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SHORT COMMUNICATION

Cardiopulmonary and anesthetic effects of the combination of butorphanol, midazolam and alfaxalone in Beagle dogs

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Abstract

Objective To evaluate the physiological variables, arterial blood gas values, induction of anesthesia quality, and recovery quality using the combination of butorphanol, midazolam and alfaxalone in dogs.

Animals Ten healthy adult Beagle dogs weighing 8.3 ± 3.1 kg.

Methods Rectal temperature (T), pulse rate (PR), respiratory rate (f_R), mean arterial pressure (MAP), and arterial blood gases were measured and recorded prior to intravenous (IV) administration of butorphanol, prior to administration of both midazolam and alfaxalone IV 10 minutes later, then every 5 minutes for 20 minutes. M-mode echocardiographic left ventricular (LV) indices were measured before and 5 minutes after administration of alfaxalone. Qualitative scores for induction of anesthesia and recovery were allocated, duration of anesthesia and recovery were calculated, and adverse events were recorded.

Results Scores for induction and recovery quality were excellent. No significant adverse events were observed. Mean ± SD time from induction to extubation and to standing (full recovery) was 29 ± 6 and 36 ± 8 minutes, respectively. There were statistically significant changes in PR, f_R and MAP after drug administration. Transient hypercarbia developed after alfaxalone injection. The echocardiographic LV indices were reduced after alfaxalone injection, although those changes were not statistically significant.

Conclusions and clinical relevance The combination of butorphanol, midazolam and alfaxalone provided excellent quality of induction of anesthesia and exerted minimal cardiopulmonary effects in healthy dogs.

Keywords alfaxalone, anesthesia, butorphanol, dog, midazolam.

Introduction

Alfaxalone (3α-hydroxy-5α-pregnane-11, 20-dione) is a neurosteroid injectable anesthetic agent that is widely used for induction of anesthesia in dogs and cats (Ferré et al. 2006; Muir et al. 2008). In contrast to propofol, alfaxalone is known to have little or no cardiovascular effects when given at clinical dose rates. In a study of compromised canine patients [American Society of Anesthesiologists (ASA) III–V] in which anesthesia was induced with alfaxalone, the cardiovascular and respiratory effects were considered as acceptable (Psatha et al. 2011). Furthermore, alfaxalone has been safely administered concomitantly with a range of drugs com-

monly used perioperatively (Pasloske et al. 2005). However, fewer studies have been conducted to evaluate the quality of anesthesia and cardiopulmonary effects of alfaxalone combined with sedatives and opioids in dogs. Therefore, this study was performed to investigate the quality of anesthesia and cardiopulmonary effects of alfaxalone combined with butorphanol and midazolam in healthy mature dogs.

Materials and methods

Approval of the animal ethics committee of Kangwon National University was obtained for this experiment prior to the commencement of the study. Ten adult Beagle dogs (five male, five female, mean body weight 8.3 ± 3.1 kg, mean age 3.8 ± 1.7 years) were used for this study. All dogs were healthy based upon physical examination, and evaluation of an electrocardiogram (ECG), and serum chemistry and hematologic analyses.

Before anesthesia, a catheter (22 or 24 gauge, BD Angiocath; Becton Dickinson, NJ, USA) was placed in a cephalic vein and in a pedal artery. Dogs were administered butorphanol (0.2 mg kg^{-1}; Jaeil Pharmaceutical, Korea) intravenously (IV), midazolam (0.2 mg kg^{-1}; Handok, Korea) IV 4 minutes after administration of butorphanol, and alfaxalone (2.0 mg kg^{-1}; Jurox, Australia) IV over 1 minute, 5 minutes after administration of midazolam. After alfaxalone administration, the tracheas of all dogs were intubated and the animals were allowed to breathe room air until extubation.

