Iranian Veterinary Surgery Association

Iranian Journal of Veterinary Surgery

Journal homepage: www.ivsajournals.com

Original Article

Clinical Evaluation of Alfaxalone in Cyclodextrin as an Intravenous Anesthetic in the Common Buzzards (*Buteo buteo*)

Nuh Kılıç*

Department of Surgery, Faculty of Veterinary Medicine, Adnan Menderes University, Aydin, Turkey.

ARTICLE INFO

Article History:

Received 10 February 2021
Revised 2 March 2021
Accepted 7 April 2021
Online 7 April 2021

Keywords:

Alfaxan-CD (R)
Anesthesia
Cyclodextrin
Intravenous buzzard
Recovery

ABSTRACT

There has not been any report about the use of the Alfaxan-CD(R) in common buzzard. The objective of this study was to evaluate the effects of Alfaxan-CD(R) as an intravenous anesthetic agent for inducing anesthesia in the common buzzard and describe some of its clinical pharmacological effects. Eight healthy adult common buzzards (*Buteo buteo*) of unknown sex, weighing 750–1000 grams, kept in captivity at the Dilek Peninsula National Park located in Aydin, Turkey, and appropriately fed (i.e.: rats, mice, rabbits, and day-old chicks) were included in this study. Birds were given alfaxalone (10 mg/kg, by 2-4 mg/kg boluses) intravenously. Variables measured before, and 5, 10, 15, 20, 30, and 90 minutes after induction were the followings: heart rate (HR, beats/min), respiratory rate (RR, breaths/min), cloacal temperature (CT), hemoglobin concentration (Hb), sodium (Na^+), potassium (K^+), ionized calcium (iCa^{++}), arterial pH (pHa), arterial oxygen tension (PaO_2), arterial carbon dioxide tension ($PaCO_2$), bicarbonate concentration (HCO_3) and base excess (BE). All buzzards survived the alfaxalone anesthesia. In this study, alfaxalone provided excellent muscle relaxation and a moderate level of anesthesia. Buzzards given alfaxalone developed primary respiratory acidosis. Base excess and HCO_3 were within the reference range and did not significantly change, indicating a primary respiratory acidosis without metabolic component. All physiologic parameters, except cloacal temperature, returned to approximate baseline values at recovery after anesthesia with alfaxalone. This study indicated that alfaxalone produced good to excellent anesthesia in buzzards, characterized by rapid induction of anesthesia, excellent muscle relaxation, unresponsiveness to noxious stimuli, and smooth, uneventful recovery from anesthesia. Hypoventilation and apnea were uncommon at clinically relevant doses but became the most important adverse effects when larger doses were administered rapidly IV.

Introduction

General anesthesia in raptors may be induced by administration of either inhalant or parenteral injectable agents.[1] Isoflurane has become the inhalant anesthetic of choice for raptors but its use requires expensive equipment such as a vaporizer and breathing system.[2,3] Injectable anesthetic agent may offer

*Correspondence to: Nuh Kılıç, Department of Surgery, Faculty of Veterinary Medicine, Adnan Menderes University, Isikli, Aydin, Turkey. E-mail: nuh_kilic44@hotmail.com

www.ivsajournals.com© Iranian Journal of Veterinary Surgery, 2021
https://doi.org/10.30500/IVSA.2021.272674.1250

advantages such as minimal equipment and low cost.

Alfaxalone is a synthetic neuroactive steroid, which interacts with the gamma aminobutyric acid $(GABA)_A$ receptor producing anesthesia and muscle relaxation. This water-insoluble molecule has been used in the past in humans and in cats and dogs in a co-formulation with alfadolone, another related steroid, and a polyoxyethylated castor oil-based surfactant.[4,5] In the cat, hyperemia or edema of the pinnae or forepaws was observed in 69% of all animals injected with the observed adverse effects being related to the Cremophor EL.[4] In dogs, Cremophor EL induces an anaphylactoid reaction with histamine release and a subsequent fall in arterial blood pressure with urticaria and skin erythema.[5] The release of histamine has been also observed in humans and led to the withdrawal of the Althesin formulation from the human medical market. A new Cremophor-free formulation of alfaxalone (without alfadolone) has been developed for use in small animals by solubilizing alfaxalone in 2-hydroxypropyl-beta cyclodextrin (HPCD).

