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Surgery

Anesthetic and cardiorespiratory effects of single-bolus intravenous alfaxalone with or without intramuscular xylazine-premedication in calves

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ABSTRACT. The anesthetic and cardiorespiratory effects of xylazine-alfaxalone combination were evaluated in calves. Six calves (age: 6–9 months old; weight: 114–310 kg) were anesthetized with intravenous alfaxalone 15 min after administration of intramuscular saline (0.5 ml/100 kg) or xylazine (0.1 mg/kg; 0.5 ml/100 kg of a 2% xylazine solution). Anesthesia induction was smooth and orotracheal intubation was achieved in all calves. The calves anesthetized with xylazine-alfaxalone required a smaller induction dose of alfaxalone (1.23 ± 0.17 mg/kg, P=0.010) and accepted endotracheal intubation for a significantly longer period (16.8 ± 7.2 min, P=0.022) than the calves anesthetized with alfaxalone alone (2.28 ± 0.65 mg/kg 7.3 ± 1.6 min). At 5 min after induction, tachycardia (heart rate: 166 ± 47 beats/min of heart rate), hypertension (mean arterial blood pressure: 147 ± 81 mmHg) and hypoxemia (partial pressure of arterial blood oxygen [PaO_2]: 43 ± 10 mmHg) were observed in the calves anesthetized with alfaxalone alone, whereas hypoxemia (PaO_2: 47 ± 7 mmHg) and mild hypercapnia (partial pressure of arterial blood carbon dioxide: 54 ± 5 mmHg) were observed in the calves anesthetized with xylazine-alfaxalone. Premedication with xylazine provided a sparing effect on the induction dose of alfaxalone and a prolongation of anesthetic effect. Oxygen supplementation should be considered to prevent hypoxemia during anesthesia.

KEY WORDS: alfaxalone, calf, intravenous anesthesia, xylazine

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Alfaxalone (3-α-hydroxy-5-α-pregnane-11,20-dione) is a synthetic neuroactive lipophilic steroid that interacts with γ-aminobutyric acid A ($GABA_A$) receptors and results in anesthesia and muscle relaxation [1]. Lower concentrations of alfaxalone facilitate the open state of the $GABA_A$ receptor channel, similar to the effect of benzodiazepines [14]. However, alfaxalone at higher concentrations could directly activate the $GABA_A$ receptor channel, similar to the effect of propofol or barbiturates [14]. Early alfaxalone products such as Saffan® were combined with alfadolone to improve the water solubility of alfaxalone and were solubilized with 20% polyoxyethylated castor oil (Cremophor EL®). However, these products were withdrawn from the veterinary and medical markets owing to the allergic side effects induced by a histamine release associated with the solubilizing agent [4, 7].

In 2000, a new formulation of alfaxalone solubilized with 2-hydroxypropyl-beta-cyclodextrin (HPCD), which does not cause a histamine release, was introduced into veterinary practice; it is currently approved as an intravenous anesthetic agent for dogs and cats in 19 countries. Pharmacokinetic studies of alfaxalone-HPCD have demonstrated that it provides a rapid and smooth induction of anesthesia and a short duration of anesthesia in rats [15], cats [27], dogs [9, 16] and horses [10, 11]. However, undesirable events, including transient muscular tremors and ataxia, were observed during recovery from anesthesia induced by alfaxalone-HPCD alone in dogs [24] and cats [25]. Premedication with centrally acting sedatives and/or analgesics reduces the dose of

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Table 1. Calves used in the present study

	Breed	Sex	Age (months)	Body weight (kg)
ALFX group				
Calf-1	Holstein	Male	6	212
Calf-2	Holstein	Female	6	129
Calf-3	Holstein	Male	6	159
Calf-4	Holstein	Male	6	114
Calf-5	Holstein	Male	6	200
Calf-6	Jersey	Male	6	178
XY-ALFX group				
Calf-1	Holstein	Male	8	310
Calf-2	Holstein	Female	8	235
Calf-3	Holstein	Male	8	227
Calf-5	Holstein	Male	8	281
Calf-7	Holstein	Male	8	240
Calf-8	Holstein	Male	9	285

