NOTE *Surgery*

Cardiorespiratory and anesthetic effects produced by the combination of butorphanol, medetomidine and alfaxalone administered intramuscularly in Beagle dogs

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ABSTRACT. This study evaluated anesthesia quality, degree of analgesia and cardiorespiratory parameters after intramuscular (IM) injection of a combination of butorphanol (0.1 mg/kg), medetomidine (10 μg/kg) and alfaxalone (1.5 mg/kg) in ten healthy adult Beagle dogs. Rectal temperature (T), heart rate (HR), respiratory rate (f_R), arterial pressure, arterial blood gases and M-mode echocardiographic left ventricular (LV) indices were measured before drug administration and every 10 min thereafter until extubation. Mean duration of anesthesia, recovery and analgesia were 89 ± 17, 6 ± 1 and 80 ± 12 min. HR, f_R, partial pressure of arterial CO_2 and O_2, arterial pressure, and LV contractility were significantly altered during anesthesia. IM administration of the drug combination provided acceptable anesthesia, but produced substantial cardiorespiratory suppression.

KEY WORDS: alfaxalone, anesthesia, butorphanol, canine, medetomidine

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Total injectable anesthesia (TIA) can be defined as a technique of general anesthesia using a combination of agents given solely by an intravenous (IV) or intramuscular (IM) route. TIA remains a common anesthetic technique in Asian countries. Alfaxalone (3α-hydroxy-5α-pregnane-11, 20-dione) is a recently developed neurosteroid injectable anesthetic agent that is gaining popularity for anesthetic induction in dogs and cats, because it provides excellent anesthetic effects with minimal cardiorespiratory suppression [4, 8, 10]. Alfaxalone is generally administered via an IV route in dogs. However, one recent study evaluated the quality of anesthesia and cardiorespiratory effects after different doses of a single IM injection of alfaxalone in dogs [11] and found that the sole use of alfaxalone by an IM route required a high dose (5–10 mg/kg) and large injection volume (0.5–1.0 m*l*/kg) to achieve surgical anesthesia. Premedication with α_2-adrenoceptor agonists (medetomidine in this study) and opioids (butorphanol in this study) can improve quality of anesthesia and can reduce the required dose of induction agents, including alfaxalone [5]. Therefore, in this study, we introduced a TIA technique for the IM route using alfaxalone, medetomidine and butorphanol and assessed the quality of anesthesia and the cardiorespiratory effects.

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 males and five females, mean body weight/age ± standard deviation 8.6 ± 1.0 kg and 4.2 ± 1.0 years old) were used for this study. All dogs were deemed healthy based upon physical examination, evaluation of an electrocardiogram (ECG), and serum chemistry and hematologic analyses.

Before administration of drugs, a catheter (22 or 24 gauge, BD Angiocath, Becton Dickinson, Franklin Lakes, NJ, U.S.A.) was placed in a dorsal pedal artery in each dog to collect arterial blood samples and provide direct arterial blood pressure monitoring. The dosage of the butorphanol, medetomidine and alfaxalone combination was established based on results of pilot studies examining different doses (butorphanol, 0.1–0.2 mg/kg; medetomidine, 5–20 μg/kg; and alfaxalone, 1–5 mg/kg; data not shown). Butorphanol (Jaeil Pharmaceutical, Seoul, Korea) 0.1 mg/kg, medetomidine (Pfizer, New York, NY, U.S.A.) 10 μg/kg and alfaxalone (Jurox, Rutherford, Australia) 1.5 mg/kg were mixed in a single syringe and injected slowly (i.e., approximately 10 m*l*/min) into the dorsal lumbar muscle of the dog using a syringe with a 23-gauge, 1-inch needle (Becton Dickinson). The tracheas of all dogs were intubated, and the dogs were allowed to breathe room air until extubation.

