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RESEARCH PAPER

Clinical efficacy and cardiorespiratory effects of intramuscular administration of alfaxalone alone or in combination with dexmedetomidine in cats

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Abstract

Objective To investigate the sedative, anaesthetic and cardiorespiratory effects of intramuscular (IM) administration of alfaxalone alone or in combination with dexmedetomidine in cats.

Study design Blinded, randomized crossover study with a washout period of 15 days.

Animals Seven adult cats, weighing 3.5 ± 0.7 kg.

Methods Cats were assigned randomly to each of three treatments: A_5 (alfaxalone 5 mg kg^{-1}), $D_{20}A_5$ (dexmedetomidine 20 μg kg^{-1} and alfaxalone 5 mg kg^{-1}) and $D_{40}A_5$ (dexmedetomidine 40 μg kg^{-1} and alfaxalone 5 mg kg^{-1}). Drugs were administered IM into the epaxial muscles. Sedation or anaesthesia scores were evaluated by a modified numerical rating scale. Times to extubation, head-lift, sternal recumbency and standing were recorded. Heart and respiratory rates, systolic arterial pressure, arterial oxygen saturation of haemoglobin, end-tidal carbon dioxide tension and rectal temperature were measured at 5, 10, 15, 20, 30, 45, 60, 90, 120 and 150 minutes after drug administration. Adverse events were recorded. Data were analysed by one-way ANOVA with Tukey's post-hoc test for parametric values and, for non-normally distributed parameters, a Kruskal–Wallis test and Mann–Whitney *U*-test for two independent samples ($p < 0.05$).

Results Sedation scores were significantly different among the treatments. Cats in A5 were deeply sedated, whereas cats administered dexmedetomidine were anaesthetized. The onset of action and the duration of anaesthesia were related to the dose of dexmedetomidine. Cardiorespiratory parameters remained stable in the A_5 group. Lower heart rates, higher systolic blood pressures and occasional low pulse oximetry readings were observed in the dexmedetomidine groups. A limited number of adverse events (hyperkinesia, emesis) occurred during recovery.

Conclusions and clinical relevance Alfaxalone administered IM induced sedation in cats. The addition of dexmedetomidine to alfaxalone induced general anaesthesia with a mild decrease in the heart rate and arterial oxygen saturation of haemoglobin.

Keywords alfaxalone, anaesthesia, cats, intramuscular, sedation.

Introduction

Cats can be particularly difficult to manage. Reliable and predictable sedation or general anaesthesia may be required to restrain fractious patients not only to

reduce the stress of handling before routine procedures but also to diminish the risk of injury to the clinician. The study of new combinations of sedatives and anaesthetics suitable for intramuscular (IM) administration can, therefore, be of interest to provide new alternatives to chemical restraint by this route in cats.

Alfaxalone is a synthetic neurosteroid anaesthetic agent with a wide margin of safety that provides good muscle relaxation, minimal cardiorespiratory effects and a rapid recovery when administered intravenously to dogs and cats (Ferré et al. 2006; Muir et al. 2009). Alfaxalone has been reintroduced in the veterinary market as a new formulation, with 2–hydroxypropyl–β–cyclodextrin (HPCD) as the excipient, to increase its aqueous solubility (Brewster et al. 1989). This formulation is chemically stable and non-irritating when administered into perivascular tissues, and no side effects were noticed upon gross necropsy of the injection sites, when injected subcutaneously at 10 mg kg^{-1} in cats (Heit et al. 2004).

$Alpha_2$-adrenoceptor agonists are widely employed to sedate cats. Medetomidine and dexmedetomidine, its active stereoisomer, induce potent sedation, analgesia and muscle relaxation in a dose dependent manner, and are also useful to reduce the doses of general anaesthetics required (Ansah et al. 1998; Mendes et al. 2003; Granholm et al. 2006). Early studies describing the effects of combinations of medetomidine and ketamine showed that medetomidine enhanced the duration of anaesthesia and the degree of analgesia, and reduced the requirements of ketamine in comparison to the sole use of ketamine in cats (Verstegen et al. 1989, 1990, 1991). Recently, the IM administration of alfaxalone, alone or in combination with other drugs, has also been described in a number of species (Thomas et al. 2012; Hansen & Bertelsen 2013; Santos González et al. 2013) including cats (Grubb et al. 2013; Ribas et al. 2015).

