ISSN 1023-1072

Pak. J. Agri., Agril. Engg., Vet. Sci., 2015, 31 (1): 93-101

COMPARISON OF EFFECTS OF XYLAZINE, DETOMIDINE AND MEDETOMIDINE ON HEART RATE, RESPIRATORY RATE AND BLOOD GLUCOSE LEVEL IN SHEEP

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ABSTRACT

The present study compared some physiological effects of three alpha$_2$-adrenergic drugs namely xylazine, detomidine and medetomidine in sheep. Each sheep was given intravenous administration of xylazine (0.2 mg/kg), detomidine (40 μg/kg) and medetomidine (6 μg/kg) in a cross over design. The results of present study showed that pulse rates decreased significantly ($P<0.05$) after administration of xylazine, detomidine and medetomidine in sheep. The respiratory rates significantly increased ($P<0.05$) for first 15 minutes and then significantly decreased ($P<0.05$) at 40 minutes with detomidine whereas xylazine and medetomedine caused significant decrease ($P<0.05$) in-respiratory rate. A trend of decrease in body temperature (although statistically insignificant) was observed after administration of xylazine, detomidine and medetomidine. There was significant increase in blood glucose level (hyperglycemia) after administration of xylazine, detomidine and medetomidine. Blood glucose level was significantly higher ($P< 0.05$) after administration of detomidine as compared to xylazine and medetomidine. It is concluded that all these alpha$_2$ adrenergic agonists studied are safe to be used in sheep.

Keywords: Alpha$_2$-adrenergic, detomidine, medetomidine, sheep, xylazine.

INTRODUCTION

Xylazine, detomidine, medetomidine are three alpha$_2$ agonists commonly used for sedative and analgesic action to facilitate restraining in several animal species. These drugs have been well known to stimulate alpha$_2$ adrenergic receptors affecting different organs. It is documented that all alpha$_2$ agonists have similar effects but the detomidine and medetomidine are more potent, longer acting and more sedative response (Dart, 1999). Xylazine, 2 (2,6 dinethyl phenyl amino)- 4H-5, 6 dihydro-1-3-thiazine hydrochloride, was the first alpha$_2$ adrenergic agonists commonly administered for sedative and analgesic actions. The specific action of xylazine is associated with CNS depression mediated by stimulation of alpha$_2$ receptors and muscle relaxation through the inhibition of

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intraneural transmission (Brikas *et al.,* 1987). Also, xylazine has been reported as anaesthetic adjunct, when administered with ketamine or other anaesthetic to induce short term surgical anaesthesia (Grant *et al.,* 1996). Combination of Xylazine with different anaesthetics has been shown to improve muscle relaxation and visceral anaesthesia and smooth emergence from anaesthesia (Hall and Clarke, 1991). In addition, xylazine causes hyperglycemia by reduction in insulin release, prolong recovery, and increase urine production by inhibition of antidiuretic hormone release. The majority of its actions develop in approximately 10 to 15 minutes after intramuscular administration, 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. It is synthetic alpha$_2$ adrenoceptor agonist primarily used as a sedative in horses. Intravenous doses of 10-20 µg/kg gave adequate sedation for about one hour and produced limited side effects in horses (Hall and Clark, 1991). The drug has also been used widely in equine for premedication prior to induction of anaesthesia with other aneasthetics such as ketamine, thiopental and propofol (Hall and Clarke, 1991). The intravenous dose of detomidine ranges from 10-20 µg/kg in swine (Thurmon *et al.,* 1992).

Medetomidine is a mixture of two optical isomers, the dextrorotatory isomer being the active component and commonly act as sedative, hypnotic, analgesic and premedicant. Previously, the drug has shown positive results when administered in sheep, cattle (I/V doses 10-20 µg/kg), buffalo and wild animals (Kalhoro *et al.,* 2000). It has also been used in combination with other drugs. The solution is non-irritant and can be administered I/V, I/M or sub-cutaneous (Hall and Clarke, 1991).

The combinations of xylazine, detomidine and medetomidine have been reported to produce cardio-respiratory effects in various ruminant and non-ruminant animal species (Jochle, 1990; Celly *et al.,* 1997; Kumar *et al.,* 1997; Kalhoro *et al*., 2000). Therefore, the present study was designed to compare the cardio-pulmonary effects of three alpha$_2$ agonists (i.e. xylazine, detomidine and medetomidine) in sheep.

MATERIALS AND METHODS

Animals and management

Eight healthy female sheep having age 19 ± 0.33 months and body weight 37.88 ± 0.64 kg, were used to study and compare the effects of three alpha$_2$ agonists (xylazine, detomidine and medetomidine) on heart rate, respiratory rate and blood glucose level in sheep. Animals were acclimated with the surroundings for a minimum period of two weeks prior to the experiment. Animals were dewormed and vaccinated against some common infectious diseases such as enterotoxaemia, contagious pleuropneumonia, and anthrax. Animals were fed jantar (sesbania) 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 administration of drugs. The hairs on left and right jugular sites were clipped with automatic hair clipper and the skin region was disinfected with antiseptic (tincture iodine). Aseptically, each drug was administered in right jugular vein.

