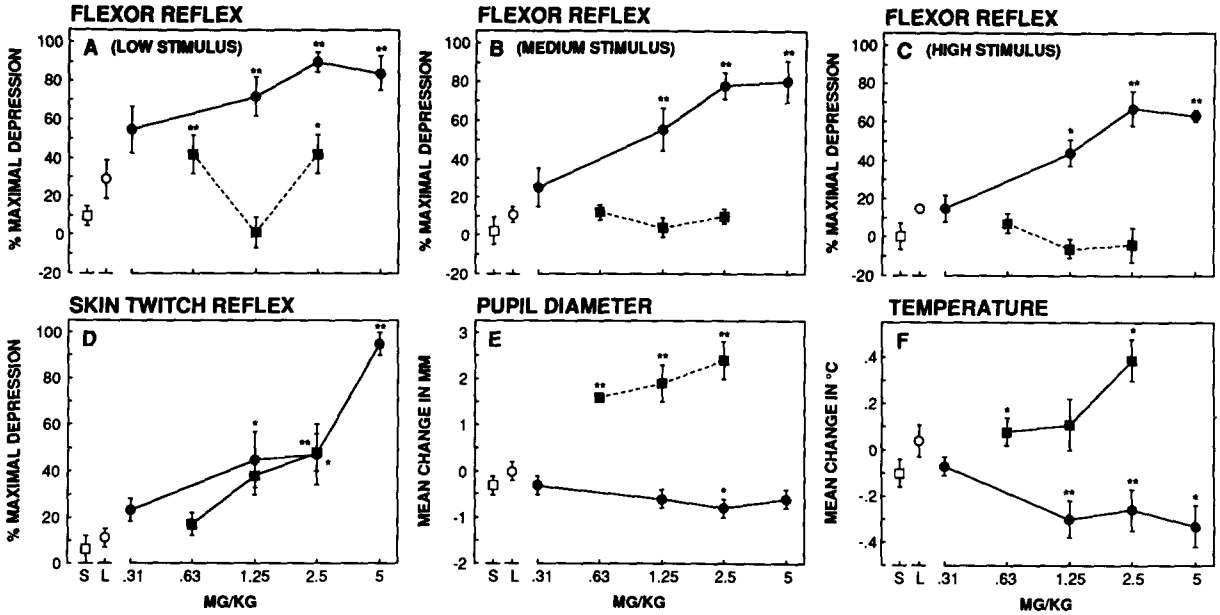

FIG. 2. Dose-response curves for single doses of pentazocine (●) and tripelennamine (■) in the dog. Responses to lactic acid/NaOH (L) and saline (S) respectively represent the pentazocine and tripelennamine vehicle controls and are shown by the open symbols. All data points represent the means and SE of the responses obtained in 6 dogs. The significance level of drug effects differing from control values as determined by paired *t*-tests is indicated by * ($p<0.05$) or ** ($p<0.01$). Those dose-response curves fulfilling the statistical criteria for a linear regression have their points connected by solid line, whereas a broken line indicates the absence of a significant linear dose-response curve.

vehicle. Postdrug observations were taken over 2½ hours at these times: 10, 20, 30, 45, 60, 90, 120 and 150 min. In the third series of experiments, the ability of opioid antagonist naltrexone to block the effects of a single dose of pentazocine or tripelennamine was determined. For these experiments, naltrexone was administered IV over 4 min prior to initiating the control period of the protocol described above.

The single dose selections of pentazocine and tripelennamine were guided by previous studies (5,17), and dose ratios for the pentazocine-tripelennamine combinations included those often employed by T's and Blues abusers. A relatively high dose of naltrexone (1 mg/kg) was used in order to antagonize both the *mu* and *kappa* type activity of pentazocine.

As the time-course data demonstrated that tripelennamine had a shorter duration of action than pentazocine in the dog, data were analyzed over the first 60 minutes following drug administration. The two nociceptive responses, the skin twitch and flexor reflex, were expressed as the percentage of maximal possible depression. Other parameters are expressed as the mean change over 60 min.

Dose-response relationships were tested using an analysis of variance that partitioned the sums of squares into linear regression (within animals) and between animal components. Regression calculations used the log of the dose so that linearity represents a log-linear dose-response curve having a significant slope ($p<0.05$). To take advantage of the crossover design, the between animals component was used to isolate the variability attributed to individual animals and reduce the error term. For the pentazocine-tripelennamine interactions, two-tailed paired *t*-tests were used to test the null hypothesis that the observed interaction response would not differ from the expected additive responses to the two single drugs. Significant differences therefore represented supra-additive or infra-additive actions. Naltrexone antagonism was evaluated by one-tailed paired *t*-tests.

