Journal of Zoo and Wildlife Medicine 35(1): 65–69, 2004

REVERSIBLE ANESTHESIA OF CAPTIVE CALIFORNIA SEA LIONS (*ZALOPHUS CALIFORNIANUS*) WITH MEDETOMIDINE, MIDAZOLAM, BUTORPHANOL, AND ISOFLURANE

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Abstract: Two adult California sea lions (*Zalophus californianus*) were effectively anesthetized 13 times with medetomidine (0.010–0.013 mg/kg), midazolam (0.2–0.26 mg/kg), and butorphanol (0.2–0.4 mg/kg) by i.m. hand or pole syringe injection. For each anesthetic event, atropine (0.02 mg/kg, i.m.) was administered 6–20 min after initial injections, and oxygen administration via face mask or nasal insufflation began at the same time. Light anesthesia was induced in 8–22 min and lasted 13–78 min. During eight of the procedures, isoflurane (0.5–2.0%) was administered via face mask or endotracheal tube for an additional 30–120 min to facilitate longer procedures or surgery. Anesthesia was antagonized with atipamezole (0.05–0.06 mg/kg) and naltrexone (0.1 mg/kg) in seven events, with the addition of flumazenil (0.0002–0.002 mg/kg) in six events. The antagonists were administered by i.m. injection 42–149 min after administration of the induction agents. All sea lions recovered to mild sedation within 4–17 min after administration of the antagonists.

Key words: *Zalophus californianus*, anesthesia, medetomidine, midazolam, butorphanol.

INTRODUCTION

Complications of short-term anesthesia in pinnipeds include apnea, poor muscle relaxation, and prolonged anesthetic recovery, but death is rare.[1–8,12] In sea lions, partial anesthetic reversal using specific antagonists of anesthetic compounds can prevent or resolve complications.[4,7] Flumazenil can stimulate respiration and reduce recovery time in South American sea lions (*Otaria byronia*) anesthetized with tiletamine and zolazepam,[7] and yohimbine may reduce recovery time in California sea lions (*Zalophus californianus*) anesthetized with detomidine, ketamine, and isoflurane.[4]

In domestic dogs, a combination of medetomidine, midazolam, and butorphanol produces anesthetic effects that can be partially antagonized with atipamezole,[9] with subsequent rapid recovery and mild residual sedation. Flumazenil and naltrexone might, if added to this protocol, produce complete reversal of effects in dogs and other carnivores, including sea lions.

MATERIALS AND METHODS

Two 23-yr-old female California sea lions (*Z. californianus*) at the Smithsonian National Zoological Park were given medetomidine (Dormitor, Pfizer Animal Health, Exton, Pennsylvania 19341, USA; 0.010–0.013 mg/kg, i.m.), along with midazolam (Versed, Roche Laboratories Inc., Nutley, New Jersey 07110, USA; 0.2–0.26 mg/kg, i.m.) and butorphanol (Torbugesic, Fort Dodge Animal Health, Fort Dodge, Iowa 50501, USA; 0.2–0.4 mg/kg, i.m.). One sea lion (M), ranging in weight from 70 to 84 kg, was anesthetized nine times for a severe bite wound and resulting panniculitis. One sea lion (E), ranging in weight from 90 to 109 kg, was anesthetized four times for recurring eye problems and myositis. The sea lions were restrained in a squeeze cage, and the anesthetic agents were administered together using pole syringe or hand injection into the caudal gluteal muscles. After administration of the induction agents, the squeeze cage containing the sea lions was covered to provide a quiet environment. If they were stimulated by noise or touch before heavy sedation, the sea lions exhibited minor head and limb trembling. Every effort was made to minimize stimulation during this period to achieve the maximal anesthetic effects.

Several time intervals were recorded, including time to onset of first signs, when the eyes closed and head and neck were lowered; time to moderate sedation, which was the time elapsed between administration and achievement of sternal recumbency with response to stimuli; time to heavy sedation, which was the interval between administration and loss of response to stimuli but retention of jaw tone; and time to light anesthesia, which was the interval between drug administration and complete relaxation of head, limbs, and jaw, with no response to handling. Total anesthesia time was defined as the time from administration of the induction agents to administration of the reversal agents.

