AgroLife Scientific Journal - Volume 9, Number 1, 2020
ISSN 2285-5718; ISSN CD-ROM 2285-5726; ISSN ONLINE 2286-0126; ISSN-L 2285-5718

THE USE OF ALFAXALONE IN COMBINATION WITH OPIOIDS FOR CAT SEDATION: PRELIMINARY RESULTS

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Abstract

This study describes a prospective, randomized, blinded clinical study on 118 cats which required chemical restraint. The protocol of sedation was based on a combination of alfaxalone and an opioid among methadone, butorphanol and pethidine in order to improve the quality of sedation, offset the lack of analgesia and reduce side effects of alfaxalone. The patients underwent clinical evaluation and each of them was randomly allocated to one of the 3 groups. The evaluation procedure lasted 30 minutes from sedation, during which cats were monitored to fill an evaluation sheet at predefined time points. The quality of recovery was influenced by the opioid, with a higher score for butorphanol and pethidine, but also by body condition score (BCS) and age. The time of lateral recumbency was affected by the American Society of Anesthesiologists score (ASA), and it was higher in ASA 1-2. Physiological parameters were influenced by the molecule over time. The molecules influenced also the degree of muscular relaxation and quality of sedation. The last parameter was also influenced by ASA status with a greater score in cats classified as ASA 3.

Key words*: alfaxalone, cat, opioid, sedation.*

INTRODUCTION

Cats are notoriously sensitive animals, whose emotionality can be upset in a veterinary environment causing anorexia, abnormal behaviour, change of physiological parameters and immunosuppression. For these reasons veterinarians often recur to chemical restraint (Pascal et al., 2013; 2015; Neagu et al., 2018).
Drugs such as ketamine and α_2-agonists represent the first choice in clinical practice, although they have an important impact on main systems of the organism, resulting not suitable in patients with head trauma, cardiac and respiratory disease, liver and kidney failure.
The present work describes a prospective, randomized, blinded clinical study on 118 cats in order to validate a safe and efficacy protocol of sedation using alfaxalone in combination with three different opioids among methadone, butorphanol and pethidine.
The aims of the study are the following: improvement of quality of sedation, finding an alternative to common protocols which use ketamine and α_2-agonist, offset the lack of analgesia and reduce side effects of alfaxalone such as tremors, hyperextension of neck and limb, opisthotonus, uncontrolled movements, maintaining an optimal cardiovascular and respiratory stability.

MATERIALS AND METHODS

One hundred and eighteen cats that needed sedation, presented at the Veterinary Teaching Hospital of the University of Perugia, were recruited for this study. The patients underwent a clinical evaluation: physiological parameters were measured, ASA status was identified and each of them was randomly allocated to one of three groups identified. The protocol of sedation was based on a combination of 3 mg/kg alfaxalone and an opioid among 0.3 mg/kg methadone (M group), 0.3 mg/kg butorphanol (B group) and 5 mg/kg pethidine (P group) administered IM.
The procedure was carried out in a quiet, silent and twilight room in order to limit the stimulations that could alter the results. The evaluation procedure lasted a maximum of 30 minutes from the time of drug administration,

during which cats were monitored to fill an evaluation sheet at predefined time points with specific scores (Figures 1-2). During this phase diagnostic and therapeutic procedures such as blood and urine samples, radiographic examination, were carried out in these groups of cats.
Drugs were administered IM with 2.5 ml syringe and 22 G needle (T0). At that time a stopwatch was activated to establish the exact time of the evaluations or occurrence of drugs were administered IM with particular effects, recorded in seconds from T0.

The time of onset of lateral recumbency, indicative of sedation, was noted and response to injection was evaluated with scores between 0 (none) to 4 (prolonged reaction).
Physiological parameters included heart rate (HR), respiratory rate (RR), rectal temperature (Temp °C), oxygen saturation of haemoglobin (SpO_2), presence of mydriasis. Parameters were evaluated at predetermined time points and beside physiological data, behavioural parameters reflective of sedation degree were scored.