Drugs

Pentazocine base, a gift from Sterling Winthrop, was dissolved in a 3:2 ratio of 8.5% lactic acid and 1 N NaOH. Saline was used as the vehicle for the hydrochloride salts of tripelennamine (CIBA Geigy, Summit, NJ) and naltrexone (NIDA Research Technology Branch). The dosages administered refer to the free base form of pentazocine and the hydrochloride salts of tripelennamine and naltrexone.

RESULTS

Duration of Action

A comparison of the time-courses for the highest doses of pentazocine and tripelennamine tested and their vehicle effects over 150 min following their administration is presented in Fig. 1. Tripelennamine-induced changes in the skin twitch reflex latency, pupil diameter and temperature were maximal within the first hour, but were still of sufficient magnitude to be statistically significant ($p<0.05$) over the entire 150-min observation period. The effects of pentazocine peaked within 1 to 2 hr of administration. However, the peak effects tended to plateau and decrease more slowly when compared to those of tripelennamine. (See the skin twitch results in Fig. 1.) Consequently, dose-response curves and the subsequent interaction experiments were evaluated based on the pharmacologic effects produced in the first 60 min after drug administration.

Single Dose Effects of Pentazocine and Tripelennamine

The pharmacologic actions of pentazocine in doses of 0.31 to 5.0 mg/kg consisted of a pronounced depression of the flexor and skin twitch nociceptive reflexes, constriction of pupils and a reduction in body temperature (Fig. 2). All these effects had linear dose-response curves over the dosages tested. The effectiveness of pentazocine in depressing the flexor reflex was stimulus-related, as its antinociceptive action decreased with increasing stimulus strength (Fig. 2A–C). Respiratory rate, heart rate and behavior scores were not affected.

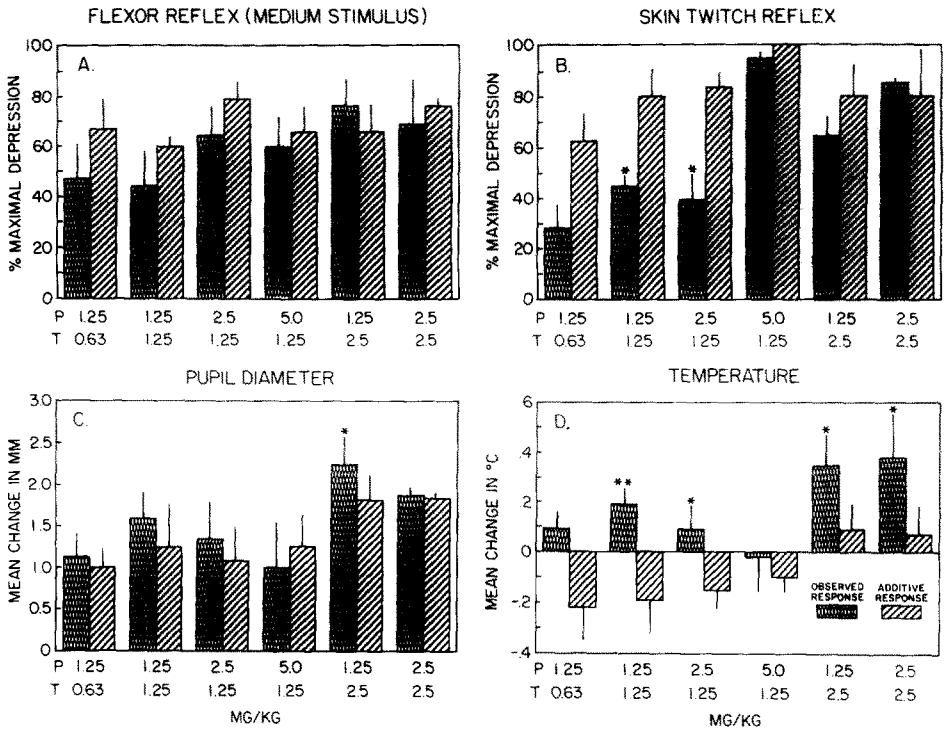

FIG. 3. Comparisons of observed and expected additive effects of different dose-ratio combinations of tripelennamine and pentazocine administered to the chronic spinal dog. Observed responses (stippled bars) are the direct measurements obtained from experiments in which the two drugs were administered together. Additive responses (hatched bars) were obtained by summing the individual effects of pentazocine and tripelennamine which were determined in separate single dose studies that are summarized in Fig. 2. Dogs which developed convulsions were not included in this data. Consequently, the bars represent the means and SE of 3 to 6 dogs. The actual number of animals for each pair of bargraphs can be determined from Table 1. Significant differences between observed responses and the statistically added responses are indicated by * and ** for $p<0.05$ and $p<0.01$, respectively.

