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# Cardiovascular and Respiratory Effects of Tiletamine–Zolazepam

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WILSON, R. P., I. S. ZAGON, D. R. LARACH AND C. M. LANG. *Cardiovascular and respiratory effects of tiletamine–zolazepam*. PHARMACOL BIOCHEM BEHAV 44(1) 1–8, 1993.—The combination of tiletamine and zolazepam is an important dissociative anesthetic-tranquilizer. However, little is known about the effects of this combination on the heart and respiration in rats. Adult, male rats anesthetized with tiletamine–zolazepam alone or tiletamine–zolazepam combined with xylazine or butorphanol were evaluated for changes in heart rate, mean arterial blood pressure, arterial blood pH, and blood gases during a 75-min period of anesthesia. Rats anesthetized with tiletamine–zolazepam had increased mean arterial blood pressure and less respiratory depression than did rats anesthetized with sodium pentobarbital. Tiletamine–zolazepam combined with xylazine at either dose produced bradycardia and a marked hypotension that persisted throughout the 75-min period. This combination produced respiratory depression comparable to tiletamine–zolazepam alone. The addition of butorphanol to tiletamine–zolazepam caused a transient hypotension and bradycardia. Tiletamine–zolazepam plus butorphanol produced a mild to severe respiratory depression that was dose and time dependent. These results demonstrate that: a) Tiletamine–zolazepam is cardiostimulatory, a property consistent with the known cardiovascular effects of other dissociative anesthetics; b) xylazine plus tiletamine–zolazepam is a potent cardiovascular depressant combination; and c) tiletamine–zolazepam plus butorphanol at specific doses is an anesthetic–analgesic combination with minimal effects on cardiovascular and respiratory function.

Tiletamine Zolazepam Xylazine Butorphanol Dissociative anesthesia Analgesia
$\alpha_2$-Adrenoceptor Opioid Hypotension Bradycardia Hypercapnia Hypoxemia

TILETAMINE HCl is an arylcyclohexylamine structurally related to phencyclidine and ketamine (27). The arylcyclohexamines produce dissociative anesthesia primarily by a "functional disorganization" of the thalamoneocortical projection system (8,23). A combination of tiletamine HCl and zolazepam HCl (Telazol®) is marketed currently as a dissociative anesthetic for use in cats and dogs. This combination is used alone or with other drugs as an anesthetic in a variety of laboratory (2,3,14,20,22) and wild animal species (16,17). Tiletamine alone produces a spectrum of CNS effects ranging from excitement and ataxia at low doses to catalepsy and finally anesthesia at higher doses in mice and rats (6). Zolazepam is a diazepine minor tranquilizer used only in combination with tiletamine and is thought to reduce the muscle hypertonicity and seizures associated with tiletamine (2,3,22).

Previous reports (26,30) indicated the usefulness of tiletamine–zolazepam as an anesthetic in rodents based upon a lack of response to surgical manipulations. However, these studies did not examine cardiovascular and respiratory effects, or rigorously evaluate nociception, in rodents anesthetized with this drug combination. Prior evaluation of tiletamine–zolazepam in our laboratory (32) suggested that it may not provide adequate antinociception for certain surgical procedures in rats but that antinociception is improved by the addition of xylazine, an $\alpha_2$-adrenoreceptor agonist, or butorphanol, an opioid agonist/antagonist. There are limited reports that have investigated combinations of xylazine and tiletamine–zolazepam in rabbits (22), horses (15), and swine (29) and a species variability in the hemodynamic response to these agents was indicated. Tiletamine–zolazepam combined with butorphanol has only been studied in sheep (13), in which it produced analgesia with minimal effect on the cardiovascular system.

The purpose of the present work was to examine the effects of tiletamine–zolazepam on cardiovascular and respiratory physiology in adult, male rats by measuring mean arterial blood pressure, heart rate, and arterial blood pH and blood gases. A second goal of our investigation was to compare these effects with those produced by tiletamine–zolazepam combined with either xylazine or butorphanol.

## METHOD

### *Animals*

Eighty adult, male Sprague-Dawley rats (Crl:SD, Charles River Laboratories, Inc., Wilmington, MA) weighing 308–429 g were used in this study. Rats were housed five to six per

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cage in temperature- (21 ± 0.5°C) and light- (12 L : 12 D cycle) regulated cubicles. Food (Rodent Laboratory Chow 5001, Purina Mills, Inc., Richmond, IN) and water were provided ad lib throughout the study. Rats were fasted 4–6 h before drug administration.

*Drugs*

The drugs and doses examined were: tiletamine–zolazepam (Telazol, A. H. Robins Co., Richmond, VA) at 20, 40, and 60 mg/kg (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); tiletamine–zolazepam plus xylazine HCl (Rompun®, Haver-Lockhart, Shawnee, KS) at either 20 + 5 or 40 + 5 mg/kg; and tiletamine–zolazepam plus butorphanol tartrate (Torbugesic®, Aveco, Fort Dodge, IA) at 20 + 1.25, 40 + 2.5, and 40 + 5 mg/kg. Sodium pentobarbital (Pentobarbital Sodium Solution, Fort Dodge Laboratories, Fort Dodge, IA) at a dose of 50 mg/kg was included in this study as a standard anesthetic for comparison.