The aim of this study was to assess the sedative quality and the cardiorespiratory effects of IM administration of alfaxalone alone or in combination with two doses of dexmedetomidine in cats. It was hypothesized that alfaxalone alone would produce a moderate sedation that could be enhanced by the addition of dexmedetomidine.

Materials and methods

This study was approved by the Local Institutional Ethics and Animal Welfare Committee of the University of Murcia, Spain. Seven experimental adult cats (four male and three female) with a weight of 3.5 ± 0.7 kg (mean ± SD) (range 3.1–4.5) and aging 3.8 ± 0.9 years (range 2.5–5) were enrolled in the study. Cats were considered healthy on the basis of a comprehensive preanaesthetic examination, which included a physical examination, haematology and serum biochemistry. The cats were housed indoors and fed with a standard commercial diet. Cats were fasted overnight before the day of the experiment, but water was always available. On the morning of the trials, the physical status of the cats was reevaluated.

In order to detect a difference between the means of 100 minutes with a standard deviation of 50 minutes in the time to lift the head during recovery (LH) with a 5% significance level and a power of 90%, seven cats were required in each treatment group (http://www.statstodo.com software).

In a blinded crossover design, all cats were administered the three treatments in a randomized order, which was determined by lottery (extracting a code from a sealed envelope). A resting period of 15 days was established between treatments. Treatment A_5 was alfaxalone 5 mg kg^{-1} (Alfaxan 10 mg mL^{-1}; Vétoquinol, France), treatment $D_{20}A_5$ was a combination of dexmedetomidine 20 μg kg^{-1} (Dexdomitor 0.5 mg mL^{-1}; Esteve, Spain) and alfaxalone 5 mg kg^{-1} and treatment $D_{40}A_5$ was a combination of dexmedetomidine 40 μg kg^{-1} and alfaxalone 5 mg kg^{-1}. The drugs were mixed in one syringe (Omnifix 5 mL; B Braun Medical, Spain) and diluted to a total volume of 3 mL with sodium chloride 0.9% solution (B Braun Medical). All injections were administered slowly into the epaxial muscles. All the data were collected by a single observer (D.R.) who was experienced in the clinical methods and scoring systems employed in this trial but who was unaware of the assigned treatments.

Once the drugs were administered (recorded as time zero, T0), the cats were left undisturbed in a dimly lit, quiet room. The levels of either sedation or anaesthesia were evaluated by a modified numerical rating scale (Young et al. 1990) obtained by adding the scores of six independent parameters (Table 1). The response to noise was assessed by clapping two hands close to the ears of the cats. The degree of muscle relaxation was evaluated subjectively by flexion and extension of the thoracic limbs. The palpebral reflex was evaluated by gently touching

Table 1 Modified numerical rating scale (Young et al. 1990) (range from 0 = low value to 4 = high value) of six independent parameters used for scoring the degree of sedation and anaesthesia after the intramuscular (IM) administration of alfaxalone alone or in combination with dexmedetomidine in cats. The sedation was judged to be poor (total score 0–3), mild (total score 4–6), moderate (total score 7–10) and deep (total score 11–15). Total scores > 15 for intubated cats were considered as an anaesthesia state

Parameter	Response	Value
Spontaneous position	Able to stand and walk	0
	Sedated but standing or sitting	1
	Lying down but able to react quickly or stand up;	2
	Lying down, but reacting slowly and having difficulty in standing up;	3
	Lying down and unable to stand up	4
Resistance to lateral recumbency	Strong resistance	0
	Moderate resistance	1
	Slight resistance	2
	No resistance	3
Response to noise	Normal response	0
	Listens and moves	1
	Listens and ear moves	2
	Hardly perceives	3
	No response	4
Jaw relaxation	Normal	0
	Slightly reduced	1
	Greatly reduced	2
Eyelid reflex	Normal	0
	Depressed reflex	1
	No reflex	2
Response to pain	Normal response (withdrawal of the limb at a minimal clamping pressure)	0
	Slow response (withdrawal at a higher clamping pressure)	1
	Very slow response (withdrawal at a higher clamping pressure maintained for 3 to 5-seconds)	2
	No response	3

