Effects of acepromazine and butorphanol on tiletamine-zolazepam anesthesia in llamas

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Objective—To evaluate sedative, antinociceptive, and physiologic effects of acepromazine and butorphanol during tiletamine-zolazepam (TZ) anesthesia in llamas.

Animals—5 young adult llamas.

Procedures—Llamas received each of 5 treatments IM (1-week intervals): A (acepromazine, 0.05 mg/kg), B1 (butorphanol, 0.1 mg/kg), AB (acepromazine, 0.05 mg/kg, and butorphanol, 0.1 mg/kg), B2 (butorphanol, 0.2 mg/kg), or C (saline [0.9% NaCl] solution). Sedation was evaluated during a 30-minute period prior to anesthesia with TZ (2 mg/kg, IM). Anesthesia and recovery characteristics and selected cardiorespiratory variables were recorded at intervals. Antinociception was assessed via a toe-clamp technique.

Results—Sedation was not evident following any treatment. Times to sternal and lateral recumbency did not differ among treatments. Duration of lateral recumbency was significantly longer for treatment AB than for treatment C. Duration of antinociception was significantly longer for treatments A and AB, compared with treatment C, and longer for treatment AB, compared with treatment B2. Treatment B1 resulted in a significant decrease in respiratory rate, compared with treatment C. Compared with treatment C, diastolic and mean blood pressures were lower after treatment A. Heart rate was increased with treatment A, compared with treatment B1 or treatment C. Although severe hypoxemia developed in llamas anesthetized with TZ alone and with each treatment-TZ combination, hemoglobin saturation remained high and the hypoxemia was not considered clinically important.

Conclusions and Clinical Relevance—Sedation or changes in heart and respiratory rates were not detected with any treatment before administration of TZ. Acepromazine alone and acepromazine with butorphanol (0.1 mg/kg) prolonged the duration of antinociception in TZ-treated llamas. (Am J Vet Res 2008;69:182–188)

Llamas (Lama glama) have become increasingly popular as companion animals and livestock in the United States during the last 20 years. Commercially, they are used as breeding animals and their fleece is used for fiber. Common husbandry procedures, such as removal of canine teeth and castration, may necessitate anesthesia, and such procedures are often performed in settings where access to inhalational anesthesia and monitoring equipment is not readily available.

The difficulties encountered with venipuncture in llamas have been reported. Venipuncture is further complicated by the lack of adequate restraint in many field settings; thus, protocols for anesthesia via IM injection are more appealing. Combinations of xylazine and ketamine are commonly used for induction of anesthesia in llamas, but this mixture is short acting.

Tiletamine, a noncompetitive N-methyl-D-aspartate antagonist, and zolazepam, a benzodiazepine, are commercially available as a 1:1 combination. This drug combination is commonly used as part of the anesthetic management of domestic animals; however, there is limited information on the effect of TZ in New World camelids. When the combination of TZ (4.4 mg/kg, IM) was administered to llamas and guanacos, adverse effects (eg, muscle tremors and rigidity, salivation, chewing, retching, vocalization, and stumbling) were detected during the recovery phase.

Butorphanol, a synthetic opioid with partial agonist activity at μ-opioid receptors and agonist activity at κ-opioid receptors, is commonly used as a premedication prior to anesthesia in many domestic species. The effects of butorphanol in awake llamas are unpredictable and may result in sedation or excitement. Butorphanol resulted in significant antinociception, compared to baseline values, against thermal nociception in awake sheep for 60 minutes after administration.

**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>TZ</td>
<td>Tiletamine and zolazepam</td>
</tr>
<tr>
<td>SpO₂</td>
<td>Pulse-oximeter-estimated hemoglobin saturation</td>
</tr>
<tr>
<td>DAP</td>
<td>Diastolic arterial blood pressure</td>
</tr>
<tr>
<td>MAP</td>
<td>Mean arterial blood pressure</td>
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</table>

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however, it did not potentiate the anesthetic effects of TZ in goats.\textsuperscript{10}

Acepromazine, a neuroleptic drug belonging to the phenothiazine group,\textsuperscript{11} is widely used in domestic animals either for sedation or as an anesthetic premedication.\textsuperscript{7,12,13} It has antagonistic properties at dopamine D\textsubscript{2} receptors, in addition to actions at catecholamine, 5-hydroxytryptamine 2, and histamine receptors.\textsuperscript{14} Acepromazine improved the induction of anesthesia with TZ in horses\textsuperscript{15} and decreased the minimum alveolar concentration of volatile anesthetics in several species, including ruminants.\textsuperscript{13} To our knowledge, there is no report of the sedative and antinociceptive effects of acepromazine in llamas.

