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Sedative and Antinociceptive Effects of Xylazine Combined with Tramadol or Pentazocine in Goats

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The aim of the study was to evaluate the quality of sedation and analgesia produced by xylazine alone and in combination with tramadol or pentazocine in goats. Four male adult West African goats weighing 8.5 ± 0.2 kg (Means \pm Standard Deviation) were sedated with each of three treatments in a randomized cross over design at one week interval between treatments. Treatments were Xylazine (0.1 mg/kg) with normal saline (XYL-SAL); with tramadol (3 mg/kg, XYL-TRA) and with pentazocine (2 mg/kg, XYL-PEN). Sedation scores, Heart Rate (HR), Respiratory Rate (RR) and Rectal Temperature (RT) were obtained before drug administration and subsequently at ten -minute intervals. Onset of sedation were 7.5 ± 0.7 min, 5.8 ± 1.3 min and 6.3 ± 1.7 min with the XYL-SAL, XYL-TRA and XYL-PEN treatments respectively. Duration of sedation was forty minutes with XYL-SAL and XYL-TRA and 50 minutes with XYL-PEN. Peak sedation occurred between thirty and forty minutes with the three treatments. At peak effect, sedation was mild with XYL-SAL, mild to moderate with XYL-TRA and intense with XYL-PEN but without analgesia. Heart and respiratory rates fell significantly from baseline values by 10 minutes post drug administration in the goats with the three treatments while rectal temperature remained unchanged. Side effects observed was drooling by all the goats with XYL-PEN and one goat with XYL-TRA. One goat had paraphimosis with XYL-TRA.

It was concluded that addition of pentazocine to xylazine in goats enhanced sedation although without analgesia and provided better sedation quality than addition of tramadol to xylazine in goats.

Keywords: Goat; Pentazocine; Sedation; Tramadol; Xylazine.

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Introduction

Sedation is an invaluable technique in veterinary medicine to facilitate many clinical procedures [1,2]. In ruminants, it is a commonly used technique in conjunction with local anesthesia for carrying out painful procedures especially for patients intractable to physical restraint [3]. Sedation also reduces stress associated with physical restraint and provides a more relaxed patient with better operating conditions [2-5]. The alpha 2 agonists, phenothiazines and benzodiazepines are all useful sedatives/tranquilizers in these species [6]. Alpha 2 agonists are particularly beneficial because they produce both sedation and analgesia [3]; however, the analgesia is usually short lived [6]. For this reason, butorphanol, an opioid with mixed agonist-antagonist action has been combined with xylazine to achieve better sedation and analgesia [6,7]. Morphine is also a commonly combined opioid with xylazine or other alpha 2 agonists [2, 6]. Indeed, the synergistic effects of opioid-sedative/tranquilizer is well recognized [4,5]. However, both butorphanol and morphine are under legal control in many countries and access to them is limited [8]. There is a need to search for more readily available opioids to utilize the synergistic sedative-analgesic effect and possibility of individual dose reduction obtainable with sedative-opioid combinations [4,5]. Pentazocine is the first synthesized mixed agonist-antagonist opioid analgesic introduced into clinical practice and still widely used in humans in poor resource environments [9] though rarely used in veterinary medicine [10]. Pentazocine has partial agonistic activity on mu and delta-opiate receptors and full agonistic activity on kappa and sigma-opiate receptors [11]. Tramadol is a mu agonist like morphine. Although, a weaker agonist than morphine having one tenth the potency of morphine, it has additional mechanisms by which it produces analgesia. It is a serotonin and norepinephrine inhibitor thereby producing analgesia by both opioid and non-opioid mechanisms [10]. Tramadol is also readily available in many countries [10]. Currently, the most popular sedative in large animal practice is xylazine [3]. The aim of this study, therefore, was to evaluate the sedation qualities of co-administration of tramadol and pentazocine with xylazine in goats as alternative sedative-opioid combinations in this species especially in developing country where access to potent opioids is limited or completely absent.

Materials and methods

Animals: Four clinically healthy adult, intact male West African Dwarf goats with weight 8.5 ± 0.2 kg (Means \pm SD) were the experimental subjects. They were obtained from a goat farm and housed together in a spacious, well-ventilated pen and fed with concentrates, cassava peels and leafy vegetables.