All drugs were diluted with sterile water to the appropriate concentration so that similar volumes were administered. Drug dilutions were calculated so that a volume of 0.5 ml/300 g body weight was administered. Rats in the control group received equivalent volumes of sterile water. All drugs were administered by IP injection into the left caudal abdominal quadrant.

*Evaluation of Cardiovascular and Respiratory Function*

Heart rate, mean arterial blood pressure, blood pH, $PaCo_2$, $PaO_2$, and base excess were measured before and at 15, 45, and 75 min after drug administration.

A left common carotid artery catheter was used for arterial blood samples and blood pressure recordings. These catheters were fabricated from 26-ga Teflon tubing and surgically inserted 24 h before testing using halothane–$O_2$ anesthesia. Rats were moved into the laboratory 2 h prior to testing to acclimate them to the room environment. All rats at the predrug time period and control rats at all time periods were restrained in an open 30 × 20 × 12.5-cm polypropylene container for blood collection and blood pressure recording. After induction of anesthesia, rats were maintained in sternal recumbancy on a 37°C circulating-water heating pad.

Arterial blood samples were collected from the carotid catheter in 135-μl capillary tubes containing sodium heparin, which were then sealed and placed on ice until analysis. The average time between collection and analysis was 10–15 min.

Following blood collection, the catheter was flushed with saline and connected to a pressure transducer. A disposable catheter adapter (Perifix Epidural Catheter Connector, Burron Medical, Inc., Bethlehem, PA) was used to attach the catheter to a three-way stopcock that in turn was connected to a 15-cm length pressure tubing leading to the pressure transducer. Arterial blood pressure was recorded on a Hewlett-Packard 7758B System (Hewlett-Packard Medical Products, Andover, MA). For each time period, a 30-s mean arterial pressure tracing and a 30-s pulse pressure tracing were recorded for each rat. The mean arterial pressure for each rat was calculated by averaging three mean arterial pressures at 10-s intervals. The heart rate for each rat was calculated from a 10-s segment of the pulse pressure recording.

Arterial blood pH, $PaCO_2$, $PaO_2$, and base excess were measured with a pH/blood gas analyzer (Instrumentation Laboratories Blood-Gas Analyzer, Boston, MA). All measurements were adjusted for body temperature at the time of blood sampling. Samples collected before drug administration and from control rats were adjusted for a resting body temperature of 37.8°C. Body temperatures were recorded in anesthetized rats by a rectal temperature probe (Laboratory Thermometer, Model BAT-4, Bailey Instruments, Inc., Saddle Brook, NJ).

The time points for measurement of mean arterial pressure, heart rate, blood pH, $PaCO_2$, $PaO_2$, and base excess were predrug administration (0 time), 15, 45, and 75 min postdrug administration. Body temperatures were only recorded from anesthetized rats at the 15-, 45-, and 75-min periods. After the 75-min recordings and blood samplings, rats were euthanized with an overdose of sodium pentobarbital.

*Statistical Analysis*

Statistical analyses were computed with a statistical software package (BMDP Statistical Software, Inc., Los Angeles, CA). Multiple-range tests were calculated manually.

Predrug values were analyzed by one-way analysis of variance (ANOVA) for mean arterial blood pressure, heart rate, arterial blood pH, arterial blood $PaCO_2$, and arterial blood $PaO_2$ with groups as the independent variable. Group × time interactions for each of the above variables were determined by ANOVA with repeated measures, with groups as the independent variable and the respective variable value at 15, 45, or 75 min as repeated measures.

Further comparisons between groups, matched for time, were computed using the Newman–Keuls multiple-comparison test for each variable. Statistical significance was accepted for $p < 0.05$.

## RESULTS

There was no significant difference among all 10 groups for mean arterial blood pressure, $F(9, 70) = 0.93$, $p = 0.51$, or heart rate, $F(9, 70) = 1.74$, $p = 0.10$, before drug administration. The mean arterial blood pressure and heart rate for all animals were 126 ± 1 mm Hg and 453 ± 6 bpm, respectively.

There was a significant drug effect on mean arterial blood pressure, $F(9, 69) = 30.63$, and heart rate, $F(9, 69) = 16.33$, and significant drug–time interaction on mean arterial blood pressure, $F(2, 18) = 11.27$, and heart rate, $F(2, 18) = 9.42$.

