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Short communication

Evaluation of Diazepam-Ketamine-Pentazocine Anaesthesia in Rabbits

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ABSTRACT: Selected anaesthetic indices of the intramuscular administration of diazepam 5mg/kg followed 10 min later by ketamine 60mg/kg, with pentazocine 10mg/kg (D-K-P) or without pentazocine (D-K) as control, were evaluated in five healthy rabbits that were not undergoing any clinical procedure. Heart rate (HR), respiratory rate (RR) and rectal temperature (RT) of the anaesthetized rabbits were also determined over the initial 60-min period.Time to loss of the righting reflex with the D-K-P (1.9 ± 0.6 min) was similar to the control value of 2.0 ± 0.0 min. Whereas D-K lacked analgesic activity, the onset and duration of analgesia with the D-K-P were respectively 3.6 ± 1.4 min and 95.0 ± 10.6 min. Recumbency time with the D-K-P (128.6 ± 9.3 min) was significantly ($P < 0.05$) shorter than the control value of 184 ± 3.3 min. Time to standing with the D-K-P (17.4 ± 1.6 min) was also significantly shorter than the control value of 42.0 ± 1.4 min. Mean HR with the D-K-P ranged between 140.8 ± 16.1 and 166.4 ± 19.9 beats/ min and were below the control range of 188.6 ± 6.4 and 201.0 ± 3.1 beats/min. Range of mean RR with the D-K-P (34.4 ± 3.1 to 68.0 ± 10.7) breaths/ min was below the control range of 71.4 ± 6.9 and 121.2 ± 12.6 breaths/min. Mean RT with the D-K-P ranged between 38.0 ± 0.4 and 39.9 ± 0.5^0C and were similar to the control range of 39.9 ± 0.1^0 C.It was concluded that the intramuscular administration of D-K-P at the dose rates employed in this study provided satisfactory immobility, analgesia and muscle relaxation of long duration, albeit with some clinically insignificant degree of cardiorespiratory depression, in healthy rabbits.

Key Words:diazepam, ketamine, pentazocine, rabbit.

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INTRODUCTION

Apart from being raised both as a source of animal protein and beloved family pets, rabbits are widely used as laboratory animals for biomedical research involving the use of anaesthetics (Flecknell, 1987). However, rabbits are known to be highly susceptible to stress and their small body size gives rise to some practical anaesthetic problems (Meredith and Crossby, 2001). Venous catheterisation can be a challenge in the awake rabbit and the delivery of volatile anaesthetic agents may be too complicated and time-consuming for the scientist who often conducts research alone without any sophisticated devices or skilled assistance (Flecknell, 1998). Thus, the ideal anaesthetic technique for the laboratory rabbit should be easy to administer, humane, efficient and safe to use. Consequently, injectable ketamine-based combinations are currently employed in rabbit anaesthesia as indicated by the number of recent publications on this technique (Henke et al, 2005; Orr et al, 2005).

When used alone, ketamine provides immobility with a marked increase in skeletal muscle tone and little or no deep analgesia during abdominal surgery in rabbits (White and Holmes, 1976). When diazepam (5-10 mg/kg) was administered 30 min prior to the injection of ketamine (60-80 mg/kg) in the rabbit, muscle relaxation was improved, duration of chemical restraint was prolonged but there was still little or no analgesic activity (Sedgwick,1986). Pentazocine, a partial opioid agonist, has been found to be an effective

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analgesic agent in rabbits (Flecknell and Liles, 1990). However, the use of this opioid with diazepam-ketamine combination is yet to be reported in the rabbit.

The aim of this study, therefore, was to evaluate the anaesthetic indices of the intramuscular administration of diazepam-ketamine-pentazocine combination (D-K-P) in rabbits not undergoing any clinical procedure. In addition, heart rate (HR), respiratory rate(RR), and rectal temperature (RT) responses of the anaesthetised rabbits were monitored as indicators of anaesthetic safety.

MATERIALS AND METHODS

Experimental Animals

Five 10-week old rabbits (1 female and 4 males), weighing 1.6 ± 0.0 kg (mean ±SEM) were acquired from a commercial rabbitery and used for the study. The experimental rabbits were housed in an indoor wooden cage with netted walls and bedding of wood shavings. They were fed on growers' mash supplemented with freshly cut leaves of either *Tridax procumbens*, *Ipomeabatatasor Talimumtriangulare* to appetite. Drinkable water was provided in the cage free choice. The rabbits were conditioned for eight weeks to acclimatise to feeding regimen and constant human handling. Just before the commencement of the trials, they were judged to be in good general health based on findings at complete physical examination of the individual rabbits.

Experimental Design

Two series of trials were carried out at random on each rabbit at one-week interval. In the first series of trials, each rabbit was premedicated with diazepam, followed 10 min later by the injection of ketamine and pentazocine. The second series of trials were similarly carried out but without the addition of pentazocine and served as control. A blinded study was employed in which the personnel monitoring the anaesthesia was not aware of the drug combination given.

Experimental Procedure

Feed and water were not withheld from the rabbits before the trials commenced. Premedication consisted of the intramuscular injection of diazepam 5mg/kg, followed 10 min later by the intramuscular injection of ketamine 60mg/kg to induce anaesthesia as recommended by Sedgwick (1986). A further intramuscular injection of pentazocine 10mg/kg was made immediately following loss of the righting reflex by the rabbit. The trial was repeated a week later but without the injection of pentazocine to serve as control.

