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Evaluation of Dexmedetomidine And Butorphanol As Pre-Anaesthetic With Alfaxalone Induced And Maintained Anaesthesia For Neutering In Cats

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Abstract
The study was conducted to evaluate the efficacy and safety of dexmedetomidine and butorphanol as pre-anaesthetic with alfaxalone induced and maintained anaesthesia for neutering in cats. All six cats were judged to be in good health based on physical examination, haemogram and blood chemical profile. The selected cats for neutering surgery were administered with dexmedetomidine at the dose rate of 20 µg per kg and butorphanol at 0.2 mg per kg body weight intramuscularly. Fifteen minutes after premedication, alfaxalone was administered @ 5mg/kg body weight intravenously over 60 seconds 'to effect' through the cephalic vein.Cats in the present study showed moderate to intense depth of sedation, smooth to very smooth anaesthetic induction and very good to excellent recovery from anaesthesia. Results revealed significant decrease in rectal temperature, respiratory rate, heart rate and pulse rate during the anaesthetic period and haematological parameters like TEC, haemoglobin, PCV, TLC and DLC varied non-significantly within in acceptable limit. The biochemical parameters namely Creatinine, BUN, ALT, TP showed a non-significant changes and blood glucose showed a significant increase by the end of anesthetic period. There was a significant decrease upto 30 minutes and then non-significant decrease in oxygen saturation; initial increase followed by decrease in mean arterial blood pressure were observed in the present study. ECG changes revealed decrease in heart rate and increase in 'T' wave amplitude after administration of dexmedetomidine and butorphanol intramuscularly and no cardiac arrhythmias attributable to the administration of intravenous alfaxalone in cats. Alfaxalone has minimal cardiovascular and respiratory depressant effects and can be used as an alternative to routinely used anaesthetic drugs in cats.

Keywords: *Dexmedetomidine, Butorphanol, Alfaxalone.*

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I. INTRODUCTION

It is a well-known fact that without ability to produce anaesthesia, surgery would still be the last option. Anaesthesia is used for a wider range of circumstances in animals than in people, due to animals' inability to co-operate with certain diagnostic or therapeutic procedures. It is required for many surgical procedures which require the patient to be immobile, unaware and without pain. Furthermore, it aims to minimize the surgical stress response. Total intravenous anaesthesia is a technique of general anaesthesia involving the induction and maintenance of the anaesthesia with drugs given solely by the intravenous (IV) route. Maintenance of anaesthesia using total intravenous anaesthesia (TIVA) is gaining popularity in small animal anaesthesia although inhalant agents are still most commonly favoured for anaesthesia maintenance. The disadvantages of inhalational anesthesia include the purchase of costly anesthetic machines, vaporizers, and breathing systems. Environmental pollution from anaesthetic-gas waste is a potential health hazard for those working around inhalant anaesthesia, and this consideration may also make IV anesthesia a better choice than an inhalant agent [1].

Dexmedetomidine, the d-enantiomer that possess all relevant pharmacological activity in racemic medetomidine, is the newest and most potent α_2-adrenoceptor agonist approved by the FDA and commercially available for use as a sedative and preanesthetic in dogs and cats[22].Dexmedetomidine is a selective and potent

α_2-adrenoceptor agonist that is used for its anxiolytic, sedative and analgesic properties[2].Butorphanol (17-cyclobutylmethyl-3,14-dihydroxymorphinan) is a mixed "agonist/antagonist" analgesic belonging to a group of morphine surrogates known as morphinans[14]. Butorphanol is a synthetic opioid with agonistic activity at κ-opioid receptors and antagonistic effects at μ receptors[12]. Butorphanol might act on the mu (μ), delta (δ) and kappa (κ) opioid receptor types, according to radio-ligand displacement studies. Furthermore, behavioural research and clinical data suggested that butorphanol might also bind to the opioid sigma (σ) receptor[9].

Alfaxalone is a synthetic neuroactive steroid that interacts with gamma aminobutyric acid ($GABA_A$) receptors to produce anaesthesia and muscle relaxation. It was previously marketed in formulations with alfadalone and a polyethoxylated castor oil surfactant (Saffan®, Schering-Plough Animal Health, Union, NJ, USA). It is now available alone, solubilised in 2-hydroxypropyl-beta cyclodextrin (Alfaxan®, Jurox Pty Ltd, Rutherford, NSW, Australia) and this formulation retains many of the advantages of alfaxalone, such as cardiovascular and respiratory safety [19, 20] without the commonly recorded side effects that were associated with histamine release resulting from the surfactant in the Saffan® formulation. The ability of steroids hormones to produce hypnosis, general anaesthesia and muscle relaxation in several species, including cats, has been recognized for almost 70 years [23]. The advantages of using steroid anaesthetic agent for induction of anaesthesia, such as rapid onset of action, minimal cardiovascular depression and high therapeutic index compared with other induction agents [8, 10, 11]stimulated interest in their use.

