TILETAMINE-ZOLAZEPAM ANESTHESIA IN NORTH AMERICAN RIVER OTTERS (LUTRA CANADENSIS) AND ITS PARTIAL ANTAGONISM WITH FLUMAZENIL


Abstract: North American river otters (Lutra canadensis) were anesthetized with tiletamine-zolazepam or tiletamine-zolazepam-flumazenil combinations in cooperation with the North Carolina Wildlife Resources Commission Otter Restoration Project for evaluation of physiologic changes during anesthesia. Sixteen otters received tiletamine-zolazepam (4 mg/kg combined, i.m.) in 1994. Induction and recovery times were recorded and physiologic data (heart rate and rhythm, respiratory rate, rectal temperature, relative oxyhemoglobin saturation, and mean arterial blood pressure) were collected at 5-min intervals. Respiratory depression developed initially in all otters, and median relative oxyhemoglobin saturation remained below 90% for the first 15 min of anesthesia. Anesthetic induction with tiletamine-zolazepam was rapid and smooth, but recovery was prolonged (median = 89 min) and characterized by persistent head motion. In 1995, flumazenil was evaluated as a partial antagonist for tiletamine-zolazepam anesthesia in otters. Sixteen otters were anesthetized with tiletamine-zolazepam (4 mg/kg combined, i.m.) and given flumazenil (1 mg per 25 mg of zolazepam) after 20 min. Flumazenil markedly shortened recovery time in all otters anesthetized with tiletamine-zolazepam (median = 65 min) with no adverse effects.

Key words: River otter, Lutra canadensis, anesthesia, tiletamine-zolazepam, flumazenil.

INTRODUCTION

Ketamine-midazolam and medetomidine-ketamine-atipamezole have been recommended previously for short-term (25–30 min) field anesthesia in river otters (Lutra canadensis). Tiletamine-zolazepam (Telazol®) has also been recommended for use in river otters, but the anesthetic effects of this combination have not been documented in this species. The potential advantages of tiletamine-zolazepam for field anesthesia include ease of administration because of small injection volume, wide margin of safety, maintenance of protective reflexes, and rapid anesthetic induction. However, the duration and quality of recovery from tiletamine-zolazepam is highly variable, dependent upon species, age, health status, and dosage.

Flumazenil competitively blocks benzodiazepine receptors in the central nervous system and has been developed for use as a specific antagonist for either therapeutic doses or overdoses of the benzodiazepine sedatives. In humans, flumazenil reverses the sedation, muscle relaxation, and respiratory depression produced by diazepam and midazolam. In domestic dogs and cats, flumazenil also reverses the sedative effects of midazolam. Flumazenil has also been used as a partial antagonist for tiletamine-zolazepam anesthesia in domestic dogs and cats to shorten recovery time. The primary objective of this study was to evaluate tiletamine-zolazepam for short-term anesthesia in otters and to compare anesthetic data with previously reported protocols for ketamine, ketamine-midazolam, and ketamine-medetomidine. A secondary objective was to evaluate flumazenil as a partial antagonist for tiletamine-zolazepam anesthesia in otters.

MATERIALS AND METHODS

Anesthesia

The protocol for this study was approved by the North Carolina State University Animal Care and Use Committee. During four winter seasons (1992–1995), 256 North American river otters were anesthetized in cooperation with the North Carolina Wildlife Resources Commission Otter Restoration Project. Multiple anesthetic protocols were evaluated during each year of the study, including isoflurane, ketamine, ketamine-midazolam, ketamine-diazepam, ketamine-medetomidine, ketamine-xylazine, azaperone-midazolam-fentanyl, and tiletamine-zolazepam. Otters were captured, housed, fed, and maintained as described previously. For anesthetic induction, each otter was transferred to a net, weighed using a hand-held metric spring scale, and
then restrained manually for i.m. injection in the cranial thigh muscles. After induction, the otter was placed in right lateral recumbency for the duration of anesthesia.

In 1994, 16 otters (8 males, 8 females) were given tiletamine hydrochloride—zolazepam hydrochloride (100 mg/ml, Telazol, Fort Dodge Laboratories Inc., Fort Dodge, Iowa 50501, USA) at a dosage of 4 mg/kg (combined, i.m.). In 1995, flumazenil hydrochloride (1 mg/ml, Hoffmann-LaRoche, Nutley, New Jersey 07110, USA) was evaluated as a partial antagonist for tiletamine-zolazepam anesthesia because of the relatively long recovery times observed during the previous year (1994). Flumazenil was given to 16 otters (5 males, 11 females) at a dosage of 1 mg per 25 mg of benzodiazepine (zolazepam), or 0.08 mg/kg for otters anesthetized with 4 mg/kg (combined) tiletamine-zolazepam. Flumazenil was administered 20 min after initial anesthetic administration.