Arterial systolic (SAP), mean (MAP), and diastolic (DAP) blood pressures, pulse rate (PR), respiratory rates (f_R), rectal temperature (T), and arterial pH and blood-gas results were recorded before administration of medications (T0), immediately after administration of butorphanol (T1), immediately after administration of midazolam (T5), immediately after administration of alfaxalone (T10), and at 5 minutes (T15), 10 minutes (T20), 15 minutes (T25), and 20 minutes after administration of alfaxalone (T30). Arterial blood samples were anaerobically collected from the pedal artery catheter and analyzed within 1 hour of collection for arterial partial pressure of oxygen (PaO_2) and carbon dioxide ($PaCO_2$), oxygen saturation (SaO_2), pH, base excess (BE), and bicarbonate (HCO_3^-) with a commercial laboratory blood gas and chemistry analyzer (i-STAT system; Abbott Laboratories, IL, USA) after correction for body temperature. The alveolar-arterial oxygen gradient ($P[A\text{-}a]O_2$) was calculated by the following formulation: $(FIO_2[P_B - P_{H2O}] - PaCO_2/RQ) - PaO_2$. P_B was the daily barometric pressure as determined from the hand-held blood–gas analyzer and $FIO_2 = 0.21$ for room air breathing, P_{H2O} was taken as 47 mmHg (saturated water vapor pressure at 37 °C) and RQ was taken as 0.8 (respiratory quotient of unfasted dogs).

Direct arterial blood pressure measurement was performed using a pressure transducer attached to a multi-parameter anesthetic monitor (VSM7; Votem, Korea). The blood pressure transducer (Transpac IV Disposable Pressure Transducer; ICU medical, CA, USA) was zeroed to atmospheric pressure at the level of the sternum with the dog in right lateral recumbency. The monitor was calibrated prior to the study according to the manufacturer's instructions. PR and f_R were obtained manually. T was measured using a rectal probe (VSM7; Votem).

Echocardiographic left ventricular (LV) indices were measured in all dogs using M-mode echocardiography at the right parasternal short axis of left ventricular papillary muscle level with an ultrasound unit (Sonoace 8000; Medison, Korea) equipped with 3.0–8.5 MHz phased-array transducers. All echocardiographic measurements were performed by the same experienced person (S-HH). Left ventricular internal diameter in systole (LVIDs), left ventricular internal diameter in diastole (LVIDd), % fractional shortening (%FS), % ejection fraction (% LVEF), stroke volume (SV, mL) and cardiac output (CO, L) were measured by M-mode echocardiography at LV papillary muscle level (Atkins et al. 1992) before administration of any medications (T0) and 5 minutes after administration of alfaxalone (T15). The CO was calculated as SV × heart rate (HR). Quality of anesthetic induction and recovery were scored using a standardized scale previously described (Sams et al. 2008): Induction score 0 (smooth uncomplicated), 1 (uncomplicated), 2 (induction difficult), and 3 (induction rough); Recovery score 0 (perfect, walking without ataxia, smooth uncomplicated), 1 (good, walking with minimal ataxia, uncomplicated), 2 (adequate, walking with moderate ataxia, recovery difficult), 3 (rough, walking with significant ataxia or crawling).

Duration of anesthesia was calculated as the time from induction to extubation. Duration of recovery was calculated as the time from extubation to standing. Total procedure time was calculated as the time from induction to standing. Evidence of adverse events noted throughout induction and

recovery were recorded, including abnormal movements and ECG alteration.

The statistical software used in statistical analysis was SPSS 15.0 for Windows (IBM, NY, USA). Normality was tested by the Kolmogorov–Smirnov test. One-way ANOVA repeated measures were performed with the same parameters between baseline and post-induction values with Dunnett's test for *post hoc* analysis. Induction quality and recovery quality were recorded. Significance was set at $p < 0.05$.

Results

Induction quality and recovery quality scores in this study population were 0 (0–0) and 0 (0–1), respectively. Only 1 adverse event was recorded, with one dog exhibiting mild signs of agitation in the recovery period. This event was short lived lasting less than 2 minutes. No morphological alterations in ECG were detected. Mean ± SD duration of anesthesia, duration of recovery and total procedure times were 29 ± 6, 7 ± 2 and 36 ± 8 minutes, respectively. There were statistically significant changes in PR, f_R, SAP, MAP and DAP after the administration of butorphanol, midazolam and alfaxalone (Table 1). Rectal temperature decreased non-significantly with time. No significant difference from baseline was seen in arterial pH, HCO_3^- and BE at any time point. The $PaCO_2$ was significantly increased above baseline readings at T15 and T20 ($p < 0.05$), but then returned to baseline by T25. The PaO_2 and SaO_2 were significantly decreased from baseline at T15 and T20 ($p < 0.05$), but then returned to baseline at T25 (Table 1).