II. MATERIAL AND METHODS

The study was carried out in healthy client owned six clinical cases of cats which were presented for routine neutering procedures to Department of Surgery and Radiology, Veterinary College Hospital, KVAFSU, Hebbal, Bengaluru. Prior to anaesthesia, all the cats underwent complete clinical examination, temperament scoring ranging from 1 (very friendly) to 5 (very aggressive) and body condition scoring (BCS). Cats were excluded from the study if they had a recent history of having been bred; were pregnant or lactating; had signs or history of systemic disease. All the cats undergoing the surgical procedure were withheld food and water for 12 hours and 6 hours respectively prior to anaesthesia and surgery. The selected cats for neutering surgery were administered with dexmedetomidine (Dexem®) and butorphanol (Butrum®) at the dose rate of 20 μg per kg and 0.2 mg per kg body weight intramuscularly. Fifteen minutes after premedication, the cephalic vein was catheterized with 24 G intravenous catheter for intravenous administration of alfaxalone. The indwelling 22 G intravenous catheter was placed in the jugular vein for collection of blood samples at different intervals during anaesthesia as per the schedule. Based on the surgical procedure (spaying or castration) that was to be performed, the surgical site was prepared aseptically in a routine manner. Alfaxalone (Alfaxan®, 10ml, inj., Jurox Pty Limited, Rutherford, Australia, 10mg/ml) was administered @ 5mg/kg BW, IV over 60 seconds 'to effect' through the cephalic vein catheter, with 0 minute being the end of the administration .The surgery was performed as per the standard technique of neutering in male or female cats. Blood samples were collected in all subjects at different time intervals(before and 0, 15, 30, 45, 60 minutes after anaesthesia) throughout the study period. All the cases were clinically assessed for quality of sedation based on the criteria given by Volpato*et al.* (2014) and scored based on a numeric descriptive scale ranging from 0-3 (0 – none, 1- mild, 2 – moderate, 3-intense). The time elapsed from the administration of the alfaxalone to the onset of anaesthesia which was evidenced by smooth transition to lateral recumbency and complete muscle relaxation with minimal or no response to noxious stimuli. The alfaxalone was administered to result in unconsciousness and loss of jaw tone sufficient to allow the patient to be intubated with endotracheal tube. Quality of induction of anaesthesia and smooth endotracheal intubation were clinically assessed in all the cases based on the criteria given by Mathis *et al*. (2012) [18]. The smoothness of induction was scored from 1 to 4, with 4 indicating the very smooth, 3 indicating smooth, 2 indicating poor induction and 1 representing the very poor induction. Depth of anaesthesia was assessed every 5 minutes and depending on outcome of the assessment, an additional bolus of alfaxalone was administered intravenously. The total dose of alfaxalone required for maintenance of anaesthesia was noted. After completion of the surgery, the cats were shifted to the recovery ward where a qualitative (non-interactive) and quantitative assessment of recovery was performed. During the recovery period, except for blood sampling, cats were left undisturbed until they were able to stand up and walk on their own. The quality of recovery was scored based on the animal's demeanor and excitability during the early post-anaesthetic period using a simple descriptive scale of 1–5 (1-excellent, 2-very good, 3-moderate, 4-poor, 5-extremely poor) as described by Zaki *et al.* (2009) [28].Variables that were monitored included: Physiological parameters such as rectal temperature, respiratory rate, heart rate and pulse rate; haematological parameters like packed cell volume (PCV percent), haemoglobin (Hb, g/dL), total erythrocyte count (TEC, 10^6/cmm. of blood), total leucocyte count (TLC, 10^3/cmm. of blood), and differential leucocyte count (DLC percent); biochemical parameters such as serum creatinine (mg/dL), blood urea nitrogen (mg/dL), alanine aminotransferase (ALT, units/liter), and total plasma protein (g/dL) were measured just before administration of the pre-anaesthetic and at 0^{th}, 15^{th}, 30^{th}, 45^{th}, 60^{th} minute after induction of general anaesthesia.The electrocardiographic tracing was recorded on a single channel

strip chart recorder using a bed side multipara patient monitor at a paper speed of 25 mm/second at the sensitivity of 1 with the voltage of 1 mV/cm. ECG was recorded once before premedication if possible and monitored throughout the course of maintenance of anaesthesia.