Atropine (Atropine sulfate, Phoenix Pharmaceutical Inc., St. Joseph, Missouri 64506, USA; 0.02 mg/kg, i.m.) was administered by hand injection 6–

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Table 1. Doses of anesthetic agents given to sea lion 1 (M) and sea lion 2 (E) during 13 anesthetic events; all sea lions (*Zalophus californianus*) were supplemented with oxygen delivered via face mask on induction.

Event no.	Sea lion no.	Weight (kg)	Medetomidine dose (mg)	Midazolam dose (mg)	Butorphanol dose (mg)	Atipamezole dose (mg)	Naltrexone dose (mg)	Flumazenil dose (mg)	Isoflurane after induction (min)
1	M1	84	0.84	16.8	16.8	4.2	10	0	0
2	M2	84	0.84	16.8	16.8	4.2	10	0	0
3	M3	78	0.84	16.8	16.8	4.2	10	0	37
4	M4	78	0.84	16.8	16.8	4.2	10	0	36[a]
5	M5	78	0.84	16.8	24	4.2	10	0	15
6	M6	75	0.90	18.7	25	4.5	10	0	26[a]
7	M7	75	0.84	16.8	24	4.2	10	0	13
8	M8	77	1.0	20	30	5.0	10	1.0	0
9	M9	82	1.1	21	33	5.5	10	0.05	31
10	E1	90	1.17	22.5	36	5.85	10	0.2	31[a]
11	E2	105	1.36	26	42	6.8	10	0.02	24
12	E3	109	1.4	27	44	6.8	10	0.04	0
13	E4	105	1.3	28	41	6.5	10	0.04	0

[a] Supplemental isoflurane was given in eight of 13 events via face mask or endotracheal tube.

20 min after administration of the induction agents, when moderate sedation was present. When animals were heavily sedated (6–20 min after administration), they were placed in lateral recumbency with their necks extended, and oxygen (2 L/min) was administered via face mask or nasal insufflation in all 13 events. Sea lions were removed from the squeeze cage for dental and ophthalmic examinations, ultrasound, and muscle biopsies, or they were transported to the veterinary hospital for further diagnostic procedures or surgery.

During eight of 13 events, supplemental isoflurane (Aerrane, Baxter Pharmaceutical Products Inc., Deerfield, Illinois 60015, USA; 0.5–2%) was delivered via face mask (five times) or endotracheal tube (three times) to maintain light anesthesia necessary for longer procedures or surgery. Isoflurane administration was discontinued in two of the events when respiratory rates decreased to 6 breaths/min.

Respiratory rates (breaths/min) and heart rates (beats/min) were measured every 5 min during light anesthesia. Rectal body temperatures were recorded using digital thermometer at the time of initial handling and on completion of all procedures. Relative arterial oxygen hemoglobin saturation (SpO_2) was monitored in all events (Nellcor, N-20, Nellcor Inc., Pleasanton, California 94588, USA).

For anesthetic reversal, a combination of two or three antagonists was administered separately in the triceps muscles: atipamezole (Antisedan, Pfizer Animal Health; 0.05–0.06 mg/kg, i.m.), naltrexone (Trexonil, Wildlife Laboratories Inc., Fort Collins, Colorado 80524, USA; 0.1 mg/kg, i.m.), and flumazenil (Romazicon, 0.1 mg/ml, Roche Laboratories Inc.; 0.0002–0.002 mg/kg, i.m., or 0.02–0.2 mg). Atipamezole and naltrexone were administered in seven events; atipamezole, naltrexone, and flumazenil were administered in six events. In the eight events in which isoflurane was administered, it was first discontinued and oxygen alone continued for a minimum of 5 min before administration of the reversal agents.

Time to initial effect was the interval between administration of reversal agents and when the head was raised in response to stimulation. Time to sternal positioning was the interval between administration of reversal agents and when the head and neck were held up and limb tone returned. Time to mild sedation was the time between administration of reversal agents and return of ambulation with slight ataxia and slightly impaired response to stimulation, and time to complete recovery was the interval between reversal administration and return to a normal or slightly excited condition.

The sea lions were recovered in a covered squeeze cage in quiet surroundings to minimize stimulation and to encourage smooth recovery before release to a dry holding area.

RESULTS

Drugs and dosages administered during the 13 anesthetic events are shown in Table 1. Induction and recovery times are listed in Table 2. No complications were noted during the 13 anesthetic events for both sea lions. Induction was gradual, and induction times were shorter using higher dosages of each drug. The most effective dosages (events nos. 5–13) were medetomidine (0.012–0.13

Table 2. Induction and reversal times of 13 anesthetic events involving two sea lions (*Zalophus californianus*).

