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Analyzing the Effects of Acepromazine-Xylazine and Acepromazine-Tramadol on Rabbit Sedation

Abstract: Six adult male rabbits, ranging in weight from 1.0 kg to 2.0 kg, were tested for the level of sedation and analgesia produced by intramuscular administration of two different mixtures: one containing 1 mg/kg acepromazine and 5 mg/kg xylazine (ACE/XYL group), and the other containing 1 mg/kg acepromazine and 2 mg/kg Tramadol (ACE/TRA group). Additionally, during the course of two hours, changes in HR, RR, and RT were measured at 10-minute intervals. The onset of sedation with ACE/XYL and ACE/TRA was not significantly different ($p > 0.05$). The duration until recumbency was achieved with ACE/XYL (7.50 ± 0.7min) was significantly shorter (19.67 ± 3.1 min) than with ACE/TRA ($p < 0.05$). More time was spent lying down with ACE/XYL (88.33± 5.7 min) compared to ACE/TRA (70.33 ± 8.1 min) ($p < 0.05$). There was no significant difference ($p>0.05$) in the onset of analgesia between ACE/XYL (30.17+ 3.3 min) and ACE/TRA (27.7 ± 2.6 min). Sedation was deep with ACE/XYL but mild with ACE/XTR. The duration of analgesia with ACE/XYL (81.67 ± 12.1min) was greater than with ACE/TRA (60.00 ± 5.8min), but there was no difference in the time to walk with ACE/XYL (13.67 ± 2.1min) and ACE/TRA (8.17 ± 1.6 min) ($p>0.05$). HR was lower with ACE/XYL compared to ACE/TRA, however RR and RT were comparable.
Both ACE/XYL and ACE/XTR were shown to be effective in sedating and analgesic healthy rabbits. For treatments that need profound sedation, ACE/XYL is the way to go.
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Keywords: xylazine, tramadol, acepromazine, rabbits

INTRODUCTION

Stress from illness or careless treatment may quickly overwhelm a rabbit (1). Death, immunosuppression, anorexia, disturbance of glucose metabolism, stomach ulceration, and catecholamine-induced cardiac arrhythmia are among conditions associated with secondary stress that may be fatal for rabbits (2). So, to make little surgical operations such abscess lancing, castration, positioning for radiographic imaging, wound bandaging, ear cleaning, and premedication prior to anesthesia induction easier to handle, rabbits are sedated (1,3, 4).

Although sedation in rabbits has been achieved with the individual use of benzodiazepines, opioids, phenothiazines, and alpha 2 agonists (1, 5), it seems that a combination of two medicines from different classes confers therapeutic benefit, particularly in rabbits. Among the phenothiazine sedatives used in veterinary medicine, acepromazine is by far the most common (6). Dosage recommendations for rabbits of 1 mg/kg only result in mild drowsiness; unlike phenothiazines, they do not alleviate pain (1, 4). Xylazine has been used in a broad range of animal species, including rabbits, and is the first alpha 2 adrenoceptor

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agonist in veterinary anesthesia. A combination of drowsiness and analgesia is produced by xylazine, whereas acepromazine does not have this feature (4). Nevertheless, when administered alone, the recommended doses of 2-5 mg/kg in rabbits cause ld to severe drowsiness but do not provide significant analgesia (1).

A synthetic analogue of codeine, tramadol is a mild agonist at the mu-receptor (7). Tramadol blocks the absorption of nor-epinephrine and 5-hydroxytryptamine by neurons in addition to its opioid effects (8). Creating analgesia via both opioid and non-opioid routes, its analgesic effectiveness is greatly enhanced by these actions on central pathways (9) (10). In order to ascertain its analgesic and anesthetic sparing effects in rabbits, its pharmacology has been investigated in a number of animal species, and there are a number of published research that address this topic (11,12). In contrast to conventional opioids, it is easily available to vets and is not yet subject to stringent regulation in many nations (13). If you take acepromazine with butorphanol, you will feel moderate to profound drowsiness and pain relief (1, 4).

It was hypothesized that combining xylazine or tramadol with acepromazine would produce deeper levels of sedation along with analgesia. This would make it a good sedative option for procedures involving pain, particularly in the stress-prone rabbit. A synergistic effect on both sedation and analgesia is an advantage of drug combinations for sedation (4). Thus, this research set out to evaluate the relative merits of acepromazine/xylazine and acepromazine/tramadol sedation in healthy rabbits that were not about to undergo any kind of therapeutic treatment, as well as their respective safety profiles.