Date: _____
Patient name: _____ M F / I N
Procedure: _____

Pediatric (0-3 months)
Young (4-12 months)
Adult (>12 months)
Geriatric (>o=10 years)

Body weight: _____
ASA STATUS: 1 – 2 – 3 – 4 – 5 – E
BCS: __/5

Treatment group random # _____
Opioid: _____ *
*Supraspinatus / Quadriceps – ri / le**

Time of IM injection____
Time of onset of lateral recumbency _____

Alfaxalone: 3 mg/kg = _____(ml) +
a) butorphanol: 0.3 mg/kg = _____(ml)
b) methadone: 0.3 mg/kg = _____(ml
c) pethidine: 5 mg/kg = _____(ml)

max IM dose 0.5 ml/kg

		pre	3′	5′	8′	12′	15′	20′	25′	30′
Temperament score (pre sedation)	- Very friendly	1								
	- Friendly but reserved/nervous	2								
	- Confident/wriggly	3								
	- Mildly aggressive	4								
	- Very aggressive	5								
Response to injection	- None	0								
	- Mild flinch/tense	1								
	- Flinches away from needle	2								
	- Vocalizes/attempts to escape	3								
	- Prolonged reaction	4								
Overall sedation	- Excellent		1	1	1	1	1	1	1	1
	- Good		2	2	2	2	2	2	2	2
	- Fair		3	3	3	3	3	3	3	3
	- Inadequate		4	4	4	4	4	4	4	4
Recovery quality	- Excellent	1	Comments:							
	- Fair	2								
	- Poor	3								

*= To be crossed ONLY at the end of the procedure for record purpose – keep the observer blinded to the treatment!!

Figure 1. Evaluation sheet with patient data, completed before sedation

PHYSIOLOGIC DATA

	basal	3′	5′	8′	12′	15′	20′	25′	30′									
HR																		
RR																		
Temp C°																		
SpO_2																		
SAP																		
Mydriasis (y/n)																		

Whenever possible!

SEDATION SCORE

		3	5	8	12	15	20	25	30
Position	- Completely alert, able to stand and walk	0	0	0	0	0	0	0	0
	- Sedated, standing or sitting	1	1	1	1	1	1	1	1
	- Lying down in sternal, looking around, able to react quickly, stand up	2	2	2	2	2	2	2	2
	- Lying down in sternal/lateral, reacting slowly, difficult standing	3	3	3	3	3	3	3	3
	- Lying in lateral/sternal, head down, unable to stand	4	4	4	4	4	4	4	4
Resistance to lateral recumbency (if in the cage, roll it)	- Strong	0	0	0	0	0	0	0	0
	- Moderate	1	1	1	1	1	1	1	1
	- Slight	2	2	2	2	2	2	2	2
	- No	3	3	3	3	3	3	3	3
Degree of muscular relaxation	- Poor	0	0	0	0	0	0	0	0
	- Moderate	1	1	1	1	1	1	1	1
	- Good	2	2	2	2	2	2	2	2
	- Excellent	3	3	3	3	3	3	3	3
Response to noise (a kiss-like sound 1m away from the cat)	- Normal response (turns head)	0	0	0	0	0	0	0	0
	- Moderate response (pronounced ear flick)	1	1	1	1	1	1	1	1
	- Weak response (slight ear flick)	2	2	2	2	2	2	2	2
	- No response	3	3	3	3	3	3	3	3

Score= **13** maximum sedation;
if **>5**→ start procedure;
if **<5** after 15′→ 3 µg/kg dexmedetomidine IM (____µg), if inadequate after further 10′→ out of study / add something else (_____)
Time of start of the procedure: _____
Catheter placement: not required yes - impossible - placed after dex
Intubation (prior instillation of the larynx with lidocaine): not required yes, with _____ ml Propofol (mg _____)
Other anesthetics required to perform the procedure: _____