Although this anesthetic has rapidly gained popularity in the veterinary medicine, its use in common buzzard has not been evaluated. Therefore, the objective of this study was to investigate Alfaxan-CD(R) as an intravenous anesthetic agent for inducing anesthesia in the common buzzard and describe some of its clinical pharmacological effects.

Materials and Methods

All of the experiments were performed according to Experimental Animal Management Law of Turkey and approved by Animal Ethics Committee of University of Adnan Menderes. A 24-gauge, 19 mm catheter (Venflon, Ohmeda, Sweden) was aseptically secured with suture material in the brachial artery and the medial tarsal vein. The buzzards were then allowed to relax. The medial tarsal vein was injected by alfaxalone (Alfaxan-CD RTU, 10 mg/ml, Jurox Pty. Ltd, Rutherford, Australia) via the catheter at a dose of 10 mg/kg during a 1-minute period followed by repeated bolus injections of 2-4 mg/kg of alfaxalone for up to 30 minutes only when birds showed signs of awakening.

Measurements

Following variables were measured before, and 5, 10, 15, 20, 30, and 90 minutes after induction: heart rate (HR, beats/min), respiratory rate (RR, breaths/min), cloacal temperature (CT), hemoglobin concentration (Hb), sodium (Na^+), potassium (K^+), ionized calcium (iCa^{++}), arterial pH (pHa), arterial oxygen tension (PaO_2), arterial carbon dioxide tension ($PaCO_2$), bicarbonate concentration (HCO_3) and base excess (BE). Respiratory rate was determined by direct observation.[6] A pulse oximeter probe was placed to the tarsometatarsus to determine the heart rate. Arterial blood samples were obtained into heparinized syringes for the measurement of electrolytes and blood gas using an automated blood gas analyzer, which corrected the reported values for body temperature to 41° C.

The quality of recovery was scored subjectively as follows:

Excellent: assumed sternal position with little or no struggle; walked without assistance or struggle; once standing, didn't fall to sternal recumbency; minimal ataxia when walking.

Satisfactory: assumed sternal position with little or no struggle; premature standing without weakness in hind limbs; once standing, falls to sternal recumbency unlikely; slight ataxia.

Poor: some struggling; repeated attempts to move from lateral to sternal recumbency; premature standing with splayed and weak hind limbs; once standing, repeatedly falls to sternal recumbency; manual restraint required to avoid injury.

The recovery period was calculated as the time between the onset of painful stimulus and the return to a standing position. Side effects were recorded.

Data Analysis

For statistical evaluation, the SPSS 15. 0 program (Statistical Products and Service Solutions) was used. Values were analyzed by using a repeated measures ANOVA to test for significant changes over time and Tukey's test was used to test for changes at specific times. Data were presented as mean ± SEM.

Results

All buzzards survived the alfaxalone anesthesia. Alfaxalone induced muscle relaxation and analgesia and buzzards were placed in dorsal recumbency immediately after the induction. Two of them began paddling their feet periodically 1-2 minutes after the induction.

After the initial bolus of alfaxalone, all buzzards were placed in dorsal recumbency. In the case of birds showing signs of awakening, additional boluses of 2-4 mg/kg of anesthesia were given as required to sustain the anesthesia with minimal response to the pinch

every five minutes. All buzzards developed transient apnea for 10 to 20 seconds after the induction bolus. Supplemental oxygen was not provided.

At the 30 minutes measurement, all buzzards had recovered from the general anesthesia although there was still some degree of sedative effects. No side effect except flapping of wings was noted during the recovery period which lasted 23.5 ± 7.2 minutes. Quality of recovery was excellent in 5 and satisfactory in the 3 remaining buzzards.

Data for the HR, RR, CT and electrolytes are summarized Table 1. There was little change in HR with time, and the values remained during the anesthesia period over 325 beats/minutes. The RR decreased significantly after induction. Cloacal temperature was evidently reduced between 15 and 30 minutes after induction. Mean ionized calcium concentration decreased evidently. Blood gas data are summarized in Table 2. After induction with alfaxalone developed a slight diminution in PaO_2 and pHa, whereas $PaCO_2$ increased.

