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Antinociceptive Properties of Tiletamine–Zolazepam Improved by Addition of Xylazine or Butorphanol

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WILSON R. P., I. S. ZAGON, D. R. LARACH AND C. M. LANG. *Antinociceptive properties of tiletamine–zolazepam improved by the addition of xylazine or butorphanol.* PHARMACOL BIOCHEM BEHAV **43**(4) 1129–1133, 1992. – A combination of tiletamine HCl and zolazepam HCl is frequently used as an anesthetic, but little is known about the antinociceptive properties of tiletamine–zolazepam. The antinociceptive properties of tiletamine–zolazepam alone or combined with xylazine or butorphanol were determined in the adult male rate using the tail-flick test. Changes in tail-flick latency were determined at 15, 45, and 75 min after IP drug administration of sterile water, sodium pentobarbital, morphine, tiletamine–zolazepam, xylazine, butorphanol, and tiletamine–zolazepam plus xylazine or butorphanol. Tail-flick latency approximated 100% maximum possible effect (MPE) at 15–75 min postinjection in morphine-treated rats. Tiletamine–zolazepam, xylazine, and butorphanol alone, at any dose utilized, produced less than 50% MPE. However, the combination of tiletamine–zolazepam with butorphanol or xylazine increased tail-flick latency approximately three times greater than tiletamine–zolazepam alone. These results demonstrate that: a) consonant with earlier findings, analgesia and anesthesia are independent states; b) tiletamine–zolazepam is not an effective combination with respect to analgesia; but c) in concert with appropriate drugs, it can exhibit potent antinociceptive properties.

Tiletamine Zolazepam Xylazine Butorphanol Antinociceptive Tail-flick test
Dissociative anesthesia Analgesia α_2-Adrenoceptor Opioid

TILETAMINE HCl is an arylcyclohexylamine structurally related to phencyclidine and ketamine (27,31,33). The arylcyclohexamines produce dissociative anesthesia primarily by a "functional disorganization" of the thalamoneocortical projection system (7,25,31). A combination of tiletamine HCl and zolazepam HCl (Telazol®) is currently marketed as a dissociative anesthetic for use in cats and dogs. Tiletamine alone produces a spectrum of CNS effects ranging from excitement and ataxia at low doses to catelepsy and finally anesthesia at higher doses in mice and rats (5). Tiletamine was more effective in producing general anesthesia in cats and nonhuman primates than other species, but muscle relaxation was only achieved at high doses (5). Zolazepam is a diazepine minor tranquilizer only used in this combination, which reduces the muscle hypertonicity and seizures associated with tiletamine (2,3,24). The tiletamine and zolazepam combination has been used alone or with other drugs as an anesthetic in a variety of laboratory (1–3,13,20,24) and wild animal species (17,18). Previous reports (26,30) indicated the usefulness of this combination as an anesthetic in laboratory rats based upon lack of response to surgical manipulations. Use of tiletamine–zolazepam at recommended doses (26) in our laboratory suggested that it may not provide adequate antinociception for certain surgical procedures. The majority of rats anesthetized with tiletamine–zolazepam for a variety of surgical manipulations (artery catheterization, ovarihysterectomy, bile duct cannulation) exhibited movement and occasionally vocalization upon incision (Wilson, unpublished observations).

The purpose of the present investigation was to examine the antinociceptive properties of tiletamine–zolazepam in adult male rats by evaluating a nociceptive reflex response. In addition, the combination of tiletamine–zolazepam with xylazine or butorphanol was examined for potentiation of antinociception in rats as has been observed in the horse (14), sheep (12), and rabbit (24). The rat tail-flick test was used to determine antinociception in this study because it a) selectively stimulates thermal nociceptors, unlike mechanical stimuli that activate both mechanonociceptors and mechanoceptors (29), and b) is independent of drug-induced changes in motor function (23).

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METHOD

Animals

One-hundred twenty-eight adult, male Sprague-Dawley rats (Crl:SD, Charles River Laboratories, Inc., Wilmington, MA) were used in this study. Rats were housed in groups of five or six per cage in temperature- (21 ± 0.5°C) and light- (12 L : 12 D cycle) controlled mass air displacement cubicles. Food (Rodent Laboratory Chow 5001, Purina Mills, Inc., Richmond, IN) and water were provided ad lib throughout the study except for a 4- to 6-h fast prior to drug administration.

