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RISK FACTORS ASSOCIATED WITH PERIANESTHETIC MORTALITY OF STRANDED FREE-RANGING CALIFORNIA SEA LIONS (*ZALOPHUS CALIFORNIANUS*) UNDERGOING REHABILITATION

Elizabeth M. Stringer, D.V.M., William Van Bonn, D.V.M., Sathya K. Chinnadurai, D.V.M., M.S., Dipl. A.C.Z.M., and Frances M. D. Gulland, M.R.C.V.S., Ph.D.

Abstract: The objective of this study was to identify risk factors associated with perianesthetic mortality of stranded free-ranging California sea lions (*Zalophus californianus*) undergoing rehabilitation. Hospital records of California sea lions that underwent heavy sedation or general anesthesia from 2004 through 2008 were reviewed, including records from 419 anesthetic events. Procedures that resulted in death during or in the subsequent 72 hr of anesthesia were classified as cases ($n = 15$). Procedures in which the animal survived were classified as controls ($n = 334$). Procedures that resulted in euthanasia ($n = 70$) were removed from subsequent analysis. The following risk factors were reviewed: gender, age class, health status, duration of anesthetic period, atropine premedication, induction protocols, maintenance protocols, and history of prior anesthesia. The prevalence of fatalities during anesthesia was 3.4% ($n = 12$) over the 5-yr period. With the inclusion of animals that died within 72 hr after anesthesia, the total mortality prevalence rose to 4.3% ($n = 15$). The most common time of death was during anesthetic maintenance. Health status was the single best predictor of anesthetic outcome, and sea lions premedicated with atropine had increased odds of anesthetic-related death.

Key words: Anesthesia, atropine, California sea lion, perianesthetic death, *Zalophus californianus.*

INTRODUCTION

Rehabilitating sea lions are commonly anesthetized for diagnostic and therapeutic procedures. Numerous anesthetic protocols have been described for otariids.[9,11,12,14,15,18,19,21–23] Some report fairly high anesthetic mortality rates.[8] However, no case control study has been done to identify risk factors of anesthetic-related mortality in pinnipeds.

Reported complications of anesthesia in pinnipeds include apnea, poor muscle relaxation, prolonged anesthetic recovery, hypothermia, hyperthermia, and death.[9,11,13,14,18,19,21,22] Prolonged and poor recoveries have been observed in California sea lions (*Zalophus californianus*) given a medetomidine and tiletamine/zolazepam combination[11] and when tiletamine/zolazepam was reconstituted more than 3 days prior to use.[9] Anesthetic deaths have been reported with various anesthetic protocols.[9,11,18,22] Therefore, understanding risk factors associated with anesthetic deaths in pinnipeds will help veterinarians identify high-risk patients and hopefully reduce mortality. The following retrospective study examined anesthetic records of rehabilitating California sea lions to determine risk factors associated with perianesthetic deaths.

MATERIALS AND METHODS

Hospital records of stranded California sea lions admitted for rehabilitation to the Marine Mammal Center in Sausalito, California, during 2004 through 2008 were reviewed for this study. The facility sees approximately 600 animals per year and admitted 2,160 California sea lions over the 5-year study period. During this time, a total of 419 heavy sedation and general anesthetic procedures were performed on 281 California sea lions. Anesthetic records from these events were reviewed, and complete medical records of animals that died during anesthesia or within the subsequent 72 hr were examined in detail.

The investigation was designed as a retrospective case-control study. All anesthetic procedures that resulted in death during or in the subsequent 72 hr of anesthesia were classified as cases ($n = 15$). All anesthetic procedures that resulted in a live sea lion for up to 10 days post anesthesia were classified as controls ($n = 334$). Seventy-two hours post anesthesia was selected based on our clinical impression that deaths during this period are related to anesthesia.

All data analyzed in the study were gathered from Marine Mammal Center medical records of the case and control sea lions. The following risk

From North Carolina State University, College of Veterinary Medicine, 4700 Hillsborough Street, Raleigh, North Carolina 27606, USA (Stringer, Chinnadurai); and the Marine Mammal Center, Marin Headlands, 1065 Fort Cronkhite, Sausalito, California 94965, USA (Van Bonn, Gulland). Correspondence should be directed to Dr. Stringer (stringer.betsy@gmail.com).

