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Research Article

Evaluation of Xylazine-Ketamine-Pentazocine Anaesthesia in the Rabbit

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Abstract

The use of ketamine drug combinations for long duration of action may be indicated in rabbits. For this purpose, the intramuscular administration of xylazine (5 mg/kg), followed 10 minutes later by ketamine (35 mg/kg) with or without pentazocine (10 mg/kg) was evaluated in 6 healthy rabbits, on the basis of selected anaesthetic indices and changes in heart rate, respiratory rate and rectal temperature over a one-hour period.

Time to loss of righting reflex by the rabbits given xylazine - ketamine-pentazocine (XKP) (1.3 ± 0.3 min) was significantly ($P < 0.05$) shorter than that with xylazine-ketamine (XK) (1.8 + 0.3 min). Duration of recumbency with XKP (110.2 + 5.2 min) was significantly longer than that with XK (73.9 2.9 min). Time to standing with XKP (5.3 + 11min) was not significantly ($P > 0.05$) different from that with XK (6.3 ± 1.3min). Mean HR ranged from 199.3 ± 6.8 to 214.8 ± 10.6 beats/ min with XKP, and from 174.8 +10.3 to 194.7 10.4 beats/ min with XK. Mean RR ranged from 18.7 ± 1.6 to 38.5 ± 6.3 breaths/min, and from 31.0 ± 2.9 to 94.5 ± 8.3 breaths/min in the XKP and XK, respectively. With XKP, mean RT ranged from 38.1 ± 0.2 to 38.4 ± 0.2 °C and from 38.2 ± 0.4° to 38.7 ± 0.3°C with XK.

The addition of pentazocine to xylazine-ketamine combination resulted in shorter induction time and longer duration of recumbency, as well as higher heart rates but lower respiratory rates which were not outside physiological limits in healthy rabbits not undergoing any clinical procedures. It was concluded that XKP combination will be useful for procedures of long duration in rabbits.

Keywords: Xylazine; Ketamine; Pentazocine; Anaesthesia; Rabbits

Introduction

The domestic rabbit is raised as a source of cholesterol-free animal protein and also as a scientific model in biomedical research. In recent times, rabbits have also become mammalian house hold pets [1,2]. Thus, practicing veterinarians are likely to be presented with rabbits that may require diagnostic, medical or surgical procedures necessitating the use of anaesthesia.

Although inhalational anaesthesia is generally considered safer than injectable anaesthesia for use in most animal species [3], the anaesthetic delivery apparatus can cause practical problems in the rabbit. Endotracheal intubation is difficult to perform in this species [4] and mask induction of anaesthesia can be stressful and result in environmental pollution with waste anaesthetic gases. In a study carried out by Flecknell and others [5], a period of apnoea lasting between 30 seconds and 2 minutes was the response to both isoflurane and halothane administered either by mask or in an induction chamber. For these reasons, injectable anaesthesia, involving the use of ketamine drug combinations [6-9] is often used in preference to volatile anaesthetic agents in rabbits. One of such ketamine drug combinations is xylazine-ketamine [10].

Ketamine is most effective when combined with an alpha 2 agonist such as xylazine because of the excellent muscle relaxing properties of the latter [11]. Although good surgical anaesthesia is produced by this combination it is only for short duration of about 30-45 minutes which may not suffice for longer procedures [12]. Butorphanol has reportedly increased the duration of anaesthesia with xylazine-ketamine and medetomidine- ketamine when included in these protocols [10,13]. Pentazocine is a mixed agonist-antagonist opioid like butorphanol [14]. It is possible that addition of pentazocine to xylazine-ketamine may also increase the duration of action of xylazine-ketamine anaesthesia. There is however, a paucity of information in literature on the use of xylazine-ketamine-pentazocine anaesthesia in rabbits.

The aim of this study, therefore, was to evaluate xylazine-ketamine- pentazocine anaesthesia in healthy rabbits not undergoing any clinical procedures, using selected anaesthetic indices and physiological parameters changes in heart rate (HR), respiratory rate (RR), and rectal temperature (RT) as indicators of anaesthetic efficacy and safety respectively.

Materials and Methods

Experimental animals

Six adult Nigerian local rabbits comprising of both sexes (4 intact bucks and 2 intact, non-pregnant, non-lactating does) with body weight 1.6 ± 0.1 kg (Mean + SD) were used for the study. The animals were purchased from a local rabbit market.