Drugs

The drugs utilized included: morphine sulfate (USP, Eli Lilly Co., Indianapolis, IN), xylazine HCl (Rompun®, Haver-Lockhart, Shawnee, KS), butorphanol tartrate (Torbugesic®, Aveco, Fort Dodge, IA), sodium pentobarbital (Pentobarbital Sodium Solution, Fort Dodge Laboratories, Fort Dodge, IA), and a 1 : 1 mixture of tiletamine HCl and zolazepam HCl (Telazol®, A. H. Robins Co., Richmond,VA). Doses of tiletamine–zolazepam reported in this article refer to the sum of the tiletamine and zolazepam doses (e.g., 40 mg/kg = 20 mg/kg tiletamine + 20 mg/kg zolazepam). Additional drug groups included combinations of tiletamine–zolazepam with either xylazine or butorphanol.

Tiletamine–zolazepam was reconstituted with sterile water. All other drugs were diluted with sterile water to the appropriate concentration so that similar volumes were administered. Drug dilutions were calculated on the basis of administering 0.5 ml/300 g body weight. Rats in the control groups received equivalent volumes of sterile water. All drugs were administered by IP injection into the left caudal abdominal quadrant.

Assessment of Antinociception

Antinociceptive tests were conducted in a room separate from the animal colony with racks containing animal cages transported into the room by 0800 h on the days of testing. During the test period, rats were kept in the same groups and cages as they were housed. Rats were left undisturbed for 3 h to acclimate to room conditions. Antinociceptive testing was conducted between 1100–1700 h.

Antinociception was evaluated by the rat tail-flick test (8) using an analgesia meter (model TF-6, Emdie Instrument Co., Maidens, VA). An intensity setting of 3.15 and cut-off time of 7.0 s were used throughout the study. These settings were determined from the results of preliminary studies to yield baseline tail-flick latencies between 2–4 s. This intensity did not produce immediate or latent burns of the tail in rats exposed to a 7 s stimulus.

Rats were restrained by hand with a small hand towel. Each rat was trained to this restraint method and the apparatus daily for 3 consecutive days. During training periods, rats were restrained for 20–30 s with no stimulation.

Baseline tail-flick latencies were measured sequentially at each of four positions on the tail (1, 2, 3, and 4 cm from the tip; marked with a dot by a black marking pen), with a 30-min interval between each measurement. From these four measurements, a mean baseline tail-flick latency was calculated for each rat.

Rats were injected with drug or sterile water as described above 1 h after the last baseline measurement. Tail-flick latencies were measured 15, 45, and 75 min after injection; each measurement was conducted at a different position on the tail, commencing with a position 1 cm from the tip. These time intervals permitted evaluation of antinociception in a period of time considered suitable for surgical procedures, while maintaining a 30-min interval between measurements. An additional tail-flick latency was measured 24 h later to determine the state of antinociception 1 day following drug administration. Antinociceptive data are expressed as the mean maximum possible effect (% MPE) for each drug group using the following formula (9):

$$\%\,\text{MPE} = \frac{\text{postdrug latency} - \text{mean predrug latency}}{7.0\,\text{s} - \text{mean predrug latency}} \times 100.$$

The loss of the righting reflex following drug administration and the time when the righting reflex returned were recorded. The onset of sleep was calculated as the difference from the time of injection to the loss of righting reflex. The duration of sleep was calculated from the difference between the time of loss of righting reflex and the time of regaining of the righting reflex. Rats that lost their righting reflex were maintained in right lateral recumbency on a 37°C circulating water blanket (Aquamatic K® Module heating pad, Gorman Rupp Industries, Belleville, OH) to minimize changes in body temperature throughout antinociceptive testing.

Data Analysis

Baseline and 24 h tail-flick latencies were analyzed using one-way analysis of variance (ANOVA). Tail-flick latencies at 15, 45, and 75 min after drug administration were analyzed using ANOVA with repeated measures. Subsequent planned comparisons were analyzed using Bonferroni multiple comparison tests. Statistical significance was considered to be $p < 0.05$.