the ventromedial canthus of the eye. The nociceptive stimulus was produced by closing a padded haemostat clamp (Kelly haemostatic forceps) on a pelvic limb digit. The applied pressure was gradually increased until the cat showed a withdrawal reflex or until the first notch of the ratchet was reached (maximum 3 seconds). Based on these signs, the sedation was judged to be poor (score 0–3), mild (score 4–6), moderate (score 7–10) or deep (score 11–15). A score was assigned at 5, 10, 15, 20, 30, 45, 60, 90, 120 and 150 minutes after administration of the drugs. Orotracheal intubation was attempted in those cats showing a depressed muscle tone and a sedation score > 11. General anaesthesia was defined when the sedation score was >15 and the trachea could be intubated.

The times from T0 to sternal (SRi) and lateral recumbency (LR) and the time to orotracheal intubation (IT) were recorded. The ease of intubation was scored subjectively as 0 (intubation not possible), 1 (intubation, minimal laryngeal reflex) or 2 (intubation, absent laryngeal reflex). After orotracheal intubation, the onset time of surgical anaesthesia (OA) was recorded. This time was calculated as the time from t0 until the time at which the animal no longer responded to a nociceptive stimulus. The end of surgical anaesthesia (AR) was determined when cats began to respond to the noxious stimulus. The time between OA and AR was considered to be the duration of anaesthesia (AD). Extubation time (ET) was defined as the time at which the orotracheal tube was removed after confirming a positive swallowing reflex. Additionally, the times to lifting of the head (LH) and regaining sternal recumbency (SRr) and a standing position (ST) were also recorded. All times were measured as the time elapsed from the time of injection of the drugs until the specific event.

The heart rate (HR) was obtained by direct auscultation of the heart with a stethoscope (Littmann Classic II S.E, 3M, Spain). A three-lead electrocardiogram (lead II) was employed to monitor

the electrical activity of the heart and to detect arrhythmias (Cardiocap II; Datex-Ohmeda, Finland). The systolic arterial pressure (SAP) was measured on the palmar common digital artery using the Doppler method (Ultrasonic Doppler flow detector; Model 811-BL; Parks Medical Electronics Inc., OR, USA), with a 2-cm paediatric cuff placed at a distance of 2 cm above the carpus. Arterial oxygen saturation of haemoglobin (SpO_2) was measured using a pulse oximeter with a probe placed on a clipped area of the ear (Heska VetOx 4404; Sensor Devices Inc., WI, USA). The end-tidal carbon dioxide tension ($P_E'CO_2$) and respiratory rate (f_R) were displayed by a side-stream gas analyzer (Monitor Vet/cap 7000; Sensor Devices Inc.). The f_R was recorded by direct observation of thoracic excursions in those cats that could not be intubated. Rectal temperature (T°) was also recorded. All data were collected at 5, 10, 15, 20, 30, 45, 60, 90, 120 and 150 minutes after administration of the drugs.

Adverse events such as salivation, emesis, micturition, bradyarrhythmias, ventricular premature complexes, muscle rigidity, hyperkinesis, hypertension (defined as SAP > 160 mmHg) or hypotension (defined as SAP < 70 mmHg) were recorded during the study.

Data are expressed as the mean ± standard deviation (SD). The statistical tests were performed using SPSS version 15.0 (SPSS Inc., IL, USA). Normality was assessed by the evaluation of descriptive statistics, plotting histograms and the Kolmogorov–Smirnov test. For normally distributed data (HR, SAP, SpO_2, f_R, T°, SR, LR, OA, DA, RA, ET, LH, SR and SR), one-way ANOVAS with Tukey's *post-hoc* test were performed. Variables with a non-normally distribution (ease of intubation and level of sedation score) are expressed as the median and range and were analysed by a Kruskal–Wallis test. When this test revealed significant differences, two-by-two comparisons were done using a Mann–Whitney *U*-test for two independent samples. A value of $p < 0.05$ was considered significant for all statistical tests.