ALFX group: alfaxalone group; XY-ALFX group: xylazine- alfaxalone group.

alfaxalone-HPCD necessary to induce and maintain anesthesia, and improves the quality of recovery from alfaxalone-HPCD anesthesia in dogs [12]. Xylazine, an α_2-adrenergic receptor agonist (α_2-agonist), has been commonly used as a sedative in cattle. The dose of xylazine in cattle (0.02–0.2 mg/kg) is one-tenth of that used in horses [5]. Therefore, it is expected that premedication with xylazine may reduce the induction dose of alfaxalone-HPCD and improve the quality of alfaxalone anesthesia.

This study evaluated an intravenous (IV) induction dose of alfaxalone-HPCD alone, the sparing effect of premedication with intramuscular (IM) xylazine on the IV induction dose of alfaxalone HPCD, and their anesthetic and cardiorespiratory effects in calves.

MATERIALS AND METHODS

Experimental animals

Six of 8 calves (age: 6–9 months; weight: 114–310 kg) were anesthetized with intravenous alfaxalone-HPCD 15 min after administration of IM saline (ALFX group) or xylazine (XY-ALFX group). Four of the 8 calves were used for each treatment, with a 2-month interval between the 2 treatments (Table 1). All calves were determined to be in good health based on a physical examination, complete blood cell counts and serum chemical analysis. Food was withheld for 12 hr before each experiment; water was continuously available. The calves were cared for according to the principles of the *Guide for the Care and Use of Laboratory Animals* prepared by Rakuno Gakuen University. The Animal Care and Use Committee of Rakuno Gakuen University approved this study (approval no. VH15C1).

Study design

In each calf, a 22-gauge, 2.5-cm catheter (Supercath®, Medikit Co., Ltd., Tokyo, Japan) was placed into the right or left posterior auricular artery and a 14-gauge, 13.3-cm catheter (BD Angiocath®, Becton Dickinson and Co., Sandy, UT, U.S.A.) was placed into the left jugular vein while the calf was in a standing position with minimal physical restraint. After instrumentation, the calf remained in the quiet induction stall for approximately 30 min. The calf then received 0.5 m*l*/100 kg IM of saline (Otsuka Normal Saline®, Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) in the ALFX group or 0.1 mg/kg IM of xylazine (0.5 m*l*/100 kg of 2% xylazine solution; Celactal® 2% injection; Bayer Yakuhin, Ltd., Osaka, Japan). At 15 min after the administration of saline or xylazine, alfaxalone-HPCD (Alfaxan®, Meiji Seika Pharma. Co., Ltd., Tokyo, Japan) was infused at a rate of 1 mg/kg/min (10 m*l*/100 kg/min) through the 14-gauge catheter into the left jugular vein until the calf lay on its side. Orotracheal intubation was then maintained until the calf showed the swallow reflex. All calves breathed room air during the experiment.

Evaluation of the anesthetic effects

The anesthetic effects were evaluated according to the degree of neuro-depression, the quality of anesthetic induction including ease of orotracheal intubation, and the quality of recovery from anesthesia. The neuro-depression produced by each treatment was subjectively evaluated using an existing composite measurement scoring system developed for dogs [23]. The scoring system consisted of 6 categories: spontaneous posture, placement on side, response to noise, jaw relaxation, general attitude and nociceptive response to toe-pinch. These categories were rated with a score of 0 to 2 for jaw relaxation; 0 to 3 for placement on side, general attitude and toe-pinch response; and 0 to 4 for spontaneous posture and response to noise, based on the responsiveness expressed by the calves [23]. The total neuro-depressive score was calculated as the sum of the scores of the 6 categories (maximum score, 19). The qualities of anesthetic induction and recovery were assessed using numerical scoring systems previously used in dogs (Table 2) [23]. A well-trained observer (S. F. E-H.) blinded to the group assignments was responsible for the