Materials and Methods

Animals

Six adult male New Zealand x American Chinchilla rabbits with weight ranging from 1.0kg to 2.0kg were used for the study.

The rabbits which were obtained from a commercial rabbitry were housed in an indoor wooden cage with netted walls and housed singly. They were allowed two weeks acclimatization period to get familiar to their new environment, feeding regime and constant human handling. They were fed ad libitum with commercial grower's mash and provided with clean, cool and clear drinkable water at all times. Just before the commencement of the procedures they were judged to be in good health based on findings at complete physical examination, haematology and serum chemistry analysis.

Drugs and supplies

The drugs used for this study were:

(a) Acepromazine maleate 1% conc. (Distributed by Vedco Inc.) supplied as a 10mg/ml aqueous sterile solution for intravenous (IV) and intramuscular (IM) injections in a 50ml multidose vial.

(b) Xylazine hydrochloride 2% conc. (Xylased ® Bioveta, Czech Republic) in 50ml multi dose vial.

(c) Tramadol hydrochloride (Distributed by Gland pharma ltd., India). It was supplied as a 50mg/ml aqueous sterile solution in 2ml ampoules for intravenous and intramuscular injections.

Design of the study

The study design was a simple randomized crossover design whereby each rabbit underwent two sets of experiments at two weeks interval. The two- week rest period was allowed for drug washout before the second set of experiments. During the first set of experiments each rabbit was injected with a combination of acepromazine and xylazine intramuscularly (ACE/XYL treatment). The second set of experiments was similarly carried

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out but by administering a combination of acepromazine and tramadol (ACE/TRA treatment).

Experimental procedure

Animals were not restricted from feed and water for any period of time before the commencement of the procedure.

For the first set of experiments, acepromazine and xylazine were administered intramuscularly at a dose of 1mg/kg and 5mg/kg respectively. The second set of experiments involved intramuscular injections of acepromazine and tramadol administered at a dose of 1mg/kg and 2mg/kg respectively. The resulting drug volume of each drug was mixed together in a syringe and were given as single injections. Immediately after drug injections, physiological parameters- baseline heart rate, respiratory rate and, rectal temperature were taken and subsequently at 10-minute intervals over a two (2) hour period.

Analgesia was assessed in the sedated rabbits using the pedal withdrawal response to pressure on the 'toe web' produced by haemostatic forceps clamped to the first ratchet for a minute. This test was carried out every 10 minutes over a period of two hours. Absence of response was interpreted as presence of analgesia.

Degree of sedation was scored using a simple descriptive sedation score scale as previously described (15) by a different person who did not know which drugs were given.

Selected sedation indices including; onset and duration of sedation, time and duration of recumbency, onset and duration of analgesia were calculated and recorded for each rabbit. Heart rate, respiratory rate and rectal temperature were determined every 10 minutes.

Measurements

The heart rate, respiratory rate and rectal temperature were determined at 10 minutes interval for 120 minutes. Heart rate (in beats/minute) was determined with the aid of a pre- cordial stethoscope, respiratory rate (in breaths/minutes) was determined by counting chest excursions. Rectal temperature (in degrees centigrade, °C) was measured using a digital clinical thermometer.

Sedation scoring system

Scoring system used in the categorization of sedation after premedication.

Sedation score description:

0. No sedation
1. Mild sedation (quiet, but still bright and active)
2. Moderate sedation (quiet, reluctant to move, ataxic but still able to walk)
3. Profound sedation (unable to walk).

Calculations

In the course of the experiments, the selected sedation indices were calculated as follows:

(a) Onset of sedation- Time interval (in minutes) between time of drug administration and onset of drug action.

(b) Time of recumbency- Time interval (in minutes) between drug administration and the assumption of sternal posture by the rabbits.

(c) Duration of recumbency-Time interval (in minutes) between the assumption of sternal posture and assumption of standing posture by the rabbits.

(d) Onset of analgesia - Time interval (in minutes) between time of drug administration and loss of pedal withdrawal response.

(e) Duration of analgesia - Time interval (in minutes) between loss and return of pedal withdrawal response.

(f) Walking time - Time interval (in minutes) between the assumption of standing position by the rabbit and when the animal starts to walk.

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Analysis of data

Data were expressed as means ± Standard deviation (SD) of the six rabbits. Sedation indices were compared using Student's T test for paired data. Means of physiological parameters for both treatment groups were compared using analysis of variance (ANOVA) for repeated measures, with least significant difference (LSD) used as post-test where appropriate. A value of $p < 0.05$ was accepted as significant for all comparisons made.