Statistical analysis was performed on parameters measured throughout the anaesthetic period. Differences in monitored parameters in cats were investigated using Paired t-test. The data interpreted as per the procedure described by Snedecor and Cochran (1996). The test of significance was fixed at five percent for all comparisons ($P \leq 0.05$).

III. RESULTS AND DISCUSSION

The study was conducted to evaluate the clinical efficacy and safety of dexmedetomidine and butorphanol as preanaesthetic with alfaxalone induced and maintained anaesthesia for neutering in cats with reference to clinical, biochemical and haematological parameters in six cats undergoing neutering surgical procedures.

All cats were judged to be in good health based on physical examination, haemogram and blood chemical profile. The mean ± SE values of age, body weight and BCS of the cats were 1.97 ± 0.81 years, 4.13 ± 0.56 kg and 3.33 ± 0.33 out of maximum score of 5 respectively. There was a significant decrease in rectal temperature[21, 25], respiratory rate[25], heart rate [13] and pulse rate [27] during the anaesthetic period (Table.1) whereas haematological parameters like TEC, haemoglobin, PCV, TLC and DLC varied non-significantly (Table.2) within in acceptable limit [20, 26,27]. The biochemical parameters namely Creatinine, BUN, ALT, TP showed a non-significant changes [5, 20, 27] and blood glucose showed a significant increase (Table.3) by the end of anesthetic period [5, 6].ECG changes revealed decrease in heart rate and increase in 'T' wave amplitude after administration of dexmedetomidine and butorphanol intramuscularly[16, 17] and no cardiac arrhythmias attributable to the administration of intravenous alfaxalone in cats[7, 20]. There was a significant decrease upto 30 minutes and then non-significant decrease in oxygen saturation; initial increase followed by decrease in mean arterial blood pressure were observed in the present study.

Table 1. Mean ± SE values of various physiological parameters recorded at different time intervals.

Parameter	Time Interval					
	15 minutes prior to induction	Post-Induction				
		0 min	15 min	30 min	45 min	60 min
Rectal temperature (^{0}F)	102.30 ± 0.30	102.18 ± 0.14	100.47 ± 0.49	99.77 ± 0.56	98.93 ± 0.74	98.38 ± 0.60
Respiratory rate (breaths/minute)	63.33 ± 7.20	35.00 ± 1.63	33.17 ± 1.47	34.83 ± 2.06	32.00 ± 3.39	34.50 ± 2.09
Heart rate (beats/minute)	122.00 ± 5.73	104.83± 5.48	90.17± 2.32	94.67± 3.92	99.67± 3.63	96.33± 6.99
Pulse rate (beats/minute)	115.33± 6.17	97.50± 4.19	89.17± 1.76	90.67± 3.29	94.50± 3.01	91.33± 5.26

Table 2. Mean ± SE values of various haematological parameters recorded at different time intervals.

	Time Interval					
	15 min prior to induction	Post-Induction				
		0 min	15 min	30 min	45 min	60 min
TEC (10^6/cmm)	8.67 ± 0.58	8.51 ± 0.53	8.06 ± 0.48	8.25 ± 0.47	8.13 ± 0.42	8.17 ± 0.44
Hb (g/dL)	12.82 ± 1.21	12.62 ± 0.92	11.60 ± 0.89	12.00 ± 0.88	11.85 ± 0.96	11.96 ± 0.92
PCV (%)	36.95 ± 3.13	37.38 ± 2.78	33.98 ± 2.19	34.63 ± 2.38	34.32 ± 2.40	34.10 ± 2.43
TLC (10^3/cmm)	12.35 ± 1.93	12.33 ± 2.09	12.75 ± 2.56	11.33 ± 2.28	10.87 ± 2.48	11.73 ± 2.21
DLC (%)						
Neutrophils (%)	46.78 ± 4.58	45.47 ± 4.15	47.58 ± 5.79	46.53 ± 5.08	43.25 ± 4.16	41.17 ± 4.02
Lymphocytes (%)	36.50 ± 3.36	32.40 ± 1.09	32.17 ± 3.21	35.85 ± 3.76	39.17 ± 3.37	39.90 ± 3.18
Monocytes (%)	4.60 ±0.37	4.13 ± 0.17	4.27 ± 0.24	4.43 ± 0.19	4.55 ± 0.18	4.45 ± 0.14
Eosinophils (%)	2.15 ± 0.31	2.23 ± 0.39	2.18 ± 0.40	2.32 ± 0.27	2.30 ± 0.38	2.37 ± 0.40
Basophils (%)	0.45 ±0.11	0.47 ± 0.04	0.37 ± 0.07	0.44 ± 0.07	0.46 ± 0.08	0.41 ± 0.08

Table 3. Mean ± SE values of various biochemical parameters recorded at different time intervals.