Table 2. Scoring systems for evaluation of the qualities of anesthetic induction and recovery in calves

Category	Conditions in calves
Induction score	
1 (Very smooth)	No swallowing, intubation on the first attempt, no coughing, no struggling, no vocalization.
2 (Quite smooth)	Some swallowing, intubation after 2–3 attempts, no coughing, some physical movement, no vocalization.
3 (Moderately smooth)	Frequent swallowing, more than 3 attempts to intubate, coughing, vocalization and/or physical movement for more than half of the induction time, some distress and excitement.
4 (Poor)	Vocalization and physical movement during the entire induction period, major distress, aggression or excitement, additional induction agent needed for intubation.
Recovery score	
1 (Very smooth)	No excitement. No paddling, vocalizing, trembling, or vomiting. No convulsions.
2 (Quite smooth)	Some excitement. Some head movement, possibly some shivering but no paddling, vocalizing, trembling, or vomiting. No convulsions.
3 (Moderately smooth)	Moderate excitement. Some paddling, vocalizing, trembling, or vomiting. No convulsions.
4 (Poor)	Extreme excitement observed: aggression, vocalizing, violent movements, or convulsions. Rescue sedation or anticonvulsant drugs necessary.

evaluation of the anesthetic effect of the treatments using these scoring systems.

In addition, the periods of time were recorded from a start of IV injection of alfaxalone-HPCD until the calves toppled down in lateral recumbency (induction time), until orotracheal intubation was complete (intubation time), until the calves showed the swallow reflex (extubation time), until the calves appeared to be in the sternal position (sternal position time), and until the calves appeared to be unaided standing (standing time). The durations of accepting endotracheal tube and lateral recumbency were also calculated as the periods between the intubation and extubation times and between the induction and sternal position times.

Measurement of cardiorespiratory valuables

The cardiorespiratory effects were evaluated in each calf before the IM injection of saline or xylazine (baseline), before and at 5, 10, 15, 30, 45 and 60 min after the start of alfaxalone-HPCD infusion. Apex-base lead electrocardiography (ECG), heart rate (HR; beats/min), rectal temperature (RT;°C), mean arterial blood pressure (MABP; mmHg), respiratory rate (RR; breaths/min) and arterial blood gas analysis were recorded before and after the drug administration. ECG, HR, and MABP were recorded by a patient monitoring system (DS-7210, Fukuda Denshi Co., Ltd., Tokyo, Japan). The HR was also determined by thoracic auscultation. The RR was counted by feeling nostril breath warmness. The RT was measured with a digital thermometer (Thermo flex for animal, Astec Co., Ltd., Chiba, Japan). The MABP was measured directly by connecting the catheter placed in the auricular artery to a pressure transducer (BD DTX^{TM} Plus DT-4812, Japan Becton and Dickinson Co., Fukushima, Japan). Arterial blood samples (1.0 m*l* each) were anaerobically withdrawn from the auricle arterial catheter into a heparinized syringe and were analyzed immediately after collection to measure arterial pH (pHa) and the partial pressures of arterial oxygen (PaO_2; mmHg) and carbon dioxide ($PaCO_2$; mmHg) using a blood gas analyzer (GEM Premier 3000, Instrumentation Laboratory, Tokyo, Japan). The pHa, PaO_2 and $PaCO_2$ were corrected for the RT determined immediately after blood collection.

