Comparison of the anesthetic effects between 5 mg/kg of alfaxalone and 10 mg/kg of propofol administered intravenously in cats

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ABSTRACT. To compare the anesthetic effects after intravenous administration of alfaxalone or propofol without premedication, either alfaxalone (5 mg/kg) or propofol (10 mg/kg) was administered intravenously over 120 sec in 6 cats. Each cat received the alternate treatment at least a 7-day interval. Anesthetic effects (tolerance of intubation, behavior changes and neurodepressive score) and physiological parameters were evaluated. Both treatments produced a rapid loss of consciousness, no apnea, and physiological parameters were maintained within clinically acceptable ranges apart from transient hypoxemia. The degree of hypoxemia was greater after the propofol treatment compared with the alfaxalone treatment. During the recovery period, more adverse events (ataxia, muscular tremors) were observed after the alfaxalone treatment compared with the propofol treatment.

KEY WORDS: alfaxalone, anesthetic induction, feline, propofol

Alfaxalone is a synthetic neuroactive steroid molecule which modulates the γ-aminobutyric acid A (GABA$_A$) receptor causing neurodepression [1, 4]. A formulation of alfaxalone in cyclodextrin has been marketed as a 10 mg/ml solution in Australia since 2001. This formulation has been approved in many countries as an intravenous (IV) anesthetic induction agent for dogs and cats, and the recommended IV dose for induction in cats is 5 mg/kg [20]. Muir *et al.* [12] reported that mild cardiovascular depressant effects without apnea were observed at doses up to 15 mg/kg of IV alfaxalone in cats. Alfaxalone is considered to be a clinically effective anesthetic induction agent [17, 21] and, similar to propofol, is commonly used to induce general anesthesia in cats [15].

Propofol has been a preferred anesthetic induction agent which also modulates the GABA$_A$ receptor. Intravenous administration of propofol in cats produces a smooth anesthetic induction despite a high incidence of apnea [11, 16]. In practice, IV induction of anesthesia in cats with either alfaxalone or propofol, followed by maintenance with isoflurane, produces a smooth induction of anesthesia and rapid recovery with similar levels of cardiorespiratory depression [9, 17]. However, there are no studies comparing the anesthetic effects of alfaxalone and propofol in cats administered at an anesthetic induction dose without premedication or an inhalation anesthetic agent. In dogs, clinically relevant differences in cardiopulmonary effects between a single bolus of alfaxalone and propofol were not observed [8]. Maney *et al.* [8] also reported that a single bolus of IV propofol resulted in shorter recovery times and fewer adverse events than a single bolus of IV alfaxalone in dogs. Conversely, Campagna *et al.* [3] reported that in cats premedicated with medetomidine, alfaxalone had less of an adverse influence on respiration than propofol. It is still controversial as to whether the quality of recovery in cats after induction with alfaxalone is poorer than that after propofol [9, 17].

The aim of this study was to compare the anesthetic effects and physiological parameters after IV administration of alfaxalone or propofol without premedication in cats. In addition, we sought to clarify differences in the pharmacological effects between a single IV anesthetic induction dose of alfaxalone and propofol in cats.

Six, 2-year-old sexually intact purpose-bred cats (3 males and 3 females) weighing from 3.1 to 5.0 kg were randomly assigned to receive either IV alfaxalone at 5 mg/kg (ALFX) or IV propofol at 10 mg/kg (PRO). The administered dose of alfaxalone (Alfaxan, Jurox Pty., Ltd., Rutherford, Australia) was the recommended dose for anesthetic induction in healthy unpremedicated cats [20], and that of propofol (Mylan, MSD Animal Health K.K., Tokyo, Japan) was adopted from the mean administration dose of propofol required to achieve tracheal intubation in unpremedicated cats, that reported by Sano *et al.* [16]. The dose of propofol in the present study coincides with the midrange of the manufacturer's recommended dose for induction in cats without premedication (based on the package insert). Both doses adopted in the present study are considered to be an anesthetic induction doses of cats in clinical practice. After a minimum interval of 7-days, each cat then received the alternate treatment. All cats were