Results

Cats showed either a sedative or anaesthetic signs compatible with an effective absorption of alfaxalone from the IM injection in all cases. Only one of the cats in the A_5 group achieved a status of general anaesthesia, which lasted for 35 minutes. The other cats in this group reached scores compatible with a

Table 2 Sedation score (scale range from 0 = no sedation to 20) over time (minutes) in cats ($n = 7$) expressed as the median (range) after intramuscular (IM) administration (time zero) of alfaxalone at 5 mg kg^{-1} (A_5), alfaxalone (5 mg kg^{-1}) with dexmedetomidine at 20 μg kg^{-1} ($D_{20}A_5$) and alfaxalone (5 mg kg^{-1}) with dexmedetomidine at 40 μg kg^{-1} ($D_{40}A_5$)

	Time (minutes)										
Group	5	10	15	20	30	45	60	90	120	150
A_5	7 (3–10)*	9 (3–14)*†	10 (7–16)*	11 (8–16)*	11 (9–16)*†	10 (5–13)*†	8 (3–11)*†			
$D_{20}A_5$	10 (2–17)	14 (7–18)*‡	15 (7–18)*	15 (6–18)	16 (13–18)‡	17 (14–18)‡	16 (14–18)*‡	15 (13–17)*	14 (11–17)	9 (4–15)
$D_{40}A_5$	16 (12–18)‡	17 (15–18)†‡	18 (16–18)‡	18 (17–18)‡	18 (17–18)†‡	18 (18–18)†‡	18 (18–18)†‡	17 (16–18)†	15 (12–18)	13 (4–18)

*Significantly different from the value after alfaxalone (5 mg kg^{-1}) with dexmedetomidine at 40 μg kg^{-1} ($p < 0.05$). †Significantly different from the value after alfaxalone (5 mg kg^{-1}) with dexmedetomidine at 20 μg kg^{-1} ($p < 0.05$). ‡Significantly different from the value after alfaxalone (5 mg kg^{-1}) ($p < 0.05$).

Table 3 Times to sternal (SRi) and lateral recumbency (LR); onset (OA), duration (AD) (time between OA and AR), end of anaesthesia (AR), head-lift (LH), sternal Recumbency (SRr) and standing Position (ST) expressed as the mean (X ± SD) after intramuscular (IM) administration (time zero) of 5 mg kg^{-1} alfaxalone (A_5), 5 mg kg^{-1} alfaxalone with either 20 μg kg^{-1} ($D_{20}A_5$) or 40 μg kg^{-1} dexmedetomidine ($D_{40}A_5$) in cats (n = 7)

	Time (minutes)							
Group	**SRi**	**LR**	**OA**	**AD**	**AR**	**LH**	**SRr**	**ST**
A_5	2.8 ± 1.6	7.4 ± 4.9				56 ± 24 *†	71.9 ± 21.5*†	81.1 ± 17.8*†
$D_{20}A_5$	1.9 ± 2.1	3.7 ± 2.7	24.7 ± 15.2*	49.13 ± 24*	73.9 ± 27.6*	134.7 ± 33.9‡	139.3 ± 33.8‡	147.9 ± 38.1‡
$D_{40}A_5$	1.6 ± 0.8	3 ± 0.9	9 ± 6†	103.1 ± 28.1†	112.1 ± 28.3†	153 ± 15.2‡	156.6 ± 13.9‡	166.1 ± 11.6‡

*Significantly different from the value after alfaxalone (5 mg kg^{-1}) with dexmedetomidine at 40 μg kg^{-1} ($p < 0.05$). †Significantly different from the value after alfaxalone (5 mg kg^{-1}) with dexmedetomidine at 20 μg kg^{-1} ($p < 0.05$). ‡Significantly different from the value after alfaxalone (5 mg kg^{-1}) ($p < 0.05$).

moderate to deep degree of sedation. Sedation scores were significantly higher (in a dosed-dependent manner) in the $D_{20}A_5$ and $D_{40}A_5$ groups. All cats receiving dexmedetomidine achieved a state of general anaesthesia (Table 2). Significant differences in the sedation score were found between groups A_5 and $D_{20}A_5$ at t10 ($p = 0.026$), t30 ($p = 0.007$), t45 ($p = 0.001$) and t60 ($p = 0.001$), between groups A_5 and $D_{40}A_5$ from t5 to t60 ($p = 0.001$), and between groups $D_{20}A_5$ and $D_{40}A_5$ at t10 ($p = 0.038$), t15 ($p = 0.038$), t60 ($p = 0.02$) and t90 ($p = 0.014$).