Water was made available ad libitum in the pen. Salt lick was also provided for the goats.

Drugs: The drugs used for this study were:

(a) Xylazine (Xylased®Bioveta, Czech Republic) supplied as 20 mg/ml solution for injection in 50 ml vials.

(b) Tramadol hydrochloride (Tramacet®, Ciron, India) supplied as 100 mg/2 ml solution for injection in 2 ml ampoules.

(c) Pentazocine (Pilata®, Belco pharmacy, India) available for parenteral injection supplied as 30 mg/ml solution for injection in

1 ml ampoules.

(d) Normal saline (0.9% sodium chloride intravenous infusion, 500 ml Unique Pharmaceuticals Ltd, Sango Ota, Nigeria).

Experimental design

The goats were assigned to three treatments in a randomized simple cross over design with a one-week washout period between treatments. Treatments were intramuscular administration of xylazine and saline (XYL-SAL), intramuscular administration of xylazine and pentazocine (XYL-TRA) and intramuscular administration of xylazine and pentazocine (XYL-PEN).

Experimental procedure

Treatment XYL-SAL consisted of xylazine (0.1 mg/kg) mixed with normal saline of equal volume of the resulting xylazine volume mixed together in the same syringe and administered as a single injection. The other treatments were xylazine (0.1mg/kg) with tramadol 3 mg/kg (XYL-TRA) and xylazine (0.1 mg/kg) with pentazocine 2 mg/kg (XYL-PEN). The drugs were mixed in the same syringe with xylazine and administered as single injections. Heart rate (HR), Respiratory Rate (RR) and Rectal Temperature (RT) were measured before drug injections and subsequently at 10 minutes' intervals over a one-hour period. Sedation was scored using a Simple Descriptive Scale (SDS) according to the grading by Kalhoro *et al.*, [13]. Analgesia was assessed using the pedal withdrawal reflex response as previously described [14].

Calculation

In the course of the experiments, some 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) Onset of analgesia - Time interval (in minutes) between time of drug administration and loss of pedal withdrawal response.

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

Scoring of sedation

The degree of sedation was graded following [13].

0 = No sedation (animal alert)

1 = Light degree of sedation (slight effect with animal becoming quieter with its head lowered below shoulder but above knees).

2 = Moderate degree of sedation (animal becoming less alert, partial closure of eyelids with its head lowered beyond knees).

3 = Deep degree of sedation (animal becoming ataxic and recumbent).

Measured physiological variables

Heart rate in beats/minute was measured with the aid of a precordial stethoscope, respiratory rate in breaths/minute was measured by observing chest movement while rectal temperature in degrees centigrade ($^{\circ}$ C) with the aid of a mercury-in-glass clinical thermometer.

Statistical analysis

Statistical analyses were performed by use of a computer software (Prism 5.0; GraphPad Software La Jolla, California, USA). Sedation indices and physiological parameters were expressed as means \pm Standard Deviation (SD) of four goats. The means of the sedative indices of the three treatment groups were compared with one way ANOVA and mean values of the measured physiological variables were compared using ANOVA for repeated measures. Tukey post hoc test was used to compare mean values of physiological variables at similar times between different treatments. For comparisons between treatments and overtime in sedation scores, a Friedman test was performed and *posthoc* analysis was conducted by use of the Dunn's test for multiple comparisons. A value of $p < 0.05$ was accepted as statistically significant for all measurements.

Results

Sedation indices and sedation scores

Onset of sedation were 7.5 ± 0.7 min, 5.8 ± 1.3 min and 6.3 ± 1.7 min with the XYL-SAL, XYL-TRA and XYL-PEN treatments respectively. Goats in all groups withdrew their legs when a pair of haemostatic forceps was used to apply pressure in the inter digital space of the hind limbs to assess analgesia.

Sedation scores of the goats following each treatment are shown in (Figure 1). By the 10th minute, following drug administration, sedation was obvious with the XYL-SAL and XYL-PEN treatments but only at the 20th minute with XYL-TRAM. At the 20th minute, one goat was moderately sedated following XYL-SAL while half of the goats were deeply sedated with XYL-PEN. Half of the goats were only mildly sedated with XYL-TRA at 20minutes. Maximum possible sedation occurred between the 30th and 40th minutes with all goats mildly sedated with XYL-SAL; two mildly and one moderately sedated with XYL-TRA; three goats deeply and one goat moderately sedated with XYL-PEN. All goats had recovered from sedation following the three treatments by the 60th minute.