	Induction time (min)					Reversal time (min)			
Event no.	Time to onset of first signs	Time to moderate sedation	Time to heavy sedation	Time to light anesthesia	Duration of injectable anesthesia	Time of reversal	Time to initial effect	Time to sternal position	Time to mild sedation
1	2	15	20	30	68	68	4	8	17
2	7	15	20	24	78	78	6	8	15
3[a]	6	12	16	18	37	68	2	3	5
4[a]	2	20	31	32	36	72	2	3	4
5[a]	2	7	7	9	15	50	2	3	5
6[a]	2	16	20	22	26	100	2	6	10
7[a]	4	9	9	11	13	50	2	3	5
8	2	8	12	17	56	56	2	4	6
9[a]	3	9	15	17	31	58	2	8	15
10[a]	2	5	6	8	31	149	2	3	4
11[a]	4	8	11	12	24	63	2	4	5
12	4	8	10	12	46	46	2	6	10
13	2	6	8	10	42	42	3	8	10

[a] Supplemental isoflurane was given in eight events.

mg/kg) combined with midazolam (0.25 mg/kg) and butorphanol (0.4 mg/kg); induction times ranged between 8 and 22 min for these nine events (Table 2). The duration of light anesthesia was variable at the range of dosages evaluated; light anesthesia lasted 13–78 min, and eight of 13 events required supplemental isoflurane to complete clinical procedures.

During induction, respiratory rates decreased from 20–24 breaths/min to 12–16 breaths/min. Apneustic breathing was common, but apnea was not observed. In all events, mucous membrane was either pink or pale pink, suggesting peripheral vasoconstriction caused by the alpha-2 agonistic effects of medetomidine. The depth and quality of respirations, as well as degree of muscle relaxation and depth of anesthesia, improved after repositioning and delivery of supplemental oxygen on induction. Respiratory rates of sea lions given isoflurane decreased with time.

Physiologic data for sea lions anesthetized with medetomidine–midazolam–butorphanol are shown in Table 3. Heart rate, respiratory rate, rectal body temperature, and relative arterial oxygen hemoglobin saturation were compared at 20 and 50 min after drug administration in eight events (four in each sea lion) using the higher dosages (medetomidine 0.012–0.13 mg/kg, midazolam 0.25 mg/kg, and butorphanol 0.4 mg/kg) (Table 3). Values were similar for heart rate (83 and 95 beats/min), respiratory rate (12 and 13 breaths/min), rectal temperature (36.2 and 35.2°C), and SpO_2 (96 and 98%) at 20 and 50 min after drug administration.

For anesthetic reversal, antagonists and dosages were adjusted with experience. Anesthetic reversal was rapid using atipamezole–naltrexone or atipamezole–naltrexone–flumazenil. In the first of 13 events, atipamezole alone was initially administered. Although this sea lion regained limb tone, it remained immobile and heavily sedated until naltrexone was administered 15 min after the atipamezole. Within an additional 15 min, the sea lion had recovered to be released from the squeeze cage to a dry holding area. Within 1 hr, reversal was

Table 3. Mean values for heart rate, respiratory rate, rectal temperature, and relative arterial oxygen hemoglobin saturation in two California sea lions (*Zalophus californianus*) anesthetized with medetomidine–midazolam–butorphanol (MMB) for eight anesthetic events, four in each of two individuals. Supplemental oxygen was administered in all events (6–20 min after drug administration); isoflurane was administered in five of eight events (24–37 min after drug administration).

Time after administration of MMB (min)	Rectal temperature (°C)	Heart rate (beats/min)	Respiratory rate (breaths/min)	Relative oxygen hemoglobin saturation (% SpO_2)
20 (range)	36.2 ± 0.9 (34.6–37.2)	83.5 ± 13.8 (68–102)	12.5 ± 4.0 (8–16)	96.1 ± 1.9 (91–100)
50 (range)	36.2 ± 1.1 (34.0–36.6)	94.5 ± 6.0 (88–100)	13 ± 5.0 (6–20)	98.5 ± 1.9 (95–100)

judged complete, although mild sedation was evident later in the day. As soon as the sea lion recovered its appetite (8 hr), it was given access to pools.

