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Effects of Xylazine or Acepromazine in dogs under constant rate infusion with alfaxalone

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Abstract

The anesthetic depth and cardiovascular effect of alfaxalone constant rate infusion in dogs premedicated with xylazine or acepromazine were evaluated. Ten dogs were randomly allocated into 2 groups. In group AA, dogs were premedicated with 0.02 mg/kg of intravenous acepromazine at 15 min before induction. In group XA 1.1 mg/kg of intravenous xylazine was premedicated at 5 min before induction. The anesthesia was maintained with 6 mg/kg/hr of alfaxalone after induction with 2 mg/kg alfaxalone in both groups. In both of groups, the qualities of induction were satisfactory without any adverse event, but adequate analgesia could not be provided, according to the withdrawal test. PaO_2 and SaO_2 implied a slight hypoxemia state in XA group, while those values of group AA were not significantly changed. The acepromazine and alfaxalone combination induce mild tachycardia. The bispectral index score were significantly decreased in group XA, compared with that in group AA. The premedication of xylazine before alfaxalone constant rate infusion in this study could provide adequate analgesia during 30 min, while the premedication with acepromazine could not.

Key words : Acepromazine, Alfaxalone, Xylazine, Bispectral index score

INTRODUCTION

Alfaxalone is a synthetic neuroactive steroid, and it produces hypnosis and minimal analgesia (Ferre et al, 2006). Many combinations for anesthesia based on alfaxalone were reported, and premedications could reduce doses of anesthetic agents and subsequently, they could alleviate adverse effects (Herbert et al, 2012; Suarez et al, 2012).

Acepromazine, a long-acting phenothiazine, has been widely and commonly used as a tranquillizer in veterinary medicine. It induces antagonism of post synaptic dopaminergic transmission in the basal ganglia and in the limbic portions of the forebrain, and it blocks α_1-receptor and also has anticholinergic effects in the periphery (Baldessarini et al, 2005). Acepromazine also has antiemetic, anti-spasmodic and a little antihistaminic effects (Lukasik et al, 2003). Dose-sparing effects on injectable anesthetic agents and inhalant agents were reported but no analgesic properties were observed in dogs (Boyd et al, 1991; Hall et al, 1999; Murrell, 2007).

α_2-adrenoceptor agonists, represented by xylazine and medetomidine, have been used as sedative, muscle relaxant and analgesic agents in small animal anesthesia. α2-agonists have analgesic effect but it last relatively shorter time than sedative duration. The analgesic period of xylazine was reported as lasting 30 to 60 min, and it depends on injection route and doses (Cullen, 1999). Xylazine provides an additive sedation, analgesia and muscle relaxation, furthermore, the dose-sparing effects of xylazine on injectable and inhalational anesthetic agent requirement for induction and maintenance have been reported (Greene, 1999; Lemke, 2004). However, the combination with xylazine and anesthetic agents

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should be used carefully because of cardiopulmonary dysfunction (Dyson et al, 1998; Cullen, 1999).

Although many studies for bispectral index score (BIS) monitoring system, the first brain function monitoring system approved by Food and Drug Administration in United States of America, were performed in various species in veterinary medicine, the use of BIS in veterinary clinics has not been well established. It seems that more data for each anesthetic regimes should be reported for exact understanding BIS.

The purpose of present study is to establish the cardiovascular effect of premedication with xylazine or acepromazine in dogs anesthetized with constant rate infusion of alfaxalone, and to present the change of BIS concurrently.

MATERIALS AND METHODS

Animals

Ten beagle dogs were randomly assigned to two groups (n=5 per group). Dogs were in clinically healthy state based on physical, biochemical and hematological examinations.

Ages of dogs were 2.3±0.7 (mean±SD) years and body weights were 8.4±0.8 kg. Before experiment, food but not water withheld for 12 hr.

Procedure

The experimental procedure was approved by the Kyungpook National University Animal Ethics Committee (KNU2016-0016). Food was withheld for 12 hr before catheter placement, but water was supplied freely. An arterial catheter (Pediatric jugular catheterization set, Arrow international, Inc., USA) was installed in the right femoral artery one day before experiment. During installation of catheter, anesthesia was induced with propofol and maintained with isoflurane under 100% oxygen. A bolus of propofol (6 mg/kg) was slowly injected over 60 sec, and isoflurane (2～2.5%) was followed. After catheter insertion, the frontal to temporal head of dogs was shaved for BIS sensor application. An Elizabethan collar was placed after catheterization.