The purpose of the study reported here was to evaluate the sedative, antinociceptive, and physiologic effects of acepromazine and butorphanol during TZ anesthesia in llamas. A question of particular interest was whether butorphanol or acepromazine increased the duration of antinociception in TZ-treated llamas. Thus, the study was designed to test the null hypothesis that acepromazine and butorphanol, alone and in combination, have no effect in increasing the duration of TZ-induced antinociception in llamas.

**Materials and Methods**

**Animals**—Five sexually intact male llamas that were 1 to 2 years old (median weight, 124 kg; range, 92 to 181 kg) were used in the study. The llamas were determined to be in good health on the basis of history and results of physical examination and serum biochemical analyses. The university-owned llamas were dewormed and vaccinated and acclimated to their premises for 10 days prior to the study. Llamas were evaluated on 5 occasions, receiving each treatment at weekly intervals, according to a Latin square design. The study was approved by The University of Tennessee Institutional Animal Care and Use Committee.

**Sedation**—Food was withheld for 24 hours before anesthesia was induced. Approximately 1 hour prior to the start of the experiment, each llama was moved to a quiet room. Baseline values for rectal temperature, pulse, and respiratory rate were recorded once the llama became accustomed to its new environment. The llama then received 1 of the following 5 treatments: A (acepromazine maleate,\textsuperscript{16} 0.05 mg/kg), B1 (butorphanol,\textsuperscript{17} 0.1 mg/kg), AB (acepromazine maleate, 0.05 mg/kg, and butorphanol, 0.1 mg/kg), B2 (butorphanol, 0.2 mg/kg), or C (physiologic saline [0.9% NaCl] solution, 5 mL). The dose of each drug was prepared separately and then combined in a syringe to 5-mL volume with physiologic saline solution; the preparation was immediately injected into the semitendinosus or semimembranosus muscle by use of an 18-gauge, 1.5-inch needle. At 5-minute intervals for a period of 30 minutes, an observer (EBB) evaluated the degree of sedation by use of a 6-point scale (Appendix) in which 0 indicated no sedation and 5 indicated maximum sedation.

**Anesthesia**—Thirty minutes after administration of the premedication treatment, and immediately prior to the administration of the TZ combination (2 mg/kg), respiratory rate and heart rate were recorded. The dose of TZ (prepared to a 5-mL volume with physiologic saline solution) was administered into the semitendinosus or semimembranosus muscle of the contralateral hind limb. The TZ combination doses are reported as the sum of tiletamine and zolazepam doses. After the llama became sterrnally recumbent and its neck could be extended without resistance, it was rolled into left lateral recumbency.

**Recording and monitoring**—Characteristics of anesthesia and recovery and selected cardiorespiratory variables were recorded for each llama during each experiment. These included times from TZ injection to sternal recumbency and to lateral recumbency, duration of antinociception, and times to subsequent sternal recumbency during recovery from anesthesia and to standing. In addition to the quality of recovery, heart rate, Sp\textsubscript{O\textsubscript{2}}, and blood pressures were monitored and recorded every 5 minutes while the llama was recumbent. Heart rate was monitored continuously by use of base-apex ECG electrodes.\textsuperscript{18} Hemoglobin oxygen saturation was estimated by use of a pulse oximetry probe\textsuperscript{19} placed on the tongue. Respiratory rate was determined by observation of thoracic excursions during a 1-minute period.

For blood gas analysis, arterial blood samples (1 mL) were collected percutaneously from the left femoral artery at 5 and 15 minutes after the llama was positioned in left lateral recumbency. Blood was collected anaerobically with a 1-mL syringe containing heparin and samples were analyzed\textsuperscript{20} with a cartridge\textsuperscript{21} within 5 minutes of collection.

During anesthesia, antinociception was assessed every 5 minutes by clamping a digit with 10-inch Vulsellum forceps.\textsuperscript{22} The forceps was closed tightly to the first or second ratchet, depending on the digit size, for a maximum period of 1 minute or released sooner if the llama made a purposeful movement during application of this stimulus. Purposeful movement was defined as gross movement of the limbs or head and was considered to represent an absence of antinociception. Stimuli were applied after cardiorespiratory measurements were recorded. The order in which digits were clamped was randomized, and no digit was clamped on more than 2 occasions.