Parameters recorded

Pulse rate (beats/minute); respiratory rate (breaths/minute), and rectal temperature (F) were recorded before administration of any drug (0), then every 5 minutes up to 30 minutes and then every 15 minutes up to 120 minutes after administration of drug. Pulse rate was determined by auscultation of heart sounds with stethoscope and the respiratory rate was determined by observing thoraco-abdominal movements with each respiration. An aliquot of blood was sampled from left jugular vein before administration of any drug (0) and then at 0.5, 1, 1.5, 2 and 24 hours after administration. Blood glucose level was determined by using Optium Xceed Glucometer using glucose oxidized kits.

Statistical analysis of data

Data (means ± SEM) were analyzed by two way analysis of variance (ANOVA) and Tukey Kramer Multiple Test by using statistical software SPSS12.0 (StatSoft, Tulsa, OK, USA), and the differences were considered significant at $P< 0.05$.

RESULTS AND DISCUSSION

The pulse rates of sheep with xylazine (69.00 ± 1.46), detomidine (69.75 ± 1.53) and medetomedine (68.25 ± 1.87) at 0 min were not different between the groups (Table 1). The pulse rate was decreased at 10 minutes with xylazine and at 5 minutes with both the detomidine and medetomidine as compared to pre-administration value. Maximum decrease in pulse rate occurred at 15, 5 and 20 minutes with xylazine, detomidine and medetomidine, respectively. The pulse rate returned towards the base line by 105 minutes with xylazine and detomidine and 60 minutes with medetomidine (Table 1). Comparison between groups revealed difference ($P< 0.05$) from 5 to 30 minutes between xylazine and detomidine, at 5 minutes between xylazine and medetomidine and from 5 to 20 minutes between detomidine and medetomidine (Table 1). The decrease in pulse rate was greater with xylazine as compared to detomidine and medetomidine. Previously, it has been reported that administration of xylazine in small and large ruminants cause reduction in pulse rate (Dehghani *et al.,* 1991; Celly *et al.,* 1997; Ahmed and Hashim, 2000 and Kijavdekar *et al.,* 2000). Also, similar effects have been reported with administration of detomidine and medetomidine. It has been shown to reduce pulse rate in ruminants (Komar *et al.,* 1989; Mohammad *et al.,* 1989) and non-ruminants (Jochle, 1990; Kramer, 1991).

Table 2 shows the effect of xylazine, detomidine and medetomidine on respiratory rate in sheep. The mean respiratory rate (33.25 ± 0.65) at 0 was not different between xylazine, detomidine and medetomedine. The respiratory rate decreased (P< 0.05) in both the xylazine and medetomedine groups whereas it initially increased (P< 0.05) from 5 to 15 minutes in detomidine and then decreased (P< 0.05) at 45 minutes compared to pre-administration value. The maximum decrease occurred at 30, 60 and 45 minutes with xylazine, detomidine and medetomidine, respectively. The respiratory rate gradually returned towards the base line at 45 minutes with xylazine and at 120 minutes with both detomidine and medetomidine respectively. Comparison between three drugs showed that the respiratory rate was higher (P< 0.05) from 5 to 25 minutes with detomidine than xylazine and lower from 60 to 90 minutes with detomidine than xylazine. There was also significant difference (P< 0.05) from 5 to 25 minutes between detomidine and medetomidine. However, no difference was observed in respiratory rates of sheep xylazine and medetomidine. The findings of this study are in agreement with previous studies. Respiratory rate initially increased and then significantly decreased after administration of detomidine in sheep (Komar, 1989). Administration of xylazine and medetomidine decreased respiratory rate in small ruminants (Dehghani *et al.,* 1991; Mohammad *et al.,* 1993; Kinjavdekar *et al*., 2000).

Table 1. Effect of xylazine, detomidine and medetomidine on pulse rate of sheep.

Time (min)	Xylazine	Detomidine	Medetomidine
0	69.00 ± 1.46	69.75 ± 1.53	68.25 ± 1.87
5	64.75 ± 1.65^{a}	37.75 ± 0.59^{b*}	54.75 ± 2.83^{c*}
10	62.00 ± 1.77^{a*}	39.50 ± 0.98^{b*}	53.50 ± 2.44^{ac*}
15	55.50 ± 0.98^{a*}	42.25 ± 1.33^{b*}	53.25 ± 2.48^{ac*}
20	55.75 ± 1.10^{a*}	43.25 ± 1.60^{b*}	52.75 ± 2.17^{ac*}
25	56.00 ± 1.00^{a*}	45.50 ± 1.88^{b*}	53.75 ± 2.15^{ab*}
30	56.50 ± 1.12^{a*}	47.25 ± 1.96^{b*}	54.75 ± 1.92^{ab*}
45	57.00 ±1.31*	50.25 ± 2.12*	55.25 ± 2.33*
60	58.50 ± 0.98*	52.25 ± 2.12*	57.50 ± 2.47
75	60.25 ± 1.10*	54.00 ± 2.39*	60.00 ± 2.14
90	61.75 ± 1.53*	57.25 ± 2.30*	62.25 ± 2.19
105	63.25 ± 1.25	60.00 ± 2.00	63.75 ± 2.12
120	65.50 ± 1.24	63.25 ± 1.65	65.75 ± 2.02

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).