RESULTS

Data for tail-flick latencies, and onset and duration of sleep where applicable, are presented in Table 1. No significant differences in tail-flick latencies were noted between groups prior to drug administration, $F(15, 110) = 0.77$, $p = 0.71$. However, at 24 h there were significant differences in tail-flick latency between groups, $F(15, 109) = 2.61$, $p < 0.05$. Tail-flick latency was significantly elevated in the morphine treated group, in comparison to controls, but was subnormal in both the 40-mg/kg tiletamine–zolazepam- and 40 mg/kg tiletamine–zolazepam + 5 mg/kg xylazine-treated groups. Tail-flick latencies at 15, 45, and 75 min after drug administration differed significantly between drug groups, $F(15, 110) = 12.15$, $p < 0.05$. However, drug–time interaction was not statistically reliable, $F(30, 220) = 1.07$, $p = 0.38$. Thus, data for the three time points were collapsed for further analysis by multiple comparison tests.

Tail-flick latencies of the control group did not differ significantly from baseline at any time point, whereas morphine-treated rats had tail-flick latencies of approximately 95% MPE at 15, 45, and 75 min after drug administration. Seven of eight rats in the morphine-treated group had latencies of 100% MPE at 15–75 min post injection.

TABLE 1

ANTINOCICEPTIVE PROPERTIES OF SELECTED ANALGESICS, ANESTHETICS, AND ANESTHETIC-ANALGESIC COMBINATIONS IN THE ADULT MALE RAT

Group*	Dose (mg/kg)	Onset (min)	Duration (min)	15-75 min MPE (%)†	24-h MPE (%)
Control	0	NA‡	NA	3.48 ± 1.41	−1.05 ± 2.15
Pentobarbital (7)	50	4.1 ± 0.7	73.9 ± 9.0	1.17 ± 6.18	6.58 ± 4.03
Morphine	15	NA	NA	95.38 ± 4.62§	16.01 ± 5.32§
Xylazine	5	NA	NA	17.48 ± 4.15	6.30 ± 5.95
Xylazine (7)	10	NA	NA	9.54 ± 3.86	−4.73 ± 4.03
Butorphanol	5	NA	NA	42.64 ± 9.15	−3.30 ± 3.93
Butorphanol	10	NA	NA	31.90 ± 10.91	1.88 ± 2.11
TZ¶	20	2.8 ± 0.6	42.2 ± 12.3	23.92 ± 4.30	6.03 ± 4.63
TZ	40	2.2 ± 0.4	112.6 ± 10.3	26.08 ± 11.91	−9.80 ± 5.39§
TZ	60	2.5 ± 0.3	115.9 ± 9.7	40.20 ± 13.91	−5.41 ± 5.31
TZ + xylazine	20 + 5	2.7 ± 0.4	129.0 ± 11.1	78.18 ± 10.61§	3.52 ± 5.06
TZ + xylazine	40 + 5	2.0 ± 0.1	201.0 ± 6.7	85.62 ± 10.95§	−7.55 ± 2.57
TZ + xylazine	40 + 10	3.0 ± 0.5	102.0 ± 18.8	68.62 ± 12.10§	−1.43 ± 5.08
TZ + butorphanol	20 + 1.25	2.0 ± 0.3	59.3 ± 5.5	58.20 ± 13.15§	10.86 ± 5.04
TZ + butorphanol	40 + 2.5	2.1 ± 0.4	141.0 ± 4.8	90.11 ± 8.07§	−1.62 ± 4.06
TZ + butorphanol	40 + 5	3.0 ± 0.8	104.8 ± 12.8	82.43 ± 9.60§	−5.18 ± 2.89

All values expressed as mean ± SEM. Time for onset and duration of sleep indicated where applicable.
*Number of animals per group equal eight unless specified in parentheses.
†MPE, maximum possible effect.
‡NA, not applicable.
§Significantly different from control ($p < 0.05$).
¶TZ, total dose of a 1 : 1 mixture of tiletamine HCl and zolazepam HCl.

Tail-flick latencies of pentobarbital- and tiletamine-zolazepam-treated rats were not significantly different from control levels at 15-75 min after drug administration. However, pentobarbital- and tiletamine-zolazepam-treated rats were anesthetized as evidenced by the loss of righting reflex and spontaneous motor activity in these rats. Of note, pentobarbital-anesthetized rats had tail-flick latencies below control levels at 45 and 75 min. Tiletamine-zolazepam alone increased tail-flick latency in a dose-dependent fashion, but even at the highest dose of 60 mg/kg did not increase tail-flick latency to levels comparable to morphine-treated rats.