Figure 2 also presents the effects of tripelennamine for comparison. Pupil dilatation and hyperthermia were the two most pronounced effects of tripelennamine. The tripelennamine-induced mydriatic responses, while marked, were not linearly related to dose as the slope for the regression line was not significant. However, body temperature increased linearly as the dose increased. Reliable antinociceptive activity for tripelennamine was measured for the skin twitch reflex (Fig. 2D). The dose-related depression of the skin twitch reflex approached 50% of maximal depression at the highest dose tested. Tripelennamine did not affect the flexor reflex evoked by either the medium or high stimulus strengths, although the 0.63 and 2.5 mg/kg doses slightly depressed the flexor reflex response to the low stimulus (Fig. 2A–C). The failure to produce significant linear regression for the three flexor reflex dose-response curves further substantiates the view that tripelennamine has little effect on spinal cord nociceptive reflexes.

Interactions of Pentazocine and Tripelennamine

The combined effects of pentazocine and tripelennamine given in different dose ratios are summarized in Fig. 3. In Fig. 3, only the antinociceptive activity of the medium stimulus evoked flexor reflex responses are illustrated since they typify the results obtained with the low and high toe pinch stimuli. Depression of the flexor reflex produced by the two drugs was not different than what would be predicted by an additive model (Fig. 3A). Since tripelennamine was previously shown to have little effect on the flexor reflex, the combined response represents primarily the effect of pentazocine. Compared to the flexor nociceptive reflex, antinociceptive interactions on the skin twitch reflex were more complex (Fig. 3B). Lower doses of tripelennamine (0.63 to 1.25 mg/kg) in pentazocine-tripelennamine ratios of 1:1 or 2:1 produced effects that were infra-additive. Increasing the ratio to 4:1 produced near maximal depression of the skin twitch which was in effect equivalent to the effect of 5 mg/kg of pentazocine given alone (Fig. 2D). When lower doses of pentazocine (1.25 and 2.5 mg/kg) were combined with higher doses of tripelennamine in ratios of 1:2 and 1:1, the skin twitch interactions were additive. The net result of pentazocine-induced miosis and tripelennamine-induced mydriasis were additive interactions with one exception when the two drugs were given together (Fig. 3C). As with effects on pupil diameter, pentazocine and tripelennamine produced opposite effects on body temperature. However, most of the temperature interaction data (Fig. 3D) show that tripelennamine interacted infra-additively with pentazocine. The net result was that tripelennamine hyperthermia physiologically antagonized pentazocine to a much greater degree than was expected. Even with the highest dose ratio of pentazocine:tripelennamine (4:1), there was essentially no decrease in body temperature (Fig. 2D).

At the inception of these experiments there was no intent to assess the convulsant interactions of pentazocine and tripelen-

TABLE 1

INCIDENCE OF CONVULSIONS PRODUCED BY PENTAZOCINE AND TRIPELENNAMINE, ALONE AND IN COMBINATION, IN CHRONIC SPINAL DOGS

		Pentazocine				
		0.3125	1.25	2.5	5.0	mg/kg
		0/6	0/6	0/6	0/6	
Tripelennamine						
0.625 mg/kg	0/6	—	0/6	—	—	
1.25 mg/kg	0/6	—	0/6	0/6	2/6	
2.5 mg/kg	0/6	—	0/6	3/6	—	

Each drug by itself did not produce convulsions as shown by the incidence ratios directly beneath the doses of pentazocine and directly to the right of the tripelennamine doses. Incidence ratios for the various drug combinations tested are shown at the intersection of the appropriate row and column. Dashes indicate dose combinations not tested.

namine, but the ability of these two drugs to potentiate the convulsant properties of each other became apparent. When administered alone, neither pentazocine nor tripelennamine produced any convulsive episodes as shown in Table 1. As higher doses of one drug were given, while keeping the dose of the other constant, the probability of producing convulsions increased.