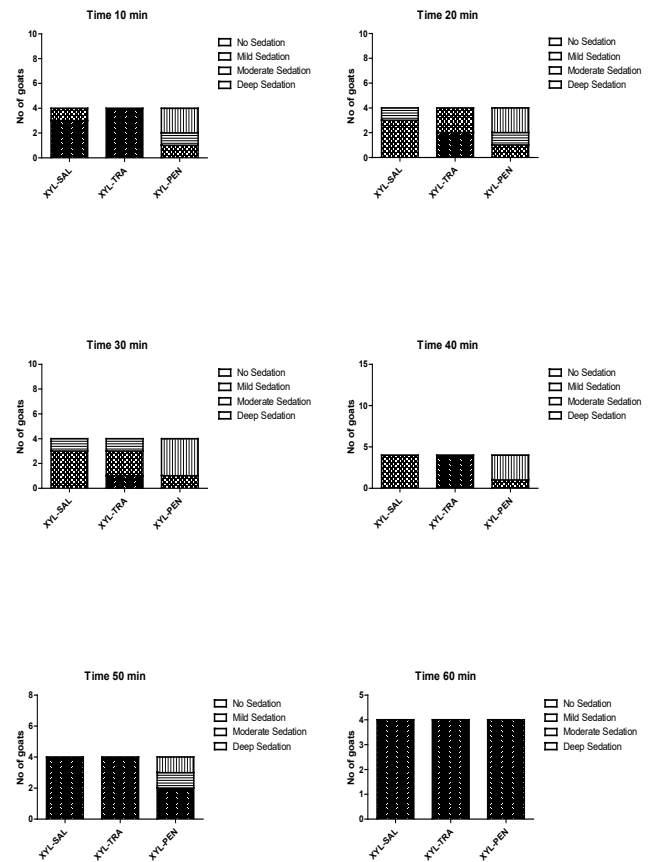


Figure 1: Distribution of sedation scores subjectively assessed by use of the simple descriptive scale (SDS) in 4 goats at 10 min after 0.1mg/kg body weight (BW) xylazine with normal saline (XYL-SAL), 0.1mg/kg xylazine with 3 mg/kg tramadol BW (XYL-TRA) and 0.1 mg/kg xylazine with 3 mg/kg pentazocine (XYL-PEN) and subsequently at 20, 30, 40, 50 and 60 min. All drugs were administered intramuscularly. The SDS ranged from 0 to 3 where 0 -no sedation; 1- mild sedation; 2-moderate sedation; and 3- deep sedation.

Table 1: Mean values of cardiovascular, respiratory, temperature responses of 4 goats to sedation with xylazine and normal saline (XYL-SAL) and combined with tramadol (XYL-TRA) or pentazocine (XYL-PEN).

Variable	Treatment	0	10	20	30	40	50	60
HR	XYL-SAL	157 \pm 40.3	113 \pm 21.1*	113 \pm 13.7	104 \pm 4.9	111 \pm 14.5	113 \pm 6.6	107.0 \pm 3.3
	XYL- XTR	168 \pm 19.99	3.3 \pm 16.1*	96 \pm 5.7	98.7 \pm 11.5	98.7 \pm 13.2	104 \pm 7.1	111.7 \pm 14.7
	XYL- XPE	162 \pm 35.5	110 \pm 12.8*	97 \pm 14.0	100 \pm 15.3	113 \pm 20.6	118 \pm 19.9	125.5 \pm 24.6
RR	XYL-SAL	62.3 \pm 2.6	48.5 \pm 28.5*	49.0 \pm 36.8	36.0 \pm 12.0	42 \pm 15.62	46 \pm 17.6	53.5 \pm 32.9
	XYL- XTR	34 \pm 2.8	22.7 \pm 5.0 *	29.3 \pm 8.2	42.7 \pm 16.8	45.3 \pm 12.4	49.3 \pm 11.1	50.0 \pm 9.1
	XYL- XPE	51 \pm 12.5	36 \pm 19.6*	32.3 \pm 2.0	34.6 \pm 22.3	31.0 \pm 12.1	36.0 \pm 17.7	42 \pm 18.0
RT	XYL-SAL	39.3 \pm 0.6	39.2 \pm 0.6	39.1 \pm 0.67	39.3 \pm 0.8	39.5 \pm 0.8	39.6 \pm 0.8	39.5 \pm 0.8
	XYL- XTR	38.0 \pm 0.3	38.2 \pm 0.3	38.0 \pm 0.4	38.0 \pm 0.6	37.8 \pm 0.1	37.9 \pm 0.3	38.0 \pm 0.3
	XYL- XPE	38.2 \pm 0.7	38.2 \pm 0.7	38.3 \pm 0.8	38.1 \pm 0.8	38.0 \pm 0.9	38.0 \pm 0.9	38.1 \pm 0.8