Acclimation times were provided to each dog for 1 hr before each experiment in the experimental room. After scrubbing with an alcohol cotton swab on the shaved head site, BIS sensor (Pediatric BIS QUATRO sensor®, Aspect Medical Systems Inc., USA) were placed with adhesive tapes. Proper pressures were given to each electrode for 5 sec for tight attachment.

A pressure transducer of polygraph (Model 7P1, Grass Instrument Co., USA) was connected with the installed catheter and baseline values were recorded in setting position, after that, an intravenous catheter (24 gauge) was placed in the cephalic vein.

In group AA, dogs were premedicated with 0.02 mg/kg intravenous acepromazine (Sedaject®, Samu median, Korea) at 15 min before induction. In group XA 1.1 mg/kg intravenous xylazine (Rompun®, Bayer Korea, Korea) was premedicated at 5 min before induction.

Anesthesia was induced with 2 mg/kg alfaxalone (Alfaxan®, Jurox Pty Ltd, Australia) and maintained with 6 mg/kg/hr of alfaxalone in both groups. The maintenance of anesthesia was lasted for one hr. Dogs were positioned at right lateral recumbency during anesthesia.

Evaluation parameters

All parameters (except BIS and electromyography) were measured and recorded baseline (unpremedicated), 5, 10, 15, 30, 45 and 60 min after induction of anesthesia.

Respiratory rate: Respiratory rates were recorded as spontaneous breaths of dogs.

Hemodynamic measurement and blood gas parameters: Blood pressure and heart rate were recorded with the polygraph (Model 7P1, Grass Instrument Co., USA). Blood gas analyses were carried out immediately after blood sampling of 0.3 ml volume through the femoral arterial catheter. Arterial blood pH, $PaCO_2$, PaO_2, SaO_2, tCO_2 and HCO_3^- were analyzed with a blood gas analyzer.

BIS and EMG: During experiment, BIS and electromyography (EMG) were recorded with BIS VISTA™

and extracted by 5 min intervals. BIS and EMG values which had signal quality indexes only above 50 were calculated. The values of BIS and EMG were recorded −5 (baseline), 0 (after induction) 5, 10, 15, 30, 45 and 60 min after induction of anesthesia.

Recovery times: After cessation of anesthetic agent, time to first head up, time to taking posture of sternal recumbency and time to walking were recorded. The walking was defined as walking at least 5 steps.

Pedal withdrawal reflex test: To determine depth of anesthesia, toe web region of hind limb was randomly pinched with a 10 cm mosquito forceps to the first-ratchet-lock for 10 sec. If there was purposeful movement, test was stopped immediately.

Statistical analysis

All data are presented as mean±SD and were analyzed with IBM SPSS Statistics Version 23 (IBM SPSS Inc, USA). Statistical differences between groups were analyzed with independent t-test. The differences within groups were analyzed with repeated measured ANOVA followed by least significance difference as post hoc comparison.

RESULTS

Respiratory rate

There were no significant differences in respiratory rate (Table 1). Incidence of apnoea was not observed in entire anesthetic periods, including during induction.

Hemodynamic measurement

Group AA had significantly decreased SAP than Group XA ($P<0.05$) at 5, 10 and 15 min, and maintained significantly decreased SAP compared with baseline. In group XA, SAP was gradually decreased at 10 min after induction (Table 1). DAP was significantly different between groups at 5, 10 and 15 min ($P<0.05$).

Table 1. Respiratory rate, blood pressures, heart rate and blood gas values in dogs anesthetized with alfaxalone