The anaesthetised rabbit was not endotracheally intubated and allowed to breathe room air without oxygen supplementation. The unconscious rabbit was placed in right lateral recumbency on a padded wooden table and covered with a towel for the duration of the trial. Analgesia was assessed at 2-min intervals in the anaesthetised rabbit using the pedal withdrawal response to pressure on the toe web produced by haemostatic forceps clamped to the first ratchet. Absence of response was interpreted as presence of analgesia.

Calculations

The anaesthetic indices selected for the study were calculated as follows:

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

(b). Onset of analgesia: time interval (in min) between injection of ketamine and loss of the pedal withdrawal reflex by the rabbit.

(c) Duration of analgesia: time interval (in min) between loss and return of the pedal withdrawal reflex by the rabbit.

(d). Recumbency time: time interval (in min) between loss of the righting reflex and the rabbit's assumption of sternal posture.

(e). Time of standing: time interval (in min) between assumption of sternal and standing postures by the rabbit.

Measurements

Following loss of the righting reflex by the rabbits, HR, RR and RT were determined at 10-min intervals over the first 1hour of anaesthesia. Heart rate (in beat/min) was determined with the aid of a precordial stethoscope . Respiratory rate (in breaths/min) was determined by counting the rabbit's chest excursions. Rectal temperature(in degrees centigrade) was measured using a mercury-in-glass clinical thermometer.

Analysis of Data.

All values are expressed as means ± standard error of mean (sem) of 5 rabbits. Mean anaesthetic indices of D-K-P were compared with the control values using students' t test for paired data. Measured HR, RR and

RT with D-K-P were compared with the control using analysis of variance (ANOVA) for repeated measures with the least significant difference (LSD) as post-test where appropriate. A p value of 0.05 was accepted as significant for all comparisons made.

RESULTS AND DISUSSION

Time to loss of the righting reflex with D-K-P (1.9 ±0.6 min) was similar to the control value of 2.0 ± 0.0 min.Recumbency time with D-K-P (128.6 ± 9.3 min) was significantly ($P < 0.05$) shorter than the control value of 184.4 ± 3.3 min. Time to standing with D-K-P (17.4 ± 1.6 min) was also significantly ($P < 0.05$) shorter than the control value of 42.0 ± 1.4 min.

Whereas D-K(control) lacked analgesic activity, the onset and duration of analgesia with D-K-P were respectively 3.6 ± 1.4 min and 95.0 ± 1.6 min.The finding of lack of analgesic activity with D-K confirms the earlier report by Sedgwick (1986). Thus, D-K would appear to provide useful chemical restraint only for non-painful procedures in rabbits. The addition ofpentazocine, a partial opioid agonist, clearly improved the anaesthetic quality of D-K in terms of provision of analgesia, shorter duration of recumbency and shorter time to standing. The long duration of analgesia means that supplemental doses of pentazocine might not be necessary during long duration procedures in rabbits.

Mean HR, RR and RT responses of the intramuscular administration of D-K and D-K-P are shown in Table 1. Whereas mean RT were similar in both groups, the D-K-P grouphad significantly ($p<0.05$) lower mean HR and RR than the D-K-P. The recorded decreases in mean HR and RR are clearly attributable to the action of pentazocine, since diazepam and ketamine are not known to produce cardiovascular and respiratory depression (Hall et al, 2001). Nonetheless, the ranges of 140.8 ± 16.1 to 166.4 ± 19.9 beats/min and (34.4 ± 3.1 to 68.0 ± 10.7 breaths/min) fall within the normal ranges of 130 to 325 beats/min and 30 to 60 breaths/min, respectively, accepted for the awake rabbit (Harkness and Wagner, 1989). In conclusion, the intramuscular administration of D-K-P provided satisfactory immobility, analgesia and muscle relaxation of long duration, albeit with some clinically insignificant degree of cardio respiratory depression in healthy rabbits not undergoing any clinical procedure.

Table 1:
Heart rate, Respiratory rate and Rectal temperature responses of rabbits to the intramuscular administration of diazepam/ ketamine [a] alone and combined with pentazocine[b].

Time (min)	Heart Rate (beats/min)		Respiratory Rate (breaths/min)		Rectal Temperature (^{0}C)	
	D-K	D-K-P	D-K	D-K-P	D-K	D-K-P
0[c]	193.0 ± 5.6	146.4 ± 9.7*	96.6 ± 15.6	68.0 ± 10.7*	39.4 ± 0.1	38.4 ± 0.4
10	205.2 ± 4.3	155.2 ± 18.2*	71.8 ± 9.1	45.0 ± 11.7*	39.2 ± 0.1	38.0 ± 0.4
20	188.6 ± 6.4	166.4 ± 19.9*	71.4 ± 6.9	34.4 ± 3.1*	39.0 ± 0.3	39.9 ± 0.4
30	196.0 ± 2.6	153.4 ± 19.0*	79.8 ± 9.5	38.4 ± 3.8*	39.2 ± 0.2	39.0 ± 0.4
40	206.0 ± 3.1	146.8 ± 16.4*	92.4 ± 8.8	43.2 ± 0.1*	39.8 ± 0.1	38.1 ± 0.5
50	203.2 ± 3.2	140.8 ± 16.1*	91.6 ± 7.1	44.8 ± 4.6*	39.5 ± 0.2	38.1 ± 0.6
60	192.0 ± 3.2	149.6 ± 20.6*	121.2 ± 12.6	50.8 ± 3.0*	39.9 ± 0.1	39.9 ± 0.5

Data are expressed as means ± SEM of 5 rabbits.

a. 5mg/ kg- diazepam/ 60mg/ kg ketamine
b. 10mg/ kg-pentazocine
c. Baseline data obtained immediately after loss of the righting reflex. * $P<0.05$, ANOVA for repeated measures.

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