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Comparative Study of Acepromazine-Xylazine and Acepromazine-Tramadol for Sedation in Rabbits

Oguntoye C.O., Adetunji A, Asudemade R.A.

Department of Veterinary Surgery and Radiology, University of Ibadan, Nigeria

Oguntoye C.O

Department of Veterinary Surgery and Radiology, University of Ibadan, Nigeria

wumcel06@yahoo.com

Abstract: The degree of sedation and analgesia produced by intramuscular administration of the mixture of 1mg/kg acepromazine and 5mg/kg xylazine (ACE/XYL group) as well as 1mg/kg acepromazine, and 2mg/kg Tramadol (ACE/TRA group) were evaluated in six adult male rabbits (New Zealand/ American Chinchilla cross-breed), weighing between 1.0kg to 2.0kg. Changes in heart rate (HR), respiratory rate (RR) and rectal temperature (RT) were also evaluated at 10- minute intervals over a 2-hour period. No significant difference ($p > 0.05$) in onset of sedation with ACE/XYL and ACE/TRA was observed. Time to recumbency with ACE/XYL (7.50 ± 0.7min) was shorter($p < 0.05$) compared to ACE/TRA (19.67 ± 3.1min). Duration of recumbency with ACE/XYL (88.33± 5.7 min) was longer ($p < 0.05$) than ACE/TRA (70.33 ± 8.1min). Onset of analgesia with ACE/XYL (30.17+ 3.3min) and ACE/TRA (27.7 ± 2.6 min) were not different ($p>0.05$). Duration of analgesia with ACE/XYL (81.67 ± 12.1min) was longer than ACE/TRA (60.00 ± 5.8min) buttime to walk with ACE/XYL (13.67 ± 2.1min) and ACE/TRA (8.17 ± 1.6 min) were not different ($p>0.05$). Sedation was profound with ACE/XYL but moderate with ACE/XTR. RR and RT were similar but HR were lower with ACE/XYL than ACE/TRA.

It was concluded that both ACE/XYL and ACE/XTR can achieve safe sedation accompanied by analgesia in healthy rabbits. ACE/XYL will be a better choice forprocedures requiring deep sedation.

Keywords: *acepromazine, rabbits, sedation, tramadol, xylazine*

I. INTRODUCTION

Rabbits are prone to stress induced by disease and inexpert handling (1). Life threatening secondary stress related factors in rabbits include: catecholamines induced cardiac arrhythmia, gastric ulceration; immunosuppression, anorexia and disruption of carbohydrate metabolism and death (2). Sedation in rabbits is therefore necessary to facilitate their handling for minor surgical procedures such as abscess lancing, castration, positioning for radiographic examination, wound bandaging, ear cleaning and premedication prior to anesthetic induction (1,3, 4).

Although the phenothiazines, alpha 2 agonists, benzodiazepines and opioids have been used individually to effect sedation in rabbits (1, 5), the combination of two drugs from different classes appears to confer clinical advantage especially in rabbits. Acepromazine is the most widely used phenothiazine sedative in veterinary medicine (6). In rabbits, the recommended dosage of 1mg/kg produces only moderate sedation without analgesia characteristic of phenothiazines (1, 4). Xylazine is the oldest alpha 2 adrenoceptor agonist in veterinary anaesthesia and has been used in a wide variety of animal species includingrabbits. Whereas acepromazine lacks analgesic property, xylazine produces both sedation and analgesia (4). However, in rabbits, the recommended dosages of 2-5mg/kg produces light to heavy sedation but without appreciable analgesia when used alone (1).

Tramadol is a synthetic codeine analog that is a weak mu - receptor agonist (7). In addition to its opioid activity tramadol also inhibits neuronal uptake of nor-epinephrine and 5-hydroxytryptamine (8). These effects on central pathways contribute significantly to its analgesic efficacy (9) thus producing analgesia by both opioid and non-opioid mechanisms (10). Its pharmacology has been studied in many animal species and several publications are available on various studies to determine its analgesic and anaesthetic sparing effects in rabbits (11,12). Unlike the traditional opioids, it is not yet under strict control in many countries and is readily accessible to veterinarians (13). Addition of butorphanol to acepromazine causes moderate to deep sedation with analgesia (1, 4).

Since drug combinations for sedation offer some advantages over single agents because of associated synergistic effect on both sedation and analgesia (4); we hypothesized that addition of either xylazine or tramadol to acepromazine may produce deeper levels of sedation accompanied by analgesia which may be a good sedative option in the stress prone rabbit especially in procedures associated with pain. The aim of this study therefore was to compare the efficacy and safety of acepromazine/xylazine and acepromazine/tramadol sedation in healthy rabbits not undergoing any clinical procedure.