	Group	0 min	5 min	10 min	15 min	30 min	45 min	60 min
Respiratory rate	XA	14.0±3.5	11.8±3.1	11.2±3.0	11.2±3.3	11.0±3.7	11.4±4.2	10.2±3.2
	AA	13.4±5.0	12.0±3.8	12.4±4.3	11.4±3.6	11.6±4.7	11.4±4.6	11.2±3.9
SAP	XA	163±14.8	170±10.6*	154±14.7*	144±19.5*	128±20.5*	118±18.9**	117±13.0**
	AA	170±10.0	111±16.4**,†	111±13.4**,†	111±16.4**,†	116±8.9**	117±8.4**	119±13.9*
DAP	XA	82±2.7	117±6.7*	104±6.5*	93±9.1	81±10.8	75±11.7	73±8.4
	AA	85±3.5	72±13.5†	73±12.0†	73±13.0†	77±12.0	81±9.6	82±12.0
MAP	XA	109±6.22	135±7.46*	121±7.67*	110±12.6	96.6±13.8	89.4±12.7*	87.0±8.37*
	AA	113±4.09	85.0±14.4*,†	85.6±12.3*,†	85.6±14.0*	89.8±11.0*	93.0±9.17*	94.0±12.6*
Heart rate	XA	82.8±5.0	81.6±18.3	86.4±21.0	87.6±25.0	92.4±17.8	88.8±18.7	93.6±21.0
	AA	91.2±19.6	142.8±14.3*,†	141.6±23.1*,†	150±39.1*,†	140.4±15.6*,†	144±19.0*,†	142.8±22.6*,†
$PaCO_2$	XA	36.32±0.70	46.40±2.31**	46.60±2.03**	46.04±2.27**	46.80±4.17*	47.14±3.70*	46.2±3.64*
	AA	35.48±3.54	40.96±2.02*,†	42.08±3.11*,†	42.26±3.40*	42.66±2.69*	42.48±3.13*	42.6±4.50*
PaO_2	XA	88.0±5.43	64.8±8.04*	74.4±8.59*	79.8±9.60*	81.8±8.11	85.8±7.79	89.8±10.33
	AA	91.8±6.91	83.6±9.53†	87.4±9.76	87.4±12.18	92.6±7.77	93.8±6.98	93.2±9.18
SaO_2	XA	96.6±0.55	89.4±2.51*	92.4±3.21*	94.0±2.92	94.4±2.51	95.0±1.73	95.6±1.52
	AA	96.8±1.10	95.8±0.84†	95.6±1.67	95.8±2.17	96.4±0.89	96.8±0.45	96.4±0.89
pH	XA	7.378±0.032	7.296±0.031**	7.296±0.031**	7.309±0.035*	7.313±0.030*	7.312±0.025*	7.309±0.022*
	AA	7.387±0.031	7.346±0.029*,†	7.344±0.023*,†	7.344±0.018*	7.337±0.038*	7.337±0.034*	7.336±0.020*
tCO_2	XA	22.6±1.95	24.2±1.92*	24.2±2.17*	24.6±1.82*	25.0±1.87*	25.2±1.64*	24.6±2.19*
	AA	22.4±1.52	23.6±2.07	24.2±2.39*	24.2±2.39*	24.2±2.68	24.0±2.45	24.2±3.42
HCO_3^-	XA	21.5±1.86	22.7±2.09	22.8±1.89	23.2±1.70	23.7±1.83	23.9±1.82	23.3±2.21
	AA	21.3±1.32	22.6±2.43	23.0±2.59	23.1±2.23	22.9±2.34	22.8±2.26	22.9±3.04

Data were expressed as mean±SD. *Significantly different from baseline ($P<0.05$), **Significantly different from baseline ($P<0.001$). †Significantly different from group XA ($P<0.05$).

Increased DAP was observed at 5 and 10 min after induction in group XA (Table 1). No changes of DAP were shown in group AA, compared with baseline. There was significant difference between groups in MAP at 5 and 10 min. The values of MAP of group AA was always under baseline after induction (Table 1).

There were statistical difference between groups in heart rate at all measured time after induction ($P<0.05$). Compared with baseline, heart rates in group XA had no changes after induction, but those of group AA significantly increased (Table 1).

Blood gas parameters

Group XA had significantly higher $PaCO_2$ values than group AA ($P<0.05$) at 5 and 10 min. The difference in $PaCO_2$ between baseline and each measuring times are expressed in Table 1. Values of $PaCO_2$ were significantly increased, compared with baseline, in all groups after induction.

There was significant difference between groups in PaO_2 only at 5 min. In group XA, PaO_2 was significantly decreased at 5 to 15 min (Table 1).

In group XA, SaO_2 was significantly decreased compared with group AA ($P<0.05$) at 5 min. Mean SaO_2 was under 90% in a 5 min after induction and significantly decreased at 5 and 10 min compared with the baseline (Table 1).

In arterial blood pH, significant decreased values were observed in both groups. The significantly decreased pH were shown in group XA at 5 and 10 min, compared with group AA ($P<0.05$). Compared with each group's baseline, both groups had significantly decreased arterial blood pH after induction (Table 1).

Compared with baseline, tCO_2 of group XA were increased after induction, but no meaningful differences between groups were noticed (Table 1). There were no significant differences within or between groups HCO_3^-.

BIS and EMG

The BIS range of alert state in this study was 95 to 98 at BIS in both groups. The BIS values of group XA significantly decreased compared with that of group AA at 5 to 45 min ($P<0.05$).

BIS was steeply decreased after induction in group XA, and mean BIS values were maintained below 75. In group AA, significant decreases, compared with baseline, were shown after induction (Fig. 1).

