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SHORT COMMUNICATION

Comparison of Two Routes of Administration of Acepromazine-Ketamine Combination in the Rabbit

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INTRODUCTION

Rabbits are widely used as laboratory animals for biomedical research (Flecknell, 1987). They have also gained popularity among urban dwellers as domestic pets (Kilic, 2004). As a result, the same level of attention in the form of cares given to other pets by veterinarians has been extended to them. Such cares include dental care, castration and ovariohysterectomy (Meredith and Crossby, 2001).

Rabbits are considered as difficult patients in relation to anaesthesia. This probably relates to the fact that the dosages needed to induce anaesthesia and those producing toxic effects are close, and to the variety of observed secondary effects related to stress including their small size, poor venous access and poor health status (Esther van Pregg, 2003, Lan self, 2007, Flecknell, 2009).Secondary effects related to stress in rabbits could be life threatening and include:

- increased risk of cardiac arrhythmia due to release of cathecholamines;
- gastric ulceration;
-immunosuppression;
_ hepatic lipidosis, liver failure and death due to stress induced anorexia and disruption of carbohydrate metabolism (Harcourt-Brown F,2005).

Ketamine is the current anaesthetic agent used in the rabbit because of its wide safety margin, cardiovascular stimulation and somatic analgesia (Flecknell, 1987). However, ketamine alone produces increased muscle tone, spontaneous movement and violent recovery (Wright, 1982; Green et al, 1987). Intramuscular administration of acepromazine/ketamine combination produces good surgical anaesthesia in rabbits (Muir, 1985;Flecknell et al, 2007). Nonetheless, the intramuscular route of drug administration is associated with more stress of physical restraint than the subcutaneous route (Flecknell, 1991). In addition, most of the anaesthetic agents in the increased dosages needed in rabbits, have irritating effect on the tissue which makes intramuscular injection painful (Flecknell et al,2007) and pain can also elicit stress in rabbits (Harcourt-B.rown,2005). In the stress prone rabbit, the subcutaneous route would seem more preferable because it is less painful and involves less stress of physical restraint. To our knowledge, the subcutaneous route of administration of the acepromazine/ketamine combination has not been evaluated.

The aim of this study was to evaluate and compare the influence of either intramuscular (IM) or subcutaneous (SC) route of administration of acepromazine/ketamine anaesthesia on selected anaesthetic indices, heart rate (HR), respiratory rate (RR) and rectal temperature (RT) in rabbits.

MATERIALS and METHODS

Animals

Six adult local rabbits of mixed sexes (3 bucks and 3 does) with a mean body weight of 1.4±0.2kg (mean± SD) were used for the study. They were obtained from the Experimental Animal Unit of the Faculty of Veterinary Medicine, University of Ibadan. They were fed ad-libitum with commercial grower's mash (Guinea feeds, Benin, Nigeria) containing 18% crude protein. Water was also given ad-libitum. The rabbits were allowed to acclimatize for three weeks before the commencement of the trials. During this period, health checks were carried out to ascertain their health status and the rabbits were judged to be in good health.

Drugs

a. Acepromazine maleate (Berkuce®, Berk Pharmaceuticals Ltd, Eastburne, England) supplied as a 2% aqueous solution for injection in 20-ml multi-dose vial.

b. Ketamine hydrochloride (Ketalar®, Rotexmedica laboratory, Trittay, Germany) supplied as a 5% aqueous solution for injection in 10-ml multidose vial.

Study Design

Two sets of randomized trials were carried out on each rabbit at one-week interval. The first set of trials consisted of premedication with acepromazine followed 30min later by ketamine injection using the SC route for both drugs. In the second set of trials which took place a week later, each rabbit was premedicated with acepromazine followed by induction with ketamine 30 minutes later. The two drugs were administered intramuscularly. In each trial, the physiological parameters were taken immediately following the loss of the righting reflex and then subsequently at 10min intervals over a period of 90 minutes. Selected anaesthetic indices were also calculated for each trial.

Experimental Procedure

In the first set of trial, each rabbit was premedicated with acepromazine at a dose of 5mg/kg subcutaneously followed 30min later by induction with ketamine at a dosage of 75mg/kg subcutaneously. Following loss of the righting reflex, each of the anaesthetized rabbits was placed in right lateral recumbent position on a wooden table and covered with a hand towel against draught for the duration of the trial. The second set of trial was carried out a week later. Each rabbit was premedicated with acepromazine at a dose of 5mg/kg using the intramuscular route for drug administration.30 minutes later; anaesthesia was induced with ketamine at a dose rate of 75mg/kg administered also through the intramuscular route.

Calculated anaesthetic indices

The anaesthetic indices evaluated were as follows:

a) Time to induction: time interval (in min) between the injection of ketamine and the loss of righting reflex of the rabbit.

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

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

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Physiological variables

Following the loss of the righting reflex by the rabbits, HR, RR, and RT were taken and thereafter, at 10min interval over a 90min period of anaesthesia. HR (in beats/min) was determined with a precordial stethoscope placed between the 3rd and 5th intercostal spaces. The RR in breaths/min was determined by observation of the rabbits' chest excursions. RT (in degrees Celsius (°C) was determined using mercury-in-glass clinical thermometer.

Data analysis

The data collected were expressed as means ± standard deviation. Mean anaesthetic indices of both acepromazine/ketamine were compared using student t-test for paired data. HR, RR and RT were compared using the analysis of variance (ANOVA) for repeated measures followed by the least significant difference (LSD) as post test.