Results

Sedation score

Table 1:

Sedation scoring description of acepromazine/xylazine and acepromazine/tramadol.

Rabbit number	Sedation score	
	ACE/XYL	ACE/TRA
1.	3	2
2.	3	2
3.	3	2
4.	3	2
5.	3	2
6.	3	2
Mean=	3	2

Mean sedation score for the ACE/XYL combination=3= profound sedation

Mean sedation score for the ACE/TRA combination=2= moderate sedation.

Sedation Indices

3.1.1 Onset of sedation: Onset of sedation with ACE/XYL (5.83 ± 0.9 min) and ACE/TRA (12.67 ±3.0min) were not significantly different ($p > 0.05$).

3.2.2. Time to recumbency: Time to recumbency with ACE/XYL (7.50 ± 0.7min) was significantly ($p<0.05$) shorter compared to ACE/TRA (10.83 ± 3.1min).

3.2.3. Duration of recumbency: Duration of recumbency with ACE/XYL (88.33 ±5.7min) was significantly ($p<0.05$) longer compared to ACE/TRA (70.33 ± 8.1min).

3.2.4. Onset of analgesia: Onset of analgesia with ACE/XYL (30.17 ±3.3min) and ACE/TRA (27.67 ± 2.6min)

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showed no significant difference ($p<0.05$).

3.2.5. Duration of analgesia: Duration of analgesia with ACE/XYL (81.67 ±12.1min) was longer than with ACE/TRA (60.00 ±5.8 min). The time to walk with ACE/XYL (13.67 ±2.1 min) was not significantly longer ($p<0.05$) than with ACE/TRA (8.17 ±1.6min).

Table 2: Selected sedation indices of the intramuscular administration of Acepromazine/ Xylazine and Acepromazine/tramadol in the six (6) Rabbits.

INDEX	TREATMENT GROUP	
	ACE/XYL[a]	ACE/TRA [b]
Onset of sedation	5.83 ± 0.9	12.67± 3.0
Time to recumbency	7.50± 0.7	19.7± 3.1*
Duration of recumbency	88.33± 5.7	70.33± 8.0*
Onset of analgesia	30.17± 13.3	27.67± 2.4
Duration of analgesia	81.67± 12.1	60.00± 5.8
Time to walk	13.67± 2.1	8.17± 1.6

Data are expressed as means + SEM of six rabbits

a. 1mg/kg acepromazine to 5mg/kg xylazine, for the ACE-XYL combination

b. 1mg/kg acepromazine to 2mg/kg tramadol for the ACE-TRA combination

*P < 0.05

Table 3: Mean heart and respiratory rate responses and temperature responses of six 6 rabbits to the intramuscular administration of Acepromazine/Xylazine[a] (ACE/XYL) and Acepromazine/Tramadol[b] (ACE/TRA)

Time interval	RR(breaths/min)		HR(beats/min)		RT(^{O}C)	
(min)	ACE/XYL	ACE/TRA	ACE/XYL	ACE/TRA	ACE/XYL	ACE/TRA
0	213.33± 15.4	195.83± 15	216.33 ± 11.8	216.17± 2.8	37.7±0.11	38.38±0.09
10	180.67± 33.8	207.00± 17.9	225.00± 14.3	210.00± 3.37.47±0.07		38.52±0.17
20	170.33± 32.1	219.33± 4.4	192.33± 11.5	210.50± 2.4	37.47±0.12	38.67±0.15
30	166.67±28.7	229.33±4.2	196.3± 13.2	211.33± 5.3	37.45±0.21	38.93±0.17

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40.	177.33± 28.2	228.17± 3.7	161.67 ± 12.2	207.67 ± 6.8*	37.47±0.19	39.03±0.11
50.	208.67± 5.3	229.83± 6.5	157.33± 14.6	215.00 ±6.1*	37.67±0.24	39.12±0.16
60.	211.00± 8.6	230.67± 5.7	164.33± 16.7	218.67 ±2.6*	37.53±0.20	39.08±0.11
70.	215.83± 15.1	210.33±16.0	165.33± 16.8	207.50± 9.5	37.53±0.20	38.05±0.09
80.	220.00± 11.2	186.67± 19.9	164.67± 17.6	223.33± 10.9	37.77±0.14	38.77±0.16
90.	224.33± 9.0	196.67± 9.3	183.33± 14.6	195.50± 6.0	37.75±0.17	38.67±0.19
100.	231.00±7.0	210.67± 7.2	178.83± 19.0	196.50± 5.7	37.73±0.24	38.68±0.18
110.	231.00± 4.8.	216.83± 5.7	168.83±14.3	203.33± 4.1	37.68±0.17	38.92±0.21
120.	233.67±7.4	210.67± 17.7	199.67± 10.0	209.00± 8.8	37.68±0.20.	38.80±0.17