Time from IM injection to lateral recumbency, orotracheal intubation, recovery and standing were recorded. Duration of anesthesia was recorded as the time from lateral recumbency to extubation. Duration of recovery was calculated as the time from extubation to standing. Quality of anesthetic induction and recovery were scored using a previously described standardized scale [9] as follows: Induction score 0 (smooth uncomplicated), 1 (uncomplicated), 2 (induction difficult) and 3 (induction rough); and recovery score 0 (perfect, walking without ataxia or smooth uncomplicated), 1 (good, walking with minimal ataxia or uncomplicated), 2 (adequate, walking with moderate ataxia or recovery difficult) and 3 (rough, walking with significant ataxia or crawling). One author (Lee) scored and a second author (Choi) confirmed the score. If the score was discrepant, a third

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author (Hyun) re-evaluated the score. Evidence of adverse events noted throughout induction and recovery were recorded, including abnormal movements and ECG alteration.

Following measurements were recorded before administration of drugs (T0) and every 10 min thereafter until extubation; arterial systolic (SAP), mean (MAP) and diastolic (DAP) blood pressures, heart rate (HR), respiratory rate (f_R), rectal temperature (T), arterial blood gas and left ventricular dimensions obtained by M-mode echocardiography. All echocardiographic measurements were taken at the LV papillary muscle level, including left ventricular internal diameter in systole (LVIDs), left ventricular internal diameter in diastole (LVIDd), % fractional shortening (%FS), % ejection fraction (%LVEF), stroke volume (SV, m*l*) and cardiac output (CO, *l*/min). Echocardiography was performed by the same experienced operator (Choi). The CO was calculated as SV × HR. Duration of analgesia was defined as time from first needle prick to time of a positive response. Needle prick with a 22-guage hypodermic needle was used to assess analgesia, as described previously [6]. The needle prick analgesic test was a "yes" or "no" response. When there was a positive response; such as limb withdrawal, skin twitching or any other purposeful movements, in reaction to the needle pricking, the response was recorded as "no" analgesia. When there was no response, the animal was considered "yes" for analgesia until the next stimulus was applied. The sequence of needle pricking was front limb near radial-ulna area, ventral midline of the abdomen and rear limb near the tibial area. The test was repeated every 5 min until the dog showed a positive response.

SPSS version 15.0 statistical software for Windows (IBM, New York, NY, U.S.A.) was used for statistical analysis. 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. Significance was set at $P<0.05$.

Median (range) scores of induction quality and recovery quality in the study population were 0 (0–1) and 1 (0–2), respectively. Three of 10 dogs were mildly agitated and staggered when they woke up. Mean ± standard deviation (SD) time from IM injection to lateral recumbency and orotracheal intubation were 319 ± 106 and 359 ± 107 sec, respectively. Three of 10 dogs had either nausea (3 dogs) or vomiting (2 dogs) after drug administration. Although no morphological alterations in ECG were detected, bradyarrhythmias were recorded in all dogs, including second-degree Type 1 atrioventricular block in 2 dogs. No dogs exhibited laryngeal complications during intubation or recovery, even though we did not desensitize the larynx with lidocaine. Mean ± SD duration of anesthesia, recovery and analgesia were 89 ± 17, 6 ± 1, and 80 ± 12 min, respectively.

There were significant changes in HR, f_R, SAP, MAP and DAP after IM administration of the drug combination (Table 1). The HR was significantly decreased from 10 min after administration (T10) to recovery ($P<0.05$). The reduction of HR persisted even after recovery (data not shown). The arterial pressure was also significantly decreased from T10 to recovery ($P<0.05$), as was the f_R ($P<0.05$). However, no dogs exhibited apnea during anesthesia. Rectal temperature was not significantly changed during anesthesia. No significant difference from baseline was seen in arterial pH, HCO_3^- and BE at any time point (Table 1). The $PaCO_2$ was significantly increased from T10 to recovery ($P<0.05$; Table 1), and the PaO_2 and SaO_2 were significantly decreased from T10 to recovery ($P<0.05$; Table 1).

Although there was no significant change in LVIDd during anesthesia, there was a significant increase in LVIDs from T10 to recovery ($P<0.05$; Table 1). All echocardiographic indices of left ventricular contractility including %FS, %LVEF, SV and CO were significantly decreased from T10 to recovery ($P<0.05$; Table 1).