Figure 2. Evaluation sheet with physiologic data and sedation score

Other information collected from each case included: catheter placement (if not required, if placed without any other drugs or after 3 μg/kg dexmedetomidine IM); orotracheal intubation (if not required or possible only after propofol); other anaesthetics needed to perform the procedure. Independently of the procedure but recording whether surgery was followed or not, recovery was scored from 1 (excellent) to 3 (poor), reporting any possible side effect.
The procedure only started if the sedation score was > 5.
Ordinal variables were evaluated with generalized linear models using a multinomial distribution and cumulative logit as a link function. For repeated variables, time was entered as a covariate, while BCS, age, ASA status and surgery were inserted when appropriate. The results are expressed as an odd ratio (OR) with 95% confidence interval (CI) and P-value. Quantitative variables were analyzed using mixed linear models evaluating the effect of the molecule (3 levels) and, for repeated variables, the impact of time (8 levels) and interaction. The basal value of each variable was entered as a covariate. The sidak correction was used for multiple comparisons. The significance was placed for $P<0.05$. The analyzes were conducted with software SPSS version 23 (SPSS Inc, Chicago, IL).

RESULTS AND DISCUSSIONS

For this study, we recruited 50 females (20 neutered and 30 intact) and 68 males (22 neutered and 46 intact). Mean body weight was 3.8±1.2 kg. Distribution according to age included more than 50% of adult cats (Table 1). Some relevant results of the recorded parameters are reported in Table 2. Most of the cats were very friendly or friendly but reserved, only 2.5% was very aggressive.
The mean time required before starting the procedure was 420±25 seconds, while the duration of the procedure was 1239±46 seconds. Orotracheal intubation was required in 52% of cats (50% in group M, 48.6% in group B, 43.2% in group P) with concomitant use of 2.7±0.2 mg/kg propofol. Surgery was done in 59.3% of cases; diagnostic and therapeutic procedures were performed in 40.7% (Table 2).

Table 1. Demographics data of the study population

GENDER n (%)	**FI**	30 (25.4%)
	FN	20 (16.9%)
	MI	46 (39.1%)
	MN	22 (18.6%)
BODY WEIGHT kg (mean±SD)		3.8±1.2
BCS n (%)	**1**	1 (0.9%)
	2	15 (12.8%)
	3	72 (61.5%)
	4	27 (23.1%)
	5	2 (1.7%)
AGE n (%)	**Pediatric**	2 (1.7%)
	Young	40 (33.9%)
	Adult	62 (52.5%)
	Geriatric	14 (11.9%)

Table 2. Results of some parameters

TEMPERAMENT SCORE n (%)	**1**	49 (41.5%)
	2	42 (35.6%)
	3	15 (12.7%)
	4	9 (7.6%)
	5	3 (2.5%)
INTUBATION n (%)	**no**	61 (52%)
	yes	56 (48%)
SURGERY n (%)	**no**	48 (40.7%)
	yes	70 (59.3%)

Catheter placement was possible in most cases, but in 3% of cats of group M, B and P was impossible, and in 9% of cats of group B was possible after use of dexmedetomidine IM.
The need to use other anaesthetics to perform the procedure occurred in 31% in group M, 50% in group B and 39% in group P.
Statistically significant differences were found in recovery quality ($P < 0.01$), with poor scores (score 3) in group B ($P < 0.01$) and group P ($P = 0.05$).
However, good recovery (score 2) occurred in most cases with a prevalence of 57.1% in group M and 68.4% in group P. Recovery quality was also analysed in association with BCS, categorized into three levels, and age.
The quality improves with increasing BCS and gets worse in adult and young cats compared to pediatric patients (Tables 3-4).
Patients classified as ASA 1-2 became recumbent more slowly than ASA 3 and ASA 4-5 ($P = 0.019$) (Table 5).

Table 3. Recovery quality according to age

Parameter	95% Wald Confidence Interval for OR		P-value
	Lower	Upper	
AGE			0.176
Young vs pediatric	1.133	56.248	**0.037**
Adult vs pediatric	1.249	49.217	**0.028**
Geriatric vs pediatric	0.798	53.848	0.080

Table 4. Recovery quality according to BCS categorized into three levels

RECOVERY QUALITY n (%)	BCS			P value
	1-2	3	4-5	
1	1 (6.3%)	23 (31.9%)	10 (34.5%)	0.068
2	12 (75.0%)	43 (59.7%)	17 (58.6%)	
3	3 (18.8%)	6 (8.3%)	2 (6.9%)	

Cats in group B achieved lateral recumbency more slowly than those in group M and group P (Table 5).