Echocardiography measurements were LVIDd (35 ± 2 at T0, 30 ± 3 mm at T15), LVIDs (21 ± 3 at T0, 19 ± 1 mm at T15), %FS (36.3 ± 8.4% at T0, 35.0 ± 7.4% at T15), %LVEF (66.4 ± 11.1% at T0, 65.2 ± 10.0% at T15), SV (30 ± 5 at T0, 24 ± 8 mL at T15), CO (3.25 ± 0.71 at T0, 3.09 ± 0.70 L at T15). The changes measured after administration of alfaxalone were not statistically significant ($p > 0.05$).

Discussion

Adverse effects identified when alfaxalone was used as a sole agent, included apnea, tachycardia, hypotension, hypoxia and excitement (Ferré et al. 2006; Muir et al. 2008), while adverse effects recorded when alfaxalone was administered after premedication with butorphanol or medetomidine were excitement, paddling, twitching, apnea, and cyanosis (Maddern et al. 2010). However, in this study, those side effects were not observed, except mild agitation during recovery in one dog. One recent study documented that dogs undergoing alfaxalone anesthesia were more likely to have ≥1 adverse event, compared to those undergoing propofol (Maney et al. 2013). Excellent quality of induction and recovery in this study might be due to butorphanol and midazolam premedication and no painful procedures involved.

The mean time from induction to extubation in this study was longer, and the alfaxalone dose required for induction lower, than when alfaxalone was used as an anesthetic induction agent without premedication (Rodríguez et al. 2012). The longer half-lives of butorphanol (1.6 hour) and midazolam (77 ± 18 minutes) than alfaxalone (24.0 ± 1.9 minutes) (Ferré et al. 2006) may suggest that sedative effects of the premedicants were persisting into the recovery period.

Muir et al. (2008) showed alfaxalone increased HR and decreased MAP in dogs when administered without premedication. Similarly in this study, PR increased and MAP decreased after anesthetic induction, but the changes were less severe. Lowering dosage of alfaxalone with premedication agents may result in less cardiovascular depression.

Maney et al. (2013) found alfaxalone without premedication did not cause hypoxemia although there was evidence for ventilation-perfusion mismatch. However, one study found alfaxalone could cause dose-related respiratory depression or apnea (Muir et al. 2008). In the current study, none of the dogs stopped breathing for longer than 30 seconds, although $PaCO_2$ concentrations were elevated. Although transient hypercarbia along with mild reduction of MAP in this study were noticed 5 minutes after alfaxalone injection and lasted for 5–10 minutes, the changes may not be clinically significant in healthy dogs. Furthermore, $P[A\text{-}a]O_2$ was less than 25 mmHg during anesthesia and there was no clinically significant impairment of gas exchange in this study group.

Cardiac output and LV contractility were not significantly decreased by administration of alfaxalone in two studies (Muir et al. 2008; Rodríguez et al. 2012). This study also measured non significant changes in SV and LV contractility after alfaxalone injection. However, there is a potential error from non-invasive measurement of CO by the M-mode echocardiography (Atkins et al. 1992).

Table 1 Cardiopulmonary and temperature measurements before (T0), and after IV administration of 0.2 mg kg^{-1} of butorphanol (T1), 0.2 mg kg^{-1} of midazolam (T5), and 2.0 mg kg^{-1} of alfaxalone (T10–T30) in Beagle dogs