Injection of sodium pentobarbital significantly decreased both heart rate and mean arterial blood pressure compared to control rats (Fig. 1). In contrast, administration of tiletamine-zolazepam had little effect on heart rate but elevated mean arterial blood pressure, the onset and duration of the hypertension depending upon the dose of tiletamine–zolazepam (Fig. 1). Rats anesthetized with combinations of tiletamine-zolazepam and xylazine had significant hypotension and bradycardia at 15, 45, and 75 min compared to control animals (Fig. 2). The degree of hypotension was comparable to that measured in sodium pentobarbital-anesthetized rats; however, the heart rate was 10–20% slower in rats anesthetized with tiletamine–zolazepam plus xylazine. The effects on mean arterial blood pressure and heart rate in rats anesthetized with tiletamine–zolazepam plus butorphanol were dependent upon the dose administered (Fig. 2). Tiletamine–zolazepam plus butorphanol at a dose of 20 + 1.25 mg/kg did not lower blood pressure and increased heart rate significantly greater than the control group at 45 and 75 min. Tiletamine-zolazepam plus butorphanol at both 40 + 2.5 and 40 + 5 mg/kg did significantly lower mean arterial blood pressure

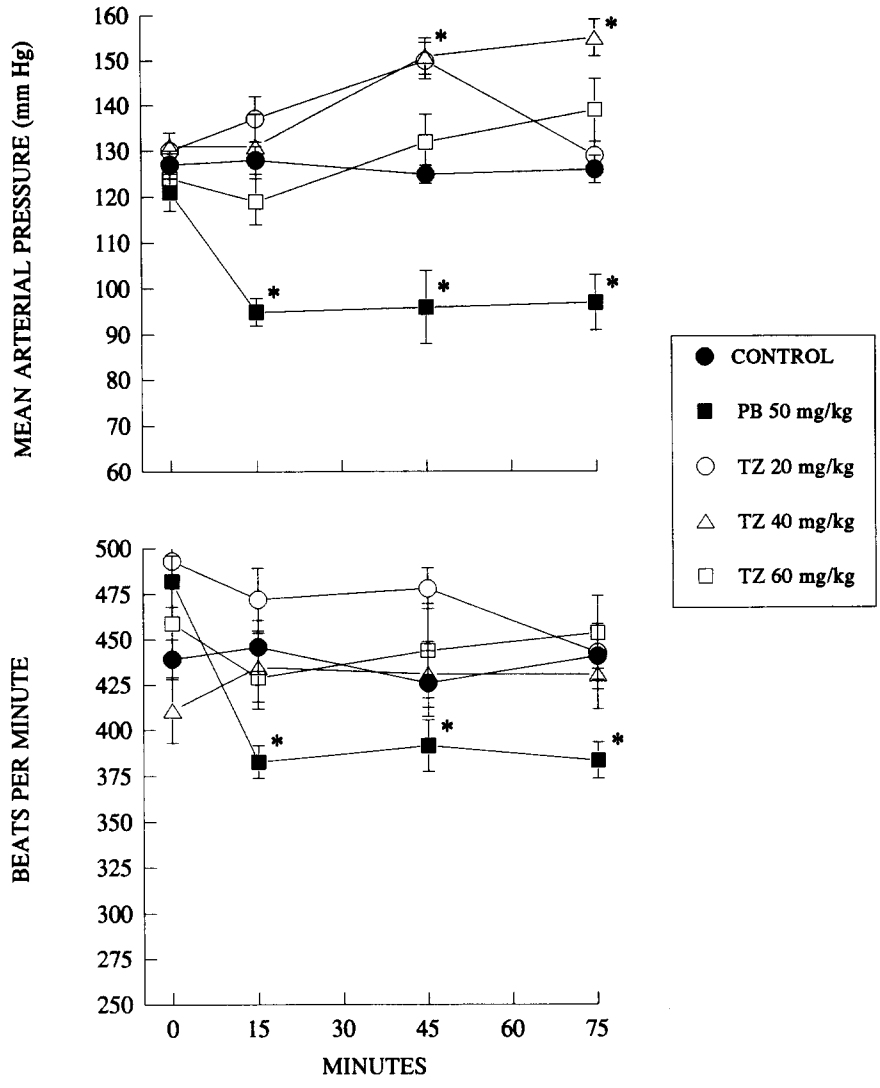


FIG. 1. Time course of effects on mean arterial blood pressure and heart rate after anesthesia with tiletamine-zolazepam (TZ) compared to control and pentobarbital (PB)-anesthetized rats. Each data point represents the mean ± SEM ($n$ = 7–8 rats per group). *Significant difference from control rats, $p < 0.05$.

and heart rate compared to control, but both heart rate and blood pressure returned to near control values at 45 min for the 40 + 2.5-mg/kg dose and 75 min for the 40 + 5-mg/kg dose.

There were no significant differences among groups before drug administration for arterial blood pH, $F(9, 69) = 1.29$, $p = 0.26$. The overall mean arterial blood pH for all rats prior to drug administration was 7.46 ± 0. Likewise, there was no significant difference among groups before drug administration for $PaO_2$, $F(9, 69) = 1.76$, $p = 0.09$. The overall mean $PaO_2$ for all rats prior to drug administration was 104 ± 1 mm Hg. There was a marginal difference among groups before drug administration for $PaCO_2$, $F(9, 69) = 2.03$, $p = 0.05$. However, no significant differences were found when groups were compared by the Newman-Kuels multiple-comparisons test. The overall $PaCO_2$ for all rats prior to drug administration was 38.2 ± 0.4 mm Hg.

All drugs significantly decreased arterial blood pH and $PaO_2$ and elevated $PaCO_2$ compared to control values at all time periods (Figs. 3 and 4). There was a significant drug-time interaction on arterial blood pH, $F(2, 18) = 11.20$, $PaCO_2$, $F(2, 18) = 2.55$, and $PaO_2$, $F(2, 18) = 1.86$.