Parameter	Time Interval					
	15 minutes prior to induction	Post-Induction				
		0 min	15 min	30 min	45 min	60 min
Creatinine (mg/dL)	1.27 ± 0.15	1.25 ± 0.82	1.32 ± 0.14	1.30 ± 0.15	1.30 ± 0.10	1.30 ± 0.12
BUN (mg/dL)	25.70 ± 0.85	25.80 ± 0.98	25.84 ± 0.9	25.56 ± 0.81	25.55 ± 0.85	25.70 ± 0.87
ALT (IU/L)	43.28 ± 2.79	43.03 ± 2.73	43.20 ± 2.94	43.08 ± 3.04	42.75 ± 3.04	42.40 ± 2.45
Total protein (g/dL)	7.40 ± 0.21	7.33 ± 0.26	7.16 ± 0.26	7.32 ± 0.38	7.15 ± 0.21	6.84 ± 0.21
Blood glucose (mg/dL)	74.66 ± 1.83	127.83 ± 6.57	158.16 ± 6.19	180.16 ± 5.65	185.16 ± 6.87	206.83 ± 4.31

The duration to attain sedation after administration of dexmedetomidine and butorphanol ranged from 8 to 15 minutes, with a mean ± SE of 11.5 ± 0.99 minutes[4]. After the onset of sedation, the cats showed reduced resistance to lie down with no responses to auditory, visual and tactile stimuli. Sedation scoring was done as per the scale given by Volpato*et al*. (2014) and the quality of sedation ranged from moderate (score 2) to intense (score 3) degree during the study. Induction of anaesthesia was characterized as quiet, uneventful and relaxed. The anaesthetic induction quality was scored using a scale proposed by Mathis *et al*. (2012) and the quality of induction was scored as smooth (score 3) to very smooth (score 4) during the study. The mean ± SE value of induction time with alfaxalone to attain the plane of anaesthesia sufficient enough to intubate the cats was 33.3 ± 1.58 seconds [20, 27]. The plane of anaesthesia achieved was characterized by unconsciousness, absence of pedal reflex and palpebral reflex, complete muscle relaxation and smooth transition to lateral recumbency. None of the cats experienced post induction apnoea (PIA) during the study. The duration of anaesthesia for completion of surgery was ranged from 22 to 55 minutes during the study with a mean ± SE of 38.83 ± 5.27 minutes. The maintenance phase of anaesthesia was characterized by ventromedial positioning of eyeball, good muscle relaxation and little or no response to noxious stimuli. The average maintenance dose of alfaxalone required for the completion of surgery was 0.6 mg/kg IV during the study. The recovery phase of anaesthesia was marked from the point of termination of alfaxalone administration during the study. The mean duration for return of pedal reflex, headlift, attainment of sternal recumbency and the duration to stand without assistance were 13.66 ± 0.66 minutes, 24.83 ± 2.07 minutes[24], 29.16 ± 1.70 minutes[15] and 36.83 ± 2.49 minutes[3], respectively. Recovery from anaesthesia was smooth, excitement free and uneventful in most of the cats under the study. However, two cats showed mild excitement and shivering. Vocalization, vomiting, tremors, seizures, or death during recovery phase were not observed in any of the cats during the study. The quality of recovery was scored as very good (score 2) to excellent (score 1) recovery using a scale given by Zaki *et al*. (2009) during the study.

IV. CONCLUSION

In conclusion, alfaxalone is effective for both the induction and maintenance of surgical anaesthesia in healthy cats following premedication with dexmedetomidine and butorphanol. Alfaxalone has minimal cardiovascular and respiratory depressant effects. Intravenous administration of alfaxalone provided rapid and smooth loss of consciousness, excellent muscle relaxation, short duration of anaesthetic effect, uneventful recovery and can be used as an alternative to routinely used anaesthetic drugs in cats.

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