Table 1. Frequency of induction protocols used in rehabilitating California sea lions (*Zalophus californianus*).[a]

Protocol no.	Induction protocol (in mg/kg i.m.)	*n*	%
1	BUT 0.1–0.2, MED 0.04–0.07	36	10.3
2	BUT 0.1–0.3, MID 0.1–0.2	52	14.9
3	BUT 0.1–0.2, MID 0.03–0.2, MED 0.03–.05	24	6.9
4	BUT 0.2, DIAZ 0.2	2	0.6
5	ISO facemask	84	24.1
6	MED 0.04–0.07	55	15.7
7	MID 0.1–0.4, ISO facemask	14	4.0
8	MID 0.1–0.15, MED 0.03–0.04	2	0.6
9	TEL 1–2	3	0.9
10	TEL 0.7–1, MED 0.04–0.07	77	22.0
	Total	349	100

[a] BUT, butorphanol tartrate; MED, medetomidine hydrochloride; MID, midazolam hydrochloride; DIAZ, diazepam; ISO, inhalant isoflurane; TEL, tiletamine hydrochloride and zolazepam hydrochloride.

factors were recorded for each anesthetic event: gender, age class (pup, yearling, subadult, or adult), health status, body weight, duration of anesthetic procedure, premedication with atropine, induction protocol, and maintenance protocol. Age classes were defined as follows: pup <1 yr, yearling 1–2 yr, subadult male 2–8 yr, subadult female 2–5 yr, adult male >8 yr, and adult female >5 yr. These classifications were based on the animal's standard length, stage of tooth development, size of flippers, and development of a sagittal crest in males.[10] Health status was categorized as good, fair, or poor by the attending clinician prior to anesthesia. Duration of anesthesia was defined as the time from the first anesthetic drug's administration until the animal was extubated, the animal was taken off the facemask, reversal agents were administered, or death occurred. The induction period was defined as the time from when the first anesthetic drug was administered until the animal was considered safe to handle.

Perianesthetic deaths were divided into three categories: anesthetic (from induction to the end of anesthesia), recovery (the 3 hr post anesthesia), and postrecovery (from 3 to 72 hr post anesthesia). Intraoperative euthanasias were not considered anesthetic mortalities and were excluded from statistical analysis.

Anesthetic induction protocols (see Table 1) included the use of i.m. butorphanol tartrate (Butorject®, Phoenix Pharmaceutical Inc., St. Joseph, Missouri 64503, USA), medetomidine hydrochloride (Domitor®, Pfizer Animal Health, Exton, Pennsylvania 19341, USA), midazolam hydrochloride (Mayne Pharma Inc., Paramus, New Jersey 07652, USA), diazepam (Roche, South San Francisco, California 94080, USA), tiletamine hydrochloride and zolazepam hydrochloride (Telazol®, Fort Dodge Animal health, Madison, New Jersey 07940, USA), or inhalant isoflurane (Abbott Laboratories, North Chicago, Illinois 60064, USA).

Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each potential risk factor. Continuous variables (body weight and duration of procedure) were tested for normality and then categorized into clinically relevant groups prior to OR analysis. Odds ratios measured the association between a risk factor and perianesthetic death. If there was no association between the factor and perianesthetic death, the OR was 1. Risk factors were those with OR $>$ 1, and protective factors had OR $<$ 1.

Dummy variables were created for all categoric variables to enable analyses of variance and covariate regressions. Univariate analyses were conducted for each potential predictor using a general linear model. Stepwise and backward regressions were then conducted to determine the best-fit model for predicting outcome. This multivariate best-fit model considered all variables that were significant predictors of outcome in the univariate analyses. Lastly, a covariate analysis using a type I SS *P* value was conducted to control for heath status as a potential confounding factor for atropine administration. A *P* value of 0.05 was considered significant. All analyses were performed with a commercially available statistical software program (SAS software, release 9.2, SAS Inc., Cary, North Carolina 27513, USA).

