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BRIEF COMMUNICATION

Tripelennamine Interactions With the Psychotomimetic *Sigma* Agonist N-Allylnormetazocine

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VAUPEL, D. B. *Tripelennamine interactions with the psychotomimetic* sigma *agonist N-allylnormetazocine*. PHARMACOL BIOCHEM BEHAV **33**(3) 717–720, 1989.—The pharmacological effects of individual and combined intravenous doses of the antihistamine tripelennamine and the psychotomimetic *sigma* benzomorphan opioid derivative, N-allylnormetazocine (NANM), on nociceptive reflexes, autonomic parameters and behavior were assessed in the chronic spinal dog. NANM (1.65 mg/kg, IV) produced antinociception, mydriasis, tachycardia, hyperthermia and behavioral signs of canine delirium. Tripelennamine (1.25 mg/kg, IV) produced antinociception, mydriasis and tachycardia without affecting behavior. The combined effects of the two drugs were additive except for heart rate. However, tripelennamine did not antagonize any of the physiological effects or the signs of canine delirium produced by NANM. The findings are inconsistent with the hypothesis that tripelennamine antagonizes the psychotomimetic NANM-like effects of pentazocine to make pentazocine-tripelennamine combinations (T's and Blues) more desirable as a heroin substitute.

N-Allylnormetazocine Tripelennamine T's and Blues Pharmacological interactions
Autonomic, antinociceptive and behavioral responses

ILLICIT use of the opioid agonist-antagonist pentazocine in combination with the antihistamine tripelennamine in the United States during the late 1970's through the mid 1980's (7) represents a unique mixture of drug classes. This drug combination, commonly known as "T's and Blues," is of pharmacological interest because it functions as a heroin substitute (8). The mechanism of action of tripelennamine in this drug interaction, however, is not completely understood. Several pharmacological strategies have been used to study the mechanism underlying the interaction including the assessment of: 1) the effects of tripelennamine and pentazocine alone and in combination on nociceptive measures (2, 15, 17, 18, 22), autonomic nervous system effects (10, 17, 18), and opioid receptor binding (10,11); 2) antagonism of the physiological effects of tripelennamine by opioid antagonists (2, 15, 17, 18); and 3) behavioral studies (10). Results from the first two types of studies have indicated that tripelennamine does not appear to interact with naloxone-sensitive opioid mechanisms in the rat and dog, although data for the mouse are less definitive.

Among the behavioral studies, discriminative stimulus generalization tests conducted in rats and squirrel monkeys have demonstrated that pentazocine has a morphine-like and an N-allylnormetazocine (NANM)-like component of action (10,21). Morphine is recognized as a naloxone-reversible *mu* opioid agonist; NANM is a benzomorphan opioid derivative, which is psychotomimetic in humans (3), and its effects are generally not antagonized by opioid antagonists. Interestingly, tripelennamine reduced the NANM-like stimulus effects of pentazocine in rats, suggesting that tripelennamine may reduce the psychotomimetic component of action of pentazocine (10). Subsequently, Su (13) demonstrated that tripelennamine had a moderate affinity for the naloxone-insensitive, *sigma* receptor as determined by inhibition of [^{3}H]-NANM binding and postulated that tripelennamine may antagonize the *sigma*-like NANM component of action of pentazocine. NANM has been proposed as the prototypic *sigma* agonist in the multiple receptor theory of opioid activity as proposed by Martin and colleagues using the chronic spinal dog model (1,5). In this model, NANM produces a characteristic pattern of autonomic and behavioral responses including antinociception, tachycardia, mydriasis and canine delirium, which distinguish it from morphine-like and ketocyclazocine-like opioids. Canine delirium consists of stereotyped head movements (head tossing and head rocking), nystagmus, vocalizations and restlessness. The following experiment directly tested the ability of tripelennamine to antagonize the canine delirium and autonomic effects produced by NANM in the chronic spinal dog model, actions which are postulated to be mediated by *sigma* receptors.