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judged to be in good health based upon a physical examination. Food was withheld for at least 12 hr before drug administration, but the cats were allowed free access to water prior to each treatment. The cats were cared for according to the principles of the "Guide for the Care and Use of Laboratory animals" prepared by Rakuno Gakuen University. This study was conducted as part of studies approved by the institutional Animal Care and Use Committee of Rakuno Gakuen University (approval numbers: VH24B8, VH24B13).

For each treatment, the IV agent was manually administered over 120 sec through a 22-gauge catheter (Supercath, Medikit Co., Ltd., Tokyo, Japan) which had been previously placed into the cephalic vein of each cat. The cats breathed room air spontaneously and, when possible, were orotracheally intubated with an endotracheal tube (Endotracheal tube with cuff [I.D. 4.0 mm], Fuji Systems Corp., Tokyo, Japan) within 5 min of commencing drug administration. After successful intubation, the endotracheal tube cuff remained uninflated. The tube was extubated when three or more coughs were elicited. The anesthetic effects and physiological parameters were measured in each cat before (baseline) and at 5, 10, 15, 20, 30, 40, 50 and 60 min after starting drug administration until the cat was able to stand unaided. The physiological parameters at baseline were measured while the cat remained sternal in its carrier. The neurodepressive effects were subjectively evaluated using an ordinal scoring system (Table 1) from a sedative scale previously used in cats [18]. An observer was not blinded, but responsible for the evaluation using this scoring system throughout the present study. The scoring system consisted of 5 categories: spontaneous posture, placement on side, response to noise, jaw relaxation and general attitude. These categories were rated in scores 0 to 2 for jaw relaxation, 0 to 3 for placement of side and general attitude, or 0 to 4 for spontaneous posture and response to noise (clapping hands by an observer) based on responsiveness expressed by the cats. The neurodepressive score was calculated as a sum of scores in the 5 categories (a maximum of 16). In addition, the times at onset of head down to the ground without head hold (head down), intubation, first appearance of spontaneous movement, spontaneous head lift, spontaneous return to sternal recumbency, unaided standing, and the durations of maintenance of intubation were recorded. Rectal temperature (RT; °C) was measured with a digital thermometer (Thermo flex for animal, Astec Co., Ltd., Chiba, Japan). Lead II electrocardiogram, heart rate (HR; beats per minute) and percutaneous oxygen saturation of hemoglobin (SpO_2; %) were recorded by a patient monitoring system (DS-7210, Fukuda Denshi Co., Ltd., Tokyo, Japan). The SpO_2 sensor was applied to the tongue. Respiratory rate (RR; breaths per minute) was counted by observing thoracic movements. Systolic arterial blood pressure (SABP; mmHg), mean arterial blood pressure (MABP; mmHg), and diastolic arterial blood pressure (DABP; mmHg) were indirectly measured by an oscillometric method (petMAP™, Ramsey Medical, Inc., Hudson, OH, USA) using a blood pressure cuff (width approximately 40% of the tail circumference) placed around the clipped tail base of each cat. Each arterial blood pressure was measured three times at each assessment, and the average of these measurements was defined as each arterial blood pressure.