Data are expressed as means ± SEM of 6 (six) rabbits

a. 1mg/kg acepromazine to 5mg/kg Xylazine, for the ACE-XYL combination

b. 1mg/kg acepromazine to 2mg/kg tramadol for the ACE-TRA combination

* $P<0.05$

Physiological parameters: The mean heart and respiratory rate responses and temperature responses of the six 6 rabbits to the intramuscular administration of ACE/XYL and ACE/TRA are shown on Table 3.

The mean heart rate with ACE/XYL ranged from 157.33± 14.6 (beats/min) to 225.00± 14.3 (beats/min) while that of ACE/TRA ranged from 195.50 ±.6.0 (beats/min) to 223.33 ± 10.9 (beats/min). Rabbits with ACE/XYL had lower mean heart rates than with ACE/TRA. The mean respiratory rates for ACE/XYL ranged from
166.67± 28.7 (breaths/min) to 233.67± 7.4 (breaths/min) and for ACE/TRA ranged from 186.67± 19.9 (breaths/min) to 230.67± 5.7(breaths /min). There was no significant difference ($p > 0.05$) between treatment

groups in terms of mean respiratory rates. The mean rectal temperature for ACE/XYL ranged from 37.45±0.21 to 37.77±0.14°C. The mean rectal temperature for ACE/TRA ranged from 38.1±0.1 to 39.1±0.2 °C. There was no significant ($p<0.05$) difference between both treatment groups.

Discussion

The result of this study shows that the administration of ACE/XYL and ACE/TRA in healthy rabbits produced profound and moderate sedation respectively accompanied by analgesia.

Although from the sedation scoring system (Table 1), ACE/XYL produced a higher degree of sedation compared to ACE/TRA both combinations can be useful in calming stress prone rabbits, to facilitate manipulative procedures. The shorter onset of sedation and

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time to recumbency with ACE/XYL (Table 2) implies that there was a more rapid uptake and distribution of the drug from the injection site compared to ACE/TRA. ACE/XYL will thus be preferred for emergency procedures where time is of essence. The longer duration of analgesia with ACE/XYL (Table 2) also makes it preferable for painful procedures than ACE/TRA. The longer duration of recumbency and time to walk (Table 2) with ACE/XYL compared with ACE/TRA may be due to the long activity of acepromazine (16) and may mean that its effect is potentiated more in combination with xylazine than tramadol. This greater potentiation of acepromazine by xylazine in the ACE/XYL is similar to the longer anaesthetic duration obtained when acepromazine is included in xylazine-ketamine anaesthesia in rabbits (1).

The lower mean heart rates by ACE/XYL (Table 2) are attributable to xylazine, an alpha 2 agonist in the combination. Xylazine causes marked bradycardia due to central stimulation and mediated through the vagus nerve (17). Overall, the mean heart rates of the rabbits with both drug combinations fell within physiological range of 130-325 beats/min in rabbits (5). Nonetheless, the ACE/XYL will need to be used with caution in rabbits with preexisting bradycardia or cardiac disease.

The recorded mean respiratory rate for both drug protocols is higher (Table 2) than the normal range of 40 to 60 breaths/min in rabbits (5). Tachypnoea sometimes could be a response to drug induced hypercapnia or hypoxemiaor both stimulating the respiratory centre. However, tachypnoea has been observed in rabbits when in unfamiliar environments (18). Stress can also induce tachypnoea but since there was no corresponding increase in heart beats stress may not be implicated in this case. Nonetheless, rabbits with these combinations may probably benefit from artificial ventilation if they are subsequently placed under general anaesthesia.

The mean rectal temperature for both ACE XYL and ACE/TRA fell within the normothermic range of 38°C to 40°C (19) in rabbits.

Conclusion

In conclusion, both ACE/XYL and ACE/XTR can achieve safe sedation accompanied by analgesia in healthy rabbits. ACE/XYL will be a better choice in procedures requiring deep level of sedation. However, it should be used with caution in rabbits with preexisting bradycardia or cardiac disease.

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