ANALGESIC, SEDATIVE AND LOCOMOTION EFFECTS INDUCED BY LUMBOSACRAL EPIDURAL INJECTION OF XYLAZINE IN GOATS

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SUMMARY

Three doses (50μg, 100μg and 150μg/kg body weight) of xylazine were evaluated for flank and perineal analgesia after epidural injection in goats. Seven clinically healthy, Small East African goats of both sexes weighing from 12.5kg to 16kg (Mean±SD; 10.8±4.6kg) were used. The seven goats were randomly assigned to each of the three doses with a one-week interval between subsequent injection. For each dose, one animal was used for sedative and locomotion study while the rest were used for analgesia studies. All doses were injected epidurally through the lumbosacral interspace with the injection taking over 20 seconds. All the three doses induced moderate to adequate analgesia of the flank and perineum within 5 minutes, and persisted for the entire 180 minutes observational period. Sedation and locomotion effects induced by lumbosacral epidural injection of xylazine at the given doses were typical of α_2-adrenergic receptor agonists. It was concluded that lumbosacral epidural injection of xylazine at doses of 50μg, 100μg and 150μg/kg body weight induced sedation and prolonged analgesia of the flank and perineum in goats. The long duration of analgesia may be useful for postoperative analgesia and procedures involving the flank and perineum. However, further work is needed to ascertain the suitability of these doses as sole agents for procedures involving the flank and perineal regions in goats.

INTRODUCTION

Xylazine is one of the α_2-adrenergic receptor agonist, commonly used as sedative, analgesic and as pre-anaesthetic in many animal species (Davis, 1980). However, its disadvantage is that, analgesia induced by parenteral (intramuscular or intravenous) injection of this agent is short lived, and the doses which induce profound analgesia may, depending on the specie induce a dose dependent cardio-respiratory depression which in some cases may be fatal. Ruminants for example had shown to be very much susceptible to xylazine. Parenteral injection of xylazine had been shown to induce an increase in airway resistance (Nolan *et al*, 1986) and cause severe lung oedema and haemorhages when given at clinical sedative doses in sheep (Celly *et al.*, 1999). Of the ruminants again, goats appear to be much more sensitive and give unpredictable responses after

xylazine injections as compared to sheep and cattle (Dhegani *et al.*, 1991 a &b). A dose of 0.05mg/kg body weight of xylazine had been reported to induce profound sedation of up to 12 hours or more in goats (Hall and Clarke, 1991). We had also experienced some deaths after parenteral administration of ≤ to 0.05mg/kg dose of xylazine in goats.

Studies on epidural injections of α_2-adrenergic receptor agonist such as xylazine in horses (Le Blanc *et al.*, 1988; Skarda and Muir, 1996), cattle (Ko *et al.*, 1989; Jean *et al.*, 1990;) and in swine (Ko *et al.*, 1992); clonidine in sheep (Eisenach *et al.*, 1987 & 1988), and metedomidine in cattle (Lin *et al.*, 1998) had shown to induce a longer duration of analgesia (>30 minutes) and less cardio-pulmonary depression effects. Flank and perineal surgeries had been performed in cattle (Zaugg and Nussbaum, 1990), and sheep (Aminkov and Hubenov, 1995; Scott and Gessert, 1997) after epidural injection of xylazine alone.

In one study, Aithal et al. (1996) recommended co-administration of ketamine (2.5mg/kg) and xylazine (50μg/kg body weight) to limit the adverse cardio-respiratory effects in goats. Same combinations, Aithal et al (1997) reported profound analgesia for perineal surgeries in 35 clinical cases in ruminants. In contrast however, Mpanduji et al. (1997) reported minimal cardio-respiratory depression effects in goats after epidural administration of xylazine at 50μg, 100μg and 150μg/kg body weight. These findings necessitated further investigations on analgesia, and behavioural effects attributable to epidural injection of xylazine alone in goats. This study was therefore carried out in order to determine the analgesia, sedation and locomotion effects induced by the three (50μg, 100μg and 150μg/kg body weight) different doses of xylazine after lumbosacral epidural injection in goats.

