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COMPARISON OF SEDATIVE AND ANALGESIC EFFECTS OF XYLAZINE, DETOMIDINE, AND MEDETOMIDINE IN SHEEP

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ABSTRACT

The present study was carried out to compare the sedative and analgesic effects after intravenous administration of xylazine (0.2 mg/Kg), detomidine (40 μg/Kg) and medetomidine (6 μg/Kg) in sheep. The onset of sedation occurred within 60 seconds, 116.25 ± 8.85 seconds and 71.25 ± 5.50 seconds which lasted for 67.13 ± 2.83 minutes, 64.63 ± 1.30 and 52.88 ± 1.74 minutes with xylazine, detomidine and medetomidine respectively. The duration of sedation was significantly higher ($P < 0.05$) with xylazine as compared to detomidine and medetomidine. Xylazine produced medium to deep degree of sedation whereas detomidine and medetomidine produced light to medium degree of sedation. Skin analgesia and recumbence were produced with xylazine while no analgesia was achieved after administration of detomidine and medetomidine. Some common side effects like salivation, frequent urination, defaecation, staggering, head drooping, wobbling, snoring and bellowing were observed after administration of xylazine, detomidine or medetomidine. It is concluded that all these alpha$_2$ adrenergic agonists studied are safe to be used in sheep. At doses studied both the detomidine and medetomidine have lesser sedative and analgesic effects in sheep.

Key words: *Sheep, Alpha$_2$-adrenergic, Sedation, analgesia*

INTRODUCTION

Alpha$_2$ agonists (xylazine, detomidine & medetomidine) stimulate alpha$_2$ adrenergic receptors affecting many systems. All alpha$_2$ agonists have similar effects but the newer alpha$_2$ agonists (detomidine and medetomidine) are more potent, longer acting and provide more predictable sedation (Dart, 1999). Xylazine, 2 (2,6 dinethyl phenyl amino) – 4H-5, 6 dihydro-1-3-thiazine hydrochloride, was the first alpha$_2$ adrenergic agonists to be used as sedative and analgesic by veterinarians. Specific action of xylazine is related to CNS depression mediated by stimulation of alpha$_2$ receptors and muscle relaxation caused by inhibition of intraneural transmission within the CNS (Kumar and Sharma, 1986 and Brikas *et al*, 1987). In ruminants, xylazine has proven to be a safe anesthetic adjunct when administered with ketamine or other anesthetic to induce short period of surgical anaesthesia (Grant *et al*, 1996). Xylazine causes hyperglycemia by reduction in insulin release, prolong recovery, and increase urine production by inhibition of antidiuretic hormone release. Depressed thermoregulation with hypo or hyperthermia will occur in sedated patients if not protected from extreme temperature conditions (Paddleford, 1999). Major effects develop in approximately 10 to 15 minutes after intramuscular administration of xylazine and within 3 to 5 minutes following intravenous administration (Grant and Upton, 2004).

Detomidine (dormosedan) is an imidazole derivative 4-(2,3- dimethyphenyl) methyl

-1H–imidazole hydrochloride is a synthetic alpha$_2$ adrenoceptor agonist primarily used as a sedative for horses. Intravenous doses of 10-20 µ/kg gave adequate sedation for about one hour with much more limited side effects in horses (Clarke and Hall, 1991). The drug has also been used widely in horses for premedication prior to induction of anaesthesia with agents such as ketamine, thiopental and propofol (Clarke and Hall, 1991). The intravenous dose of detomidine ranges from 10-20 µ/kg in swine (Thurmon *et al.* 1992). Medetomidine is a mixture of two optical isomers, the dextrorotatory isomer being the active component and is used as sedative, hypnotic, analgesic and premedicant. There are some reports of its use in sheep and cattle (I/V doses 10-20 µ/kg), buffalo and wild animals (Kalhoro, *et al.* 2000). The solution is non-irritant and can be administered I/V, I/M or sub-cutaneous (Clarke and Hall, 1991).

The sedative and analgesic effects of xylazina, detomidine and medetomidine have been examined individually in various ruminant and non-ruminant species (Kalhoro *et al*., 2000; Memon, 1999; Tunio, 1999; and Shahani, 1998) under varying experimental conditions but the comparative study of these alpha$_{-2}$ agonists have not been examined under the same conditions. Therefore, the present study has been designed to compare the sedative and analgesic effects of three alpha$_{-2}$ agonists (xylazine, detomidine and medetomidine) in sheep.

MATERIALS AND METHODS

Animals and Management

Eight healthy female sheep having 19±0.33 months age and 37.88 ± 0.64 kg body weight , were used to study and compare the sedative and analgesic effects of three alpha-2 agonists (xylazine, detomidine and medetomidine) . Animals were acclimated with the surroundings for a minimum period of two weeks prior the experiment. Animals were dewormed and vaccinated against some common infectious diseases such as enterotoxaemia, contagious pleuropneumonia, and anthrax. Animals were fed Jantar grass during adaptation as well as experimental period.