In the A_5 group, two cats (2/7) could be intubated, one of them with a sedation score of 13. In contrast, all cats in the $D_{20}A_5$ and $D_{40}A_5$ groups were intubated. Furthermore, it was significantly easier to intubate the cats in the $D_{40}A_5$ group compared to those of the A_5 ($p = 0.033$) and $D_{20}A_5$ ($p = 0.037$) groups. The onset of anaesthesia was faster ($p = 0.027$) and the duration of anaesthesia longer ($p = 0.002$) in the $D_{40}A_5$ group compared to the $D_{20}A_5$ group (Table 3). The $D_{40}A_5$ group showed a longer ET compared to A_5 ($p = 0.011$). The LH, SRr and ST were significantly shorter in the A_5 group compared to the $D_{20}A_5$ and $D_{40}A_5$ groups, but there were no differences in those times between the two dexmedetomidine groups.

Cardiorespiratory data are presented in Table 4. The HR values in the alfaxalone group were significantly higher than those observed for the $D_{20}A_5$ and $D_{40}A_5$ groups at t5 ($p = 0.027$, $p = 0.015$), t10 ($p = 0.01$, $p = 0.001$), t15, t20, t30, t45 and t60 ($p < 0.001$, $p < 0.001$), respectively. The SAP in $D_{40}A_5$ was significantly higher at t10 ($p = 0.002$, $p = 0.016$), t15 ($p = 0.023$, $p = 0.011$) and t20 ($p < 0.001$, $p = 0.021$) compared to A_5 and $D_{20}A_5$, respectively. Moreover, SAP at t30 was significantly lower in the A_5 group compared to the $D_{20}A_5$ ($p = 0.036$) and $D_{40}A_5$ ($p = 0.002$) groups.

The respiratory frequency was significantly lower at t20 ($p = 0.045$) and t30 ($p = 0.014$) in the A_5 compared to the $D_{40}A_5$ group. The SpO_2 remained above 90% in the A_5 and $D_{20}A_5$ groups, although it decreased below this level (down to 87%) from t15 to t60 in the $D_{40}A_5$ group.

Adverse effects observed during the recovery phase consisted in one case of dysphoria and a short period of ataxia in two cats of the A_5 group. There were two episodes of vomiting in cats of the $D_{20}A_5$ group. Adverse effects observed in the $D_{40}A_5$ group consisted of vomiting in one cat, urination and prolonged ataxia with hyperkinesia in another cat and salivation with hyperkinesia in another. All other cats showed a smooth and progressive recovery from sedation/anaesthesia without excitement.

Discussion

The present study was based on the hypothesis that the IM administration of alfaxalone alone would induce sedation in cats and that this effect would be enhanced by the addition of dexmedetomidine. The results from this study suggested that the IM administration of alfaxalone alone was effective to provide sedation in most cats (6/7), whereas the combinations of alfaxalone and dexmedetomidine induced a state of general anaesthesia in all cats (14/14). Cardiorespiratory parameters were well maintained in the alfaxalone group and only minor side effects were observed. However, the addition of

Table 4 Cardiorespiratory parameters and rectal temperature measured from 5 to 150 minutes in seven cats after intramuscular (IM) administration of alfaxalone at 5 mg kg^{-1} (A_5), alfaxalone (5 mg kg^{-1}) with dexmedetomidine at 20 μg kg^{-1} ($D_{20}A_5$) and alfaxalone (5 mg kg^{-1}) with dexmedetomidine at 40 μg kg^{-1} ($D_{40}A_5$).