MATERIALS AND METHODS

Test drug, doses and allocation procedures

Three doses (50μg, 100μg and 150μg/kg body weight) of xylazine (Chanazine^R, Chanelle pharmaceuticals Ireland) were used in this study. The test drug was diluted to the final concentrations of 500μg/ml using water for injection. This concentration was achieved by adding 2.5ml of 20mg/ml xylazine to 97.5ml of water. It is from this solution that pre-calculated doses of xylazine were drawn for epidural administration.

Experimental animals

Seven clinically healthy, adult Small East African goats of both sexes with body weights ranging from 12.5kg to 16kg (Mean±SD; 10.8±4.6kg) were used. Of these, 4 were female and 3 were males. The goats were confined in well-ventilated spacious pen at night and allowed to graze freely for 8 hours daily. Twelve hours prior to experiment, animals were confined and fasted but provided with water. The seven goats were randomly assigned to each of the three doses with a one-week interval between

subsequent injection.

Preparation of the animal for epidural injection

The lumbosacral region was prepared asceptically to avoid introduction of pathogens into the lumbosacral epidural space. The area was cleaned, shaved and disinfected using Savlon^{R} (cetrimide and chlorhexidine), 70% alcohol and iodine in that order. A sterile, 18 gauge, 10 cm spinal needle was inserted into the epidural space through the lumbosacral interspace as described by Gray and McDonell (1986). A pre-calculated dose of xylazine adjusted to total volume of 5ml by addition of water for injection was administered slowly with the injection taking over 20 seconds through the needle previously positioned epidurally. After epidural injection of the test dose, animals were positioned in right lateral recumbency and analgesia was determined and recorded. The animals scheduled for sedation and locomotion study were left undisturbed and observed from a distance.

Sedation, analgesia and locomotion effects

Sedation was defined as decreased mental alertness, lowered head, drooping of the lower lip and ears, and partial to complete closure of eyes, while locomotion was assessed by allowing the animal to move around in a calm environment and any signs of abnormality in the gaits such as swaying movements, ataxia, partial to complete paralysis of hind limbs, and recumbency were observed. The onset of these signs were noted and recorded. Analgesia was determined at time 0, 5, 10, 15, 30, 60, 120 and 180 minutes. The degree of sensory perception to needle pricks in the perineal and flank regions was graded using a scoring system of 0 to 3 as described by Skarda and Muir (1996). The spread of analgesia to the thorax, neck, forelimbs and head was also determined and recorded. A score of 0 (no analgesia) was given if there was an avoidance response on pricking the surface of the skin. A score 1 (mild analgesia) was given if there was no avoidance response to superficial skin pricks by the needle. A score of 2 (moderate analgesia) was given if there was no avoidance to the insertion of half the needle length and a score of 3 (adequate analgesia) was given if there was no avoidance response to inserting the needle through the skin and the underlying tissues (deep muscle pricks). During each test period, superficial skin prick and deep muscular pricks were performed using a 1.5 inches, 21-gauge needle.

Data analysis

The mean analgesia data for the three doses were statistically compared using analysis of variance. The least square mean (LSM) was used for multiple comparison of means. All data were handled as described in SAS/STAT. (1988) and a p value of less than 0.05 was considered significant.

RESULTS

Sedation and locomotion effects

Lumbosacral epidural injection of xylazine resulted in variable levels of sedation and locomotion effects. Signs of sedation appeared 15 minutes after injection of 50μg/kg dose of xylazine and were characterized by low head carriage. Twenty minutes later, the animal showed intermittent sternal to lateral recumbency, tail flaccidity and swaying movements. Later on, the animal preferred sternal recumbency posture with its head held flat on the floor. At this moment the animal was profusely salivating. However, when aroused, the animal was able to stand and walk. Thirty-nine minutes later, movement resumed to normal although the animal preferred sternal recumbency to standing. Tail strength returned 92 minutes post xylazine injection.

Tail flaccidity and ataxia developed within 3 minutes for the goat that was given 100μg/kg xylazine dose. Seventeen minutes later, complete hind limb paralysis ensured and the animal acquired a dog sitting posture. This culminated to sternal recumbency. At this time, the animal showed complete closure of eyes, droopy ears and profuse salivation. At about 23 minutes, the animal was able to stand and walk for few seconds before returning to sternal recumbency. At the end of 180 minutes observational period, the animal was still sedated and salivation was evident to some extent.