The neurodepressive scores are reported as median ± quartile deviation. The neurodepressive scores at each time point was compared with the baseline value using a Kruskal-Wallis test and Steel test for each treatment. Differences in the neurodepressive scores between the treatment were compared using the Kruskal-Wallis test. Differences in the neurodepressive scores between males and females were compared using the Kruskal-Wallis test for each treatment. The times related to the anesthetic effects and physiological parameters are reported as mean ± standard deviation. The times related to the anesthetic effects between treatments

Table 1. Ordinal scoring system evaluating for neurodepressive effects in cats [18]

Spontaneous posture	Score		Jaw relaxation	Score
Standing	0		Poor	0
Tired and standing	1		Slight	1
Lying but can rise	2		Good	2
Lying with difficulty rising	3		General attitude	Score
Unable to rise	4		Excitable	0
Placement on side	Score		Awake and normal	1
Resists strongly	0		Tranquil	2
Modest resistance	1		Stuporous	3
Slight resistance	2		Sedation score*	0–16
No resistance	3			
Response to noise	Score			
Jump	0			
Hears and moves	1			
Hears and twitches ear	2			
Barely perceives	3			
No response	4			

This scoring system was consisted 5 categories (spontaneous posture, placement on side, response to noise, jaw relaxation and general attitude). These categories were rated in score 0 to 2, 0 to 3, or 0 to 4 based on responsiveness expressed by the cats. *The sedation score was calculated as a sum of scores for the 5 categories: spontaneous posture, placement on side, response to noise, jaw relaxation and general attitude.

were compared using a paired *t*-test. The physiological parameters were analyzed using a two-way (treatment and time) repeated measures ANOVA followed by a Bonferroni test. Adverse events observed during recovery period between treatments were compared using a Wilcoxon signed-rank test. The level of significance was set at $P<0.05$.

No cat showed behavioral responses considered to be a pain during either injection, such as withdrawal of the leg, attempting to bite at the injection site, or vocalization. The median neurodepressive score peaked at 5 min post-injection and then gradually decreased for both treatments (Table 2). A higher neurodepressive score occurred between 5 min and 40 min post-injection compared with the score at baseline ($P<0.001$), and no significant difference was detected between treatments. There is no sex difference of neurodepressive scores in either the ALFX treatment ($P=0.512$) or the PRO treatment ($P=0.701$). Times related to the anesthetic effects are shown in Table 3. The ALFX treatment produced a faster onset of head down ($P=0.005$). Other times related to anesthetic effects did not significantly differ between treatments. Four out of 6 cats could be intubated following each treatment. Particularly, 2 cats (one male and one female) were intubated for both treatments. Only one cat in the PRO treatment was intubated smoothly, while the other intubated cats exhibited coughing or a swallowing reflex during the intubation attempt. During recovery from the ALFX treatment, ataxia in 6 cats, transient muscular tremors in 5 cats, and opisthotonos-like posture in one cat were observed. After the PRO treatment, ataxia in one cat, transient muscular tremors in one cat, and paddling in one cat were observed during recovery. There was a significant difference in the number of cats exhibiting ataxia during recovery ($P=0.020$). Transient muscular tremors, ophishotonos-like posture, and paddling were exhibited intermittently during the early recovery phase from the onset of first movement to the return to sternal recumbency. Ataxia was improved in all cats within 60 min after standing unaided. The physiological parameters are summarized in Table 2. RT gradually decreased after each treatment ($P<0.001$).

Table 2. Changes in neurodepressive score and physiological parameters before and after starting intravenous administration of alfaxalone at 5 mg/kg or propofol at 10 mg/kg in cats