TABLE 1

EFFECTS OF NANM AND TRIPELENNAMINE (T), ALONE AND IN COMBINATION, IN CHRONIC SPINAL DOGS

	Saline	NANM 1.65 mg/kg	T 1.25 mg/kg	NANM + T Observed	NANM + T Expected
Flexor reflex, low stim. % maximal depression	8 ± 6	60 ± 20*	−3 ± 8	56 ± 22	57 ± 17
Flexor reflex, med stim. % maximal depression	0 ± 4	46 ± 15*	1 ± 4	45 ± 17*	47 ± 16
Flexor reflex, high stim. % maximal depression	−1 ± 2	40 ± 12*	−8 ± 5	35 ± 13*	33 ± 13
Skin twitch reflex % maximal depression	9 ± 6	41 ± 11*	32 ± 5*	52 ± 11*	68 ± 10[A]
Pupil diameter change in mm	−0.3 ± 0.3	0.8 ± 0.3*	1.7 ± 0.4*	1.8 ± 0.4*	2.5 ± 0.6
Heart rate change in beats/min	−3 ± 2	29 ± 6*	12 ± 3*	26 ± 3*	41 ± 7*
Temperature change in °C	−0 ± 0.1	0.1 ± 0.0*	0.1 ± 0.1	0.3 ± 0.0*	0.3 ± 0.1
Stereotypy + nystagmus incidence/5 dogs	0/5	3/5*	0/5	4/5*	3/5

Values in the table are the mean responses ± SE obtained over 1 hr following drug administration in the same 5 dogs. Except for stereotypy + nystagmus measurements, the paired *t*-tests were used for comparisons. NANM and T were compared with Saline; 1-tailed, $*p<0.05$. The effects of NANM + T Observed were compared with Saline; 2-tailed, $*p<0.05$. The NANM + T Expected additive effects were calculated by summing the individual effects of NANM and T and they were compared with NANM + T Observed responses using 2-tailed tests, $*p<0.05$. Similar comparisons of the incidence of simultaneously occurring stereotypy and nystagmus were made using chi-square tests, $*p<0.05$. [A]The expected additive value does not approximate 73% because the sum for one dog was 124%. Since the maximal depression cannot exceed 100%, 100% was used to determine the expected value shown above.

METHOD

Six female beagle dogs were used. Their spinal cords had been transected at the T-10 level according to published methods (5) at least two years before this study. Dogs weighed between 7 and 11 kg, and their health was monitored using periodic physical examinations, blood cell counts, blood chemistry analyses and urinalyses. Physiological and behavioral responses were obtained using objective and subjective procedures (5,19). The measures included two nociceptive reflexes, the flexor and the skin twitch reflexes, respiratory rate, heart rate, pupil diameter, rectal temperature, general behavior activity, secretory activity, covalizations, nystagmus and stereotypic head movements. The flexor reflex of the left hindlimb was evoked by a pneumatically driven toe pinch that delivered either a low, medium or high stimulus strength pinch that corresponded to 4.5, 9, and 18 pounds per square inch, respectively. Evoked flexions were displayed on a polygraph. The latency of the skin twitch reflex was determined by focusing a heat lamp on a shaved area of the left shoulder until the skin twitched or rolled when the heat stimulus became noxious.

Single-drug and two-drug interaction experiments were conducted using a complete crossover design. Experiments consisted of 3 observations made at 10-min intervals during a 30-min control period, the IV administration of either NANM or tripelennamine alone, NANM and tripelennamine given in rapid succession or the saline vehicle over 4 min, and 8 postdrug observations taken over 2½ hr. Dosages were selected from the ascending phase of dose-response curves determined in previous studies (17–19). The 1.65 mg/kg dose of NANM produces well-developed *sigma* effects including canine delirium (stereotypic head movements, nystagmus and vocalizing), but at less than a maximal response level (16,19). This dose would permit the determination of either additive, infra-additive or supra-additive effects resulting from interactions with tripelennamine. The 1.25 mg/kg dose of tripelennamine was selected because it represented a moderate dose in the dog capable of producing antinociception on the skin twitch reflex and autonomic nervous system changes (17,18). Data were analyzed over the first 60 min following drug administration due to the relatively short duration of action of tripelennamine in the dog. Antinociception, measured as depression of the flexor reflex amplitude and prolongation of the skin twitch reflex, was expressed as a percentage of maximal possible depression over 60 min. Other measures were expressed as the mean change over 60 min. One- and two-tailed paired *t*-tests were used to test the statistical significance of differences between single drug responses as compared to the effects of vehicle, and the null hypothesis that the observed NANM + tripelennamine response did not differ from expected additive responses, respectively. Expected additive responses were the sums of the individual tripelennamine and NANM responses. For the interaction comparisons, significant differences represented supra-additive or infra-additive effects; lack of significance demonstrated an additive effect. The criterion for significance statements was $p<0.05$.