The highest dose of tiletamine-zolazepam plus butorphanol (40 + 5 mg/kg) differed significantly from all other drugs at 15, 45, and 75 min with respect to blood pH, $PaCO_2$, and $PaO_2$ (Fig. 4). $PaCO_2$ values for anesthetized rats in this group were elevated approximately 60% above control values at all three postdrug periods. Three of eight rats (38%) in this group had $PaCO_2$ values greater than 60 mm Hg at 15 and 45 min postdrug administration. No other drug elevated $PaCO_2$ to this magnitude in any individual animal.

Changes in arterial blood gases and pH in tiletamine-zolazepam-anesthetized rats were comparable to rats anesthetized with sodium pentobarbital (Fig. 3). Rats anesthetized with

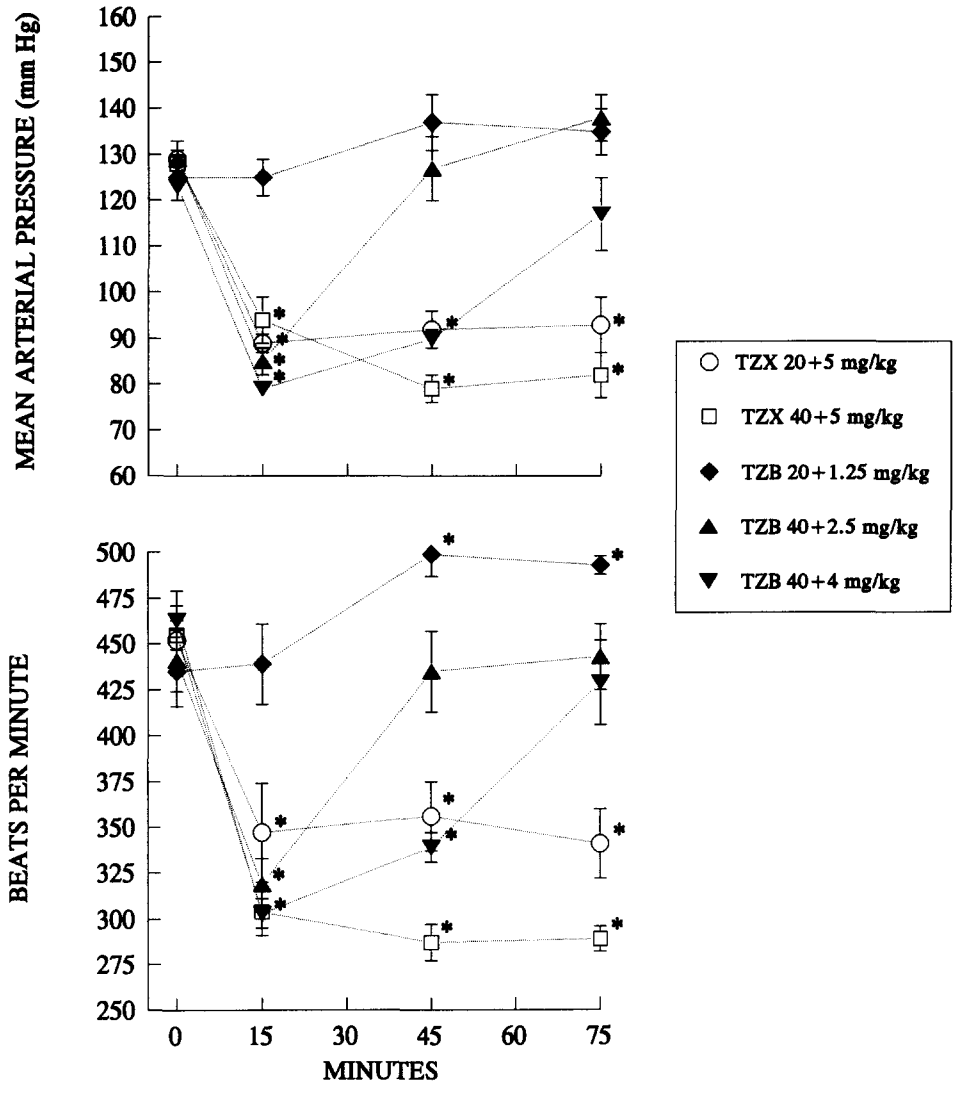


FIG. 2. Time course of effects on mean arterial blood pressure and heart rate after anesthesia with tiletamine-zolazepam combined with either xylazine (TZX) or butorphanol (TZB). Each data point represents the mean ± SEM ($n$ = 8 rats per group). *Significant difference from control rats, $p < 0.05$.

either dose of tiletamine-zolazepam plus xylazine or with 20 + 1.25 and 40 + 2.5 mg/kg of tiletamine-zolazepam plus butorphanol had greater changes in arterial blood pH and blood gases initially but recovered to levels comparable to pentobarbital-anesthetized rats (Fig. 4).

Base excess was measured for all groups except the 40-mg/kg tiletamine-zolazepam group. Predrug values ranged from −1.2 to 6.9. Base excess after drug administration ranged from −3.8 to 7.6. No individual value was ≤ −5.0, which was established in this protocol as a possible indicator of a metabolic component to any acidosis detected.