Quality of recovery was subjectively evaluated by use of a 3-point scale as follows: score 1 = minimal struggling or paddling and standing on the first or second attempt; 2 = mild to moderate struggling and 3 attempts to stand; and 3 = moderate to excessive struggling or paddling during recovery and standing after ≥ 4 attempts.

**Statistical analysis**—A mixed-model ANOVA was used to examine the effect of treatment (ie, sedation) on physical and biochemical values among treatments. The independent variables treatment, time, and interaction...
between treatment and time were evaluated for their effect on the dependent variables heart and respiratory rate; \( \text{PaO}_2 \), \( \text{PaCO}_2 \), \( \text{SpO}_2 \), and DAP, systolic arterial blood pressure, and MAP. Week of treatment, llama, and the 3-way interaction between treatment, llama, and week of treatment were used as the error term in the model. A second mixed-model ANOVA was used to evaluate the effect of treatments on anesthetic and antinociceptive effects. The independent variables were treatment, llama, week of treatment, and body mass were evaluated for their effect on the following dependent variables: time from induction of anesthesia until sternal recumbency, time from induction of anesthesia to lateral recumbency, time from induction of anesthesia to the end of antinociception, duration of lateral recumbency, time from induction of anesthesia to standing, and quality of recovery. By use of the W statistic of Shapiro-Wilk and bency, time from induction of anesthesia to the end of antinociception were evaluated for their effect on the following dependent variables: heart rate, respiratory rate, \( \text{PaO}_2 \), \( \text{PaCO}_2 \), and DAP, systolic arterial blood pressure, and MAP.

**Table 1**—Effect of IM treatment (least squares mean ± SEM) with acepromazine (0.05 mg/kg; A), a low dose of butorphanol (0.1 mg/kg; B1), a combination of acepromazine (0.05 mg/kg) and butorphanol (0.1 mg/kg; AB), a high dose of butorphanol (0.2 mg/kg; B2), or saline (0.9% NaCl) solution (5 mL; C) on times to sternal and lateral recumbency and duration of antinociception, time to standing, and quality of recovery following IM administration of a TZ combination (2 mg/kg) in 5 llamas (each of which received each treatment once).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Time to sternal recumbency (min)</td>
<td>2.9 ± 1.7a</td>
</tr>
<tr>
<td>Time to lateral recumbency (min)</td>
<td>2.9 ± 3.8a</td>
</tr>
<tr>
<td>Duration of antinociception (min)</td>
<td>35 ± 7a</td>
</tr>
<tr>
<td>Duration of lateral recumbency (min)</td>
<td>84 ± 10a</td>
</tr>
<tr>
<td>Time to standing (min)</td>
<td>97 ± 11a</td>
</tr>
<tr>
<td>Quality of recovery</td>
<td>2.3 ± 0.15a</td>
</tr>
</tbody>
</table>

*Duration of lateral recumbency was the interval after injection of TZ to subsequent sternal recumbency.
* Within a variable, row values with the same letter are not significantly \( (P > 0.05) \) different.

**Table 2**—Effect of treatments A, B1, AB, B2, or C on cardiovascular and respiratory variables (least squares mean ± SEM) following IM administration of a TZ combination in 5 llamas (each of which received each treatment once).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>54 ± 3a</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>135 ± 7a</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>70 ± 9a</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>90 ± 9a</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>24 ± 2a</td>
</tr>
</tbody>
</table>

*For this variable, difference between the values at 5 and 15 minutes for each treatment are not significantly \( (P > 0.05) \) different.

\( \text{SAP} = \text{Systolic arterial blood pressure.} \)

See Table 1 for remainder of key.
eral recumbency (ie, interval after injection of TZ to subsequent sternal recumbency) was significantly (P = 0.046) longer for treatment AB (97 ± 10 minutes) than for treatment C (50 ± 10 minutes).

Time to standing did not differ among treatments (Table 1). Recovery was considered smooth on most occasions, and there was minimal struggling or paddling; however, 3 llamas that received treatment A and 1 each that received treatments B1 and B2 made 4 attempts to stand. The quality of recovery did not differ among treatments.

Although cardiorespiratory function was monitored throughout the period of lateral recumbency, regardless of its duration, only the first 30 minutes of cardiovascular and respiratory data are reported (Table 2). During lateral recumbency, heart rate was increased significantly (P = 0.007) for treatment A (34 ± 3 beats per min), compared with treatments B1 (42 ± 3 beats per min) and C (40 ± 3 beats per min). The DAP and MAP values were significantly lower for treatment A than for treatment C.