The rabbits were housed in three indoor locker-type cages provided with a bedding of wood shaving to keep the animals warm and to facilitate hygienic maintenance of the cages. Feed and water troughs were also provided in each cage. The rabbits were fed on commercial grower mash feed containing 18.0% crude protein (Vital feed® Grand cereals, Lagos, Nigeria) which was supplemented with fresh leaves of *Tridax procumbens*. They were fed ad libitum twice daily and fresh water provided free choice in the cages. The animals were kept for four weeks to get them familiar with their new environment, feeding regime and constant human handling. During this period, they were also dewormed with ivermectin (Ivomec super® Merial, Germany) at a dosage of 400mcg/kg body weight. Just before the start of the trials, the rabbits were judged to be in good health based on normal findings at comprehensive physical examination, haematology and serum chemistry evaluations.

Drugs

The drugs used for the experiment were

- Xylaxine-M2 injectable solution (VMD, Arendonk, Belgium) available as a 2% aqueous solution in 25 ml multidose vial for parenteral administration
- Ketamine hydrochloride injection USP vial ketamine®, ROTEX-MEDICA, Trittau, Germany) supplied as a 5 percent aqueous solution for parenteral administration in 10 ml multidose vial.
- Pentazocine (Pentalab®, LABORATE pharmaceutical, India) available for parenteral administration injection in 1 ml ampoule.

Experimental design

The study design was a randomized cross over design where each rabbit underwent two sets of experiments at one-week intervals in between experiments for drug washout. The first experiment involved premedication with xylazine followed 10 minutes later by administration of ketamine which served as control. The second experiment involved premedication with xylazine followed 10 minutes later by concurrent administration of ketamine and pentazocine. The physiological parameters were taken immediately following the loss of righting reflex and subsequently at 10 minutes interval over a period of 60 minutes. Selected anaesthetic indices were also recorded.

Experimental procedure

Food and water were not withheld from the rabbits before the trials. For the control (XK), rabbits were premedicated with intramuscular injection of 5mg/kg followed ten minutes later by intramuscular administration of Ketamine at a dose rate of 35 mg/kg body weight. For the XKP group rabbits were administered xylazine at 5mg/kg intramuscularly and ten minutes by the concurrent intramuscular administration of Ketamine at a dose rate of 35 mg/kg and pentazocine at a dose rate of 10 mg/kg. Following loss of righting reflex by the anaesthetized rabbits, they were placed on right lateral recumbency on a wooden table and covered with a towel. The physiological parameters were measured and anaesthetic indices calculated.

Calculated anaesthetic Indices

In this trial, the following anaesthetic indices were calculated:

- **Time to loss of righting reflex:** time interval (in minutes) between the injection of ketamine and the loss of righting reflex by the rabbits.
- **Duration of recumbency:** time interval (in minutes) between the loss of righting reflex and assumption of sternal posture by the rabbit.
- **Time to standing** time interval (in minutes) between the assumption of sternal and standing postures by the rabbit.

Measured physiological parameters

Heart rate, respiratory rate and rectal temperature were measured immediately after the loss of righting reflex and subsequently at 10 min intervals over a period of 60 min. Heart rate (in beats/min) was evaluated with the aid of precordial stethoscope. Respiratory rate (in breaths/min) was determined by counting the rabbit's chest movements and rectal temperature (in °C) was measured using a mercury- in- glass clinical thermometer.

Data analysis

Data were expressed as means + SD of six rabbits. Mean anaesthetic indices of XK and XKP were compared, using student's t-test for paired data. The mean values of the measured physiological parameters were compared using analysis of variance (ANOVA) for repeated measures followed by the least significant difference (LSD) as post- test. $P < 0.05$ was accepted as statistically significant.

Results

Anaesthetic indices

Time to loss of the righting reflex by the anaesthetized rabbits with XKP (1.3 ± 0.3 min) was significantly ($P < 0.05$) shorter than that with XK (1.8 ± 0.3min) Duration of recumbency with XKP (110.2 ± 5.2 min) was significantly longer than that with XK (73.9 ± 2.9min). Time to standing with XKP (5.3 + 1.1 min) was not significantly ($P > 0.05$) different from that with XK (6.3 ± 1.3 min).

Physiological parameters

Table 1 shows the mean HR, RR and RT responses of the anaesthetized rabbits to XK and XKP. The mean HR ranged from 199.3 ± 68 to 214.8 ± 10.6 beats/ min with XKP and from 174.8 ± 10.3 to 194.7 ± 11.4 beats/min with XK. The mean respiratory rates ranged from 18.7 ± 1.6 to 38.5 ± 6. 3 breaths/ min and from 31.0 ± 2.9 to 94.5 ± 8.3 breaths/min in the XKP and XK group of rabbits respectively. Whereas HRs were significantly higher with XKP than the corresponding control (XK) values; the RR values were significantly lower with XKP than the corresponding control values throughout the duration of the trials. Rectal temperature values showed no significant difference ($p > 0.05$) between the two treatment groups and ranged from 38.1 ± 0.2 to 38.4° ± 0.2 °C with XKP and 38.2 ± 0.4 to 38.7 ± 0.3°C with XK.