RESULTS

Two hundred and eighty-one animals were anesthetized in 419 different anesthetic events for a variety of medical procedures, including wound debridement, radiography, sonography, magnetic resonance imaging, endoscopy, laparoscopy, and surgery. The majority of anesthetic procedures (79.7%, $n = 334$) resulted in a successfully recovered live animal.

Sixty percent of the procedures were performed on males ($n = 212$; female $n = 137$). Age class distribution of procedures included 41 pups (11.7%), 101 yearlings (28.9%), 146 subadults (41.8%), and 61 adults (17.5%). Animals weighed from 13.6 kg to 254 kg, with a median of 36 kg. Physical status prior to immobilization was scored as good ($n = 143$, 41%), fair ($n = 190$, 54.4%), or poor ($n = 16$, 4.6%). The duration of procedures ranged from 10 to 340 min, with a median of 69 min. Duration was not recorded in two anesthetic events.

Induction protocols used at the Marine Mammal Center during the study period are listed in Table 1. The most commonly used induction protocols included inhalant isoflurane via facemask (24.1%, $n = 84$) or a combination of tiletamine hydrochloride and zolazepam hydrochloride and medetomidine hydrochloride (22%, $n = 77$). Animals were most commonly maintained on inhalant isoflurane via endotracheal tube (65.6%, $n = 229$) or facemask (22.9%, $n = 80$). No additional drugs were used for anesthetic maintenance in 11.5% of anesthetic events ($n = 40$). Atropine was used (at a dosage of 0.015–0.02 mg/kg) in 155 procedures (44.4%) and was the only antimuscarinic used as a premedication in this facility.

The prevalence of fatalities during anesthesia was 3.4% ($n = 12$). Of these, no animals died during induction, 9 died during maintenance, and 3 died during recovery but prior to extubation. Two animals died during the 3-hr postextubation recovery period, and one additional animal died in the subsequent 2 days. Thus, with the inclusion of animals that died within the 72 hr post anesthesia, the prevalence of anesthetic-related fatalities rose to 4.3% ($n = 15$).

The complications that led to death were cardiac and/or respiratory arrest ($n = 9$), poor perfusion ($n = 1$), or not recorded ($n = 2$). Upon review of necropsy records, the underlying medical problems leading to death for the 12 animals that died under anesthesia were trauma ($n = 3$), domoic acid toxicosis ($n = 2$), cerebral hemorrhage ($n = 2$), malnutrition ($n = 2$), leptospirosis ($n = 2$), verminous pneumonia ($n = 1$), septicemia ($n = 1$), and pneumothorax ($n = 1$) (Table 2). Both animals that died within 3 hr of extubation were found dead in their recovery pen. Necropsy records reported malnutrition or white muscle disease as the underlying cause of death for these two individuals. The animal that died in the postrecovery period experienced seizures for the 2 days following the anesthetic procedure, and the ultimate cause of death was determined to be malnutrition.

Of the 15 anesthetic-related deaths, 6.7% had a health status of good ($n = 1$), 73.3% fair ($n = 11$), and 20% poor ($n = 3$). Five of the animals were juveniles and 10 were subadults; no adults or pups suffered anesthetic mortalities.

Odds ratios for perianesthetic risk factors are summarized in Table 3. Factors associated with increased odds of perianesthetic death included premedication with atropine, intubation, poor health status, and maintenance with inhalant isoflurane via endotracheal tube. Differences between years were examined, and no effect was found. Protective factors included the lack of atropine premedication and a good preanesthetic health status.

Univariate analyses showed the following significant associations with perianesthetic death: premedication with atropine ($P = 0.02$), intubation ($P = 0.02$), poor health status ($P = 0.003$), subadult age class ($P = 0.05$), and maintenance with inhalant isoflurane via endotracheal tube ($P = 0.02$). There was also a significant association with perianesthetic survival and good health status ($P = 0.006$).