Statistical analysis

The total dose of alfaxalone-HPCD required for intubation (induction dose); the induction, intubation and standing times; and the durations of endotracheal tube acceptance and lateral recumbency were expressed as mean ± standard deviation of 6 calves in each group, and were compared between the ALFX and XY-ALFX groups using an unpaired *t*-test or Welch's *t*-test following the results of the Kolmogorov-Smirnov test and F test. Cardiorespiratory and blood gas data were expressed as mean ± standard deviation of 6 calves in each group, and their time-dependent changes were analyzed between groups using a two-way repeated measures ANOVA or Friedman test following the results of the Kolmogorov-Smirnov test and the Bartlett test. In each group, the cardiorespiratory and blood gas data at each time point were compared with the baseline value using the Kruskal-Wallis test and Steel test or a one-way ANOVA and Dunnett test following the results of the Kolmogorov-Smirnov test and Bartlett test. The total neuro-depressive, anesthetic induction and recovery scores were expressed as median and range of the 6 calves in each group. The time-dependent changes of the total neuro-depressive score were analyzed between groups using the Friedman test. In each group, the total neuro-depressive score at each time point was compared with its baseline value using the Kruskal-Wallis test and Steel test. The anesthetic induction and recovery scores were compared between groups using the Mann-Whitney *U* test. For all analyses, *P* values <0.05 were considered significant.

RESULTS

Immediately before the administration of alfaxalone-HPCD, all calves in the ALFX group were standing and showed poor jaw relaxation. In the XY-ALFX group, a calf was unable to rise, 3 calves were lying with difficulty rising, and 2 calves were standing but all calves showed poor jaw relaxation at the immediately before the IV administration of alfaxalone-HPCD. Therefore, it was judged that orotracheal intubation was impossible for all calves in both groups. The induction dose of alfaxalone-HPCD,

Table 3. Induction dose of alfaxalone-HPCD, times related to anesthetic effects, and quality of induction and recovery in calves anesthetized with alfaxalone-HPCD alone (ALFX group) or xylazine-alfaxalone-HPCD (XY-ALFX group)

	ALFX group	XY-ALFX group
Induction dose of alfaxalone-HPCD (mg/kg)	2.28 ± 0.65	1.23 ± 0.17[aa)]
Induction time (sec)	66 ± 14	75 ± 8
Intubation time (min)	4.8 ± 1.8	5.8 ± 3.2
Duration of endotracheal tube acceptance (min)	7.3 ± 1.6	16.8 ± 7.2[a)]
Duration of maintaing lateral recumbency (min)	18.9 ± 3.4	21.8 ± 3.9
Standing time (min)	34.0 ± 7.2	36.8 ± 13.1
Induction score	2 [1, 2]	2 [2]
Recovery score	3 [3]	2 [2][aa)]

Induction dose of alfaxalone-HPCD and times related to anesthetic effect are expressed as mean ± standard deviation of 6 calves in each group. The induction and recovery scores are expressed as median [range] of 6 calves in each group. Significant differences between groups: a) $P<0.05$; aa) $P<0.01$.

times related to anesthesia, and induction and recovery scores of each group are summarized in Table 3. The induction dose of alfaxalone-HPCD was significantly smaller in the XY-ALFX group than the ALFX group ($P=0.010$). The duration of endotracheal tube acceptance was significantly longer in the XY-ALFX group ($P=0.022$). There was no significant difference in the induction or standing times, or the duration of lateral recumbency between groups. In the ALFX group, anesthetic induction was smooth, and the quality of anesthesia induction was scored as a 1 in one calf and a 2 in 5 calves. However, anesthetic recovery was characterized by hyperkinesia, including tremors, paddling, seizure-like activity and thrashing, and the quality of recovery from anesthesia was scored as a 3 in all calves. In the XY-ALFX group, the qualities of induction and recovery were scored as a 2 in all calves. The quality of recovery from anesthesia was significantly better in calves of the XY-ALFX group ($P=0.001$).