Table 1: Heart rate, respiratory rate and rectal temperature responses of the rabbits to intramuscular administration of xylazine-ketamine and xylazine-ketamine-pentazocine.

Time interval (minutes)	HR (beats/minute)		RR (breaths/minute)		RT(0C)	
	XK	XKP	XK	XKP	XK	XKP
0[a]	194.7 ± 11.4	214.8 ± 10.6*	37.7 ± 5.2	26.7 ± 3.2*	38.4 ± 0.4	38.4 ± 0.1
10	185.3 ± 7.1	215.7 ± 9.1*	31.0 ± 2.9	18.7 ± 1.6*	38.7 ± 0.3	38.3 ± 0.2
20	184.0 ± 10.2	212.3 ± 8.5*	31.7 ± 3.2	19.7 ± 2.1*	38.5 ± 0.4	38.4 ± 0.2
30	174.8 ± 9.3	209.7 ± 8.8*	38.3 ± 4.9	20.5 ± 1.8*	38.4 ± 0.4	38.4 ± 0.2
40	174.8 ± 10.3	205.7 ± 7.2*	54.0 ± 6.9	28.7 ± 4.3*	38.2 ± 0.4	38.3 ± 0.2
50	188.7 ± 12.0	201.7 ± 5.2*	68.7 ± 7.2	33.3 ± 5.3*	38.3 ± 0.3	38.1 ± 0.2
60	191.7 ± 12.3	199.3 ± 6.8	94.5 ± 8.3	38.5 ± 6.3*	38.3 ± 0.3	38.2 ± 0.2

Data were expressed as means ± SD of 6 rabbits.

*$P \leq 0.05$.

Discussion

The results of this study showed that the concurrent administration of pentazocine with xylazine-ketamine anaesthesia was associated with shorter time to induction and longer duration of recumbency than the control values in healthy rabbits that were not subjected to any clinical procedure.

The shorter time to loss of righting reflex in the rabbits when given XKP than when given XK rabbits is interesting. This finding implies a more rapid uptake or distribution, or both of the drugs through the intramuscular sites of injection. The mechanism by which this was achieved is not quite clear. However, the noticed faster onset of action attributable to the addition of the opioid pentazocine to xylazine-ketamine combination in this study is similar to what was observed when tramadol, an opioid with opioid and non-opioid mechanisms of action, was added to midazolam-ketamine combination in rabbits [15]. Increases in mean heart rates associated with XKP (Table 1) would be expected to cause an increase in cardiac output and hence blood flow, unless increases in heart rate are offset by a corresponding decrease in stroke volume. However, this is unlikely to be the case in this study considering that rabbits generally have small, noncompliant heart with fixed stroke volume just like other small mammals [16]. The longer duration of recumbency with XKP suggests that pentazocine has a potentiating effect on xylazine-ketamine anaesthesia in the rabbits. Synergistic association between opioids and sedatives/tranquiliz-

ers have been the rationale for these combinations instead of single use of either a sedative/tanquilizer or an opioid in neuroleptanalgesia [11,14].

Although mean heart rates of the rabbits given XKP which ranged from 199.3 ± 6.8 to 214.8 ± 10.6 beats/ min were higher than corresponding values with XK (Table 1) the values obtained with XKP fell within normal range of 130 to 235 beats min accepted for awake rabbits (Harkness and Wagner, 1989). Thus, the recorded increases in heart rates were considered to be of no clinical significance in this study. The lower mean respiratory rates of the rabbits treated with XKP, 18.7 ± 1.6 to 38.5 ± 6.3 breaths/min than with XK (Table 1) also fell within the normal range of 30 to 60 breaths/minute for awake resting rabbits [16]. This lower respiratory rate is not surprising because the use of typical opioids is associated with some level of respiratory depression [13]. Mean rectal temperatures of the anaesthetized rabbits with both XKP and XK (Table 1) fell within the normal range of 38.0 to 40.0°C for awake resting rabbits [16].

Conclusion

There was an interaction between xylazine-ketamine and pentazocine which led to a faster onset of anaesthetic induction evidenced by a shorter time to loss of the righting reflex and a longer duration of recumbency when compared to XK. The inclusion of pentazocine in xylazine-ketamine for anaesthesia in rabbits produced a longer duration of anaesthesia than that produced by xylazine - ketamine alone and will be useful in rabbits undergoing medical or surgical procedures of long duration.

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