The multivariate best-fit prediction model for perianesthetic outcome (death, survival), in order of significance, included good health, atropine, and poor health. This model had a P value of 0.002. Intubation, subadult age class, and inhalant isoflurane via endotracheal tube were no longer significant variables in this model. Furthermore, the covariate analysis found that when controlling for good health or poor health, atropine was not a significant predictor of outcome ($P = 0.07$).

DISCUSSION

Pinnipeds have many adaptations to allow for extended breath holding and deep diving, which makes their anesthetic management different than that of terrestrial mammals. Such features include myoglobin-rich muscles that continue to perform in an oxygen-poor environment.[9] Pinnipeds also have approximately twice the blood volume of similarly sized terrestrial mammals, as well as larger erythrocytes and higher hemoglobin concentrations.[9] The pinniped dive reflex is a complex set of physiologic adaptations that allow for the conservation of oxygen for use by the brain and heart while breath holding.[11] This reflex causes bradycardia and shunting of blood.[9,11,19] Lactic acid produced by skeletal muscle is prevented from returning to the heart by venous constriction and pooling of the blood in the peripheral venous

Table 2. Characteristics of all recorded perianesthetic deaths in rehabilitating California sea lions from 2004 through 2008.[a]

Patient	Working diagnosis	Procedure	Health status	Atropine	Induction	Maintenance	Duration (min)	Time of death	Necropsy COD
29.5 kg Subadult male	Encephalitis	Radiographs, ultrasound	Poor	Yes	BUT 0.2, MID 0.15	ISO facemask	70	Maintenance	Domoic acid toxicity
32.5 kg Subadult male	Cellulitis	Radiographs	Fair	Yes	BUT 0.2, MED 0.04	ISO ET tube	32	Maintenance	Spinal cord trauma
32 kg Subadult male	Ocular disease	Ophthalmic surgery	Fair	No	ISO facemask	ISO ET tube	55	Maintenance	Malnutrition
71 kg Subadult male	Lethargy of unknown origin	Radiographs, ultrasound	Poor	Yes	ISO facemask	ISO ET tube	85	Recovery, prior to extubation	Leptospirosis
16.5 kg Yearling male	Corneal rupture	Enucleation	Poor	Yes	ISO facemask	ISO ET tube	55	Maintenance	Septicemia, malnutrition
14.5 kg Yearling female	Subcutaneous emphysema	Radiographs	Fair	Yes	ISO facemask	ISO ET tube	17	Maintenance	Pneumothorax
35 kg Subadult male	Humeral fracture	Orthopedic surgery	Fair	Yes	MID 0.2, ISO facemask	ISO ET tube	125	Maintenance	Trauma
96 kg Subadult male	Renal failure	Laparoscopy for renal biopsy	Fair	Yes	TEL 1, MED 0.04	ISO ET tube	130	Recovery, prior to extubation	Leptospirosis, renal failure, domoic acid toxicity
40 kg Subadult female	Encephalitis	Magnetic resonance imaging	Fair	No	TEL 1, MED 0.07	ISO ET tube	139	Maintenance	Cerebral hemorrhage
46 kg Subadult male	Domoic acid toxicosis	Radiographs, cerebrospinal fluid tap	Fair	Yes	MED 0.07	ISO ET tube	37	Recovery, prior to extubation	Cerebral hemorrhage
25.5 Yearling male	Flipper trauma	Abscess lancing	Fair	Yes	ISO facemask	ISO ET tube	20	Maintenance	Trauma, osteomyelitis
27 kg Subadult female	Humeral fracture	Brainstem auditory evoked response test	Good	No	BUT 0.15, MID 0.15	ISO ET tube	n/a	Maintenance	Verminous pneumonia
23 kg Yearling male	Paresis of hind flippers	Radiographs	Fair	Yes	TEL 1, MED 0.07	ISO ET tube	57	1 hr post extubation	Paralysis, malnutrition
57 kg Subadult male	Skull trauma	Radiographs, ultrasound	Fair	Yes	TEL 1, MED 0.04	ISO ET tube	70	3 hr post extubation	White muscle disease
16 kg Yearling male	Ocular and renal disease	Enucleation	Fair	Yes	ISO facemask	ISO ET tube	65	2 days post anesthesia	Malnutrition

[a] COD, cause of death; BUT, butorphanol tartrate; MID, midazolam hydrochloride; ISO, inhalant isoflurane; MED, medetomidine hydrochloride; ET, endotracheal; TEL, tiletamine hydrochloride and zolazepam hydrochloride; n/a, not available.