IM injection of alfaxalone is generally not recommended in dogs. However, IM administration of injectable agents is often only the option for fractious, fearful or excited dogs. Tamura *et al.* evaluated different doses of alfaxalone by IM administration in dogs without other premedicants and found a dose-dependent anesthetic effect with relatively mild cardiorespiratory depression [11]. Opioids (butorphanol) and sedatives (medetomidine) can provide analgesia and thus can improve quality of anesthesia and extend its duration [5, 7]. Therefore, in this study, we evaluated the quality of anesthesia after IM administration of alfaxalone combined with butorphanol and medetomidine.

The dose of alfaxalone used in this study was 1.5 mg/kg, which was lower than the minimal IV recommended dose. Tamura *et al.* found that 5 mg/kg of alfaxalone alone administered by the IM route in dogs was insufficient to produce anesthesia, although the authors did observe a brief period of sedation and immobilization [11]. In contrast, we found that 1.5 mg/kg alfaxalone administered in combination with butorphanol and medetomidine was sufficient to produce deep sedation and immobilization. The duration of anesthesia was 89 ± 14 min, which was similar to that reported by Tamura *et al.* following a single IM injection of 7.5 mg/kg alfaxalone [11]. This indicates that co-administration of alfaxalone with butorphanol and medetomidine may dramatically reduce the dose of alfaxalone necessary to achieve anesthesia. However, there was a wide range of individual variation in the duration of anesthesia after IM administration in the present study, which was similarly observed by Tamura *et al.* [11]. Because butorphanol (1.6 hr) [6] and medetomidine (1 to 1.6 hr) [2] have longer half-lives than alfaxalone (24.0 ± 1.9 min) [4], the present results might also suggest that the sedative effects of butorphanol and medetomidine also had a greater effect on the duration and quality of recovery.

Although 3 dogs had either nausea or vomiting after IM administration, the induction and recovery quality in this study were acceptable. Gastrointestinal adverse effects might have been due to medetomidine, as reported previously [2]. Previously identified adverse effects of alfaxalone as a sole agent include apnea, tachycardia, hypotension, hypoxia and excitement [4, 8], and adverse effects of alfaxalone after premedication with butorphanol or medetomidine were excitement, paddling, twitching, apnea and cyanosis [7]. None of these side effects was observed in the present study,

Table 1. Changes in vital signs, blood gas parameters and left ventricular echocardiographical measurement before (T0) and after IM administration of 0.1 mg/kg of butorphanol, 10 μg/kg of medetomidine and 1.5 mg/kg of alfaxalone in Beagles