		Time (minutes)									
Variable	**Group**	**5**	**10**	**15**	**20**	**30**	**45**	**60**	**90**	**120**	**150**
HR (beats $minute^{-1}$)	A_5	194 ± 23*†	180 ± 31*†	181 ± 19*†	169 ± 20*†	173 ± 25*†	184 ± 20*†	190 ± 30*†			
	$D_{20}A_5$	160 ± 2‡	141 ± 20‡	132 ± 22‡	122 ± 13‡	111 ± 15‡	104 ± 14‡	99 ± 15‡	104 ± 17	100 ± 15	97 ± 18
	$D_{40}A_5$	156 ± 23‡	126 ± 12‡	123 ± 9‡	137 ± 27‡	117 ± 9‡	113 ± 9‡	106 ± 8‡	102 ± 7	98 ± 7	103 ± 15
f_R (breaths $minute^{-1}$)	A_5	46 ± 8	39 ± 8	38 ± 8	34 ± 7*	29 ± 4*	29 ± 10	29 ± 9			
	$D_{20}A_5$	43 ± 14	37 ± 7	36 ± 6	36 ± 5	35 ± 5	31 ± 5	30 ± 6	27 ± 3	24 ± 5	29 ± 5
	$D_{40}A_5$	48 ± 10	49 ± 9	46 ± 10	41 ± 4‡	37 ± 4‡	36 ± 5	33 ± 4	32 ± 4	29 ± 5	30 ± 5
SAP (mm Hg)	A_5		103 ± 15*	122 ± 18*	114 ± 8*	115 ± 11*†	122 ± 19	124 ± 24			
	$D_{20}A_5$		115 ± 7*	120 ± 20*	135 ± 23*	142 ± 23‡	136 ± 24	129 ± 22	115 ± 26	109 ± 22	121 ± 44
	$D_{40}A_5$		155 ± 12†‡	161 ± 16†‡	138 ± 26†‡	157 ± 16‡	146 ± 25	141 ± 23	126 ± 23	114 ± 20	113 ± 32
SpO_2 (%)	A_5		97 ± 1	93 ± 2	93	92 ± 2	93 ± 2	92 ± 2			
	$D_{20}A_5$		88 ± 4	90 ± 3	90 ± 2	90 ± 3	92 ± 1	92 ± 2	92 ± 3	92 ± 3	93 ± 2
	$D_{40}A_5$		91 ± 3	87 ± 5	87 ± 5	87 ± 4	88 ± 4	89 ± 6	90 ± 4	91 ± 4	91 ± 4
T° (C°)	A_5	38.4 ± 0.3	38.3 ± 0.4	38.1 ± 0.6	38 ± 0.5	37.8 ± 0.3	37.7 ± 0.5	37.2 ± 0.3			
	$D_{20}A_5$	38.3 ± 0.6	38.2 ± 0.8	38.2 ± 0.6	38 ± 0.5	38 ± 0.7	37.7 ± 0.5	37.4 ± 0.6	37 ± 0.8	36.4 ± 0.6	36.6 ± 0.4
	$D_{40}A_5$	38.8 ± 0.8	38.8 ± 0.9	38.5 ± 0.8	38 ± 0.7	38.3 ± 0.8	38 ± 0.8	37.8 ± 1	37.5 ± 1	37.2 ± 1	36.9 ± 0.8

HR, heart rate; f_R, respiratory rate; SAP, systolic arterial pressure; SpO_2, oxygen haemoglobin saturation; T^a, Rectal temperature. The mean ± SD. *Significantly different from the value after alfaxalone (5 mg kg^{-1}) with dexmedetomidine at 40 μg kg^{-1} ($p < 0.05$). †Significantly different from the value after alfaxalone (5 mg kg^{-1}) with dexmedetomidine at 20 μg kg^{-1} ($p < 0.05$). ‡Significantly different from the value after alfaxalone (5 mg kg^{-1}) ($p < 0.05$).

dexmedetomidine resulted in some negative cardiovascular and respiratory effects, as previously described for alpha-2 adrenoceptor agonist drugs.

In the present study, a marked clinical effect ranging from moderate sedation to general anaesthesia (according to the treatment group) was observed in all cats with each of the three combinations injected in the epaxial muscles. Only one cat showed a violent reaction to the injection, a behaviour that was most likely related to the particularly fractious temperament of this animal. In a previous puplication, the IM administration of alfaxalone/alfadolone was found to be clinically less predictable when it was injected into the biceps compared to the quadriceps muscle (Evans et al. 1972). This difference was attributed to the fascial plane that lies between the adductor muscle and the biceps muscle (Baxter & Evans 1973). A recent study showed that the injection of alfaxalone into the right quadriceps muscle in cats premedicated with dexmedetomidine or dexmedetomidine/hydromorphone was able to induce a light plane of anaesthesia (Grubb et al. 2013). These authors also described that most cats (8/12) reacted during the IM administration of alfaxalone, even when they were already sedated, and did not recommend this route of administration (Grubb et al. 2013). Recently, Ribas et al. (2015) demonstrated that the lumbar IM administration of alfaxalone and butorphanol was effective to sedate cats. The differences found in the level of pain experienced after IM injection of alfaxalone could be related to anatomical differences in the muscles employed to perform these studies. In the present study, injection in the epaxial muscles produced not only minimal pain responses in most cases, despite the large volume injected (3 mL), but also a clinically significant absorption of alfaxalone.