Experimental design and procedure

Each animal received three treatments: xylazine (0.2 mg/kg, AnaSed, Bayer Corporation, USA), detomidine (40 µg/kg, Dormosedan, Orion Corporation, Finland) and medetomidine (6 µg/kg, Zalopine, Orion Corporation, Finland) intravenously in a cross-over design in a way that a minimum interval two weeks was given between two treatments. Animals were off fed for 12 hours before injection. The hairs over the left and right jugular sites were clipped with electric hair clipper and the skin site was disinfected with antiseptic (tincture iodine). Each drug was administered by injection through disposable syringe in right jugular vein.

Parameters recorded:

The onset, degree and duration of sedation and analgesia were recorded for each animal. Onset of recumbency, nature and duration of recovery and standing time was recorded also for each animal. The analgesic effect was noted by no response to deep needle pricking and deep incision with the help of scalpel. Degree and level of sedation was quantified as follows: Score (0) for no sedation and sheep was alert. Score (1) for light sedation and sheep was standing quite, staggering a bit with its head lowered below shoulders but above knees. Score (2) for medium sedation when sheep was drowsy and staggering with its head lowered beyond knees and animal eventually went into sternal recumbence. Score (3) for deep sedation, as sheep dropped its head beyond knees, staggering and eventually went into lateral recumbence.

Other clinical features like salivation, regurgitation, snoring, bellowing, urination, defecation, tympany, head drooping, jugular pulsation, wobbling, staggering, arrythmias, ruminal movements and protrusion of tongue were noted. Palpebral reflex, corneal reflex, nystagmus, swallowing, jaw tone, pedal reflex, movement of limb and movement of tail (if any) were noted after the administration of sedative and analgesic agent for each animal.

Statistical analysis

The data obtained was analyzed using two ways analysis of variance (ANOVA) and Tukey Kramer Multiple Range Test.

RESULTS AND DISCUSSION

The onset of sedation was rapid ($P < 0.05$) with xylazine (60 ± 0.00 sec) and medetomidine (71.25 ± 5.50 sec) as compared to detomidine (116.25 ± 8.85 sec) (Table 1). There was no significant difference in onset of sedation between xylazine and medetomidine. The onset of optimal sedation also was rapid ($P < 0.05$) with xylazine (7.37 ± 0.42 min) compared to deteomidine (19.25 ± 0.49 min) and medetomidine (11.75 ± 0.45 min). Kumar and Thurmon (1979) and Shokry et al. (1976) reported rapid onset of sedation after intramuscular administration of xylazine at the rate of approximately 0.2 mg/kg body weight. The onset of sedation with detomidine is dose dependent. Intravenous administration of detomidine produced rapid onset of sedation (within 60 sec) at higher dose (140 μg/Kg) in sheep (Komar, 1989) whereas the onset of sedation was delayed (335 ± 16.27 sec) at low dose (40 μg/kg) in goats (Tunio, 1999). Shahani (1998) reported onset of sedation in 185, 63.33 and 40.83 sec with 5, 8 and 10 μg/kg of medetomidine in buffalo calves, respectively. Memon (1999) observed onset of sedation in 250 seconds, 120 seconds and 57.50 seconds with 4, 5 and 6 μg/kg of medetomidine in goats, respectively.

The total duration of sedation was higher ($P < 0.05$) with xylazine (67.13 ± 2.83 min) and detomidine (64.63 ± 1.30 min) compared to medetomidine (52.88 ± 1.74 min) (table 1). There was no significant difference in total duration of sedation between xylazine and detomidine. The duration of optimal sedation also was longer ($P < 0.05$) with xylazine (27.25 ± 0.31 min) compared to detomidine (23.00 ± 0.57 min) and medetomidine (17.13 ± 0.51 min), respectively. Coulson *et al.,* (1989) observed sedation and effective anaesthesia for 15 minutes with 0.1 mg/kg of xylazine administered intravenously in sheep. Carter, *et al*., (1990) reported marked sedation with xylazine, 1.1 mg/kg administered intravenously in foals. Tunio (1999) observed total duration of

Table 1. Sedative effects of xylazine, detomidine and medetomidine in sheep.

Items	Xylazine	Detomidine	Medetomidine
Onset of sedation (sec)	60 ± 0.0^{a}	116.25 ± 8.85^{b}	71.25 ± 5.50^{a}
Total duration (min)	67.13 ± 2.83^{a}	64.63 ± 1.30^{a}	52.88 ± 1.74^{b}
Onset of optimal sedation (min)	7.37 ± 0.42^{a}	19.25 ± 0.49^{b}	11.75 ± 0.45^{c}
Duration of optimal sedation (min)	27.25 ± 0.31^{a}	23 ± 0.57^{a}	17.13 ± 0.51^{b}
Degree of sedation	2.63 ± 0.18^{a}	1.37 ± 0.18^{b}	1.25 ± 0.16^{b}

Sheep were intravenously administered with xylazine (0.2 mg/kg), detomidine (40 μg/kg), and medetomidine (6 μg/kg). Animals were off-fed for 12 hours before administration. Values are mean ± standard error (SE, n=8)

$^{a-c}$within column without a common letter differ ($P < 0.05$)

sedation 68.83 minutes after intravenous administration of detomidine (40 μg/kg) in goats. Shahani, (1998) reported total duration of sedation 29.5, 90.83 and 105 minutes with 5, 8 and 10 μg/Kg of medetomidine in buffalo calves, respectively. Memon (1999) observed total duration of sedation 60.58, 83.50 and 104.33 minutes with 4 , 5 and 6 μg/kg of medetomidine in goats, respectively.

