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EFFECTS OF FUROSEMIDE ON XYLAZINE-KETAMINE ANAESTHESIA IN CATS

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ABSTRACT
The aim of this study was to evaluate the effects of furosemide on xylazine-ketamine anaesthesia in cats. Fifteen cats assigned to two groups, namely Xylazine-Ketamine-Furosemide (XKF) of 8 cats and Xylazine-Ketamine (XK) of 7 cats were used for the study. They were studied for their physiologic responses following intramuscular administration of xylazine at 0.5 mg/kg, ketamine at 15 mg/kg and furosemide at 2.5 mg/kg (XKF group), and xylazine at 0.5 mg/kg and ketamine at 15 mg/kg (XK group). They were observed over a period of one hour for changes in heart and respiratory rates and rectal temperature as well as time to induction, duration of recumbency and time to standing. There was no significant (P>0.05) difference in induction time of XKF (4.6±2.2 min) and XK (3.2±2.1 min) groups. There was significant (P<0.05) difference in duration of recumbency in groups XKF (54.8±12.8 min) and XK (80.0±15.3 min). There was no significant (P>0.05) difference in time to standing of group XKF (6.0±1.1 min) and XK (7.8±3.7 min). Mean heart rates for XKF and XK groups ranged from 107.1±8.3 to 132.6±15.8 beats/min and from 107.8±19.6 to 116.4±27.9 beats/min respectively. Mean respiratory rates for XKF and XK groups ranged from 23.0±3.5 to62.4±3.8 breaths/min and from 18.8±1.3 to 54.8±4.2 breaths/min respectively. Mean rectal temperature for XKF and XK groups ranged from39.4±0.7 to 41.0±1.2 ^{0}C and from 38.9±0.6 to 40.3±1.3 ^{0}C respectively. There were no significant (P>0.05) changes in the rectal temperature, the heart and respiratory rates. In conclusion, furosemide influenced the duration of recumbency but did not influence time to standing.

***Keywords*:** Cats, Effects, Furosemide, Xylazine, Ketamine.

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INTRODUCTION

In feline practice, injectable anaesthetic agents are used to provide humane restraint for non-painful clinical procedures, as well as analgesia for noxious diagnostic, manipulative and surgical procedures [1,2]. Ketamine hydrochloride (ketamine) has proved to be the most useful injectable anaesthetic agent in the cat because it can be given intramuscularly [3]. It has wide safety margin and cardiovascular stimulating activity [4,5,6]. However, ketamine is most frequently used clinically in combination with either an alpha$_2$–agonist, a benzodiazepine or a phenothiazine derivative in order to reduce the anaesthetic

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dose of ketamine, prolong the duration of anaesthesia, provide muscle relaxation and promote smooth anaesthetic recovery [6,7,8].

It is an accepted standard that an animal undergoing surgery be placed on fluids. However, the small size of cats makes them prone to accidental fluid overload that may manifest as pulmonary oedema [9,10]. This condition may necessitate immediate intraoperative administration of furosemide to treat [9,10]. Ketamine has been reported to be predominantly excreted in the urine either as an unchanged drug or as an active metabolite in the cat [11,12,13]. Therefore, it is logical to expect a clinically significant ketamine-diuretic interaction to occur somewhat by renal mechanisms.

This study was therefore designed to evaluate the effect of furosemide on xylazine-ketamine anaesthesia in cats.Specifically, the effect of xylazine-ketamine-furosemide (XKF) was compared with that of xylazine-ketamine (XK) in the cats by monitoring of some anaesthetic indices like time to induction, duration of recumbency and time to standing as well as changes in rectal temperature (RT), heart rate (HR) and respiratory rate (RR) over a 60- minutes period of anaesthesia.

MATERIALS AND METHODS

Fifteen adult domestic short-haired cats (8 intact males and 7 intact females), weighing between 1.2 kg and 1.6 kg (1.4±0.2 kg, mean ± SD) were used for this study. The cats were housed individually in the cattery section of the Experimental Animals Unit of the Faculty of Veterinary Medicine, University of Ibadan. Prior to the commencement of the experiments, the animals were examined clinically and adjudged to be apparently healthy.