In the present study, the IM injection of alfaxalone alone induced a moderate to deep degree of sedation, and in only one cat (1/7) a state compatible with general anaesthesia was achieved. Evans et al. (1972) employed a mixture of alfaxalone and alfadolone by the IM route to induce a deep sedation and in some cases suitable anaesthesia for minor surgical procedures in cats. However, the onset of action and the duration of the clinical effects of this combination at a dose of 12–18 mg kg^{-1} in cats were dose-related and, therefore, variable effects were reported (Jones 1979). Despite the fact that there are no known published studies about the IM use of the newer alfaxalone formulation administered as a sole anaesthetic agent in cats, some studies reported clinical effects with alfaxalone ranging from good sedation to anaesthesia in different species of mammals (Thomas et al. 2012; Santos González et al. 2013; Giral et al. 2014).

The addition of dexmedetomidine in the present study showed results that are in agreement with a recent study performed in cats where the anaesthetic effect of IM injection of alfaxalone and dexmedetomidine was assessed by bispectral index monitoring (Grubb et al. 2013). Furthermore, the score compatible with anaesthesia reached by the dexmedetomidine groups showed a significant dose-response effect in terms of onset of action, duration of action and ease of intubation. The dose-dependent sedative effects and the anaesthetic sparing effects of IM administration of three different doses of dexmedetomidine in cats are well described in the literature (Ansah et al. 1998).

One limitation of the present study is the lack of two groups sedated only with the dexmedetomidine doses. However, a study in cats showed a decrease in the sedative and analgesic effect of IM dexmedetomidine after 60 minutes (Granholm et al. 2006), whereas in the present study the sedation score remained above 15 until 120 minutes after injection in both dexmedetomidine groups, suggesting an additive effect of alfaxalone and dexmedetomidine.

In the present study, the HR values remained stable when alfaxalone was administered IM as a sole agent. This is in agreement with previously published findings, as the intravenous (IV) administration of alfaxalone in cats (2–5 mg kg^{-1}) produced clinically irrelevant decreases in haemodynamic values and only with larger doses (15, 25 or 50 mg kg^{-1}) was a decrease in the heart rate observed (Muir et al. 2009; Zaki et al. 2009). Nevertheless, the results of the present study showed that the addition of dexmedetomidine decreased the HR equally in all cases, regardless of the dose. It has indeed been shown that the HR decrease is not attenuated when lower doses of dexmedetomidine are administered in cats, although the reduction in HR is of a shorter duration (Ansah et al. 1998; Selmi et al. 2003; Granholm et al. 2006; Monteiro et al. 2009; McSweeney et al. 2012). Interestingly, the IM use of alfaxalone in cats premedicated with dexmedetomidine (0.01 mg kg^{-1}) and hydromorphone (0.1 mg kg^{-1}) showed that the studied combination had a minimal effect on the pulse rate (Grubb et al. 2013).

The blood pressure remained within an acceptable clinical range in all the groups. Caulkett et al. (1998) showed that the Doppler technique is an accurate predictor of the mean arterial blood pressure and correlates well with the direct arterial pressure in anaesthetized cats. Nevertheless, interpretation of the values should be performed with caution (da Cunha et al. 2014). Clinical doses of alfaxalone (2–5 mg kg^{-1}) administered IV in unpremedicated cats caused mild suppressive effects on the arterial blood pressure (Muir et al. 2009). In the present study, a traditional biphasic pattern was seen in the SAP values, with higher values for blood pressure during the first 20 minutes, followed by a slight decrease over time. It is well known that activation of post-synaptic alpha2-receptors in peripheral vascular smooth muscle produces an initial increase in blood pressure resulting from peripheral vasoconstriction, followed by a decrease in the sympathetic tone owing to a central effect and a subsequent reduction in blood pressure (Dobromylskyj 1996). Grubb et al. (2013) reported a normal-to-slightly elevated blood pressure after IM administration of alfaxalone (5 mg kg^{-1}) with dexmedetomidine (0.01 mg kg^{-1}) in cats, although data were not collected until 30 minutes after endotracheal intubation.