## DISCUSSION

Drugs used for anesthesia must be carefully evaluated for their analgesic properties and effects on basic physiology in each species for which they will be used. This report is the first to examine objectively the cardiovascular and respiratory effects of tiletamine-zolazepam anesthesia in rats. Rats anesthetized with tiletamine-zolazepam exhibit a time- and dose-dependent hypertension consistent with the known cardiostimulatory effects of dissociative anesthetics (31,34) and its effects in other species (11,12,18). Results of the present study also demonstrate that although the addition of analgesic drugs to anesthetics may improve analgesia the analgesic drug may markedly alter the physiological effects of the anesthetic.

The marked, persistent hypotension and bradycardia observed in rats anesthetized with tiletamine-zolazepam plus xylazine is consonant with this combination's cardiovascular effects in other species (22) and with the cardiovascular effects of xylazine combined with a related dissociative anesthetic, ketamine (19,22,24,33). The decreases in blood pressure and heart rate observed in these studies have been attributed to xylazine, which by itself produces an initial hypertension fol-

lowed by a prolonged hypotension and bradycardia in most species (1,9). Our results, in agreement with previous findings (5,22,24,33), demonstrate that although the addition of xylazine to dissociative anesthetics improves analgesia xylazine has dramatic effects on the cardiovascular system that can reverse the cardiostimulatory properties of the dissociative anesthetics. It should be noted, however, that tiletamine-zolazepam plus xylazine had transient and minimal effects on hemodynamic variables in horses (15) and swine (29), suggesting possible species differences in response to this combination.

The hypotension and bradycardia due to anesthesia with a combination of butorphanol and tiletamine-zolazepam were transient and the magnitude dose-dependent. The initial hypotension and bradycardia detected in rats anesthetized with tiletamine-zolazepam plus butorphanol could be due to a transient effect of the butorphanol, as rats anesthetized with tiletamine-zolazepam exhibited hypertension at the same time points. Previous studies of the cardiovascular effects of butorphanol have reported no significant effects on hemodynamic function in humans (10) to anywhere from minimal (21) to marked cardiovascular depression (25) in dogs. Therefore, it is possible that the degree of cardiovascular depression due to