**Anesthesia intervals**

The following intervals were defined and monitored during induction and recovery from tiletamine-zolazepam anesthesia in 1994: 1) initial effect, first appearance of ataxia or sedation; 2) induction time, loss of righting reflexes resulting in lateral recumbency; 3) first sign of recovery, return of purposeful head and limb movement; 4) time to sternal, return of righting reflexes resulting in sternal recumbency; 5) time to standing, return to ambulatory state; and 6) total anesthesia time, length of time from anesthetic induction to when the animal became fully alert. In 1995, first sign of recovery, time to sternal, time to standing, and total anesthesia time were recorded for otters recovering from tiletamine-zolazepam-flumazenil.

**Physiologic monitoring**

Heart rate, respiratory rate, rectal temperature, electrocardiogram, relative oxyhemoglobin saturation, and indirect blood pressure were monitored on all anesthetized otters. Physiologic data for each otter were recorded at 5-min intervals from 5 to 30 min in 1994. Heart rate was measured by cardiac auscultation, respiratory rate by direct observation of thoracic excursions, and temperature by rectal thermometer. Electrocardiograms were recorded using a portable electrocardiograph unit (MPE Escort, Hewlett-Packard, Andover, Massachusetts 01810, USA) with standard three-lead placement. Systolic and diastolic blood pressure were measured indirectly, and mean arterial blood pressure was calculated using a Dinamap 1846 blood pressure unit (Critikon Inc., Tampa, Florida 33634, USA). A neonatal no. 4 or 5 cuff was positioned at the base of the tail. Relative percent oxyhemoglobin saturation was monitored using a Nellcor N-100 pulse oximeter (Nellcor Inc., Hayward, California 94545, USA) with a D-20 probe placed on the tongue. Calibration of the pulse oximeter was not performed, and, therefore, percent oxyhemoglobin saturation readings were considered relative and not absolute values.

Apnea was defined as the absence of respiratory effort for 1 min or more. Otters were considered hypoxic if relative percent oxyhemoglobin saturation was less than 80% for ≥5 min, tachycardic if heart rate exceeded 170 beats per min for ≥5 min, and tachypneic if respiratory rate exceeded 40 breaths per min. Hypothermia was subdivided into mild (39.4–40.0°C), moderate (40.1–40.5°C), and severe (40.6–41.1°C).

**Data analysis**

The data were not distributed normally. Therefore, median and 25th and 75th percentiles were used as summary statistics. Microsoft Excel 4.0 for Macintosh (Microsoft Corporation, Redmond, Washington 98052-6399, USA) was used to graph summary statistics for physiologic data from 1994. Anesthetic recovery times (time to first signs of recovery, time to sternal, and time to standing) for tiletamine-zolazepam in 1994 and tiletamine-zolazepam-flumazenil in 1995 were compared using the Wilcoxon signed rank test.11

**RESULTS**

**Tiletamine-zolazepam (1994)**

Anesthetic induction with tiletamine-zolazepam (4 mg/kg, combined) was rapid and smooth in all 16 otters. First anesthetic effects occurred within 1–2 min (median = 1.3 min), and induction was complete within 3 min in most otters (median = 2.4 min). During anesthesia, myorelaxation was generally good. Some otters maintained limb or neck tone, and minor tongue motion persisted in eight otters, interfering intermittently with pulse oximetry recordings. Hypersalivation (mild to moderate) was noted in all otters, and their eyelids remained open throughout the anesthetic period.

The duration of anesthesia with tiletamine-zolazepam was variable. Otters began to show first signs of recovery (return of jaw tone, purposeful limb and head movement) 16–42 min postinjection (median = 29.0 min, Table 1). During the initial stages of recovery, otters exhibited repetitive "co-bralike" head motions before regaining a sternal position. Most otters were responsive to external
Table 1. Comparative recovery times (min) for North American river otters (*Lutra canadensis*) anesthetized with tiletamine-zolazepam (4 mg/kg, combined) with and without partial antagonism by flumazenil (0.08 mg/kg, i.m.) administered after 20 min (n = 16 per group).

<table>
<thead>
<tr>
<th>Interval</th>
<th>Tiletamine-zolazepam</th>
<th>Tiletamine-zolazepam-flumazenil</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Median</td>
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<tr>
<td>First</td>
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<tr>
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* Wilcoxon signed rank test.

stimuli within 45 min but remained ataxic and sedated. Full recovery to an ambulatory state was also variable, ranging from 60–129 min after anesthetic administration (median = 89.0 min, Table 1). Regardless of recovery time, all otters appeared mildly sedated for the remainder of the day.