						Minutes after starting treatment				
		Baseline	5	10	15	20	30	40	50	60
Neurodepressive core	Alfaxalone	3.0 ± 0.8	$16.0 \pm 0.4^*$	$16.0 \pm 0.4^*$	$13.0 \pm 1.1^*$	$12.5 \pm 0.5^*$	$11.0 \pm 0.4^*$	$9.0 \pm 2.8^*$	5.5 ± 1.3	3.5 ± 0.3
	Propofol	3.0 ± 0.4	$15.5 \pm 0.5^*$	$16.0 \pm 0.8^*$	$14.5 \pm 0.9^*$	$14.0 \pm 0.4^*$	$10.5 \pm 1.3^*$	$8.0 \pm 1.8^*$	4.0 ± 0.5	6
RT (°C)	Alfaxalone	38.2 ± 0.6	37.8 ± 0.4	37.7 ± 0.5	37.6 ± 0.5	37.4 ± 0.6	$37.1 \pm 0.5^*$	$37.2 \pm 0.4^*$	$37.1 \pm 0.5^*$	$37.0 \pm 0.1^*$
	Propofol	38.0 ± 0.4	37.7 ± 0.4	37.8 ± 0.4	37.6 ± 0.3	37.5 ± 0.3	37.2 ± 0.3	37.2 ± 0.1	37.3 ± 0.4	36.8
HR (beats/min)	Alfaxalone	187 ± 28	186 ± 13	174 ± 15	163 ± 27	$163 \pm 34^\dagger$	$183 \pm 36^\dagger$	194 ± 22	$216 \pm 44^\dagger$	$224 \pm 24^\dagger$
	Propofol	180 ± 25	160 ± 10	149 ± 20	136 ± 23	$129 \pm 25^*$	135 ± 24	181 ± 33	180 ± 9	196
RR (breaths/min)	Alfaxalone	59 ± 16	$14 \pm 6^*$	$16 \pm 4^*$	$17 \pm 6^*$	$17 \pm 6^*$	$19 \pm 11^*$	$26 \pm 11^*$	34 ± 14	37 ± 6
	Propofol	67 ± 42	$14 \pm 6^*$	$18 \pm 5^*$	$22 \pm 12^*$	$18 \pm 5^*$	$21 \pm 6^*$	$27 \pm 7^*$	$32 \pm 10^*$	24
SABP (mmHg)	Alfaxalone	180 ± 33	141 ± 20	$128 \pm 33^*$	$124 \pm 25^*$	$131 \pm 20^*$	141 ± 19	166 ± 30	172 ± 34	209 ± 35
	Propofol	183 ± 16	137 ± 25	$118 \pm 19^*$	$119 \pm 18^*$	$129 \pm 17^*$	140 ± 16	169 ± 34	189 ± 22	183
MABP (mmHg)	Alfaxalone	121 ± 18	101 ± 10	87 ± 21	87 ± 16	89 ± 11	98 ± 13	109 ± 19	118 ± 26	131 ± 42
	Propofol	118 ± 17	96 ± 26	$78 \pm 13^*$	$76 \pm 17^*$	83 ± 12	98 ± 19	108 ± 26	121 ± 18	102
DABP (mmHg)	Alfaxalone	91 ± 13	80 ± 8	63 ± 18	68 ± 12	67 ± 11	76 ± 13	82 ± 13	93 ± 26	93 ± 46
	Propofol	87 ± 18	72 ± 24	59 ± 12	56 ± 14	58 ± 16	77 ± 24	77 ± 28	86 ± 21	59
SpO$_2$ (%)	Alfaxalone	N.D.	$82 \pm 11^\dagger$	$89 \pm 7^\dagger$	93 ± 5	95 ± 3	96 ± 1	N.D.	N.D.	N.D.
	Propofol	N.D.	72 ± 8	79 ± 9	88 ± 6	90 ± 3	92 ± 4	N.D.	N.D.	N.D.

Neurodepressive scores are expressed as median ± quartile deviation. Physiological parameters are expessed as mean ± standard deviation. RT: rectal tempareture, HR: heart rate, RR: respiratory rate, MABP: mean arterial blood pressure, SpO$_2$: percutaneous oxygen saturation. N.D.: not done. The observation was finished when the cat was able to stand unaided. *Significant difference from baseline value ($P<0.05$). †Significant difference from the propofol treatment ($P<0.05$).