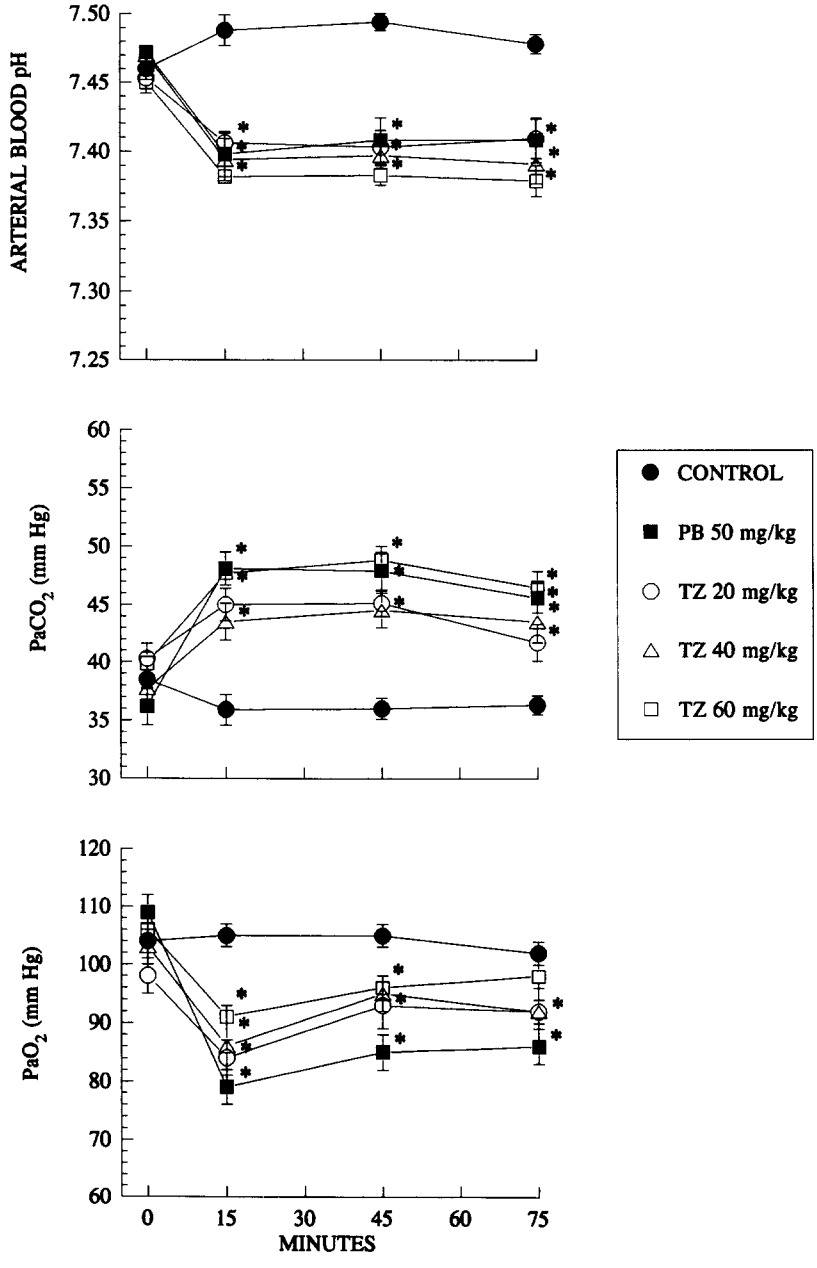


FIG. 3. Time course of effects on arterial blood pH, $PaCO_2$, and $PaO_2$ after anesthesia with tiletamine-zolazepam (TZ) compared to control and pentobarbital (PB)-anesthetized rats. Each data point represents the mean ± SEM ($n$ = 7–8 rats per groups). *Significant difference from control rats, $p < 0.05$.

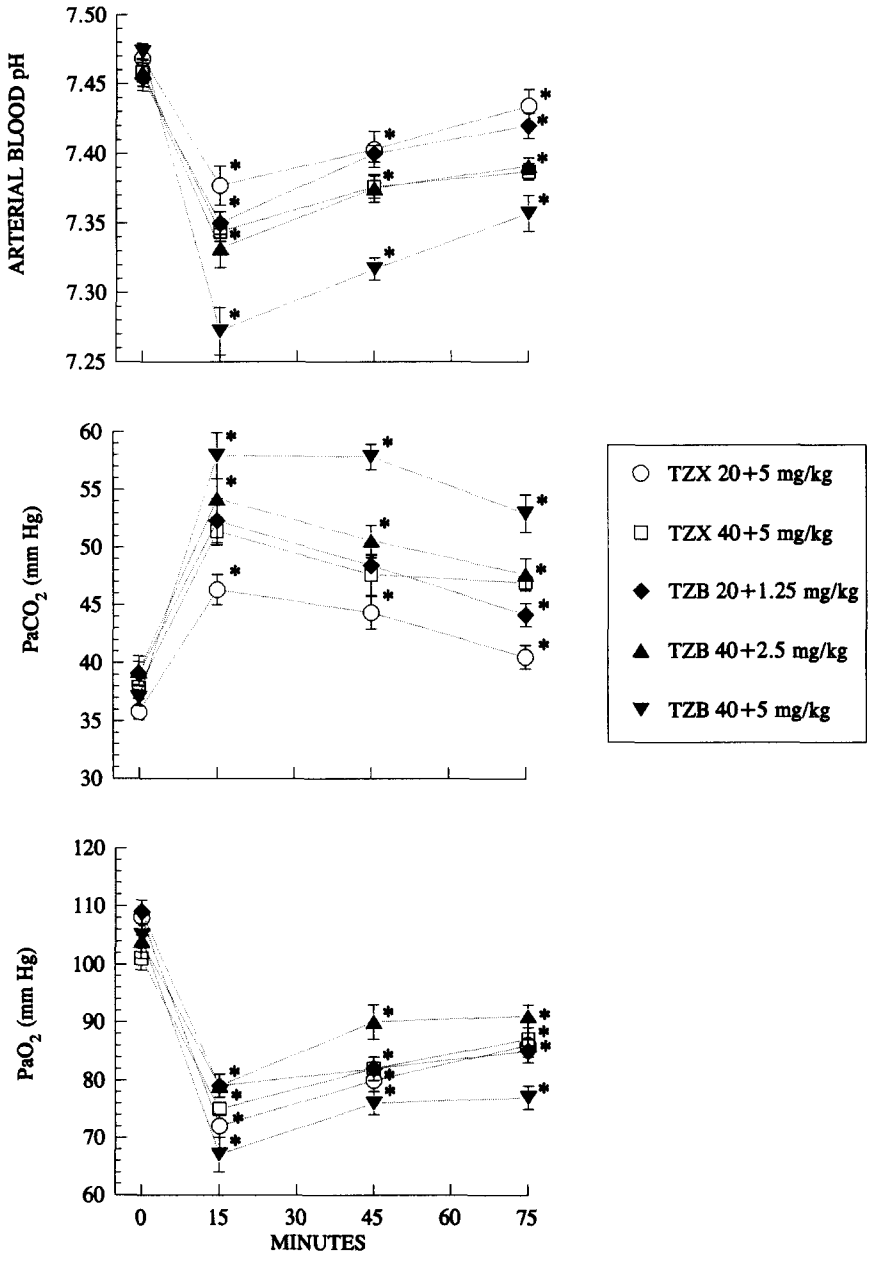


FIG. 4. Time course of effects on arterial blood pH, $PaCO_2$, and $PaO_2$ after anesthesia with tiletamine-zolazepam combined with xylazine (TZX) or butorphanol (TZB). Each data point represents the mean ± SEM ($n$ = 8 rats per group). *Significant difference from control rats, $p < 0.05$.

the addition of butorphanol may depend upon the species also. In the only other evaluation of the hemodynamic effects of combining tiletamine-zolazepam and butorphanol, Howard et al. (13) reported an 18% average decrease in mean arterial blood pressure from baseline levels in anesthetized sheep. Our findings did show that, with time, the cardiac depressant effects of the butorphanol are counteracted by the cardiostimulatory actions of tiletamine-zolazepam in anesthetized rats.