Values of EMG were significantly different between groups at 0 to 25 min ($P<0.05$). In group XA, significant changes from baseline were revealed after premedication, except at 50 and 55 min (Fig. 2). In most times, values of group AA showed no differences be-

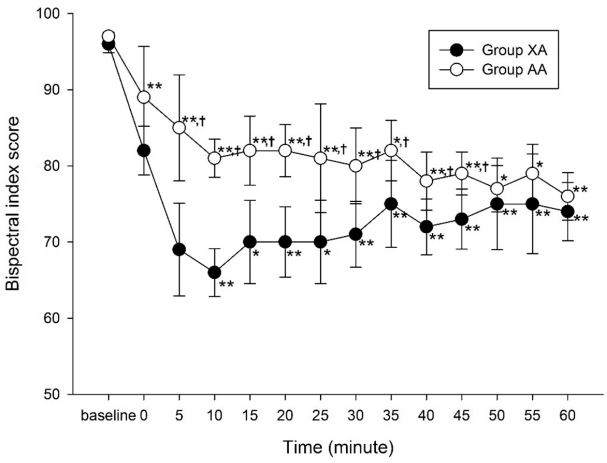

Fig. 1. Bispectral index scores in dogs anesthetized with alfaxalone. Data were expressed as median±SD. *Significantly different from baseline ($P<0.05$) and **Significantly different from baseline ($P<0.05$). †Significantly different from groups XA ($p<0.05$).

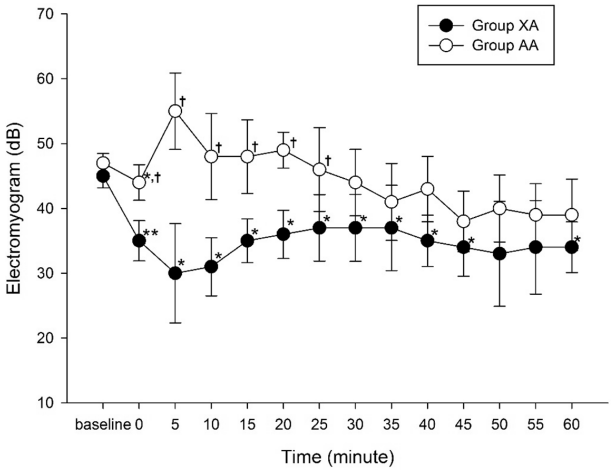

Fig. 2. Electromyograms in dogs anesthetized with alfaxalone. Data were expressed as median±SD. *Significantly different from baseline ($P<0.05$) and **Significantly different from baseline ($P<0.05$). †Significantly different from groups XA ($P<0.05$).

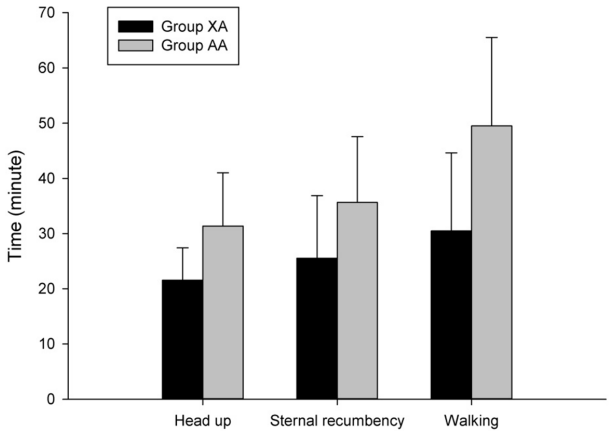

Fig. 3. Recovery times in dogs anesthetized with alfaxalone. Data were expressed as mean±SD.

tween baseline and each value.

Recovery time

Although mean recovery times of group AA were longer than those of group XA, no significant difference were observe between groups (Fig. 3).

Pedal withdrawal reflex test

Group XA showed inadequate analgesia after 45 min, and group AA could not provide proper analgesia during anesthesia. The result of withdrawal test is shown in Table 2.

DISCUSSION

Previously mentioned, the total intravenous anesthesia using the combinations with other anesthetics or analgesic agents could reduce the required dose of alfaxalone for induction or maintenance, however, co-administered drugs should be pondered on relative advantage or disadvantage on the systemic function, such as respiratory and cardiovascular system.

In the periods after premedication and before induction, deep sedated states were observed in most of group XA dogs but variable sedative states appeared in group AA. Induction of anesthesia was satisfactory without any adverse event in both groups.