II. Materials and Methods

2.1 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.

2.2 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.

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

2.4 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.

2.5 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.

2.6 Sedation scoring system

Scoring system used in the categorization of sedation after premedication.

2.6.1 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).

2.7. 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.

2.8 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.

III. Results

3.1 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.

3.2 Sedation Indices

3.2.1 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) 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
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± 5.737.73±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

3.3 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.

IV. 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 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.

V. 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.

References

[1.] Flecknell, *Laboratory Animal Anaesthesia* (3rd edn Elsevier, London, 2009)
[2.] Harcourt-Brown, F. *Textbook of Rabbit Medicine*. (Butterworth Heinemann Oxford 2002) PP 98
[3.] Virginia C.G. and Richardson M.A. Rabbit: *Health, Husbandry and Diseases Blackwell Science Limited*, (Gershington road, Oxford 2000)
[4.] Clarke, K.W. Trim, C.M. Hall, L.W. *Veterinary Anaesthesia* (Saunders Elsevier, London 2014).

[5.] Thomas J. A. and Philip, L. Rodent and Rabbit Anaesthesia in *Anesthesia and Analgesia for Veterinary Technicians (5th Edition* Elsevier, St Louis Missouri 2017) pp340-360.

[6.] Posner, L.P, Sedatives and Tranquilizers. In *Veterinary Pharmacology and Therapeutics. 9th edition*. Edited by Riviere JE, Papich MG. Iowa: Wiley Blackwell (2009)

[7.] Gutstein, H.B., and Akil, H. Opioid analgesics in HarmanJG, Limbird LE, Goodman Gilman A eds. Goodman Gilman's *The pharmacological basis of therapeutics 10th edition* (New York. McGraw Hill 2001) 569-619

[8.] Grond, S. Sablotzki A, Clinical pharmacology of tramadol. *Clin Pharmacokinet*.2004;**43**(13):879–923.

[9.] Desmeules, J.A. Piguet, V. Collart, L. Dayer, P. Contribution of monoaminergic modulation to the analgesic effect of tramadol. *Br. J Clin Pharmacol* 41, 1996,7-12.

[10.] A. N. Edinoff, L.A. Kaplan, S. Khan, M. Petersen, E. Sauce, C. D. Causey, E. M. Cornett,F. Imani, O.M Moghadam, A.M. Kaye, and A.D. Kaye , Full opioid agonists and tramadol: Pharmacological and clinical considerations *Anaesthesia and Pain Medicine, 11(4),* 2021, 1-11.

[11.] C. M. Egger, M. J. Souza, C. B. Greenacre, S. K. Cox, B.W. Rohrbach, Effect of intravenous administration of tramadol hydrochloride on the minimum alveolar concentration of isoflurane in rabbits *American Journal of Veterinary Research, 70 (8),* 2009, 945-949.

[12.] S.A. Abid, AL-Redah and N. F. Hass. Efficacy of tramadol as analgesic and mixed with ketamine, xylazine as anesthetic in rabbits.Kufa. *Journal For Veterinary Medical Sciences* (2011)

[13.] Ajadi, R.A. Olusa, T.A. Smith O.F. Ajibola, E.S. Adeleye, O.E. Adenubi, O.T. Makinde F.A. Tramadol improved the efficacy of ketamine–xylazine anaesthesia in young pigs. *Vet. Anaesth. Analg*. 36, 2009,562–566.

[14.] Longley, L.A. Anaesthesia of Exotic Pets, *Elsevier Saunders*, (London 2008). Pp 47

[15.] Monteiro, E.R., Lobo, R.B., Nunes Jr., J.S., Rangel, J.P.P., Bitti, F.S. Tramadol does not enhance sedation induced by acepromazine in dogs *Can. J. Vet. Res*. 80:323–328 (2016).

[16.] Zuurbier, C.J. Koeman, A. Houten, SM et al. Optimizing anesthetic regimen for surgery in mice through minimization of hemodynamic, metabolic, and inflammatory perturbations.*Exp Biol Med (Maywood)* 2014; 239(6):737–746.

[17.] Hall, L.W. Clarke, K.W. and Trim, C.M. *Veterinary Anaesthesia*. 10th Ed. Saunders, (London, 2001) 392.

[18.] P. A. Flecknell, I. J. Cruz, J. H. Liles & G. Whelan. Induction of anaesthesia with halothane and isoflurane in the rabbit: a comparison of the use of a face-mask or an anaesthetic chamber. *Laboratory Animal Anaesthesia*30(1) 1996, 67-74

[19.] Harkens, J.E. Wagner, J.E. Biology and husbandry- the rabbit. In Williams & Wilkins, (4thedn) *Biology and Medicine of Rabbits and Rodents*. (Baltimore, 1995)