Variable	Time Points (min)										
	T0	T10	T20	T30	T40	T50	T60	T70	T80[b)]	T90[b)]	T100[b)]
HR (beats/min)	136±29	61±32[a)]	57±21[a)]	49±22[a)]	46±19[a)]	48±25[a)]	51±22[a)]	47±21[a)]	39±22[a)]	38±27[a)]	36±19[a)]
SAP (mmHg)	138±22	115±16[a)]	102±19[a)]	104±11[a)]	102±21[a)]	106±12[a)]	105±16[a)]	99±13[a)]	104±17[a)]	102±15[a)]	100±11[a)]
MAP (mmHg)	118±7	96±6	87±6[a)]	84±4[a)]	92±7[a)]	89±4[a)]	86±5[a)]	86±4[a)]	83±5[a)]	84±4[a)]	87±4[a)]
DAP (mmHg)	109±18	87±22[a)]	79±11[a)]	74±17[a)]	87±11[a)]	81±16[a)]	77±18[a)]	79±21[a)]	72±22[a)]	75±12[a)]	80±13[a)]
T (°C)	38.3±0.3	38.3±0.4	38.3±0.5	38.2±0.7	37.8±0.6	38.4±0.5	38.0±1.6	38.1±0.9	37.9±0.6	37.9±0.9	38.4±0.4
f_R (breaths/min)	26±6	17±11[a)]	17±8[a)]	20±10[a)]	19±8[a)]	17±9[a)]	20±6[a)]	18±10[a)]	19±8[a)]	19±11[a)]	20±8[a)]
pH	7.36±0.03	7.35±0.06	7.35±0.06	7.35±0.05	7.36±0.03	7.35±0.05	7.35±0.07	7.35±0.04	7.36±0.04	7.36±0.08	7.37±0.02
$PaCO_2$ (mmHg)	34.8±2.5	35.2±4.1	34.3±4.2	39.6±3.9[a)]	41.2±1.9[a)]	42.0±3.2[a)]	40.3±2.8[a)]	39.6±2.7[a)]	41.2±1.5[a)]	40.2±1.7[a)]	40.0±1.1[a)]
PaO_2 (mmHg)	94±3	80±5[a)]	80±10[a)]	82±8[a)]	81±7[a)]	83±6[a)]	78±11[a)]	79±12[a)]	81±10[a)]	83±12[a)]	83±8[a)]
SaO_2 (%)	98±2	93±4[a)]	93±1[a)]	93±3[a)]	93±2[a)]	92±3[a)]	91±3[a)]	91±5[a)]	93±1[a)]	92±3[a)]	92±2[a)]
P (A-a) O_2 (mmHg)	12.2±1.8	25.7±5.2[a)]	26.9±3.3[a)]	18.2±3.8[a)]	17.2±4.4[a)]	14.2±1.8	21.4±4.8[a)]	21.2±3.4[a)]	17.2±2.7[a)]	16.5±2.1[a)]	16.7±3.6[a)]
HCO_3^- (mmol l^{-1})	20.6±1.4	21.7±1.2	21.2±1.3	21.3±0.9	19.6±1.7	20.4±0.8	22.0±1.1	21.3±1.6	21.6±2.0	20.6±3.1	22.8±1.6
BE (mmol l^{-1})	−3.7±1.2	−5.8±0.9	−4.4±2.2	−2.7±2.8	−3.4±2.5	−4±1.7	−3.4±1.4	−4.7±1.3	−3.4±1.1	−4.4±0.7	−4.2±2.3
LVIDd (mm)	39.1±2.1	42.4±3.2	40.2±2.1	38.8±0.7	38±1.4	40.5±2.8	39.9±4.1	39.4±2.3	42.5±2.8	41.5±1.8	40.1±1.3
LVIDs (mm)	26.2±3.5	34.6±2.8[a)]	33.5±4.3[a)]	32.1±2.9[a)]	32.2±1.2[a)]	33.5±4.8[a)]	33.6±2.8[a)]	32.9±1.3[a)]	30.5±0.9[a)]	31.9±1.3[a)]	30.9±1.1[a)]
FS (%)	32.9±5.3	18.3±4.3[a)]	16.7±6.7[a)]	17.3±3.9[a)]	15.2±7.1[a)]	17.2±2.1[a)]	15.7±3.4[a)]	16.5±2.9[a)]	21.8±3.1[a)]	23.1±2.9[a)]	24.8±4.2[a)]
LVEF (%)	58.9±10.3	39.6±7.1[a)]	35.7±3.4[a)]	41.6±5.2[a)]	32.4±11.3[a)]	37.1±13.8[a)]	43.8±5.8[a)]	40.2±7.1[a)]	36.6±4.8[a)]	43.6±5.8[a)]	48.6±4.7[a)]
SV (m*l*)	27.8±3.1	24.8±4.2[a)]	21.2±5.7[a)]	22.6±6.3[a)]	19.9±2.7[a)]	19.5±4.8[a)]	20.5±2.9[a)]	21.4±1.1[a)]	22.5±5.3[a)]	23.1±3.7[a)]	27.2±3.3
CO (*l*/min)	2.86±0.43	1.51±0.34[a)]	1.21±0.52[a)]	1.11±0.23[a)]	0.92±0.42[a)]	0.94±0.21[a)]	1.05±0.47[a)]	1.01±0.21[a)]	0.88±0.11[a)]	0.88±0.12[a)]	1.02±0.44[a)]

Mean ± SD. a) Significant difference from baseline (T0). HR, heart 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-a) O_2, alveolar-arterial oxygen gradient; HCO_3, standard bicarbonate, BE, base excess; LVIDs, Left ventricular internal diameter in systole; LVIDd, left ventricular internal diameter in diastole; %FS, % fractional shortening; %LVEF, %ejection fraction; SV, stroke volume; CO, cardiac output. b) n=7 in T80, n=7 in T90, n=3 in T100.

although some dogs did exhibit transient muscular tremors and staggering gait during recovery. Tamura *et al.* [11] have reported similar quality of recovery after IM administration of alfaxalone alone.