RESULTS

The 1.65 mg/kg dose of NANM significantly depressed the flexor and skin twitch reflexes, dilated pupils, increased both heart rate and rectal temperature and produced stereotypic head movement and nystagmus (Table 1). Vocalizations, scored as whining, occurred in 2 of 5 dogs and did not represent a statistically significant effect. General behavioral activity was not affected, as the NANM treatment group was rated as quiet throughout the postobservation period. In the same group of dogs, 1.25 mg/kg of tripelennamine depressed the skin twitch reflex, enlarged pupil diameter and increased heart rate, but did not affect the flexor

reflex or behavioral signs (Table 1). The small increase in rectal temperature was not statistically significant. When administered together, NANM and tripelennamine produced antinociception as demonstrated by depression of the flexor and skin twitch reflexes, mydriasis, tachycardia, hyperthermia, stereotypy and nystagmus (Table 1). One of six dogs receiving NANM and tripelennamine developed seizures; therefore, data for this animal were not included in Table 1. Comparisons of the observed effects to the expected additive effects of the NANM + tripelennamine combination demonstrated that the effects were mostly additive except for the effects on heart rate. In this case, the interaction response was infra-additive with the observed heart rate being equivalent to that produced by NANM alone (Table 1). In no instance was any response to NANM significantly reduced by tripelennamine to levels below those established for NANM alone.

DISCUSSION

The findings demonstrated that tripelennamine generally was not effective in reducing the pharmacological actions of NANM in the dog and that most of the effects produced by the interactions of the two drugs were additive. It is noteworthy that two elements of NANM-induced canine delirium, stereotypy and nystagmus, as well as NANM-induced depression of the flexor reflex were not antagonized by a dose of tripelennamine that lacked a direct effect on these measures, yet affected other parameters. Higher doses of tripelennamine were not tested with NANM to avoid further production of seizure activity. The present data do not, therefore, support the hypothesis, based upon previous behavioral observations (10) and receptor binding data (13), that tripelennamine antagonizes *sigma* receptor-mediated effects. Thus, in the pentazocine-tripelennamine interaction, tripelennamine may not function as an antagonist to block the NANM-like effects of pentazocine.

For measures directly affected by tripelennamine, the observed additive effects of tripelennamine and NANM on the skin twitch reflex, pupil diameter and temperature and their infra-additive effect of heart rate could result if tripelennamine functioned as a weak partial agonist at *sigma* receptors. Although no direct evidence is available to support this speculation, it is interesting to note that a low dose of tripelennamine, which did not generalize to the NANM discriminative stimulus cue in rats, enhanced the NANM-like generalization of low doses of pentazocine and antagonized the generalization produced by higher doses of pentazocine (10). Alternatively, the contribution of tripelennamine to the additive and infra-additive NANM-tripelennamine interaction may be through other neurotransmitter-receptor systems (e.g., cholinergic, adrenergic or histaminergic).

It is also possible that the effects of NANM in the dog may be an inappropriate model for assessing the psychotomimetic effects of pentazocine. Radioreceptor studies have identified two distinct binding sites at which NANM and phencyclidine cross-react, the phencyclidine receptor and the *sigma* receptor, (9, 12, 19, 23). Further, phencyclidine and NANM produce identical pharmacological profiles in the dog (16). Therefore, NANM-induced canine delirium may represent an action with phencyclidine receptors rather than with *sigma* receptors, and the negative results with tripelennamine may reflect its inability to bind to phencyclidine receptors and to effect an antagonism.

An alternative hypothesis is that pentazocine-induced dysphoria and psychotomimetic properties are mediated by *kappa* opioid receptors and not *sigma* receptors. Supporting evidence includes the demonstration that racemic pentazocine and its enantiomers bind to *kappa* receptors (14) and the report that (−)MR2033, a selective benzomorphan *kappa* agonist, but not the (+)-enantiomer, produces dysphoric and psychotomimetic effects in humans (6). Tripelennamine does not bind to *kappa* receptors (14) and, therefore, would not be expected to antagonize *kappa*-mediated effects of pentazocine.

Pharmacokinetic explanations cannot be altogether discounted, though they are assumed to be less likely. Tripelennamine could antagonize NANM at the *sigma* receptor while concomitantly increasing CNS or blood levels of NANM to offset the antagonism by competing with NANM at other sites. Possible mechanisms include reducing NANM's renal clearance, decreasing its hepatic metabolism or displacing plasma protein-bound NANM.

It is difficult to associate the mechanism of action of tripelennamine with opioid or *sigma* receptors to pharmacodynamically explain the effects of NANM-tripelennamine or pentazocine-tripelennamine drug interactions. Therefore, the physiological and behavioral effects of tripelennamine may be mediated through other transmitter systems. However, an indirect opioid mechanism cannot be entirely excluded at present, since tripelennamine itself was identified by experienced drug users as an opioid based on subjective liking and the production of euphoria (4). Yet, the inability of the opioid antagonist naltrexone to antagonize the antinociceptive and autonomic effects of tripelennamine in the dog suggests otherwise (17,18). From these findings, it is concluded that the pharmacological mechanism of action underlying tripelennamine-pentazocine use remains to be elucidated.

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