The study protocol was approved by the Ethics Committee for Animal Experiments of the Faculty of Veterinary Medicine, University of Ibadan, Nigeria (Protocol No.03/03/14). Food was withheld overnight from the cats while water was allowed up to the time of drug administration. The cats were randomly divided into two groups XKF (8 cats comprising of 4 tom cats and 4 queens) and XK (7 cats comprising of 4 tom cats and 3 queens). The group XKF cats were given atropine sulphate (Nonproprietary 0.6 mg/ml, Antigen Ltd, Eire) at a dose rate of 0.04 mg/kg and xylazine hydrochloride (Xylax$^{(R)}$ 20 mg/ml, Farvet Laboratories, Holland) at a dose rate of 0.5 mg/kg, followed10 min later by induction of anaesthesia with injection of ketamine hydrochloride (Vetalar$^{(R)}$ 50 mg/ml, Parke Davis & Co Ltd, UK) at a dose rate of 15 mg/kg and 2.5 mg/kg of furosemide (Lasix$^{(R)}$ 10 mg/ml, Hoechst, UK) intramuscularly (IM). Seven XK group cats which served as control were also given IM injections of atropine and xylazine at the same dose rate used for the XKF group but without the addition of furosemide. Induction of anaesthesia was done 10min later with the IM administration of ketamine alone at a dosage of 15mg/kg body weight. The intramuscular injections were given at the quadriceps group of muscles. Following anaesthetic induction, the anaesthetized cats were placed in right lateral recumbency on a foam padded table as soon as they lost the righting reflex and then covered with a towel.

The baseline values for HR, RR and RT of the cats were determined immediately before induction of anaesthesia (time 0 min), and subsequently at 10 min intervals over the first 60 min period of anaesthesia. Heart rate (in beats/min) was evaluated with the aid of a precordial stethoscope and respiratory rate (in breaths/min) was determined by observing the cats' chest movement. Rectal temperature ($^{\circ}$C) was measured using a mercury-in-glass thermometer inserted into the rectum.

The anaesthetic indices recorded for each cat were defined as follows:

Time to induction: Time interval (in min) between ketamine injection and loss of righting reflex by the cat.

Duration of recumbency: Time interval (in min) between the loss of righting reflex and assumption of sternal posture by the cat.

Time to standing: Time interval (in min) between assumption of sternal and standing postures by the cat.

Statistical Analysis
All data were expressed as mean ± standard deviation (SD). The means of the anaesthetic indices between the XKF and XK groups were compared using student's t-test for unpaired data. The respective means of the HR, RR and RT were compared using analysis of variance for repeated measures followed as appropriate by Tukey-Kramer multiple comparisons test [14]. A P value of less than 0.05 was accepted for statistical significance in all comparisons. Number Cruncher Statistical Software (NCSS) 2004 statistical package was used [14].

RESULTS
The times to induction (4.6±2.2 min) and standing (6.0±1.1 min) with XKF were similar to the respective XK values of 3.2±2.1 min and 7.8±3.7 min, whereas the duration of recumbency (54.8±12.8 min) with XKF was significantly ($P < 0.05$) shorter than XK value of 80.0±15.3 min (Table 1).

Table 1: Mean anaesthetic indices of cats anaesthetized with the intramuscular administration of xylazine-ketamine alone (XK) and with furosemide (XKF).

Anaesthetic indices	Treatment groups	
	XK	XKF
Time to induction (min)	4.6± 2.2	3.2±2.1
Time to standing (min)	6.0±1.1	7.8±3.7
Duration of recumbency (min)	54.8±12.8	80.0±15.3

The physiological responses of the cats during XK and XKF anaesthesia are shown on table 2. The mean HR ranged between 107.1±8.3 and 132.6±15.8 beats/min with XKF while XK values ranged between107.8±19.6 beats/min and 116.4 ±27.9 beats/min. Apart from the 60th min time interval, the mean HR values with XKF were not significantly ($p > 0.05$) different from the corresponding XK values throughout the period of the study. Also in both groups, the mean HR was not significantly ($p > 0.05$) different from the baseline values in the first 20 min and later rose steadily till it became significant in XKF cats only at the 60th min time interval. The mean RR with XKF ranged from 23.0±3.5 to 62.4±3.8 breaths/min and the XK values ranged from 18.8±1.3 to 54.8±4.2 breaths/min. The mean RR values with XKF were similar to the corresponding XK values, except higher values that were recorded at 50thand 60thmin time intervals. In both groups, the mean RR values were significantly ($P < 0.05$) lower than the baseline values at 10 min and later rose significantly ($P < 0.05$) 30 min later and remained so to the end of the study. The mean RT with XKF ranged between 39.4±0.7 and 41.0±1.2^{0}C while the XK values ranged between 38.9±0.6 and 40.3±1.3^{0}C. Although there was no significant ($p > 0.05$) difference between the mean RT values of both XKF and XK cats throughout the period of the trials, there were steady increases from the baseline values until it became significant in XKF and XK groups at the 50th and 60th min time intervals respectively.

DISCUSSION
In this study, times to induction of the cats following the administration of ketamine were similar for both XKF (4.6±2.2 min) and XK (3.2±2.1 min) as expected. Verstegen*et al*. [15] also recorded induction time of 4.25min in cats following xylazine-ketamine administration. Ketamine provides good analgesia and has a rapid onset of action and short duration of action. In similar studies in rabbits, Kilic[16] had reported the onset of action and duration of recumbency to be 2.0 min and 120.0 min respectively, while Adetunji and Lawal[17] reported 3.4 min and 62.0 min. The duration of recumbency recorded in this study,80.0±15.3 min (64.7 to 95.3min), is lower than the 120 ± 25min recorded by Kilic [16] probably as a result of the higher dosage of ketamine (50mg/kg) used in the previous study. However, onset of action

obtained by both Kilic [16] and Adetunji and Lawal [17] were similar to our finding in which the onset of action following administration of ketamine was 3.2 min.