Tail-flick latencies of rats receiving either 5 or 10 mg/kg xylazine ranged from 10–17% MPE (Table 1). However, administration of xylazine plus tiletamine-zolazepam produced tail-flick latencies comparable to that recorded with morphine treatment and differing significantly from control values (Table 1 and Fig. 1). Injection of 5 mg/kg xylazine plus either 20 or 40 mg/kg tiletamine-zolazepam increased tail-flick latencies approximately twofold greater than the expected additive effect of the two drugs.

Butorphanol increased tail-flick latencies to a greater extent than xylazine but still not comparable to morphine-treated animals. Tail-flick latencies of rats injected with either 5 or 10 mg/kg butorphanol ranged from 32–43% MPE (Table 1). Administration of butorphanol plus tiletamine-zolazepam at all doses significantly increased tail-flick latencies from control levels but comparable to that obtained with morphine (Table 1 and Fig. 1). Tiletamine-zolazepam at a dose of 40 mg/kg with the addition of either 2.5 or 5 mg/kg butorphanol increased tail-flick latencies approximately three times greater than tiletamine-zolazepam alone (Table 1).

It should be noted that the duration of sleep increased with administration of higher concentrations of tiletamine-zolazepam. The combination of either xylazine or butorphanol with tiletamine-zolazepam increased the duration of sleep in rats to an even greater extent (Table 1). However, addition of analgesics to tiletamine-zolazepam did not have any effect on the onset of sleep.

DISCUSSION

The major result of the present study is that tiletamine-zolazepam, which produced states consistent with anesthesia, had minimal effects on nociception. Even at a dose one and one-half times that previously recommended for rats (26), nociception was only moderately affected. Tiletamine-zolazepam produced periods of immobility, loss of consciousness, and loss of righting reflex in the adult male rat as demonstrated in earlier studies (26,30). The time to onset of sleep (2–3 min) was consistent with that demonstrated in other reports (26,30). The duration of sleep in the present study was dose dependent, a property consistent with findings in rats (26,30) and other laboratory animal species (2,3,13,20). The durations of sleep were approximately double those noted in an earlier study (26); however, the rats used in our experiments were older and of greater weight. The durations of sleep in this investigation were within the range of durations noted previously (30).

The lack of appreciable antinociception at any dose of tiletamine-zolazepam detected in these experiments is in contrast to the findings of previous studies (26,30). This discrepancy may be due to the type of nociceptive test used in each investigation. One prior study evaluated nociception based upon the subjective response of rats to surgical and experimental ma-