Table 3. Times related to anesthetic effects after starting intravenous administration of alfaxalone at 5 mg/kg or propofol at 10 mg/kg in cats

	Treatment		*P* value
	Alfaxalone	Propofol	
Time to onset of head down (sec)	25 ± 8	36 ± 9	0.005
Time to intubation (sec)*	227 ± 47	247 ± 54	0.588
Time to the first appearance of spontaneous movement (min)	26 ± 12	18 ± 7	0.216
Time to spontaneous head lift (min)	38 ± 9	32 ± 8	0.242
Time to spontaneous return to sternal recumbency (min)	41 ± 9	39 ± 7	0.323
Time to unaided standing (min)	44 ± 9	44 ± 11	0.852
Duration of maintenance of intubation (min)*	4 ± 2	9 ± 11	0.399

Data are expressed as mean ± standard deviation. *Four out of 6 cats could be intubated after each treatment.

Spontaneous breathing was maintained in all cats, but the RR markedly decreased from baseline after each treatment ($P<0.001$). SABP decreased from baseline in both treatment groups ($P<0.001$). MABP decreased from baseline in the PRO treatment ($P<0.001$). There was no significant difference in RT, RR, SABP, MABP, or DABP between the treatments. Heart rates at 20 min and 30 min after starting drug administration were significantly lower after the PRO treatment compared to those after the ALFX treatment ($P=0.027$). In addition, 4 cats in the ALFX treatment and all cats in the PRO treatment showed a clinically relevant hypoxemia. The lowest SpO_2 value recorded in each cat were 68%, 75%, 75%, 85%, 95%, and 95% in the ALFX treatment. In the PRO treatment, those were 62%, 65%, 66%, 71%, 79%, and 82%. The SpO_2 levels at 5 min and 10 min after starting drug administration were significantly lower after the PRO treatment compared to those after the ALFX treatment ($P=0.014$).

Intravenous administration of alfaxalone or propofol produced smooth and rapid loss of consciousness in the present study. The onset of head down after the ALFX treatment was slightly faster compared to that after PRO treatment, although the difference is unlikely to be clinically significant. The durations of neurodepressive effects and maintenance of lateral recumbency were similar between treatments (approximately 40 min), and all cats were able to stand unaided within 60 min. Mean IV doses of alfaxalone and propofol required to permit tracheal intubation in a clinical situation were reported as 4.3 mg/kg (range 2.7 to 5.8) and 10.1 ± 2.8 mg/kg (mean ± standard deviation), respectively, in unpremedicated cats [16, 21]. In both studies, lidocaine was topically applied to the vocal folds [16, 21]. On the other hand, tracheal intubation was achieved in 4 out of 6 cats after either the ALFX or the PRO treatments. The freedom of information summary for propofol released by the United States food and drug administration (NADA 141-070) shows that only 6 out of 10 cats administered IV propofol at 9.9 mg/kg could be intubated. A higher anesthetic induction dose of alfaxalone and propofol, compared to those used in the present study might be required to achieve tracheal intubation in all cats. In addition, the rate of administration of propofol or alfaxalone might have also affected the anesthetic induction dose requirement [2]. A slower rate of administration for both drugs than that used in the present study should be considered to achieve successful tracheal intubation. Previous studies have reported that the IV dose of alfaxalone or propofol required to achieve tracheal intubation in cats was decreased by premedication [11, 21]. In clinical practice, topical lidocaine is usually applied on to the arytenoids in order to control the laryngeal reflex [14]. We concluded that premedication and/or topical application of local anesthetic prior to intubation would produce a smoother and more reliable anesthetic induction in order to achieve tracheal intubation following either alfaxalone or propofol administration in cats.