Naltrexone Antagonism Studies

Naltrexone, given as a 1 mg/kg pretreatment before the administration of pentazocine or tripelennamine, did not by itself produce any significant effects, as shown by the bar graph comparisons for the saline control in the four panels of Fig. 4. Depression of the flexor reflex, miosis and hypothermia produced by 2.5 mg/kg of pentazocine were completely antagonized by naltrexone as shown in Fig. 4. The antinociceptive effect of naltrexone + pentazocine on the skin twitch did not differ from the appropriate naltrexone + saline control, representing antagonism. However, this antagonism was only partial since the saline + pentazocine and naltrexone + pentazocine treatments were not different ($p<0.2$). In contrast to its effectiveness in blocking pentazocine, naltrexone failed to antagonize the antinociceptive, mydriatic and hyperthermic actions of tripelennamine.

DISCUSSION

The pharmacologic profiles of effects of pentazocine and tripelennamine in the dog were readily distinguishable. Pentazocine produced miosis, hypothermia and antinociception as demonstrated by depression of the flexor and skin twitch reflexes, replicating previous work in this species (5). In contrast, mydriasis and hyperthermia were the most pronounced autonomic effects of tripelennamine. Notably, tripelennamine was not effective as an antinociceptive agent at the level of the spinal cord thereby differing from pentazocine. Yet, tripelennamine did exhibit antinociceptive activity on the skin twitch reflex suggesting that supra-spinal levels of integration were critical to its antinociceptive action. Both tripelennamine and pentazocine did not significantly alter canine behavior.

The combination of tripelennamine and pentazocine affected spinal and supra-spinal nociceptive reflexes differently. Depres-

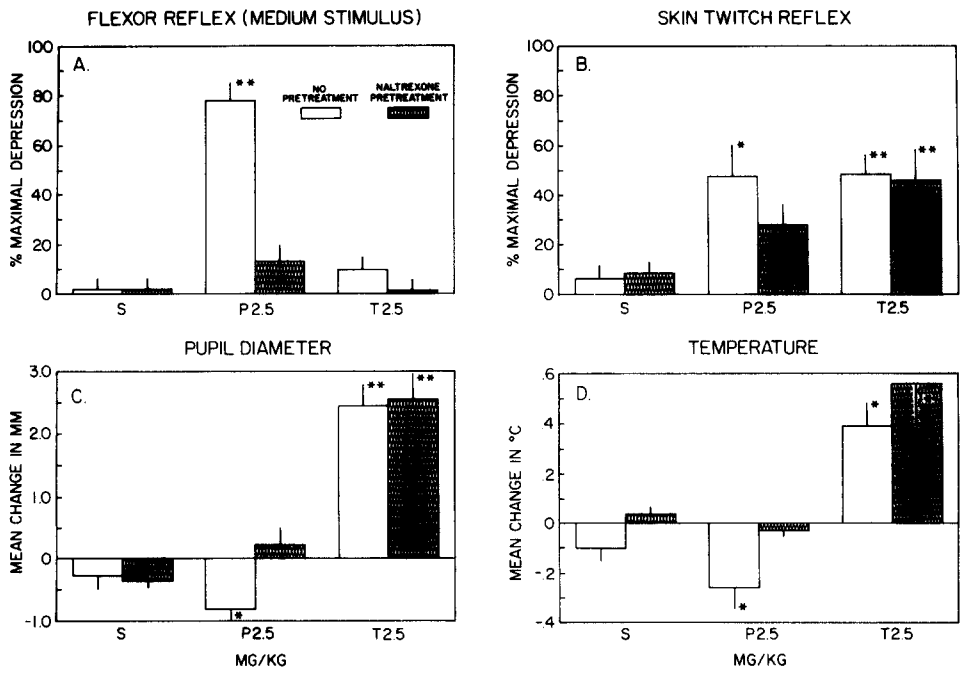

FIG. 4. The effect of naltrexone pretreatment on responses to single doses of pentazocine (P) and tripelennamine (T). Each bar represents the mean and SE of the responses obtained in 6 dogs. The two control conditions (S) did not differ from each other. Determinations of the significance of the effects of pentazocine and tripelennamine following saline (open bars) or naltrexone (stippled bars) pretreatment were based on comparisons with the appropriate saline control (S). Significant effects are indicated by * for $p<0.05$ and ** for $p<0.01$.

sion of the flexor reflex produced by the combination represented almost entirely the effects of pentazocine. This was consistent with the general lack of efficacy of single doses of tripelennamine on this reflex. Interactions on the skin twitch were characterized as either infra-additive or additive. In comparison both additive and potentiated antinociceptive responses have been reported in rats and mice for pentazocine-tripelennamine combinations (1, 6, 22, 27).