Tail flaccidity developed immediately following lumbosacral epidural injection of 150μg/kg xylazine. Intense sedation manifested by droopy ears, complete closure of the eyes and lateral recumbency followed within 5-7 minutes. Deep sedation (sleep like state) and dropping of the lower lip was noted 13 minutes after epidural injection of 150μg/kg xylazine. Sixty minutes thereafter, the animal recovered and managed to stand and walk. Signs of sedation (low head carriage, partial closure of the eyes and salivation) were still evident. These conditions persisted until the end of observational period. Bloat of variable onset and magnitude occurred at least twice in all three-dose regimens.

Analgesia

Epidural injection of xylazine induced moderate to adequate analgesia that extended to the thorax, head and forelimbs within 5 minutes. In all dose regimens, the levels of analgesia tended to decrease with time and did not differ ($P>0.05$) significantly between doses except at t=180 minutes and at t=120 minutes for the flank and perineal region respectively. At these time points, the mean analgesia score for the 50μg/kg and 150μg/kg xylazine treatments were significantly lower ($P<0.05$) compared to that of 150μg/kg and 100μg/kg treatments on the flank and perineum respectively. The means of the various levels of analgesia scores in response to needle pricks at different time intervals are shown in Table 1.

DISCUSSION

In the present study, xylazine at 50μg, 100μg and 150μg/Kg body weight adjusted to total volume of 5ml by addition of sterile water were used. These doses have earlier been evaluated by Mpanduji *et al.* (1999) for their effects on cardiopulmonary and rectal temperatures after lumbosacral epidural injection in goats and were found to have variable cardiopulmonary and rectal temperature depression effects, which were not harmful to the well being of the animals. Higher doses of xylazine (200 to 300μg/Kg body weight) are reported to have severe cardiopulmonary depression effects (Mpanduji *et al.*, 1997). It is from these observations that xylazine at doses of 50μg, 100μg and 150μg/kg body weight were selected further to evaluate their analgesic, sedative and locomotion effects after lumbosacral epidural injection in goats.

All the three doses of 50μg, 100μg and 150μg/kg body weight of xylazine induced generalized analgesia and sedation within 5 minutes. These effects continued for the entire 180 minutes observational period. No differences were noted on the duration of analgesia between the three doses. Sedation and analgesia are believed to be mediated by α_2A-adrenergic receptor subtypes in the *locus coerelus* (Sallinen *et al.*, 1997). The *locus coerelus* has both the ascending projections in the cortical, limbic and to the cerebellum as well as the descending projections to the spinal cord (Moore and Bloom, 1979). Since substantial amount of xylazine do enter the general circulation to the central nervous system (Ko et al., 1989; Jean et al., 1990) and then the α_2-adrenergic receptors are present on the dorsal horn of the spinal cord (Unnerstall *et al.*, 1984, Giron *et al.*, 1985), it is therefore possible for the epidurally administered α_2-adrenergic receptor agonists to have direct inhibitory effects to *locus coerelus*. The descending inputs from the locus coerelus to the dorsal horn of the spinal cord (Sternberg, 1986), are also suspected to be responsible for the α_2-receptor mediated analgesia apart from the local analgesic effects (Aziz and Martin, 1978) and spinal inhibition of a neuro- transmitter, substance p (Pernow, 1983). Deep sedation and generalized analgesia seen after epidural injection of xylazine in the present study may have been caused by combinations of these effects.

The low mean analgesia score for the flank region seen in the 100μg/kg dose regimen was probably due to struggling in the first goat, and pregnancy in the second goat. Struggling may have caused deposition of some of the anaesthetic drug outside the epidural space. Pregnancy and/or presence of large abdominal mass have been reported to cause compression of the vena cava, in such cases blood is diverted to the spinal veins. The absorption of anaesthetic from the epidural space thus increases and hence the amount of drug needed to produce blockade (Cruz, 1992).