The respiratory rate of llamas that received treatment B1 decreased significantly (P = 0.022) from baseline, compared with changes in respiratory rate of llamas that received treatment C (Table 2). The PaO2, Paco2, and SpO2 values did not differ significantly within treatments at 5 and 15 minutes, and values did not differ among treatments at either time point. One llama that received each of treatments A, B2, and AB had severe hypoxemia at 5 minutes (PaO2 = 24, 28, and 26 mm Hg, respectively); however, there was no significant difference in these values among groups.

### Discussion

On the basis of results of the present study, butorphanol, acepromazine, or their combination did not induce sedation in llamas by 30 minutes after IM administration of the doses evaluated. To reduce variability in drug uptake, care was taken to ensure that drugs were injected deep into the muscle and that the same site was used for all administrations. A 30-minute period was considered adequate to allow IM premedications to take effect, because most drugs that are administered as aqueous solutions achieve peak plasma concentrations within that interval. For butorphanol, this supposition is supported by published data, which indicate that the mean plasma butorphanol concentration at 15 minutes was higher than the value at 30 minutes following IM administration of the drug to llamas.

The doses of butorphanol used in our study were based on published information that describes the pharmacokinetics and pharmacodynamics of single IV and IM doses (0.1 mg/kg) of butorphanol in llamas. Interestingly, it was reported that 2 llamas became sedated and 2 became excited following butorphanol administration; however, it was not mentioned whether these effects occurred following IV or IM administration. Behavioral effects associated with administration of butorphanol (0.1 or 0.2 mg/kg, IV) in awake sheep have also been reported; in those animals, butorphanol caused restlessness, chewing, and vocalization. No such behavioral effects were observed in the present study, perhaps because these effects are less likely to occur if the drug is given IM.

The reported sedative effects of butorphanol alone, or in combination with other agents, indicate that the drug’s effects are variable. Butorphanol improved the quality of sedation in horses treated with the α2-adrenoceptor agonist romifidine. The inability of butorphanol to potentiate the sedative effects of acepromazine in the present study may be a result of differences in drug interactions or species differences in response.

Acepromazine is widely used for premedication and sedation of domestic species; however, the degree of sedation achieved via acepromazine administration is variable, and the drug cannot be relied upon to induce sedation on every occasion. The dose of acepromazine used in the present study was within the accepted dose range for domestic species. It is possible that a higher dose of acepromazine may have resulted in sedation in the study llamas; however, it is generally accepted that there is little benefit in the use of high doses of acepromazine. Another possibility for the lack of a sedative effect following acepromazine administration was that insufficient time was allowed for signs of sedation to become obvious. This seems unlikely because the onset of sedation following IV administration of acepromazine to horses was approximately 20 minutes, although maximum sedation was not achieved until 33 minutes. In another study, IM administration of acepromazine to horses 23 minutes prior to induction of anesthesia with ketamine improved the quality of induction, indicating that considerable absorption of acepromazine had occurred by that time. The inability to detect a sedating effect for acepromazine or butorphanol in the llamas in the present study could also be attributed to the lack of sensitivity of the sedation assessment scale. This llama sedation scale has been used for a decade in the authors’ workplace and is based on clinical signs; however, it may not suitable for identifying subtle changes in behavior.

Administration of the TZ combination alone resulted in only a brief period of antinociception, making it unsuitable at this dose for most surgical procedures. The TZ combination dose was chosen on the basis of the findings of other experiments by one of our group, in which TZ administered IM at a dose of 2 mg/kg resulted in lateral recumbency and a short period of antinociception in llamas. The combination of TZ appears to have poor antinociceptive effects even at doses capable of causing immobilization. In llamas, higher doses of the TZ combination (4.4 mg/kg) failed to block the response to noxious stimuli; however, the type of nociceptive stimulation was not described. A study in rats revealed that TZ, at doses that resulted in a general anesthesia-like state (ie, caused immobility, loss of consciousness, and loss of the righting reflex), had only minimal effects on the tail-flick test.

Butorphanol did not improve the antinociceptive effects of the TZ combination in our study. In contrast, butorphanol significantly enhanced the antinociceptive effect of TZ in the tail-flick test in rats. This discrepancy may be attributable to the difference in the methods used to measure antinociception and the type of nociceptive stimulus between studies. Butorphanol seems to be efficacious in thermal nociceptive assessments, such as the tail-flick test in rats; in sheep, the drug was...
The lack of significant differences in SpO₂, PaO₂, and PaCO₂ between the butorphanol treatments used in our study indicated that butorphanol-induced respiratory depression in the llamas was not dose dependent.