Discussion

In this study alfaxalone provided excellent muscle relaxation and a moderate level of anesthesia. Early studies evaluating the anesthetic and cardiorespiratory effects of alfaxalone in dogs and cats determined that they produced minimal cardiorespiratory depression, good muscle relaxation, pleasant, uneventful recovery, and possessed a high therapeutic index.[7-9] Adverse effects were uncommon other than pain upon injection (hydroxydione), a variable duration (minutes) to maximal drug effect, and, rarely, vomiting during recovery.[7] Neurosteroids, including alfaxalone, modulate

Table 1. Heart rate, respiratory rate, cloacal temperature and electrolytes (Na^+, K^+, and iCa^{++}) in adult common buzzard before (baseline) and after intravenous administration of alfaxolone.

Parameters	Heart rate (beats/min)	Respiratory rate (breaths/min)	Cloacal temperature (° C)	Na^+ (mmol/L)	K^+ (mmol/L)	iCa^{++} (mmol/L)
0 (baseline)	322.7 ± 8.2	24.5 ± 2.5	41.2 ± 0.1	163.6 ± 0.5	4.18 ± 0.25	1.44 ± 0.01
5 min AI	358.5 ± 11.6	55.5 ± 11.2[c]	41,1 ± 0.2	161.0 ± 1,1	3.89 ± 0.32	1.33 ± 0.02 [a]
10 min AI	355.5 ± 10.3	51.1 ± 8.8[c]	40,9 ± 0.6	160.8 ± 1.5	3.85 ± 0.28	1.30 ± 0.02 [a]
15 min AI	351.6 ± 15.6	49.2 ± 6.7[b]	40.0 ± 0.3[a]	162.0 ± 2.3	3.61 ± 0.16	1.29 ± 0.02 [b]
20 min AI	352.3 ± 16.7	40.5 ± 7.3[b]	39.9 ± 0.3 [b]	161.5 ± 2.3	3,68 ± 0.24	1.25 ± 0.01[c]
30 min AI	344.2 ± 12.1	32.5 ± 4.7[a]	39.9 ± 0.3 [b]	161.7 ± 1.8	3.72 ± 0.30	1.34 ± 0.02 [a]
90 min AI	334.0 ± 14.8	26.5 ± 2.5	40.9.5 ± 0.3 [c]	160.3 ± 1.6	3.68 ± 0.27	1.38 ± 0.02

Values are reported mean ± SE. [a] Mean value differs significantly ($p < 0.05$) from baseline value, [b] Mean value differs significantly ($p < 0.01$) from baseline value, [c] Mean value differs significantly ($p < 0.001$) from baseline value. AI= after induction. Na^+=natrium, K^+= potassium, iCa^++= ionized calcium.

Table 2. Blood gas values (pH, $PaCO_2$, PaO_2, HCO_3, BE, Hb) in adult common buzzard before (baseline) and after intravenous administration of alfaxolone.

Parameters	Arterial pH (units)	$PaCO_2$ (mmHg)	PaO_2 (mmHg)	Bicarbonate concentration (mEq/L)	Base excess (units)	Hemoglobin concentration (g/dl)
0 (baseline)	7.43 ± 0.04	39.9 ± 4.3	87.2 ± 1.8	24.4 ± 0.7	3.8 ± 0.8	15.2 ± 0.7
5 min AI	7.34 ± 0.02[b]	57.6 ± 5.7 [c]	68.3 ± 1.4 [c]	24.6 ± 0.6	3.0 ± 0.6	14.8 ± 0.7
10 min AI	7.32 ± 0.02[c]	59.1 ± 6.7 [c]	67.9 ± 1.3 [c]	25.7 ± 0.6	2.8 ± 0.9	14.7 ± 0.7
15 min AI	7.32 ± 0.03[c]	61.0± 5.9[c]	57.2 ± 2.2 [c]	25.3 ± 0.7	2.2 ± 0.7	14.5 ± 0.6
20 min AI	7.33 ± 0.03[c]	62.5 ± 4.0 [c]	54.5 ± 2.3 [b]	26.5 ± 0.8	2.9 ± 0.5	14.4 ± 0.6
30 min AI	7.30 ± 0.02[c]	59.9± 3.1 [c]	54.6 ± 3.1 [b]	25.5 ± 0.5	2.8 ± 0.3	14.4 ± 0.6
90 min AI	7.42 ± 0.02	43.4 ± 2.7	84.0 ± 3.7	25.7 ± 0.2	2.9 ± 0.4	14.3 ± 0.6

Values are reported mean ± SE. [a] Mean value differs significantly ($p < 0.05$) from baseline value, [b] Mean value differs significantly ($p < 0.01$) from baseline value, [c] Mean value differs significantly ($p < 0.001$) from baseline value. AI= after induction. PaO_2 = arterial oxygen tension, $PaCO_2$ = arterial carbon dioxide tension.