In the present study, haemoglobin oxygen saturation values remained above the clinically acceptable level (≥ 90%) in the A_5 and $D_{20}A_5$ groups. The highest dose of dexmedetomidine produced a marked reduction in the SpO_2 values. In the present study design, it was decided not to provide oxygen supplementation to the patients to assess the potential influence of the different treatments on this variable. Our results suggested that oxygen supplementation is always recommended to prevent the risk of hypoxaemia, particularly if higher doses of dexmedetomidine are used in combination with alfaxalone. Nevertheless, low pulse oximetry saturation levels could also be explained by the vasoconstrictive effects of dexmedetomidine or by the effect on the local circulation produced by the probe (Moens & Coppens 2007).

In the present study, apnoea was not observed in any case. It has been described that post-induction apnoea is an uncommon finding when alfaxalone is administered IV to young and adult cats (Zaki et al. 2009; O'Hagan et al. 2012; Beths et al. 2014). Similarly to our study, apnoea has not been reported after IM administration of alfaxalone in combination with dexmedetomidine in cats (Grubb et al. 2013). In the present study, the f_R was high immediately after dexmedetomidine/alfaxalone administration but decreased over time. The $P_E'CO_2$ values were not reported because they were obviously too low to be an accurate representation of alveolar CO_2. A limitation of $P_E'CO_2$ monitoring, given the superficial breathing pattern observed in most cats, is the likelihood that the $P_E'CO_2$ underestimated the alveolar CO_2 tension. Ansah et al. (1998) described an initial increase in the f_R in cats after IM administration of dexmedetomidine and medetomidine, followed by a gradual decrease to normal values. Recently, the combination of IM dexmedetomidine and alfaxalone in cats was shown to decrease the respiratory rate, with no abnormalities in $P_E'CO_2$ values (Grubb et al. 2013).

The rectal temperature tended to decrease in all three groups in the present study. Hypothermia induced by alpha 2 adrenoceptor agonists has been related to decreasing heat production owing to less muscular activity and to a direct effect on noradrenergic hypothalamic mechanisms implicated in thermoregulation (Pypendop & Verstegen 2001). In the present study, a decrease over time in the rectal temperature in the A_5 group could be as a result breathing room air, muscle relaxation and heat loss induced by vasodilatory effects (Whittem et al. 2008; Muir et al. 2009).

Although the recovery period was, in general, smooth in the present study, some minor adverse effects were observed in the three groups: hyperkinesia was more frequently observed in cats of the A_5 and $D_{40}A_5$ groups, whereas emesis was the main adverse event during the recovery phase in the $D_{20}A_5$ group. Excellent recoveries were described in cats after IV administration of alfaxalone (5 and 15 mg kg^{-1}), although higher doses (50 mg kg^{-1}) caused fatal consequences (Muir et al. 2009). Zaki et al. (2009) showed an improvement in the quality of recovery when IV alfaxalone was combined with acepromazine and butorphanol in young cats, most probably as a result of either the use of a lower alfaxalone induction dose or a direct contribution of the drugs used for premedication. Vomiting is regarded as the most common side effect when dexmedetomidine is administered IM in cats (Granholm et al. 2006; McSweeney et al. 2012). Grubb et al. (2013) reported that the combination of alfaxalone with dexmedetomidine resulted in a high incidence of hyper-reactivity, ataxia and excitement during recovery. In the present study, the use of 20 μg kg^{-1} dexmedetomidine seemed to reduce the

incidence of twitching and paddling potentially produced by the effect of alfaxalone.

In conclusion, IM administration of alfaxalone as a sole agent in cats produced mild to moderate sedation characterized by a stable cardiorespiratory function, which may favour its use by this route to facilitate sedation for non-invasive procedures in cats. The addition of dexmedetomidine enhanced the alfaxalone effects, inducing a state compatible with general anaesthesia, but resulted in some cardiorespiratory side effects. Lower pulse oximetry readings and hypocapnia may occur. The use of a moderate dose of dexmedetomidine was found to be useful to prevent the incidence of hyperkinesia during recovery from anaesthesia. Further investigations of the pharmacokinetic properties of IM administration of alfaxalone in cats should be conducted.

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