The mean values for degree of sedation were 2.63±0.18, 1.37±0.18 and 1.25±0.16 with xylazine, detomidine and medetomidine, respectively (Table 1). The degree of sedation was light to medium with detomidine and medetomidine, whereas xylazine produced medium to deep degree of sedation. The degree of sedation was higher ($P < 0.05$) with xylazine compared to detomidine and medetomidine. Tunio (1999) reported medium to deep degree of sedation with the similar dose of detomidine in goats. Memon (1999) reported deep degree of sedation with the similar dose of medetomidine in goats. Komar (1989) observed a profound sedation after 60 seconds, which lasted for 60-90 minutes with muscular relaxation and salivation when he injected detomidine at the dose rate of 140 μg/Kg in sheep. Muhammad *et al.,* (1993) observed sedation, recumbence, good analgesia and marked muscle relaxation in 6 male Awassi sheep after intramuscular administration of medetomidine at dose rate 40 mg/kg. It seems to have species variation in response to detomedine and medetomidine. Sheep are less sensitive to the detomedine and medetomidine compared to goats.

Xylazine produced analgesia within 6.00±1.76 min which lasted for 10.87±3.19 minutes whereas no analgesia was observed in sheep that received detomidine or medetomidine. Grant and Upton (2004) reported rapid onset of analgesia after intravenous administration of 2.5 mg/kg of xylazine, which lasted for 25 minutes. Coulson et al (1989) observed analgesia and effective anaesthesia for 15 minutes after intravenous administration of 0.1 mg/kg xylazine in sheep. Tunio (1999) reported onset of analgesia within 22.66 minutes after administration of detomidine (40 μg/kg), which lasted for 10 minutes in goats. Memon (1999) reported the onset of analgesia in 12 minutes, which lasted for 31.50 minutes with 6 μg/Kg of medetomidine in goats. There also seems to have species variation in response to detomedine and medetomidine. Sheep are less sensitive to the detomedine and medetomidine compared to goats.

Salivation and frequent urination were seen in all animals after administration of xylazine, detomidine or medetomidine (Table 2). Pedal and palpebral reflexes were present in animals of all groups after administration of xylazine, detomidine and medetomidine, except for the sheep in xylazine group which did not show pedal reflexes. Staggering, wobbling, protrusion of tongue, tail movement, mild tympany, snoring and defecation were only found in sheep after administration of xylazine. Bellowing was observed only with xylazine and medetomidine but no bellowing was seen in sheep of detomidine group. Jaw tone was absent in animals with xylazine while present after administration of detomidine and medetomidine. Previous studies have also reported various side effects with xylazine, detomidine and medetomidine. Ali *et al*., (1989) reported frequent urination and defecation after administration of xylazine in camels. Tunio (1999) reported similar findings, when he used detomidine (40, 50 and 60 μg/kg) in goats. Singh *et al*., (1991) reported salivation after administration of detomidine in goats. Head drooping with detomidine had also been reported in horses (Jochle *et al*., 1989 and Skarda *et al*., 1996) and sheep (Singh *et al*.,

Table 2. Effect of xylazine, detomidine and medetomidine on selected clinical signs in sheep

Clinical signs	Xylazine	Detomidine	Medetomidine
Recumbence	Present	Absent	Absent
Salivation	Present	Present	Present
Frequent urination	Present	Present	Present
Defecation	Present	Absent	Absent
Staggering	Present	Absent	Absent
Wobbling	Present	Present	Absent
Snoring	Present	Absent	Absent
Bellowing	Present	Present	Present
Mild Tympany	Present	Absent	Absent
Pedal Reflex	Absent	Present	Present
Palpebral Reflex	Present	Present	Present
Protrusion of Tongue	Present	Absent	Absent
Jaw Tone	Present	Present	Present
Tail Movement	Present	Absent	Absent

Sheep were intravenously administered with xylazine (0.2 mg/kg), detomidine (40 μg/kg), and medetomidine (6 μg/kg). Animals were off-fed for 12 hours before administration. Values are mean ± standard error (SE, n=8)

1994). Memon (1999) reported similar findings, when he used medetomidine at dose rate of 6 μg/kg in goats.

In the present study, detomidine and medetomidine produced light to medium sedation in sheep which may be useful for physical examination, biopsy, tagging, and application of surface medication and for pre-anaesthetic medication. Xylazine produced medium to deep degree of sedation which may be useful for physical examination, biopsy, tagging, application of surface medication, pre-anaesthetic medication, performing diagnostic procedures, dressing of wounds, and drainage of abscesses, application of plaster casts, passing of urinary catheters, dental problems and removal of stitches.

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