HR: Heart Rate; RR: Respiratory Rate; RT: Rectal Temperature. * $p < 0.05$

Physiological variables: Heart rate, respiratory rate and rectal temperature of the goats are shown on Table 1.

Heart rate: There was no significant difference ($p>0.05$) among the baseline HR values. There was significant reduction in HR between the base line values and values at ten minutes after drug administration. Heart rates started increasing between the 40th and 50th minutes post drugs administration (Table 1).

Respiratory rate: RR decreased significantly ($p<0.05$) from baseline values after all the treatments but had all increased significantly ($p<0.05$) by the 50th minute (Table 1).

Rectal temperature: The RT appeared unchanged in the goats among the treatment groups at all time points and between the base line values (Table 2).

Side effects: The side effects observed in the goats following administration of the drugs included drooling (all dogs with XYL-XPE and one goat with XYL-XTR; none with XYL-SAL) and paraphimosis in one goat with XYL-TRA.

Discussion

Sedation produced by xylazine alone at the dosage of 0.1 mg/kg was only mild without analgesia while addition of 2 mg/kg pentazocine also administered intramuscularly caused intense sedation but without analgesia. Addition of tramadol at the intramuscular dosage of 3 mg/kg body weight used in combination with xylazine in this study did not produce analgesia nor any appreciable sedation. The dosages of the drugs used were according to literature, xylazine [6], pentazocine [15] and tramadol [16].

The duration of sedation with XYL-SAL, XYL-TRA and XYL-PEN was between 40 and 50 minutes (Table 1). This duration is shorter than the one hour obtained with xylazine in another study that compared sedative and physiological effects of alpha 2 agonists in goats [17]. The reason for this may be because of the higher dosage in that study. The study administered 0.1 mg/kg xylazine intravenously whereas our study administered the same dosage intramuscularly since intravenous dosages are usually lower than intramuscular dosages of the same drug for the same clinical effect [6]. Although, higher intramuscular dosage of 0.2 mg/kg has been quoted in literature, we used a lower dosage because the principle of balanced analgesia/anaesthesia is a reduction of dosages of the drugs in combination than when given singly [4]. The lower heart rates following administration of the sedative and sedative-opioid combinations in this study is expected because alpha 2 agonists are associated with bradycardia [6] by central stimulation and mediated via the vagus nerve. Side effects observed with opioids also include bradycardia and respiratory depression [6], thus the reduction in respiratory rates of the goats was also not surprising. However, none of the goats had heart or respiratory rate lower than the respective minimum physiological values of 70 beats/minute and 10 breaths/minute quoted for goats [18].

The dosage reduction of individual drugs afforded in sedative-opioid combinations usually helps in reduction of side effects of each drug associated with the higher dosages employed when the drugs are used individually [4,5]. Drooling observed in all the goats with XYL-PEN and one goat with XYL-TRA are consistent with side effects observed in goats in similar experiments where medetomidine, another alpha 2 agonist was combined with pethidine,

morphine, tramadol, and methadone in goats [19]. However, paraphimosis observed in one goat with XYL-TRA was not recorded in the medetomidine-opioid study [19]. It was concluded that addition of pentazocine to xylazine in goats enhanced sedation although without analgesia and provided better sedation quality than addition of tramadol to xylazine in goats.

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