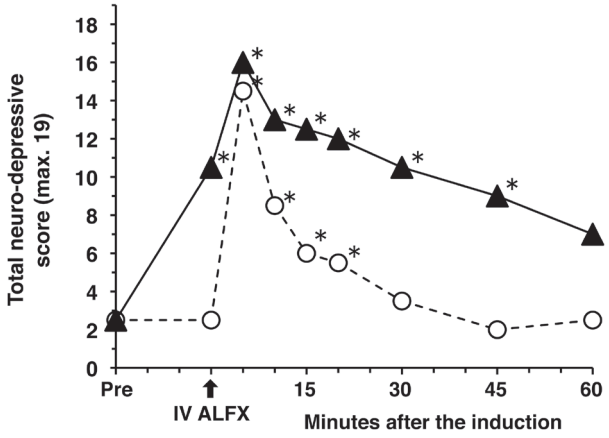

Fig. 1. Time-dependent changes in the neuro-depressive scores of 6 calves anesthetized with alfaxalone-HPCD alone (ALFX group) or with xylazine and alfaxalone-HPCD (XY-ALFX group). Plots are the median values of 6 calves in the ALFX (○) or XY-ALFX-groups (▲). There was a significant difference in the time-dependent changes of the total neuro-depressive scores between the ALFX and XY-ALFX groups ($P<0.001$). *Significant difference from the baseline value ($P<0.05$).

Changes in the total neuro-depressive score are shown in Fig. 1. The median score in the ALFX group significantly increased at 5 min (14.5 [range: 9–18], $P=0.023$), 10 min (8.5 [range: 6–11], $P=0.022$), 15 min (6 [range: 5–9], $P=0.021$), and 20 min (5.5 [range: 5–7], $P=0.021$) after administration of alfaxalone-HPCD. In the XY-ALFX group, the calves were moderately sedated immediately before administration of alfaxalone-HPCD (median neuro-depressive score: 10.5 [range: 7–15], $P=0.024$). In these calves, the median score significantly increased at 5 min (16 [range: 10–18], $P=0.025$), 10 min (13 [range: 9–17], $P=0.025$), 15 min (12.5 [range: 7–15], $P=0.025$), 20 min (12 [range: 7–12], $P=0.025$), 30 min (10.5 [range: 7–12], $P=0.025$), and 45 min (9 [range: 7–10], $P=0.023$) after the IV administration of alfaxalone-HPCD. There was a significant difference in the time-dependent change of the total neuro-depressive score between the ALFX and XY-ALFX groups ($P<0.001$).

The time-dependent changes in the cardiorespiratory valuables are summarized in Table 4. There were significant differences in the time-dependent changes in RT, HR, MABP and pHa between the ALFX and XY-ALFX groups ($P<0.001$, $P<0.001$, $P<0.001$ and $P=0.017$, respectively) but the changes in RT and pHa were not clinically relevant in either group. In the ALFX group, the HR and MABP increased significantly after the administration of alfaxalone-HPCD ($P<0.001$ and $P<0.001$, respectively), and tachycardia and hypertension were observed. In the XY-ALFX group, the HR decreased significantly immediately before the administration of alfaxalone-HPCD ($P=0.008$), and MABP decreased significantly after the administration of alfaxalone-HPCD ($P=0.004$), but clinically relevant hypotension was not observed. There was no significant difference in the time-dependent changes of RR, $PaCO_2$ or PaO_2 between the ALFX and XY-ALFX groups. The PaO_2 decreased significantly after administration of alfaxalone-HPCD in the ALFX and XY-ALFX groups ($P<0.001$ and $P<0.001$, respectively) and severe hypoxemia occurred. In the XY-ALFX group, PaO_2 increased significantly immediately before and after the administration of alfaxalone-HPCD ($P<0.001$), and mild hypercapnia was observed.