All dogs in the present study had reduced HR after induction and then significantly reduced HR with time. In contrast, after administration of alfaxalone alone, Muir *et al.* [8] reported increased HR in dogs. Therefore, profound bradycardia in the dogs in our study might have been due to the a_2-agonistic effect of medetomidine, which has been reported previously [2]. Mild decrease in HR after administration of butorphanol has been also described [5]. The duration of action of medetomidine in dogs is up to 1–1.6 hr, and many dogs in the present study had persistent bradycardia even after recovery. Furthermore, 2 of 10 dogs exhibited benign second-degree heart block during anesthesia. Therefore, it must be emphasized that continuous ECG monitoring is necessary in the clinical setting, especially for sick dogs, if anesthesia is achieved by this combination.

We observed persistent reduction in f_R, although no dogs had apnea and hypercapnea ($PaCO_2$ >45 mmHg) during the maintenance of anesthesia. Two other studies have also found that alfaxalone caused dose-related respiratory depression or apnea [7, 8], and in the present study, many dogs had ventilation-perfusion mismatch (>25 mmHg P[A–a]O_2) during anesthesia, especially at T10 and T20, although all maintained a P[A–a]O_2 value of <25 mmHg after T20, even while breathing room air. Therefore, continuous f_R, SaO_2 and end tidal CO_2 monitoring is also necessary in the clinical setting for early detection of clinically significant impairment of gas exchange.

The arterial blood pressure was significantly decreased from baseline during anesthesia. Dose-dependent cardiovascular depression after alfaxalone injection without premedication in dogs has been described previously [8]. Profound bradycardia due to medetomidine might have contributed to hypotension in the present study, in spite of vasoconstriction related to the a_2-agonistic effect. It has been common to observe hypotensive (MAP <60 mmHg) phases of short duration that respond to an increased rate of fluid administration. However, all dogs in the present study maintained MAP >60 mmHg, and clinically significant hypotension was not observed.

CO and LV contractility were dramatically reduced during anesthesia, contrary to results of several other studies, in which CO and LV contractility were not significantly decreased after administration of alfaxalone [8]. It has been reported that medetomidine increases inotropy and vascular resistance during autonomic blockade in dogs [3]. The reduction of CO associated with medetomidine is usually attributed to a decrease in HR and an increase in vascular resistance, and not to a direct depression of myocardial contractility [2]. However, the present results have demonstrated that alfaxalone and medetomidine in combination were associated with a direct depression of myocardial contractility, as evidenced by the decreased LVIDs and SV during anesthesia, although it remains unclear which drug is more responsible for this myocardial depression. Furthermore, there is a potential error in non-invasive measurement of CO by M-mode echocardiography [1]. Therefore, continuous monitoring of vital

signs reflecting changes in CO is necessary in the clinical setting, and this combination of anesthesia may not be suitable for dogs with heart disease.

There are several limitations to the present study. The study population was limited to a small number of healthy colony dogs and could not achieve sufficient statistical power to prove minimal cardiovascular detrimental effects. In addition, the depth of anesthesia (degree of analgesia) was only assessed by needle prick. More accurate methodology using an algometer or nerve stimulator to assess the degree of analgesia is warranted. Lastly, there was no control group for comparison in this study.

In conclusion, the present study found the combination of butorphanol, medetomidine and alfaxalone administered through an IM route provided a reasonable quality of anesthesia, although cardiorespiratory suppression from this combination was substantial and persistent. Therefore, continuous monitoring of vital signs should be mandatory in all cases.

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