In events nos. 2–7, atipamezole–naltrexone was administered simultaneously, and recovery was smooth and complete within 30 min; however, similar to the first event, mild sedation persisted throughout the day. Flumazenil was added to the eighth and all subsequent events. Different dosages of flumazenil were used (0.0002–0.002 mg/kg), and all were effective; no residual sedation was observed when flumazenil was included in the reversal protocol. Retching or mild vomiting was observed within 4 hr of reversal in four of the 13 events.

Time to initial effect of reversal, time to sternal positioning, and time to mild sedation after administration of naltrexone, atipamezole, and flumazenil (six events) were 2.1 ± 0.4 min (range: 2–6 min), 5.3 ± 2.1 min (3–8 min), and 8.1 ± 3.8 min (4–15 min), respectively.

DISCUSSION

The maximum effect of the medetomidine, midazolam, and butorphanol combination in sea lions at the dosages evaluated was heavy sedation to light anesthesia. Anesthetized sea lions are prone to develop apnea, hypoxemia, and poor muscle relaxation,[1–8,12] but no anesthetic complications were noted in this study. Cardiopulmonary depression is a common complication of alpha-2 agonist administration in a variety of species, including pinnipeds.[9,11] For this reason, low medetomidine dosages were chosen for this protocol. Significant bradycardia was not recorded, respiratory rates remained steady, muscle relaxation was excellent, and isoflurane was easily administered to deepen the plane of anesthesia when necessary.

Atropine was administered between 6 and 20 min after administration of immobilizing agents to control respiratory secretions. The effect of atropine on heart rates in sea lions anesthetized with medetomidine–butorphanol–midazolam was not evaluated in this study. However, initial values for heart rates were lowest at the beginning of each procedure (first measurements were obtained 15–20 min after drug administration) and subsequently increased. Further studies are necessary to gather physiologic data earlier during induction and to evaluate the effect of atropine given either on induction or as a premedicant. Atropine premedication did not prevent bradycardia in southern elephant seals (*Mirounga leonine*) given xylazine or medetomidine (using similar dosages).[10,11]

In sea lions of this study, respiratory depression was observed during induction, including apneustic breathing. Because of the known tendency for anesthetized sea lions to develop hypoxemia, oxygen supplementation via face mask was initiated as soon as the sea lion was safe to handle in all 13 anesthetic events. Vasoconstriction and movement often precluded reliable pulse oximetry readings on induction; oxygen was administered regardless of pulse oximetry recordings. The best oximetry readings were obtained with a rectal reflectance probe, although standard transmission y-clip probes were also placed on the vulva, tongue, or ear pinna. All sea lions were supplemented with oxygen or oxygen and isoflurane, and all reached 100% relative oxygen hemoglobin saturation based on pulse oximetry. Respiratory rates were considered an important indicator of anesthetic depth, and concentrations of isoflurane were adjusted to maintain rates at 6 breaths/min. In two instances, isoflurane administration was discontinued until respiratory rates increased.

In dogs anesthetized with medetomidine–butorphanol–midazolam, reversal was judged complete after atipamezole administration alone.[9] In sea lions, heavy sedation persisted in one event using atipamezole alone, and mild sedation was observed in two events using atipamezole and naltrexone. Low doses of flumazenil (0.02–0.2 mg) were effective in eliminating residual sedation when added to the reversal protocol in sea lions. Administration of flumazenil (0.5–1 mg) prevented respiratory depression in South American sea lions anesthetized with tiletamine–zolazepam; at higher dosages (1 mg per 25 mg of benzodiazepine), flumazenil shortened recovery time.[7]

Further evaluation of safe and effective medetomidine, midazolam, and butorphanol dosages, as well as reversal protocols for sea lions in field situations, is warranted.

CONCLUSIONS

Captive sea lions can be safely anesthetized with medetomidine (0.013 mg/kg, i.m.), midazolam (0.25 mg/kg, i.m.), and butorphanol (0.4 mg/kg, i.m.), and anesthesia can be effectively reversed with atipamezole (0.06 mg/kg, i.m.), flumazenil (0.002 mg/kg, i.m.), and naltrexone (0.1 mg/kg, i.m.).

Atropine (0.2 mg/kg, i.m.) should be given on induction to control airway and oral cavity secretions, and administration can be repeated if bradycardia occurs. Supplemental oxygen should be administered to prevent hypoxemia.

Acknowledgments: We thank the National Zoo's pinniped animal care staff and the staff of the Department of Animal Health for their help with these cases.

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Received for publication 19 November 2001