Table 4. Time-related changes in the cardiorespiratory valuables of calves anesthetized with alfaxalone-HPCD alone (ALFX group) and xylazine-alfaxalone-HPCD (XY-ALFX group)

Cardiorespiratory valuable	Group	Baseline	Time after intravenous administration of alfaxalone-HPCD (min)						
			0	5	10	15	20	30	45	60
Rectal temp. (°C)[aa)]	ALFX	38.6 ± 0.7	38.6 ± 0.7	38.5 ± 0.7	38.4 ± 0.7	38.4 ± 0.7	38.3 ± 0.9	38.3 ± 0.7	38.3 ± 0.5	38.4 ± 0.5
	XY-ALFX	39.3 ± 0.4	39.4 ± 0.5	39.1 ± 0.6	39.0 ± 0.6	39.2 ± 0.3	39.1 ± 0.3	39.1 ± 0.4	39.0 ± 0.4	39.1 ± 0.5
Heart rate (bpm)[aa)]	ALFX	68 ± 10	68 ± 9	167 ± 45[b)]	149 ± 34	143 ± 34	122 ± 30	107 ± 31	91 ± 16	79 ± 13
	XY-ALFX	73 ± 5	57 ± 8[b)]	73 ± 6	74 ± 10	77 ± 14	70 ± 10	65 ± 4	62 ± 5	65 ± 4
Respiratory rate (bpm)	ALFX	23 ± 15	19 ± 7	36 ± 12	33 ± 18	41 ± 19	37 ± 11	32 ± 10	23 ± 6	25 ± 8
	XY-ALFX	38 ± 14	24 ± 6[b)]	40 ± 9	41 ± 16	33 ± 7	32 ± 11	25 ± 6	27 ± 7	20 ± 5
MABP (mmHg)[aa)]	ALFX	106 ± 9	101 ± 4	147 ± 8[bb)]	122 ± 12	115 ± 9	112 ± 4	111 ± 7	106 ± 10	105 ± 14
	XY-ALFX	118 ± 4	115 ± 11	96 ± 16[b)]	95 ± 17[b)]	94 ± 8[b)]	99 ± 12	102 ± 13	95 ± 10[b)]	103 ± 10
pHa[a)]	ALFX	7.442 ± 0.013	7.452 ± 0.029	7.423 ± 0.048	7.395 ± 0.067	7.410 ± 0.037	7.378 ± 0.036[b)]	7.425 ± 0.029	7.453 ± 0.019	7.462 ± 0.029
	XY-ALFX	7.475 ± 0.040	7.448 ± 0.029	7.417 ± 0.025	7.457 ± 0.019	7.465 ± 0.023	7.465 ± 0.027	7.465 ± 0.015	7.493 ± 0.039	7.475 ± 0.031
$PaCO_2$ (mmHg)	ALFX	44.0 ± 3.9	43.8 ± 4.4	47.8 ± 6.1	46.8 ± 8.4	41.0 ± 5.6	44.2 ± 6.6	39.8 ± 3.3	39.7 ± 3.6	40.2 ± 4.4
	XY-ALFX	40.3 ± 3.1	47.7 ± 2.9[b)]	53.7 ± 5.2[bb)]	47.0 ± 4.1	47.3 ± 4.1	47.0 ± 4.1	47.5 ± 3.3[b)]	45.2 ± 3.7[b)]	47.5 ± 2.7
PaO_2 (mmHg)	ALFX	86.2 ± 5.2	84.7 ± 10.2	42.8 ± 10.2[bb)]	56.2 ± 13.3[bb)]	68.3 ± 13.0	75.2 ± 12.1	83.7 ± 13.4	85.2 ± 6.1	87.2 ± 5.5
	XY-ALFX	97.7 ± 6.2	78.8 ± 13.6	47.2 ± 7.1[bb)]	50.0 ± 6.6[bb)]	53.7 ± 13.7[bb)]	56.0 ± 12.2[bb)]	65.7 ± 10.1[bb)]	74.5 ± 13.1[b)]	77.0 ± 9.9[b)]

Data are expressed as mean ± standard deviation of 6 calves in each group. bpm: beat/minute; MABP: mean arterial blood pressure; $PaCO_2$: partial pressure of arterial carbon dioxide; PaO_2: partial pressure of arterial oxygen. Significant differences observed between groups: a) $P<0.05$; aa) $P<0.01$. Significant differences observed from baseline value: b) $P<0.05$; bb) $P<0.01$.