Influence of BCS influences the time in which the subjects become recumbent with more significant impact in animals with values placed at the extremities of this scale (Table 5).

Table 5. Influence on the time of lateral recumbency Values with the same letter in each subcolumn are statistically not relevant.

Parameter		TIME OF ONSET OF LATERAL RECUMBENCY (sec)	P-value
OPIOID	**Group M**	222±23	0.359
	Group B	270±37	
	Group P	200±22	
ASA STATUS	**1-2**	252^{a}±21	**0.019**
	3	169^{b}±18	
	4-5	157^{ab}±39	
BCS	**1-2**	240±60	0.180
	3	204±15	
	4-5	275±41	

About physiological parameters, only HR and SpO_2 were influenced by the opioid used ($P < 0.01$). HR was maintained within physiological ranges in cats of group P compare to group M ($P < 0.05$) with mean values of 169±6, 171±6 and 162±6 (in P, M and B group respectively).

HR and RR were influenced by ASA status: HR was lower in cats classified as ASA 1-2 (157±2) compared to ASA 3 (158±3) and ASA 4-5 (166±7); RR was lower in cats classified as ASA 3 (24±1) compared to ASA 1-2 (28±0) and ASA 4-5 (28±2). The rectal temperature didn't change in the three study groups.

Regarding the sedation score, only the degree of muscular relaxation and the overall sedation were influenced by the opioid ($P < 0.05$) and ASA status ($P < 0.001$). The degree of muscular relaxation was poor (score 0) in group B compared to group M, overall sedation was poor (score 3) in group B compared to group M. This latter parameter was excellent (score 0) in cats classified as ASA 3 compared to ASA 1-2.

In agreement with other studies, reported in the literature, we recorded side effects typically described after alfaxalone, such as opisthotonos, hyperextension of the limbs and neck, myoclonus, pedalling, ataxia and vocalizations at recovery (Figure 3).

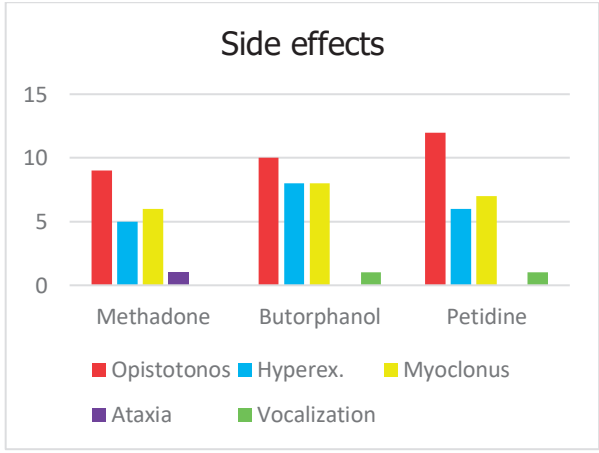

Figure 3. Side effects during the study

CONCLUSIONS

The protocols used in this study was considered safe due to the excellent cardiorespiratory stability and trifling side effects and efficient due to the good sedation effect.

Moreover, most patients were slightly intolerant by the large volume of injection and required adequate physical restraint since alfaxalone is only available at 10 mg/ml formulation.

Lateral recumbency was achieved unexcitedly and in a short time. It was judges as excellent as premedication for patients undergoing general anaesthesia before surgery, but it was evaluated as not entirely suitable for radiographic and CT examinations or blood and

urine samples, that required excessive stimuli. However, in these cases, the administration of a low dose of dexmedetomidine in cats (3 μg/kg IM) was enough to achieve deeper sedation without interfering with physiological parameters evaluated.

Data showed that the best association was alfaxalone-methadone, with greater sedation quality in the shortest time and best recovery, without the use of other anaesthetics. The combination alfaxalone-pethidine showed good results, but more attention is required at the IM injection because accidental IV administration of the opioid could induce an anaphylactic reaction. The association with butorphanol was the least effective of the three in terms of efficacy of sedation and recovery.

Regarding the choice of the opioid used in combination with alfaxalone, it is imperative to consider the patient's age, BCS and ASA status, but also the environment (absence of external stimuli) and the procedure to be performed.

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