$GABA_A$ receptor activity and may act in a paracrine fashion to locally and selectively influence different neurons and $GABA_A$ receptor pools with different receptor isoforms.[9] These drug specific differences in $GABA_A$ activity are likely responsible for the intensity and spectrum of pharmacologic and anesthetic effects produced by each drug, including sedation, anxiolysis, muscle relaxation, and general anesthesia. Neurosteroid $GABA_A$ subunit specificity may be also be responsible for their wide therapeutic range and high therapeutic index (> 30 mg/kg), and the comparatively mild cardiovascular depressant effects we observed at dosages up to three times (15 mg/kg) the recommended dose of alfaxalone.[5,8]

An increase in $PaCO_2$ compared with baseline indicated hypoventilation despite an increased respiratory rate. Apnea may result from direct respiratory depressant effects of the anesthetic and/or by relaxation of the respiratory muscles.[2,9,10] In birds, apnea may also be caused by high oxygen concentrations.[2] Compression of air sacs by abdominal viscera when the birds are in dorsal recumbency may also restrict ventilation.[11]

Alfaxalone maintained a constant heart rate in dogs, buzzards and cats as well.[12-14] Collectively, previous reports and our data suggest that the IV administration of clinically relevant doses of Alfaxan (10 mg/kg) caused mild vasodilatory effects resulting in minimal changes in heart rate and cardiac output, while larger doses (> 15 mg/kg) cause vasodilation and negative inotropic effects with subsequent decreases in arterial blood pressure and cardiac output. Alfaxalone holds a number of characteristics, such as rapid induction of hypnosis, short duration of anesthesia, and a rapid predictable recovery that are valuable in a safe anesthetic drug. All physiologic parameters, except cloacal temperature, returned to approximate baseline values at recovery after anesthesia with alfaxalone. No warming devices were used in the present study as the aim was to determine the effects of these agent on body temperature. However, their use is strongly advised in order to prevent dangerous decreases in body temperature.

Buzzards given alfaxalone developed primary respiratory acidosis. Base excess and HCO_3 were within reference range,[15] and did not significantly change, indicating a primary respiratory acidosis without metabolic component.

In this study, the linear relationship observed between the pH and the end-tidal partial pressure of carbon dioxide suggest that the monitoring of end-tidal partial pressure of carbon dioxide can also be useful to prevent respiratory acidosis.[16]

In our study, mean ionized serum calcium concentration decreased significantly during anesthesia. Hypocalcemia can be regularly observed using inhalational and injectable anesthetics in dogs, cats, buzzards and horses.[17-19] Although the myocardial depressant effects of injectable anesthetics seem to be a combination of both direct effects on calcium homeostasis in cardiac myocytes (specifically on L-type calcium channels) and calcium permeability of the sarcoplasmic reticulum, supplementation of calcium during anesthesia can reverse these effects, even in the absence of clinical hypocalcemia.[18,19]

This study suggested that alfaxalone produced good to excellent anesthesia in buzzards, characterized by rapid induction of anesthesia, excellent muscle relaxation, unresponsiveness to noxious stimuli, and smooth, uneventful recovery from anesthesia. Hypoventilation and apnea were uncommon at clinically relevant doses but became the most important adverse effects when larger doses were administered rapidly IV. Heart rate, rhythm and hemodynamic values remained stable following the IV administration of clinically relevant doses (10 mg/kg) of alfaxalone.

Acknowledgement

The author is grateful to all the staff at Dilek Peninsula National Park for helping with the birds.

Conflict of Interest

The author report no conflicts of interest. The author alone is responsible for the content and writing of the paper.

References

1. Redig PT. Recommendation for anesthesia in raptors with comments on trumpeter swans. *Seminars in Avian and Exotic Pet Medicine,* 1998; 7(1): 22-29.
2. Ludders, JW, Matthews N. Anesthesia and immobilization of specific species: Birds. In: Thurmon, JC, Tranquilli, WJ, Benson G. Eds, *Veterinary Anesthesia*, 3rd edn. Williams & Wilkins, Baltimore, USA, 1996; 645–669.
3. Straub J, Neil AF, Thielebein J, Pees M, Krautwald-Junghanns ME. The effects of isoflurane anesthesia on some Doppler-derived cardiac parameters in the common buzzard (*Buteo buteo*). *Veterinary Journal*, 2003; 166(3): 273-276.