RESULTS and DISCUSSION

Time to induction with the SC route (3.2±0.3min) was longer than with the IM route (2.0±0.2 min). Duration of recumbency with SC route (89.5±24.0 min) was shorter than 102.5±34.8min with the IM route. The time to standing with SC route (42.0±2.01min) was also shorter than with IM route (53.7±35.4min). The finding of a slower time to induction with the subcutaneous route of drug administration is intersting. In theory, the uptake of a drug from its site of administration depends on the rate of its absorption into the circulation which, in turn, is dependent on blood supply to the area. Since the subcutis is less vascularized than the muscle, the consequent slower rate of drug absorption from the former site would be expected to result in longer time to induction (3.2±0.3min) than with the intramuscular route (2.0± 0.2min). However, the recorded time difference between the two routes of drug administration appears insignificant for practical purposes. These close times to induction with both routes of drug administration may be explained in part by the vasodilatory effect of acepromazine that might have increased blood flow to the subcutis thereby enhanced drug absorption from this site as well. The longer duration of recumbency with the intramuscular route (102.5±14.2min) than with the subcutaneous route (89.5±9.8min) is not surprising. The faster rate of drug absorption from the intramuscular site would be expected to result in a higher plasma level of the drugs and hence a deeper plane of narcosis and more delayed recovery than from the subcutaneous site.

Mean HR, RR and RT responses of the rabbits to the IM and SC routes of administration of acepromazine/ketamine are shown in Tables I, II and III respectively. Although the intramuscular route of drug administration appears to produce lower mean heart rates in the rabbits than the subcutaneous route, all the heart rates still fell within the normal range of 130 to 325 beats/min for rabbits TABLE I Heart rate responses of the rabbits to the IM and SC routes of administration of acepromazine/ketamine (Harkness and Wagner, 1989). These normal mean heart rate values imply that the apparent increase in the mean respiratory rate may be of no clinical significance. The reason for higher mean respiratory rates than the acceptable normal range of 30-60 breaths/min accepted for awake rabbits (Harkness and Wagner, 1989) observed after the 50th minute interval in the experimental rabbits is not quite clear. Although it could be due

TABLE I
Heart rate responses of the rabbits to the IM and SC routes of administration of acepromazine/ketamine

Time interval (minutes)	Heart rate (beats/minute) IM	SC
0[a]	...	191.0±28.9
10	189.0±21.0	195.2±29.7
20	184.6±22.3	200.0±24.1*
30	184.3±30.2	181.2±45.8
40	191.8±15.1	208.0±13.6*
50	183.2±27.5	204.0±27.0*
60	186.2±30.7	202.0±24.4*
70	191.0±27.5	191.2±26.7
80	184.3±31.2	207.7±23.6*
90	186.0±29.5	209.0±18.2*

Data are expressed as means ± SD of 6 rabbits.
[a] Data obtained immediately after loss of righting reflex. * P<0.05

TABLE Ⅱ
Respiratory rate responses of the rabbits to the IM and SC routes of administration of acepromazine/ketamine.

Time interval (minutes)	Respiratory rate (breaths/min) IM	SC
0a	65.2±33.2	77.7±51.3
10	48.3±10.9	47.3±8.7
20	50.5±12.2	60.3±23.9
30	51.5±13.1	67.2±26.7*
40	53.7±14.1	69.0±24.8*
50	70.0±37.4	78.3±31.3*
60	77.0±22.8	91.7±33.7*
70	97.3±48.8	111.2±43.7*
80	82.7±35.5	151.3±55.6*
90	118.3±59.5	161.7±66.1*

Data are expressed as means ± SD of 6 rabbits.
[a] Data obtained immediately after loss of righting reflex. * P<0.05

TABLE III
Rectal temperature responses of the rabbits to the IM and SC routes of administration of acepromazine/ketamine.

Time interval (minutes)	Rectal temperature °C IM	SC
0a	38.6±0.3	39.2±0.2
10	38.8±0.2	38.9±0.6
20	38.7±0.3	39.1±0.3
30	38.8±0.4	39.0±0.4
40	38.8±0.5	39.1±0.4
50	38.7±0.6	39.3±0.4
60	38.7±0.7	39.2±0.4
70	38.7±0.8	39.3±0.4
80	38.6±0.8	39.3±0.3
90	38.7±0.9	39.2±0.4

Data are expressed as means ± SD of 6 rabbits.
[a] Data obtained immediately after loss of righting reflex. * P<0.05

to stress, ambient temperature, hypoxaemia or other factors; in this study, it is unlikely to be caused by stress because the animals were under anaesthesia. Increase in ambient temperature can increase the respiratory rate in order to eliminate the excess body heat produced in the animal. However, this is unlikely the reason in this study since the mean rectal temperatures recorded did not show hyperthermia. The increased mean respiratory rate might be due to hypoxaemia but this could not be confirmed because blood gas analysis was not carried out. Nonetheless, tachypnea has been observed frequently in rabbits following removal from their cage or pen and exposure to unfamiliar surroundings (Flecknell, 1987).

The higher mean rectal temperature produced by the subcutaneous route of administration throughout the period of

the trial except at the 10th and 30th minutes time intervals were still within the normal range of 38.5 to 40.0°C for awake resting rabbits (Harkness and Wagner, 1989).

CONCLUSION

It was concluded that the time to induction as well as duration of recumbency were only slightly influenced by the route of administration of acepromazine/ketamine combination in clinically healthy rabbits not undergoing any clinical procedure. Since the observed differences were not of such magnitude to be of clinical concern, the SC route of administration of acepromazine/ketamine will be a better choice in practice than the IM route because it is associated with less stress of physical restraint of rabbits and also less painful.

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