Mathis *et al.* [9] reported that twitching, paddling, face rubbing, opisthotonos, and tremors were observed during recovery in cats that had been administered IV alfaxalone or propofol for anesthetic induction. In addition, more episodes of paddling and tremors were observed in cats administered alfaxalone compared with those administered propofol [9]. In that study, all cats were premedicated with intramuscular acepromazine and buprenorphine and maintained with isoflurane [9]. In our study, a single bolus of IV alfaxalone produced more ataxia compared with that with propofol, although no cats became excited or behaved aggressively. In addition, a high incidence of transient muscular tremors was observed with ALFX treatment, although there was no significant difference between treatments ($P=0.072$). A high incidence of ataxia, muscular tremors, and opisthotonus-like posture was observed during the recovery period from the sedative effects of a single intramuscular administration of alfaxalone in cats [18]. These results may be related to the differences in the pharmacokinetic variables and the proportion of occupied $GABA_A$ receptors between alfaxalone and propofol [5]. Premedication and/or use of an inhalant anesthetic agent has been shown to improve the quality of recovery from alfaxalone anesthesia [19].

In the present study, RT, HR, SABP, MABP, and DABP were maintained within clinically acceptable ranges in all cats after each treatment, although slightly lower HR was observed during the PRO treatment. Both alfaxalone and propofol cause respiratory depression or apnea [12, 16]. In the present study, RR decreased without apnea but transient hypoxemia was detected after each treatment except for 2 cats in the ALFX treatment. In particular, SpO_2 at 5 min and 10 min after starting drug administration was lower after the PRO treatment compared with after the ALFX treatment. Muir *et al.* [12] reported that IV administration of alfaxalone at 5 mg/kg in cats produced transient hypoxia associated with hypoventilation mainly caused by a decrease in RR. In dogs, induction with propofol may result in decreased oxygenation associated with ventilation perfusion mismatching compared with induction using alfaxalone [8]. We changed the SpO_2 sensor site on the tongue periodically to avoid the influence on tissue perfusion caused by the sensor clip to minimize the measurement errors. However, there are some limitations of SpO_2 measurement such as animal movement. In the present study, the SpO_2 at 5 min (immediately after tracheal intubation) and after 20 min (most cats started showing spontaneous movement) might be affected by animal movements. Further sophisticated cardiorespiratory measurements including arterial blood gas analysis and the measurement of cardiac output or tidal volume is required to compare the cardiopulmonary effects of both drugs in cats. As is recommended when performing all general anesthetsia, supplemental oxygen should be administered to prevent hypoxemia.

The main elimination pathway of alfaxalone or propofol is biotransformation by cytochrome P450s and conjugation enzymes in the liver [19]. Propofol undergoes extrahepatic metabolism in the lungs of cats [10]. Alfaxalone is also considered to undergo extrahepatic metabolism [14]. The limitation of our study is that plasma biochemistry, including hepatic enzyme activity, was not performed before each treatment, although clinical signs of liver failure including ascites, jaundice, hypoactivity and anorexia were not observed. However, the intensity and the duration of the anesthetic effect observed in the present study are similar to those reported previously [7, 16, 19, 20]. In addition, sex differences in pharmacokinetics and pharmacodynamics of drugs used in the present study should be considered. In humans, males are more sensitive than females to propofol [13]. Althesin®, which is a mixture of alfaxalone and alfadrone, is 4 times more potent an anesthetic in the male rats than that in the female rats [6]. To the best of our knowledge, there are no reports of sex difference in pharmacokinetics and pharmacodynamics of alfaxalone or propofol in cats. Whittem *et al.* [20] did not mention sex difference in their studies that used both male and female cats to determine

the pharmacokinetics and pharmacodynamics of alfaxalone and propofol, respectively. In the present study, there are no sex difference in neurodepressive scores for both drugs. Further investigations on the gender difference for the pharmacokinetics and pharmacodynamics of alfaxalone or propofol in cats will be required.

Both IV alfaxalone at 5 mg/kg and IV propofol at 10 mg/kg produced a smooth and rapid loss of consciousness and a similar duration of neurodepressive effects (approximately 40 min). Cardiorespiratory changes after the ALFX treatment were milder than those after the PRO treatment, although care should be taken to avoid hypoxemia immediately after induction. During the recovery period, a single bolus of IV alfaxalone resulted in more adverse events, including ataxia and muscular tremors, compared with a single bolus of IV propofol.

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