Table 3. Risk factors associated with perianesthetic deaths in 349 California sea lions (*Zalophus californianus*) in a rehabilitation facility.[a]

Risk factor	Categories	No. of cases	No. of controls	Odds ratio	95% Confidence interval
Health status	Good	1	142	0.1	0.01–0.74
	Fair	11	179	2.38	0.74–7.63
	Poor	3	13	6.17	1.55–24.57
Age group	Pup	0	41	0	–
	Yearling	5	96	1.24	0.41–3.72
	Subadult	10	136	2.91	0.97–8.71
	Adult	0	61	0	–
Weight (kg)	≤20	3	46	1.57	0.43–5.76
	21–50	9	176	1.35	0.47–3.87
	51–75	2	66	0.62	0.14–2.84
	76–100	1	25	0.88	0.11–6.99
	>100	0	21	0	–
Sex	Male	12	200	2.68	0.74–9.68
	Female	3	134	0.37	0.1–1.35
Intubation	ET tube	14	215	7.75	1.01–59.66
	No ET tube	1	119	0.13	0.02–0.99
Atropine	Yes	11	144	3.63	1.13–11.63
Premedication	No	4	190	0.28	0.09–0.88
Induction	1	1	35	0.61	0.08–4.78
protocol	2	2	50	0.87	0.19–3.99
	3	0	24	0	–
	4	0	2	0	–
	5	6	78	2.19	0.76–6.34
	6	1	54	0.37	0.05–2.88
	7	1	13	1.76	0.22–14.45
	8	0	2	0	–
	9	0	3	0	–
	10	4	73	1.3	0.4–4.2
Maintenance	ISO via ET tube	14	215	7.75	1.01–59.66
	ISO via facemask	1	79	0.23	0.03–1.78
	None required	0	40	0	–
Duration	≤30 min	2	38	1.29	0.28–6.0
	31–60 min	5	106	1.19	0.39–3.64
	61–90 min	4	87	1.13	0.35–3.7
	91–120 min	0	57	0	–
	121–180 min	3	36	2.25	0.6–8.45
	181–240 min	0	7	0	–
	>240 min	0	2	0	–
Year	2004	4	109	0.75	0.23–2.41
	2005	6	69	2.56	0.88–7.44
	2006	3	47	1.53	0.42–5.61
	2007	2	65	0.64	0.14–2.89
	2008	0	44	0	–
Prior anesthesia	Yes	4	120	0.65	0.2–2.08
	No	11	214	1.54	0.48–4.95

[a] ET, endotracheal; ISO, inhalant isoflurane.

circulation during the dive.[19] Although the majority of dives utilize aerobic metabolism, pinnipeds tolerate elevations in carbon dioxide by increasing cerebral blood flow.[6,7]

Perianesthetic complications and mortalities of pinnipeds have been attributed to an inappropriate elicitation of this dive reflex.[11,19] Profound bradycardia and prolonged apnea have been observed just before death.[19] Bradycardia will occur if anesthetized pinnipeds become hypoxic, but it develops more slowly than the bradycardia observed during diving. Therefore, the anesthetist

needs to distinguish between acceptable periods of apnea and prolonged apnea that may result in hypoxia.[19]

The objective of this study was to identify risk factors that predispose California sea lions to perianesthetic mortality. Health status was the single best predictor of outcome. Good health status was found to be a protective factor, and poor health status was associated with increased risk. Of the anesthetic-related deaths, disease condition and severity varied (Table 2) and certainly affected the anesthetic outcome. The relationship between patient health status and anesthetic death has been documented in many small animal, equine, and human studies[3–5,17,20] and plays a significant role in pinnipeds as well. The animals in this study were injured or ill rehabilitating California sea lions, often quite debilitated at the time of their anesthetic procedure, and therefore are likely not representative of pinnipeds in captivity.