All drugs examined in this investigation produced acidosis and hypercapnia and lowered $PaO_2$. Similar outcomes have been reported previously for barbiturate and ketamine-tranquilizer anesthesia in rats (5,7,28,33). Some degree of acidosis, hypercapnia, and hypoxemia is to be expected in anesthetized, spontaneously breathing animals (4,27). In general, the respiratory depression was no greater than that produced by sodium pentobarbital, with the exception of the highest dose of tiletamine-zolazepam plus butorphanol.

The degree of respiratory depression caused by tiletamine-zolazepam appears to depend upon the species anesthetized. Tiletamine-zolazepam in dogs caused minimal depression of respiration (12,30), while cats exhibited dose-dependent de-

creases in respiratory rate, acidosis, hypercapnia, and hypoxemia (11). The addition of either xylazine or butorphanol to tiletamine-zolazepam at most doses produced minimal changes in arterial blood gases and pH from those seen with tiletamine-zolazepam alone. The exception was the 40 + 5-mg/kg dose of tiletamine-zolazepam plus butorphanol. This dose and combination produced changes in $PaCO_2$, $PaO_2$, and pH and significantly different from tiletamine-zolazepam, tiletamine-zolazepam plus xylazine, or sodium pentobarbital at all postdrug time periods. A possible explanation for the dramatic effect of the highest dose of tiletamine-zolazepam plus butorphanol may be an additive or synergistic action of the two drugs with respect to their individual respiratory depressant effects.

The minimal change in respiratory function produced by the addition of xylazine to tiletamine-zolazepam agrees with the finding of minimal effect on arterial blood gases and pH of xylazine alone in most species (1,9). This contrasts with the moderate to marked hypoxia, hypercapnia, and acidosis produced by ketamine-xylazine in rats (33) and rabbits (19,24). Hubbell et al. (15) reported significant increases in $PaCO_2$ and decreases in pH and $PaO_2$ in tiletamine-zolazepam- and xylazine-anesthetized horses, leading the authors to suggest that the respiratory depression was a combination of the CNS sedative effects of xylazine plus a dose-dependent respiratory depression associated with dissociative anesthetics.

In summary, the results of this investigation suggest that the addition of analgesic drugs can markedly change the physiological effects of an anesthetic. Further, analgesic drugs of different classes combined with the same anesthetic may have different effects on basic physiology. Finally, this study confirms the importance of evaluating both analgesic and physiological effects of anesthetic-analgesic combinations.