Table 2: Mean Heart rate, respiratory rate and rectal temperature responses of cats to intramuscular administration of xylazine-ketamine alone (XK) and with furosemide (XKF).

Time interval	HR(beats/min)		RR (breaths/min)		RT(^{0}C)	
(min)	XK	XKF	XK	XKF	XK	XKF
0[a]	116.4±27.9	112.2±11.3	26.6±3.1	28.4±3.4	38.9±0.6	39.4±0.7*
10	114.0±13.3	109.0±5.7	18.8±1.3	23.0±3.5*	39.1±0.6	39.6±0.8*
20	108.0±12.6	107.1±8.3	26.6±1.7	25.0±3.6	39.3±0.8	39.9±0.8*
30	108.4±6.5	112.2±13.0	34.0±2.7	31.8±4.1*	39.5±1.0	40.2±0.9*
40	114.2±8.6	119.3±16.9	43.4±4.6	39.6±4.3*	39.7±1.1	40.5±1.2*
50	111.2±12.3	121.6±14.5	50.2±4.5	56.0±4.3*	39.9±1.1	40.9±1.2*
60	107.8±19.6	132.6±15.8*	54.8±4.2	62.4±3.8*	40.3±1.3	41.0±1.2

The shorter duration of recumbency associated with the XKF group than the XK group in this study is interesting because it is contrary to the findings of Hanna *et al.* [18] who reported that, on the basis of measured pharmacokinetic parameters, the concurrent use of diuretics such as furosemide prolonged the renal excretion of ketamine in cats. However, these authors administered ketamine alone without xylazine. Furosemide is a potent loop diuretic which acts on the ascending limb of the loop of Henle to inhibit active re-absorption of tubular contents, leading to increased output of urine [19]. Also in the cat, intramuscular administration of 1.1 mg/kg xylazine causes 6-fold increase in urine production [19]. Thus the recorded shorter duration of recumbency with XKF in this study might be due to rapid clearance of ketamine and its anaesthetic effect by furosemide and xylazine [20,21,22,3,24].

Although ketamine administration usually causes an increase in the heart rate and arterial blood pressure due to ketamine's increased sympathetic afferent activity [25].It is surprising that the range of mean HR recorded in this study for both XKF and XK groups (Table 2) were lower than the range of 112 to 198 beats/min quoted for anaesthetized cats [26]. This finding is most likely to be due to the bradycardic effect of xylazine [21,22,23,24], in spite of the co-administration of recommended clinical dose of an anticholinergic, atropine. McLeish and Steffey [27] have similarly reported in cats that the injection of 0.4 mg/kg xylazine resulted in an immediate significant reduction in HR, which could not be modified by pre-atropinization. Lower RR recorded for the XKF and the XK in the early period of the trial (Table 2) may relate to the pharmacological effects of both xylazine and ketamine on the respiratory system [6,21,23,24,26,28,29]. In a previous report by Hatch [30], ketamine has been shown to decrease RR and/or tidal volumes in cats. In dogs anaesthetized with ketamine administration, respiratory rate and minute volume decreased initially, but both returned to baseline values within 15 min [31] as recorded in this study. Although these findings are contrary to what has been reported before in cats with acepromazine premedication, Ingwersen*et al*. [32] reported non-significant changes in respiratory and heart rates while Farver*et al*. [33] reported a significant increase in heart and respiratory rates following ketamine anaesthesia in dogs. Xylazine's effects on respiratory function are usually clinically insignificant, but at high dosages, it can cause respiratory depression with decreased tidal volumes and respiratory rate and an overall decreased minute volume [24].

The apparent hyperventilation that occurred in the latter part of the trials might relate to progressive fall in plasma concentration of xylazine and ketamine due to elimination and attendant recovery of the cats. Mean RT recorded for both XKF and XK groups (Table 2) were higher than the range of 38.1 to 39.2 ^{0}C quoted for awake cats [35]. This was expected because it was reported that ketamine may cause either hypothermia or hyperthermia. Hypothermia is due to its effects on thermoregulatory centers, and hyperthermia due to increased muscle activity or hyperactive behavioural change [20,29]. Hyperthermia was recorded in this study (Table 2).

In conclusion, administration of furosemide to xylazine-ketamine anaesthetized cats hastened recovery and without significant effect on the rectal temperature, respiratory and heart rates of the cats. It is therefore advisable to use alternative anaesthetic regimen for procedures that will last for more than one hour, otherwise incremental doses of ketamine will be needed when furosemide is concurrently used with xylazine-ketamine anaesthesia.

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