All otters were apneic for a brief period following anesthetic induction with tiletamine-zolazepam (3–5 min postinjection). Initial respiratory rates after 5–10 min were highly variable among individual otters, ranging from 6–60 breaths/min (Fig. 1A). Eight otters were tachypneic (respiratory rates above 40 breaths/min), with shallow respirations for the first 1.5 min of anesthesia. At 5 min postinjection, relative oxyhemoglobin saturation was less than 90% in all otters, and five otters were hypoxemic (relative oxyhemoglobin saturation less than 80%). Relative oxyhemoglobin saturation increased gradually in all otters during the anesthetic period, and median values rose above 90% after 15 min (Fig. 1B).

Initial heart rates in all otters were greater than 150 beats per minute, and 10 otters were tachycardic (heart rate greater than 170 beats per minute). No other arrhythmias were noted, and median heart rate declined during anesthesia (Fig. 1C). In seven otters, initial mean arterial blood pressures were low (48–72 mm Hg) and then increased (range = 80–140 mm Hg). In the remaining nine otters, mean arterial pressures ranged from 81–125 mm Hg. Mild hypothermia developed in six otters (39.4–40°C), and moderate hyperthermia developed in two (40.1–40.5°C). Rectal temperatures decreased during anesthesia (Fig. 1D).

Given the small sample size, no statistical correlations between physiologic parameters and anesthetic intervals were made. Subjectively, tiletamine-zolazepam produced variable effects in otters with no apparent relationship between anesthetic depth, physiologic changes (e.g., tachycardia, hypertension), and duration of recovery.

Tiletamine-zolazepam-flumazenil (1995)

Recovery times were markedly shortened after flumazenil administration (median = 65.0 min, Table 1). Less ataxia was observed during recovery, and most otters were alert and ambulatory within 70 min of initial anesthetic administration.

**DISCUSSION**

Both dissociative anesthetics and benzodiazepine sedatives are known respiratory depressants, and their effects are dose-dependent in most species.

In North American river otters, marked respiratory depression developed initially after anesthetic induction with tiletamine-zolazepam (4 mg/kg, combined). This pattern is typical of other injectable anesthetics in this species at doses appropriate for short-term anesthesia. After a brief period of apnea, respiratory rates were highly variable among individual otters given tiletamine-zolazepam. Tachypnea, characterized by shallow respirations at rates up to 60 breaths per min, occurred during half of the cases. Tachypnea has also been documented in dogs and cats anesthetized with tiletamine-zolazepam.

For this study, hyperemia was defined as relative oxyhemoglobin saturation below 80%, but values in the range 80–90% were considered undesirable and indicative of depressed cardiopulmonary function. In otters anesthetized with tiletamine-zolazepam, median relative oxyhemoglobin saturation remained below 90% for the first 15 min postinjection, and five otters were hypoxemic. Similar results were obtained in otters anesthetized with ketamine alone. By comparison, otters given a combination of ketamine and midazolam or ketamine and medetomidine had deeper, more regular respirations with higher relative oxyhemoglobin saturation (greater than 90% within 10 min postinjection) than otters given tiletamine-zolazepam.

When possible, supplemental oxygen should be given via facemask, and an endotracheal tube...
Figure 1. Median values for A, respiratory rate, B, relative percent oxyhemoglobin saturation, C, heart rate, and D, rectal temperature at 5-min intervals for 16 North American river otters (Lutra canadensis) anesthetized with tiletamine-zolazepam (4 mg/kg, combined). Error bars represent the 25th and 75th percentiles.
should be available when injectable anesthetics are used in otters.

Heart rates were elevated in all otters anesthetized with tiletamine-zolazepam and were higher than those recorded for otters anesthetized with ketamine, ketamine-midazolam, or ketamine-medetomidine.\textsuperscript{16,17} Aside from tachycardia, no arrhythmias occurred with tiletamine-zolazepam, and heart rates declined gradually during anesthesia. A biphasic change in mean arterial blood pressure (decrease followed by an increase) occurred in half of the cases. High mean arterial blood pressures (120–140 mm Hg) were also recorded in otters anesthetized with ketamine.\textsuperscript{17} Dissociative anesthetics are known to increase sympathetic tone and thereby produce cardiovascular stimulation.\textsuperscript{5,10} To avoid further increases in heart rate and blood pressure, we did not administer atropine. Although most otters developed mild to moderate hypersalivation, no increased airway secretions were detected. For longer procedures using isoflurane for maintenance anesthesia, anticholinergics should be given when necessary.