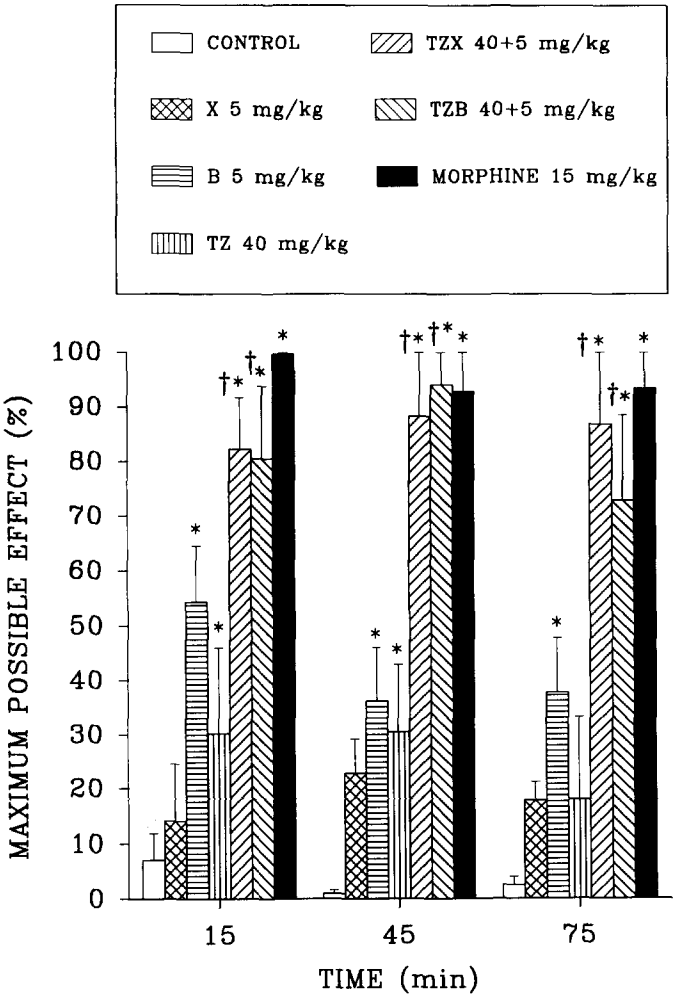

FIG. 1. Effects of xylazine (X), butorphanol (B), tiletamine-zolazepam (TZ), and tiletamine-zolazepam combined with xylazine (TZX) or butorphanol (TZB) on tail-flick latency in rats. Each bar represents mean ± SE of group (n = 7-8/bar) tail-flick latency expressed as maximum possible effect (MPE %). *Significantly different from control ($p < 0.05$). †Not significantly different from morphine-treated rats ($p > 0.05$).

nipulations (30). However, surgical stimuli are complex, not easily quantified, and likely to vary depending upon the particular procedure. Another investigation utilized an abdominal pinch test, a stab incision in the abdominal region, and a skin incision in the cervical area to evaluate nociception in each subject (26). Understandably, the lack of precision of these techniques produced variability, making quantitation and statistical evaluation difficult. Another possible explanation for the minimal increase in tail-flick latency in tiletamine-zolazepam-anesthetized rats recorded in the present study may be due to the doses utilized. Tiletamine alone did not produce any analgesic effect in rats except at a dose of 150 mg/kg (5). In the present experiments, changes in tail-flick latency were not different between the 20- and 40-mg/kg doses but tail-flick was approximately doubled with a dose of 60 mg/kg, indicating some dose dependency. The effect of higher doses of tiletamine-zolazepam on tail-flick latency needs to be evaluated with the possibility of developing a dose-response curve. Tiletamine-zolazepam has an apparent wide margin of safety in the rat; fatalities were not noted in an earlier report until a dose of 200 mg/kg was administered (30).

Our results demonstrated a synergistic effect with respect to antinociception when xylazine or butorphanol was administered in combination with tiletamine-zolazepam. The tail-flick latencies produced by the combination of xylazine or butorphanol with tiletamine-zolazepam were of a similar magnitude to latencies in morphine-treated rats. This magnitude of change in tail-flick latency was not achieved with tiletamine-zolazepam, xylazine, or butorphanol individually. Xylazine alone did not significantly alter nociception despite being considered a potent nonnarcotic analgesic in several species (20). The lack of antinociceptive action in the present report may have been due to the doses (5 or 10 mg/kg) used compared to a dose of 30 mg/kg IP employed in a prior study (4,21). Butorphanol produced an increase in tail-flick latency midway between the control and morphine groups. Even though butorphanol is considered five to seven times more potent than morphine as an analgesic (11,22), some animal tests, including the rat tail-flick test, have found butorphanol to be less potent than morphine (11). The ED_{50} of butorphanol for the rat tail-flick test is 23.3 mg/kg (22), a dose much higher than either dose used in these experiments.

The mechanism of enhanced antinociception produced by tiletamine-zolazepam in conjunction with xylazine or butorphanol is unknown but may be due to action at different sites by the components of the combinations. Xylazine is an agonist at central and spinal α_2-adrenoceptors, which in turn modulate spinal sensory function (34). The combination of agonist activity at central and spinal opiate receptors by tiletamine (16,28) and central and spinal adrenoceptors by xylazine may account for the synergism. However, it is possible that the synergistic action upon tail-flick latency is entirely the result of the drugs' actions at the spinal level. The additive effect of butorphanol and tiletamine-zolazepam could also involve interaction at different spinal opiate sites. Butorphanol is an agonist at κ-opiate receptors, which are associated with spinal analgesia (15).

Data recorded in this investigation also suggest that tail-flick latency is independent of anesthetic state. Therefore, there is a need to specifically define the antinociceptive properties of drugs used to induce anesthesia. Loss of consciousness, motor function, and muscle tone does not necessarily alter the tail-flick response (23). Sodium pentobarbital did not change tail-flick latency relative to control levels despite causing loss of consciousness and righting reflex in drug-treated rats. This finding is in agreement with other studies that demonstrated a lack of antinociceptive properties in pentobarbital-anesthetized rats using thermal (6) or mechanical (32) noxious stimuli and is consistent with the generally poor analgesic properties of barbiturates in man (19). In the present investigation, morphine produced near maximum effect on tail-flick latency in treated rats while not producing loss of righting reflex or loss of consciousness. This finding further supports the independence of tail-flick latency from other properties of anesthesia.

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