Pupil diameter and temperature provided an assessment on autonomic function in the dog. When administered individually, tripelennamine and pentazocine produced opposite effects on both measures. The pupillary effects of pentazocine-tripelennamine combinations were almost uniformly additive in the dog as they were in rats (16). Stated another way, tripelennamine-induced mydriasis physiologically antagonized the pupilloconstrictor effects of pentazocine. This observation is consistent with the ability of tripelennamine to partially antagonize pentazocine-induced miosis in humans (9).

In contrast, interactions on body temperature demonstrated a potentiation of the hyperthermic effect of tripelennamine in 4 of 6 comparisons. That is, the hyperthermic effect of tripelennamine reversed the hypothermic effect of pentazocine to a significantly greater degree than was expected.

The most consistent interaction observed was potentiation of the convulsant properties of pentazocine and tripelennamine. The interaction was manifested in the development of convulsive activity since none of the individual doses selected produced convulsions when administered alone. Seizures represent the most life-threatening toxic effect for T's and Blues abusers according to Poklis and Mackell (14). Seizures in the dog were treated rapidly with IV diazepam and no fatalities occurred. Lethality studies in mice (15,25) have demonstrated that pentazocine-tripelennamine combinations were more lethal than expected based on their individual effects with deaths often preceded by convulsions. Neither diazepam nor naloxone effectively reduced these lethal effects in rodents (25). However, the observation that convulsive seizures produced by pentazocine and tripelennamine combinations were effectively terminated by diazepam in the dog suggests that potential fatalities may be avoided. Overall, the effects of pentazocine and tripelennamine interactions on the autonomic nervous system and seizure activity observed in the dog were consistent with the available human data.

Experiments targeted at determining if tripelennamine interacts with opioid receptors have been a logical outgrowth of the T's and Blues problem, and strategies utilizing antinociception and stimulus discrimination have attempted to assess the role of tripelennamine on the opioid effects of pentazocine. In acute studies, the opioid antagonist naloxone antagonized tripelennamine antinociception in mice (6,22), but not in rats (18,27). The longer acting opioid antagonist naltrexone, in a dose sufficient to antagonize both *mu* and *kappa* opioid effects of pentazocine, antagonized neither antinociception nor the prominent pupil dilatation or hyperthermia produced by tripelennamine in the dog. Drug discrimination studies have consistently shown that tripelennamine did not generalize to opiates in rats (16,18) and pigeons (20). These results suggested there may be a species difference in the acute antinociceptive activity of tripelennamine with the mouse differing from the rat, dog and other species. Using a classical opioid bioassay, inhibition by pentazocine of evoked guinea pig ileum twitches was antagonized by naloxone but not by tripelennamine. In addition to this physiological and behavioral evidence, receptor binding data indicate lack of a direct interaction with opioid receptors (16,18) although there is a lack of agreement concerning the ability of tripelennamine to modify opioid receptor interactions (16,18). The preponderance of data have demonstrated that the acute effects of tripelennamine do not result from a direct interaction with opioid receptors.

In conclusion, pharmacologic interactions of pentazocine and tripelennamine in the dog were typically additive or infra-additive without any supra-additive interactions. Mechanistically, the actions of tripelennamine did not involve opioid receptors since naltrexone did not effectively antagonize them. A toxic interaction manifested by seizures may represent potentiation, since neither of the individual doses employed elicited seizures. Therefore, the acute pentazocine-tripelennamine interactions are complex, depending upon the physiological parameter measured and the dose ratio used. Complex interactions also appeared to characterize human responses to this drug combination. In a controlled clinical study (9), inspection of the peak euphoria and dysphoria measured for two doses each of pentazocine and tripelennamine, administered alone and in combination, showed the following trends: euphorigenic effects of pentazocine-tripelennamine combinations appeared to be either additive or supra-additive, whereas for dysphoria, all interactions appeared to be infra-additive. As it is not possible to associate the subjective effects of the pentazocine-tripelennamine combinations with a pharmacological mechanism, such as an interaction of tripelennamine with opioid receptors, reinforcing properties or other behavioral factors may contribute to the euphorigenic effects of pentazocine-tripelennamine combinations.

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