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## REFERENCES

1. Booth, N. H. Non-narcotic analgesics. In: Booth, N. H.; McDonald, L., eds. Veterinary pharmacology and therapeutics. Ames, IA: Iowa State University Press; 1988:351-359.
2. Bree, M. M. Dissociative anesthesia in *Macaca mulatta*—clinical evaluation of CI 744. J. Med. Prim. 1:256-260; 1972.
3. Bree, M. M.; Cohen, B. J.; Rowe, S. E. Dissociative anesthesia in dogs and primates: Clinical evaluation of CI 744. Lab. Anim. Sci. 22:878-881; 1972.
4. Brobst, D. Pathophysiologic and adaptive changes in acid-base disorders. J. Am. Vet. Med. Assoc. 183:773-780; 1983.
5. Buelke-Sam, J.; Holson, J. F.; Bazare, J. J.; Young, J. F. Comparative stability of physiological variables during sustained anesthesia in rats. Lab. Anim. Sci. 28:157-162; 1978.
6. Chen, G.; Ensor, C. R.; Bohner, B. The pharmacology of 2-(ethylamino)-2-(thienyl)-cyclohexamine·HCl (CI 634). J. Pharmacol. Exp. Ther. 168:171-179; 1969.
7. Ching, M. Comparison of the effects of althesin, chloralose-urethane, and pentobarbital on mammalian physiologic responses. Can. J. Physiol. Pharmacol. 62:654-657; 1984.
8. Corssen, G.; Reves, J. G.; Stanley, T. H. Intravenous anesthesia and analgesia. Philadelphia, PA: Lea and Febiger; 1988:99-173.
9. Greene, S.; Thurmon, J. Xylazine—a review of its pharmacology and use in veterinary medicine. J. Vet. Pharmacol. Ther. 11:295-313; 1988.
10. Heel, R. C.; Brogden, R. N.; Speight, T. M.; Avery, G. S. Butorphanol: A review of its pharmacological properties and therapeutic efficacy. Drugs 16:473-505; 1978.
11. Hellyer, P.; Muir, W.; Hubbell, J.; Sally, J. Cardiorespiratory effects of the intravenous administration of tiletamine-zolazepam to cats. Vet. Surg. 17:105-110; 1988.
12. Hellyer, P.; Muir, W.; Hubbell, J.; Sally, J. Cardiorespiratory effects of the intravenous administration of tiletamine-zolazepam to dogs. Vet. Surg. 18:160-165; 1989.
13. Howard, B. W.; Lagutchik, M. S.; Januszikiewicz, A. J.; Martin, D. G. The cardiovascular response of sheep to tiletamine-zolazepam and butorphanol tartrate anesthesia. Vet. Surg. 19:461-467; 1990.
14. Hrapkiewicz, K. L.; Stein, S.; Smiler, K. L. A new anesthetic agent for use in the gerbil. Lab. Anim. Sci. 39:338-341; 1989.
15. Hubbell, J. A. E.; Bednarski, F. M.; Muir, W. W. Xylazine and tiletamine-zolazepam anesthesia in horses. Am. J. Vet. Res. 50: 737-742; 1989.
16. Kreeger, T. J.; Seal, U. S.; Callahan, M.; Beckel, M. Physiological and behavioral responses of gray wolves (*Canis lupus*) to immobilization with tiletamine and zolazepam. J. Wildl. Dis. 26: 90-94; 1990.
17. Kreeger, T. J.; Seal, U. S.; Tester, J. R. Chemical immobilization of red foxes (*Vulpes vulpes*). J. Wildl. Dis. 26:95-98; 1990.
18. Lin, H. C.; Thurmon, J. C.; Benson, G. J.; Tranquilli, W. J.; Olson, W. A. The hemodynamic response of calves to tiletamine-zolazepam anesthesia. Vet. Surg. 18:328-334; 1989.
19. Lipman, N. S.; Marini, R. P.; Erdman, S. E. A comparison of ketamine/xylazine and ketamine/xylazine/acepromazine anesthesia in the rabbit. Lab. Anim. Sci. 40:395-398; 1990.
20. Payton, A. J.; Pick, J. R. Evaluation of tiletamine and zolazepam as an anesthetic for ferrets. Lab. Anim. Sci. 39:243-246; 1989.
21. Pircio, A. W.; Gylys, J. A.; Cavanaugh, R. L.; Buyinski, J. P.; Bierwagen, M. E. The pharmacology of butorphanol, a 3,14-dihydroxymorphinan narcotic antagonist analgesic. Arch. Int. Pharmacodyn. Ther. 220:231-257; 1976.
22. Popilskis, S. J.; Oz, M. C.; Gorman, P.; Florestal, A.; Kohn, D. F. Comparison of xylazine with tiletamine-zolazepam (Telazol) and xylazine-ketamine anesthesia in rabbits. Lab. Anim. Sci. 41: 51-53; 1991.
23. Reves, J. G.; Glass, P. S. A. Nonbarbiturate intravenous anesthetics. In: Miller, R. D., ed. Anesthesia. New York: Churchill-Livingstone; 1990:243-279.
24. Sanford, T. D.; Colby, E. D. Effect of xylazine and ketamine on blood pressure, heart rate, and respiratory rate in rabbits. Lab. Anim. Sci. 30:519-523; 1980.
25. Sederberg, J.; Stanley, T. H.; Reddy, P.; Liu, W. S.; Port, F. J.; Gilmor, S. Hemodynamic effects of butorphanol-oxygen anesthesia in dogs. Anesth. Analg. 60:715-719; 1981.
26. Silverman, J.; Huhndorf, M.; Balk, M.; Slater, G. Evaluation of a combination of tiletamine and zolazepam as an anesthetic for laboratory rodents. Lab. Anim. Sci. 33:457-460; 1983.
27. Soma, L. R. Preanesthethic medication. In: Soma, L. R., ed. Textbook of veterinary anesthesia. Baltimore, MD: Williams and Wilkins; 1971:147-151.
28. Svendsen, P.; Carter, A. M. Influence of injectable anaesthetic combinations on blood gas tensions and acid-base status in laboratory rats. Acta Pharmacol. Toxicol. 57:1-7; 1985.
29. Thurmon, J. C.; Benson, G. J.; Tranquilli, W. J.; Olson, W. A.; Tracy, C. H. The anesthetic and analgesic effects of telazol and xylazine in pigs: Evaluating clinical trials. Vet. Med. 38:841-845; 1988.
30. Ward, G. S.; Johnson, D. O.; Roberts, C. R. The use of CI744 as an anesthetic for laboratory animals. Lab. Anim. Sci. 24:737-742; 1974.
31. White, P. F.; Way, W. L.; Trevor, A. J. Ketamine—its pharmacology and therapeutic uses. Anesthesia 56:119-136; 1982.
32. Wilson, R. P.; Zagon, I. S.; Larach, D. R.; Lang, C. M. Antinociceptive properties of tiletamine-zolazepam improved by addi-

tion of xylazine or butorphanol. Pharmacol. Biochem. Behav. 43:1129–1133; 1992.
33. Wixson, S. K.; White, W. J.; Hughes, H. C.; Lang, C. M.; Marshall, W. K. The effects of pentobarbital, fentanyl-droperidol, ketamine-xylazine and ketamine-diazepam on arterial blood pH, blood gases, mean arterial blood pressure and heart rate in adult male rats. Lab. Anim. Sci. 37:736–742; 1987.
34. Wright, M. Pharmacologic effects of ketamine and its use in veterinary medicine. J. Am. Vet. Med. Assoc. 180:1462–1471; 1982.