For all 5 treatments, PaO₂ was low 5 minutes after lateral recumbency and values ranged from 35 to 57 mmHg.
acepromazine, -28 drugs -o o -2 Proceedings. 50 27-29. 27 o o or - - - combination consistent with published values for llamas. AJVR, Scoring Appendix gen delivery, the authors do not considered this to be a of llamas in relation to hemoglobin saturation and oxy hypoxemia; however, because of the unique physiology acepromazine and butorphanol may develop transient ed with TZ alone or TZ with either acepromazine or 86x210 combination of TZ, compared with the effect of treatment with sa enhanced kinetics of oxygen use. 86x226 attitude living, hemoglobin of llamas has a high affinity mm Hg, respectively. As an adaptation to high-alti hemoglobin saturation values of 94%, 90.4%, 84.8%, 86x305 previous study , oximeter in llamas. Nevertheless, the Sp 86x347 pulse oximeter used in our study was not validated of llamas maintained arterial oxygen values of 71.7, 86x368 pulmonamy vasoconstriction. 86x557 After all 5 treatments, the Sp2 values remained relatively high despite the low values for Pa2. The pulse oximeter used in our study was not validated for use in llamas, and we are unaware of any study to validate the use of any commercially available pulse oximeter in llamas. Nevertheless, the Sp2 values are consistent with published values for llamas. 86x589 Additionally, anesthesia causes changes in lung perfusion secondary to decreases in cardiac output and pulmonamy vascular resistance and inhibition of hypoxic pulmonary vasoconstriction.

After all 5 treatments, the Sp2 values remained relatively high despite the low values for Pa2. The pulse oximeter used in our study was not validated for use in llamas, and we are unaware of any study to validate the use of any commercially available pulse oximeter in llamas. Nevertheless, the Sp2 values are consistent with published values for llamas. In a previous study, llamas maintained arterial oxygen hemoglobin saturation values of 94%, 90.4%, 84.8%, and 71.3% at Pa2 values of 71.7, 57.3, 43.1, and 31.9 mm Hg, respectively. As an adaptation to high-altitude living, hemoglobin of llamas has a high affinity for oxygen (P50 value [Pao2] at 50% saturation of hemoglobin) of approx 21 mm Hg at sea level) and enhanced kinetics of oxygen use.

In adult male llamas, acepromazine, butorphanol, or the combination of those drugs did not induce sedation at the doses evaluated in the present study. Prior administration of acepromazine and acepromazine with butorphanol significantly prolonged the analgesic effect of TZ, compared with the effect of treatment with saline solution, but butorphanol alone had no significant effect on TZ-induced antinociception. Llamas treated with TZ alone or TZ with either acepromazine or acepromazine and butorphanol may develop transient hypoxemia; however, because of the unique physiology of llamas in relation to hemoglobin saturation and oxy gen delivery, the authors do not considered this to be a serious problem.

### Appendix

Scoring system used to evaluate sedation in llamas following IM administration of acepromazine, butorphanol, or both drugs in combination or saline (0.9% NaCl) solution.

<table>
<thead>
<tr>
<th>Sedation score</th>
<th>Description of behavior</th>
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<tbody>
<tr>
<td>0</td>
<td>No sedation.</td>
</tr>
<tr>
<td>1</td>
<td>Standing with head below the level of the scapulae.</td>
</tr>
<tr>
<td>2</td>
<td>Standing with head below the level of the scapulae; wide-base stance</td>
</tr>
<tr>
<td>3</td>
<td>Standing with head below the level of the scapulae; swaying of the body.</td>
</tr>
<tr>
<td>4</td>
<td>Sternal recumbency; able to hold head up.</td>
</tr>
<tr>
<td>5</td>
<td>Sternal recumbency with neck extended; can be rolled into lateral recumbency without resistance.</td>
</tr>
</tbody>
</table>

a. Telazol, Fort Dodge Animal Health, Madison, NJ.
c. Acepromazine, 10 mg/ML, VEDCO Inc, St Joseph, Mo.
d. Butorphanol, Fort Dodge Animal Health, Madison, NJ.
e. Passport-XG, Datasearch Corp, Paramus, NJ.
f. Nellcor N-20V pulse oximeter, Nellcor, Pleasanton, Calif.
g. Dinamap veterinary blood pressure monitor 8300, Critikon Inc, Tampa, Fla.
h. i-STAT portable clinical analyzer, Heska Corp, Fort Collins, Colo.
i. i-STAT-Precision-CG+4-07G02, Abbott Laboratories, Abbott Park, Ill.
j. Milteix, Lake Success, NY.

### References