	Time points							
Variable	**T0**	**T1**	**T5**	**T10**	**T15**	**T20**	**T25**	**T30**
PR (beats $minute^{-1}$)	117 ± 21	85 ± 13*	99 ± 23	146 ± 19*	135 ± 18*	106 ± 21	89 ± 13	74 ± 10*
SAP (mmHg)	133 ± 31	123 ± 32	118 ± 29	103 ± 22*	101 ± 20*	105 ± 18*	93 ± 15*	102 ± 22*
MAP (mmHg)	102 ± 24	88 ± 24	95 ± 24	81 ± 16	76 ± 17*	75 ± 16*	76 ± 13*	74 ± 18*
DAP (mmHg)	89 ± 24	70 ± 22	83 ± 25	74 ± 15	67 ± 17*	63 ± 12*	65 ± 14*	60 ± 16*
T (°C)	38.8 ± 0.5	38.7 ± 0.3	38.6 ± 0.3	38.0 ± 1.3	38.0 ± 0.4	38.0 ± 0.4	37.8 ± 0.4	36.6 ± 1.6
f_R ($breaths\ minute^{-1}$)	28 ± 7	35 ± 18	42 ± 18	43 ± 11	46 ± 13	51 ± 12	55 ± 5	32 ± 9
pH	7.44 ± 0.02	–	7.43 ± 0.01	7.43 ± 0.01	7.39 ± 0.05	7.40 ± 0.04	7.43 ± 0.05	7.41 ± 0.04
$PaCO_2$ (mmHg)	32.6 ± 3.5	–	33.7 ± 0.7	33.3 ± 0.7	40.5 ± 6.4*	38.6 ± 4.9*	33.4 ± 7.8	36.2 ± 4.9
$PaCO_2$ (kPa)	4.4 ± 0.5		4.5 ± 0.1	4.4 ± 0.1	5.4 ± 0.8*	5.2 ± 0.5*	4.5 ± 1.1	4.8 ± 0.7
PaO_2 (mmHg)	98 ± 4	–	100 ± 9	107 ± 20	89 ± 15*	91 ± 18*	98 ± 6	98 ± 22
PaO_2 (kPa)	13.1 ± 0.5		13.3 ± 1.2	14.3 ± 2.7	11.8 ± 2.0*	12.1 ± 2.4*	13.0 ± 0.8	13.1 ± 2.9
SaO_2 (%)	97.3 ± 4.2	–	97.3 ± 1.4	96.1 ± 4.2	90.3 ± 2.8*	91.6 ± 6.4*	97.5 ± 9.2	90.7 ± 10.6
$P(A\text{-}a)O_2$ (mmHg)	12 ± 3		8 ± 8	8 ± 6	10 ± 6	10 ± 2	10 ± 3	7 ± 2
$P(A\text{-}a)O_2$ (kPa)	2.5 ± 0.4		1.1 ± 1.1	1.1 ± 0.7	1.3 ± 0.7	1.3 ± 0.3	1.3 ± 0.4	0.9 ± 0.3
HCO_3^- ($mmol\ L^{-1}$)	20.4 ± 1.2	–	20.5 ± 0.1	20.7 ± 0.1	22.3 ± 0.9	21.6 ± 0.6	20.3 ± 2.1	21.3 ± 0.8
BE ($mmol\ L^{-1}$)	−1.7 ± 0.21	–	−1.8 ± 0.00	−1.8 ± 0.35	−1.8 ± 0.78	−2.2 ± 0.64	−2.3 ± 0.07	−2.0 ± 0.64

PR, pulse rate; SAP, systolic arterial pressure; MAP, mean arterial pressure; DAP, diastolic arterial pressure; T, rectal temperature; f_R, respiratory rate; $PaCO_2$ and PaO_2, partial pressures of arterial carbon dioxide and oxygen; SaO_2, hemoglobin oxygen saturation; $P(A\text{-}a)O_2$, alveolar-arterial oxygen gradient; HCO_3^-, bicarbonate, BE, base excess. n = 10 except for T30 where n = 4. Mean ± SD. *Significant difference from baseline (T0).

There are several study limitations for applying the results to clinical practice. The study population was limited to a small number of healthy colony dogs and not capable of obtaining sufficient statistical power to prove minimal cardiovascular detrimental effects. In clinical practice, the induction dose of alfaxalone is generally administered to effect for each individual dog. However, we administered a full 2.0 mg kg^{-1} of alfaxalone, IV over 1 minute for all dogs. Therefore, the study results might have been different if the alfaxalone was administered by titrating to effect. In addition, no painful stimulus was applied to the dogs during anesthesia. Studies in clinical populations could address these issues.

In conclusion, in this study the combination of butorphanol, midazolam and alfaxalone provided excellent quality of induction of anesthesia, good to excellent recovery, and exerted minimal cardiopulmonary effects in healthy dogs.

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