Table 2. Number of dogs showing negative in pedal withdrawal reflex test in dogs anesthetized with alfaxalone (n=5)

Time (min)	5	10	15	30	45	60
Group XA	5	5	5	5	4	1
Group AA	4	3	3	1	2	1

In respect of respiratory rate, there was no significant difference between groups. In both groups, arterial CO_2 pressures were increased throughout anesthetic periods, and values of $PaCO_2$ in group XA were higher than those of in group AA at 5 and 10 min. Although mean PaO_2 and SaO_2 implied a slight hypoxemia state in XA group at first 10 min of anesthetic periods, those values of group AA was not significantly changed. The phenothiazines, including acepromazine, did not contribute to pulmonary depression in previous studies (Popovic et al, 1972; Turner et al, 1974), and it was consistent with our results.

In group XA, the analgesic effects were not sufficient after 45 min, and most dogs showed positive reflexes in withdraw test. It was reported that analgesic effect of xylazine was prolonged 30 to 60 min, according to administration route and dose, and duration of analgesia of xylazine might not be changed by co-administration with alfaxalone. In group AA, no adequate analgesia was noted after induction. It had been reported that acepromazine has no anti-nociceptive property (Barnhart et al, 2000; Bergadano et al, 2009). There was no synergistic analgesic effect on the combination of acepromazine and alfaxalone, and that provided poor analgesic effect in this study. Based on the previous study, increasing the dose of a phenothiazine did not make enhancement of the degree of sedation and increase of adverse effect (Hall et al, 2001), therefore, an elevation of the dose of acepromazine does not seem to produce adequate analgesia in this combination. In the anesthetic regimes of this study, additional anesthetics or analgesic agents should be considered to achieve complete analgesia or prolonged anesthetic period.

Transient hypertension were observed in group XA just after xylazine injection and arterial blood pressures were continuously decreased since 10 min after induction and similar result was observed in single injection of xylazine in a previous study (Ilback et al,

2003). It also reported that bradycardia and a brief period of hypertension followed by a prolonged decrease in arterial blood pressure are common events after the administration of xylazine (Tranquilli et al, 1992). Whereas, early decreased arterial blood pressure and gradual increase of arterial pressures were shown in group AA.

It is best known that one of negative cardiovascular effect of xylazine is bradycardia, however, the heart rate of group XA was not changed compared with baseline, and it implies that xylazine administration could alleviate the effect of tachycardia of alfaxalone. On the other hand, acepromazine and alfaxalone combination induce mild tachycardia.

The BIS were significantly decreased at most measured point in group XA compared with those in group AA. Compared with each baseline, all values of BIS were decreased in both groups, except values 5 min after induction in group AA. BIS alterations after premedication was identified just in xylazine treated group.

The facial EMGs in group AA showed no changes except the time point of 0 min, but in group XA significant decreased values were recorded with the exception in 50 to 55 min. The results of BIS, EMG and pedal withdrawal test implied that analgesia was more closely correlated with EMG than BIS.

In a previous study, it was suggested that BIS to determine surgical anesthetic depth is imprudent in dogs (Bleijenberg et al, 2011), and the result of this study was corresponded with the previous study. BIS and EMG has weak correlations with pedal withdrawal reflex test and was not reflected precisely analgesia and could not determine the depth of surgical anesthesia. The BIS system is a basically hypnosis monitor, because anesthesia consisted with hypnosis and analgesia and muscle relaxation, precise quantification of analgesia is difficult or impossible by BIS system alone (Singh, 1999), because hypnosis is not a same concept with analgesia, although hypnosis induced analgesia is also a part of anesthetic analgesia (Montgomery et al, 2000).

There were steep increases of BIS and EMG after cessation of infusion in all dogs, and it is thought that insufficient doses of anesthetics to maintain hypnosis could be detected by BIS, and it is carefully supposed that BIS could reduce the frequency of awareness during anesthesia.

The qualities of recovery were satisfactory in most dogs without severe adverse events in both groups. Although there was no statistical differences in recovery times, delayed mean recovery times were observed in group XA, and this seems to be affected by prolonged sedative effect of acepromazine.

In summary, mild hypoxia and transient hypertension were noticed during anesthesia with combination of xylazine and alfaxalone, while mild tachycardia was observed in the anesthesia with acepromazine and alfaxalone. The changes of BIS and EMG were greater in dogs with premedication of xylazine than those with acepromazine. EMG showed close correlation with pedal withdrawal test. The premedication of xylazine before alfaxalone CRI in this study could provide adequate analgesia during 30 min, while the premedication with acepromazine could not.

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