DISCUSSION

In the present study, all calves could be anesthetized and orotracheally intubated by induction of anesthesia with IV alfaxalone-HPCD, with or without IM xylazine premedication. As we hypothesized, xylazine premedication reduced the IV anesthetic induction dose of alfaxalone-HPCD. Furthermore, the longer duration of endotracheal tube acceptance, and the time-dependent changes with the higher neuro-depressive scores observed in the calves anesthetized with alfaxalone-HPCD after xylazine premedication indicated a prolonged anesthetic effect. However, oxygen supplementation should be considered to prevent hypoxemia during anesthesia.

Alpacas, goats and sheep are among the ruminants in which the anesthetic effect of alfaxalone-HPCD alone has been investigated [2, 3, 6, 8]. del Álamo *et al.* [6] reported that the dose sufficient to allow endotracheal intubation was 2.1 ± 0.1 mg/kg, and the time from induction to standing was 34.1 ± 3.2 min in 5 alpacas (weight: 96.7 ± 19.9 kg) anesthetized with alfaxalone-HPCD alone. These results were similar to those observed in the calves in this study anesthetized with alfaxalone-HPCD alone. In addition, undesirable recovery characteristics such as tremors, paddling, seizure-like activity and thrashing observed in alpacas [6] were similar to those observed in the calves anesthetized with alfaxalone-HPCD alone in this study. Greater attention to the recovery environment is advisable when using alfaxalone-HPCD for the induction of anesthesia in dogs when minimal premedication has been used [13]. In contrast, calm and uneventful recoveries were observed in goats [8] and sheep [2] anesthetized with alfaxalone-HPCD alone (goats: 3.0 mg/kg; sheep: 2.0 mg/kg). Although further studies are necessary to determine the reason for the differences in the recovery characteristics from the alfaxalone-HPCD anesthesia among ruminants, IV induction with alfaxalone-HPCD alone should be avoided in calves and alpacas.

In the present study, IM xylazine premedication reduced the anesthetic induction dose of alfaxalone-HPCD sufficient to allow endotracheal intubation in calves by 46% (mean: 1.23 mg/kg) compared to that of calves anesthetized with alfaxalone-HPCD alone (mean: 2.28 mg/kg). As expected, xylazine premedication reduced the induction dose of alfaxalone-HPCD. In addition, xylazine premedication prolonged the duration of endotracheal intubation acceptance by 57% (mean: 16.8 vs. 7.3 min), although recovery from anesthesia was not prolonged (mean duration of lateral recumbency: 34.0 vs 36.8 min). Furthermore, xylazine premedication improved recovery from alfaxalone-HPCD anesthesia in calves. Xylazine is an α_2-agonist commonly used for prolonged sedation in cattle [5]. The α_2-agonists are sympathomimetic agents that selectively stimulate α_2-adrenergic receptors and mimic the action of adrenaline and noradrenaline signaling in the heart, smooth muscle, and central nervous system [5]. The IV induction dose of alfaxalone-HPCD in cats was effectively reduced by premedication with other α_2-agonists such as medetomidine and dexmedetomidine [17, 21]. It was also reported that the quality of recovery from alfaxalone-HPCD anesthesia was improved by premedication with α_2-agonists such as medetomidine and dexmedetomidine in dogs [23] and cats [17, 19, 20]. Waterman [26] reported that premedication with xylazine (0.2 mg/kg IM) did not significantly affect the half-life of ketamine (5 mg/kg IV) but reduced the volume of distribution and the clearance rate of ketamine by approximately 50%. The IV administration of alfaxalone-HPCD

after premedication with xylazine may be useful for short-duration anesthesia or anesthetic induction for orotracheal intubation in calves.