4. Dodman NH. Complications of Saffan anesthesia in cats. *Veterinary Record*, 1980; 107(21): 481–483.
5. Child KJ, Currie JP, Davis B, Dodds MG, Pearce DR, Twissell DJ. The pharmacological properties in animals of CT1341 – a new steroid anaesthetic agent. *British Journal of Anesthesia*, 1971; 43(1): 2–13.
6. Kilic N, Pasa S. Cardiopulmonary effects of propofol compared with those of a medetomidine-ketamine combination in the common buzzards (*Buteo Buteo*). *Revue Medicine Veterinaire,* 2009; 160(3): 154-159.
7. Campbell D, Forrester AC, Miller DC, Hutton I, Kennedy JA, Lawrie TD, Lorimer AR, McCall D. A preliminary clinical study of CT1341 – a steroid anaesthetic agent. *British Journal of Anesthesia*, 1971; 43(1): 14–24.
8. Sear JW. Steroid anesthetics: Old compounds, new drugs. *Journal of Clinical Anesthesia,* 1996; 8(Suppl 3): 91–98.
9. Lambert JJ, Belelli D, Peden DR, Vardy AW, Peters JA. Neurosteroid modulation of $GABA_A$ receptors. *Progress in Neurobiology,* 2003; 71(1): 67–80.
10. Kilic N. A comparison between medetomidine-ketamine and xylazine-ketamine anesthesia in rabbits. *Turkish Journal of Veterinary Animal Sciences*, 2004; 28(5): 921-926.
11. King AS, Payne DC. Normal breathing and the effects of the posture in *Gallus domesticus*. *The Journal of Physiologie,* 1964; 174(11): 340-347.
12. Ferre PJ, Pasloske K, Whittem T, Ranasinghe MG, Li Q, Lefebvre HP. Plasma pharmacokinetics of alfaxalone in dogs after an intravenous bolus of Alfaxan-CD RTU. *Veterinay Anesthesia and Analgesia*, 2006; 33(4): 229–236.
13. Schubart MA. The short-term anesthesia with alphaxolone/alphadolone in crossbreeds and gyrandperegrine falcon -Quality of anesthesia, influence on respiratory and metabolic parameters-. *Dissertations*, Leipzig, Germany, 2005.
14. Zaki S, Ticehurst KE, Miyaki Y. Clinical evaluation of Alfaxan-CD (R) as an intravenous anaesthetic in young cats. *Australian Veterinary Journal*, 2009; 87(3): 82-87.
15. Kollias GV, Mcleish I. Effects of ketamine hydrochloride in red-tailed hawks (*Buteo jamaicensis*). II-Biocemical and haematologic. *Comparative Biochemistry and Physiology Part C: Comperative Pharmacology*, 1978; 60(2): 211-213.
16. Desmarcheiler M, Rondenay Y, Fitzgerald G, Lair S. Monitoring of the ventilatory status of anesthetized birds of prey by using end-tidal carbon dioxide measured with a microstream capnometer. *Journal of Zoo and Wildlife Medicine,* 2007; 38(1): 1-6.
17. Brainard B, Campbell V, Drobatz JK, Perkowski SZ. The effects of surgery and anesthesia on blood magnesium and calcium concentrations in canine and feline patients. *Veterinay Anesthesia and Analgesia,* 2007, 34(2): 89-98
18. Grubb TL, Benson GJ, Foreman JH, Constable PD, Thurmon JC, Olson WO, Tranquilli WJ, Davis LE. Hemodynamic effects of ionized calcium in horses anesthetized with halothane or isoflurane. *American Journal of Veterinary Research*, 1999; 60(11)**:** 1430–1435.
19. Hysing ES, Chelly JE, Jacobson L, Doursout MF, Merin RG. Cardiovascular effects of acute changes in extracellular ionized calcium concentration induced by citrate and $CaCl_2$ infusions in chronically instrumented dogs, conscious and during enflurane, halothane, and isoflurane anesthesia. *Anesthesiology*, 1990; 72(1)**:** 100–104.