Mild to moderate elevations in rectal temperature occurred in half of the otters anesthetized with tiletamine-zolazepam. Even higher rectal temperatures were recorded in otters given ketamine or ketamine-midazolam, and one third developed moderate to severe hypothermia (40.1–41.1°C) after induction. Rectal temperatures were lowest in otters anesthetized with ketamine-medetomidine.\textsuperscript{16} No complications occurred secondary to hyperthermia, and rectal temperatures declined gradually during anesthesia in otters regardless of anesthetic protocol.

Anesthetic induction with tiletamine-zolazepam in river otters was smooth and rapid (2–3 min), similar to induction with ketamine-midazolam and medetomidine-ketamine (2–5 min).\textsuperscript{16,17} In our experience, adequate restraint for i.m. injection of the anesthetic was essential and was best accomplished with the otter in a net. A thick woven mat was used for added protection during hand injection in the cranial thigh muscle. Alternative methods include the use of a modified squeeze cage or pole syringe. Given the relatively large amount of subcutaneous space in otters, as well as their strength and agility, manual restraint is not recommended, and net restraint should be performed only by experienced handlers. Subcutaneous administration of any injectable anesthetic to an otter can be expected to result in prolonged induction and reduced anesthetic depth.

For otters anesthetized with tiletamine-zolazepam, the duration of effect was variable, and complete recovery was prolonged. Several otters required more than 120 min before recovering to an ambulatory state. The appearance of early recovery signs did not necessarily reflect shorter total recovery time: three of seven otters with the longest recoveries (greater than 100 min) began spontaneous movements within 20 min of initial anesthetic administration. Most otters exhibited persistent side-to-side head motion during recovery, and mild sedation persisted in all otters for the remainder of the day. For procedures requiring more than 25 min, higher initial dosages of tiletamine-zolazepam would be required, which could further prolong recovery. Alternatively, supplemental isoflurane or ketamine (5 mg/kg, i.m.) can be used to increase anesthetic depth and lengthen anesthesia time following induction with tiletamine-zolazepam.

Although gradual anesthetic recoveries are often preferable in captive zoo situations, more rapid recoveries are advantageous in the field as they reduce the risk of postanesthetic complications. When flumazenil was given 20 min after initial injection of tiletamine-zolazepam, median recovery time (65 min) was considerably shorter than for otters not given the antagonist (89 min). No adverse effects of the dissociative anesthetic were observed, and no resedation was noted following flumazenil administration. The dosage of flumazenil was based upon practical experience in other species and upon published information.\textsuperscript{5,6,7,12} Recovery times for otters anesthetized with ketamine (45 min), ketamine-midazolam (55 min), and medetomidine-ketamine-atipamezole (38 min) were shorter than with tiletamine-zolazepam-flumazenil.\textsuperscript{16,17}

In otters anesthetized with tiletamine-zolazepam, flumazenil produced the desired effect by decreasing recovery time. However, limited success has been achieved with dissociative anesthetic-benzodiazepine-flumazenil combinations in other species. The half-life of flumazenil is relatively short (70 min in people), and resedation may occur with longer-acting sedatives such as diazepam or zolazepam.\textsuperscript{7,14} In addition, antagonism of the benzodiazepine component may unmask the excitatory effects of the dissociative component, producing tonic-clonic convulsions or seizures. If the plasma half-lives of tiletamine and zolazepam are known, the likelihood of adverse effects following flumazenil reversal can be predicted. The plasma half-lives of zolazepam and tiletamine are 4.5 hr and 2.5 hr in the cat and 1 hr and 1.2 hr in the dog.\textsuperscript{10} When flumazenil was evaluated in these species, both recovered more rapidly from tiletamine-zolazepam-flumazenil, but dogs often exhibited excitatory behavior during recovery.\textsuperscript{4,10} Our results sug-
gest that the metabolism of tiletamine-zolazepam in North American river otters is more similar to the domestic cat than to the dog.

We recommend tiletamine-zolazepam (4mg/kg combined, i.m.) for short-term anesthesia in otters. Flumazenil (1 mg per 25 mg of zolazepam) can be administered after a minimum of 20 min as a partial antagonist. When possible, supplemental oxygen should be supplied via mask or endotracheal tube to correct hypoxemia. Caution should be used when administering flumazenil as a partial antagonist for tiletamine-zolazepam anesthesia for the first time in any species. A suitable interval should be allowed between anesthetic induction and administration of the benzodiazepine antagonist.

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LITERATURE CITED


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