Results of this study also suggest that sea lions premedicated with atropine had increased odds of anesthetic-related death. Although health status was a confounding factor in the covariate analysis, atropine administration does still appear to be a predictor of outcome when included in a multivariate model. The combination of several predictors was more powerful than any of them on their own. Although statistically significant, this result could be confounded due to a clinician's choice of using atropine when suspecting a case to be at high risk of anesthetic complications. Atropine has been shown to decrease respiratory secretions and some of the detrimental side effects of the dive reflex, such as bradycardia.[9,11,19] However, its action in otariids is not completely understood.

Atropine premedication in dogs sedated with an α-2 agonist induces tachycardia and hypertension.[1,2,16] In addition, premature ventricular complexes and pulsus alternans have been reported in dogs given this drug combination.[2,16] The increased heart rate may cause excessive increases in oxygen consumption by the myocardium, leading to myocardial hypoxia and arrhythmias.[2] High oxygen demand during a period of oxygen conservation (i.e., a dive response) may be a possible explanation for the increased mortality observed in California sea lions premedicated with atropine.

Although duration was not a risk factor in our study, understanding the timing of the anesthetic death is important for identifying high-risk periods. Our study found that the majority of anesthetic-related deaths occurred during the maintenance period ($n = 9$, 60%). The remaining deaths occurred at various stages of recovery ($n = 3$ prior to extubation, $n = 2$ in the 3 hr post extubation, and $n = 1$ in the 3 days following extubation). No animals died during the induction period. Timing of anesthetic death has also found to be variable in small animals.[4]

Due to the retrospective nature of this study, the patient's anesthetic depth was not consistently available for all anesthetic events. In addition, supportive care during anesthesia, including fluid therapy, external heat sources, and ventilation, were not consistently recorded. Thus, these data were not included in the statistical analyses, a recognized limitation of the study.

Pinnipeds have less cartilaginous tracheal tissue than terrestrial mammals, predisposing them to tracheal collapse under anesthesia.[19] Most species also have a fleshy pharyngeal region that can lead to respiratory obstruction.[19] Intubation is important for maintaining an airway, ensuring adequate oxygenation, and preventing aspiration of regurgitated material in all species but may be especially important for apnea-prone marine mammals.[13] Although intubation and maintenance with isoflurane via endotracheal tube were initially identified as risk factors for perianesthetic death, these variables fell out in the best-fit model. Clinicians may have been more likely to intubate animals that they deemed to be high-risk patients.

Due to difficult vascular access, induction of otariids is primarily through i.m. injection or inhalation.[13] A variety of induction protocols were used during our study period, but none were associated with increased risk. Anesthetic maintenance was achieved most commonly with isoflurane. These drugs have been previously described for use in pinnipeds[9,11,12,14,15,18,19,21,23] and appear to be safe.

The prevalence of anesthetic death in this population of California sea lions (4.3%) was higher than that reported in other species. Estimates of anesthetic mortality rates in dogs and cats are 0.1–0.2%,[4,5] 0.1–1% in horses,[3] and 0.008% in humans.[17] However, these studies include a large number of healthy patients undergoing elective procedures when compared with our population of rehabilitating sea lions. Perianesthetic deaths can result from pre-existing disease, surgical or procedural causes, and the anesthesia itself, or it can be multifactorial.[4] Cardiovascular and respiratory complications are the most commonly reported in the small

animal literature,[4] which is consistent with what was observed in this population of pinnipeds.

This study provides insight into the risk associated with various patient demographics and anesthetic protocols. Health status was the single best predictor of anesthetic outcome, and sea lions premedicated with atropine had increased odds of anesthetic-related death. Understanding risk factors associated with anesthetic deaths in pinnipeds will help veterinarians identify high-risk patients and improve patient care during anesthesia and recovery.

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