Ataxia and hind limb paralysis observed in all treatments have previously been reported after epidural injection of xylazine in horse (Le Blanc *et al.*, 1988), cattle (Ko *et al.*, 1989) and swine (Ko *et al.*, 1992). This effect is thought to be mediated by the strong local analgesic effect of xylazine on the motor neurons of the hind limb (Skarda *et al.*, 1990; Ko *et al*, 1992). Dose dependent sedation and recumbency have also been reported in swine (Ko *et al.*, 1992) after lumbosacral epidural injection and in calves (Raidurg, 1995) after caudal epidural administration of detomidine and xylazine, respectively. In contrast, epidural administration of xylazine is reported to cause only mild degree of sedation, non-significant ataxia and bilateral analgesia of variable cranial extension in horses and cattle (LeBlanc *et al.*, 1988, Fikes *et al.*, 1989, Ko *et al.*, 1989, Zaugg and Nusbaum, 1990).

Bloat of variable onset developed in all treatments regardless of the dose. Rumeno-reticular atony, bloat and occasionally loose faeces are commonly seen in all ruminants after xylazine medication (Davis, 1980). The decrease in rumeno-reticular motility is attributed to the inhibition of acetylcholine release from the auerbachs plexus (Vizi, 1974). Since epidural administration of xylazine depressed the rumeno-reticular motor functions, appropriate precautions for its prevention should be taken. It can therefore be concluded that epidural injection of all three doses (50μg/kg, 100μg/kg and 150μg/kg body weight) of xylazine induces sedation and long duration analgesia adequate for flank and perineal manipulations in goats and for postoperative analgesia. However, further work is needed to ascertain the suitability of these doses as sole agents for flank and perineal surgeries in goats.

ACKNOWLEDGEMENT

The authors are grateful to the Norwegian Agency for Development (NORAD) through Sokoine University of Agriculture (SUA) for financing the study. Further thanks are due to the Department of Veterinary Surgery and Theriogenology, Faculty of Veterinary Medicine, Sokoine University of Agriculture for provision of facilities used in this study.

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Table 1: The mean analgesic scores in response to needle pricks at the flank and perineal regions after lumbosacral epidural injection of xylazine in goats.

REGION	DOSE (μg/kg)	Time after treatments (minutes)						
		0 5	10	15	30	60	120	180
FLANK	50	0 2.67 ± 0.19^{a*}	3.00 ± 0.19^{a*}	3.00 ± 0.19^{a*}	3.00 ± 0.19^{a*}	2.67 ± 0.19^{a*}	2.50 ± 0.19^{a*}	1.67 ± 0.19^{a*}
	100	0 2.67 ± 0.19^{a*}	2.67 ± 0.19^{a*}	2.83 ± 0.19^{a*}	2.67 ± 0.19^{a*}	2.50 ± 0.19^{a*}	2.17 ± 0.19^{a*}	2.00 ± 0.19ab*
	150	0 3.00 ± 0.19^{a*}	3.00 ± 0.19^{a*}	3.00 ± 0.19^{a*}	3.00 ± 0.19^{a*}	2.83 ± 0.19^{a*}	2.67 ± 0.19^{a*}	2.33±0.19^{b}
PERINEUM	50	0 2.67 ± 0.13^{a*}	3.00 ± 0.13^{a*}	3.00 ± 0.13^{a*}	3.00 ± 0.13^{a*}	2.83 ± 0.13^{a*}	2.83 ± 0.13^{ab*}	2.50 ± 0.13^{a*}
	100	0 3.00 ± 0.13^{a*}	3.00 ± 0.13^{a*}	3.00 ± 0.13^{a*}	3.00 ± 0.13^{a*}	3.00 ± 0.13^{a*}	3.00 ± 0.13^{a}	2.67 ± 0.13^{a*}
	150	0 3.00 ± 0.13^{a*}	3.00 ± 0.13^{a*}	3.00 ± 0.13^{a*}	3.00 ± 0.13^{a*}	3.00 ± 0.13^{a*}	2.50 ± 0.13^{b}	2.33 ± 0.13^{a*}

Note: Data are expressed as means±se (n=6) adjusted to two decimal places. Values significantly different (P<0.05) from the base line are indicated (*). Means in the same column, same regions having different superscripts are significantly different (P<0.05)