Tachycardia was accompanied by hypertension in the calves anesthetized with alfaxalone-HPCD alone. An increase in HR after the administration of alfaxalone-HPCD alone was observed in alpacas [6] and sheep [2]. The increase in HR after the IV administration of alfaxalone-HPCD alone was accompanied by hypertension in alpacas [6], similar to that in the calves in this study. In sheep, the increase in HR after the IV administration of alfaxalone-HPCD (2 mg/kg) alone was not accompanied by significant changes in arterial blood pressure [2]. In goats, HR and arterial blood pressure were maintained within clinically acceptable limits after IV administration of alfaxalone-HPCD [8]. There was a distinct lack of detailed cardiovascular data, including cardiac output and systemic vascular resistance, in the present study and in these previous studies of ruminants. Although further studies of ruminants are necessary to confirm the cardiovascular effects of alfaxalone-HPCD, the effects of alfaxalone-HPCD on vascular resistance in calves seem to be similar to those in alpacas and different from those in goats or sheep.

Severe hypoxemia occurred in the calves anesthetized with IV alfaxalone-HPCD alone. Similar hypoxemia occurred in alpacas anesthetized with IV alfaxalone-HPCD alone [6]. However, no respiratory depression occurred in goats [8] or sheep [2] anesthetized with the IV alfaxalone-HPCD alone. It was reported that mild hypoxemia (PaO_2, 77.8 ± 11.9 mmHg) occurred in cattle physically restrained in lateral recumbency [22]. The oxygenation of the calves anesthetized with IV alfaxalone-HPCD alone might deteriorate into severe hypoxemia due to a combination of respiratory depression caused by lateral recumbency and alfaxalone-HPCD.

IM xylazine premedication decreased the HR in the calves, but HR and MABP were maintained within clinically acceptable limits after the administration of alfaxalone-HPCD. Severe hypoxemia was prolonged and mild hypercapnia was observed. Similar cardiorespiratory changes have been reported in calves anesthetized with xylazine (0.088 mg/kg IV) and ketamine (4.4 mg/kg IV) [18]. Ventilation-perfusion mismatching and hypoventilation are the predominant causes of hypoxemia in cattle [5]. The present data suggest that there was only a minimal decrease in alveolar ventilation during alfaxalone-HPCD anesthesia following IM xylazine premedication, because $PaCO_2$ values remained within the acceptable range. Therefore, the reduction of PaO_2 during IV alfaxalone-HPCD anesthesia following IM xylazine premedication might be attributed to ventilation-perfusion mismatching. As there may be minimal cardiovascular depression during IV alfaxalone-HPCD anesthesia following IM xylazine premedication, increasing the inspired oxygen concentration may effectively minimize the reduction of PaO_2. Although no overt problems attributable to hypoxemia were observed in any calf, supplemental oxygen is recommended during IV alfaxalone-HPCD anesthesia following IM xylazine premedication.

The present study has several limitations. First, there were differences in the body weights and ages of the calves between the ALFX and XY-ALFX groups. The cardiorespiratory measurements in the XY-ALFX group may have been affected by their larger body weight. Second, there was a lack of detailed cardiovascular data, including cardiac output and systemic vascular resistance, in the present study. We cannot confirm the cardiovascular effects in calves anesthetized with IV alfaxalone-HPCD with or without the xylazine premedication. Finally, the neuro-depressive score used in the present study was originally developed for dogs. Because of these limitations, the results of the present study should be interpreted with caution. Further investigations are necessary to confirm the anesthetic and cardiorespiratory effects of single-bolus IV alfaxalone with or without IM xylazine premedication in calves.

In conclusion, IM xylazine premedication decreased the IV anesthetic induction dose of alfaxalone-HPCD and prolonged the anesthetic effect. The administration of IV alfaxalone-HPCD following IM xylazine premedication may be useful for short-duration anesthesia or for the induction of anesthesia for orotracheal intubation in calves when oxygen supplementation is available.

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