*difference between 0 and the corresponding time-point within the group (P< 0.05).
$^{a-c}$within column without a common letter differ (P < 0.05).

Table 2. Effect of xylazine, detomidine and medetomidine on respiratory rate of sheep.

Time (min)	Xylazine	Detomidine	Medetomidine
0	33.25 ± 0.65	33.25 ± 0.65	33.25 ± 0.65
5	21.88 ± 1.56^{a*}	59.50 ± 1.50^{b*}	28.25 ±1.62^{ac*}
10	21.00 ± 1.73^{a*}	53.00 ± 2.00^{b*}	26.50 ± 1.64^{ac*}
15	20.50 ± 1.63^{a*}	48.13 ± 2.51^{b*}	24.75 ± 1.56^{ac*}
20	20.25 ± 1.53^{a*}	42.00 ± 3.25^{b*}	24.00 ± 1.31^{ac*}
25	20.75 ± 1.36^{a*}	35.50 ± 2.87^{b*}	23.50 ± 1.40^{ac*}
30	20.00 ± 1.60*	27.75 ± 3.69	23.00 ± 1.00*
45	25.75 ± 0.96	19.75 ± 2.34*	21.50 ± 0.63*
60	27.75 ± 0.59^{a}	17.38 ± 1.92^{b*}	22.75 ± 0.65^{ab*}
75	27.75 ± 1.62^{a}	18.13 ± 1.14^{b}	24.75 ± 0.65^{ac*}
90	27.00 ± 1.41^{a}	19.75 ± 1.20^{b*}	26.25 ± 0.70^{ab*}
105	26.25 ± 2.15	21.50 ± 1.05*	28.00 ± 0.65*
120	29.00 ± 2.20	24.25 ± 0.96	29.75 ± 0.80

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).
*difference between 0 and the corresponding time-point within the group (P< 0.05).
$^{a-c}$within column without a common letter differ (P< 0.05).

Table 3. Effect of xylazine, detomidine and medetomidine on rectal temperature of sheep.

Time (min)	Xylazine	Detomidine	Medetomidine
0	103.32 ± 0.20	103.55 ± 0.18	103.53 ±0.14
15	102.90 ± 0.25	103.28 ± 0.19	103.31 ± 0.13
30	102.41 ± 0.29	102.98 ± 0.21	103.13 ± 0.13
45	102.18 ± 0.26	102.70 ± 0.26	102.98 ± 0.13
60	102.07 ± 0.28	102.46 ± 0.30	102.85 ± 0.12
75	101.92 ± 0.35	102.28 ± 0.22	102.86 ± 0.12
90	102.15 ± 0.30	102.48 ± 0.22	102.95 ± 0.14
105	102.29 ± 0.23	102.62 ± 0.24	103.15 ± 0.14
120	102.45 ± 0.17	102.80 ± 0.26	103.30 ± 0.14

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).

The rectal temperature of sheep at various time-points was not different from the pre-administration values and also not different between the groups (Table 3). Previous studies have shown variable thermoregulatory effects after administration of alpha-2 agonists. Administration of xylazine decreased rectal temperature in sheep (Robertson *et al*., 1990) and increased total temperature in cattle (Fayed *et al*., 1989; Dehghani *et al*., 1991). Administration of medetomidine decreased rectal temperature in goats (Mohammad *et al.,* 1989) and sheep (Kijavdekar *et al.,* 2000). The small variation has been observed in body temperature when detomidine was administered in sheep (Singh *et al*., 1994) and calves (Gracia *et al*., 1991).

Table 4. Effect of xylazine, detomidine and medetomidine on blood glucose level (mg/dl) of sheep.

Time (h)	Xylazine	Detomidine	Medetomidine
0	82.88 ± 0.79	82.00 ± 1.00	82.00 ± 0.98
0.5	93.63 ± 0.80^{a*}	119.37 ± 1.33^{b*}	93.00 ± 0.87^{ab*}
1	104.25 ± 1.91^{a*}	142.25 ± 1.13^{b*}	105.25 ± 1.29^{ab*}
1.5	96.87 ± 1.08^{a*}	132.87 ± 3.44^{b*}	95.75 ± 1.53^{ab*}
2	89.13 ± 1.64^{a*}	102.75 ± 0.99^{b*}	90.37 ± 0.92^{ab*}
24	79.87 ± 0.79	81.50 ± 0.80^{b*}	79.25 ± 1.32^{ab*}

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).
*difference between 0 and the corresponding time-point within the group (P< 0.05).
$^{a-c}$within column without a common letter differ (P < 0.05).

Blood glucose concentration

The mean pre-administration value (82.29 ± 0.81) of blood glucose concentration was not different between the groups. The administration of xylazine, detomidine and medetomedine caused an increase in blood glucose level. The maximum increase occurred at 1 h with all the drugs then gradually returned towards the base line at 24 h. Comparison between three treatments showed that blood glucose level was lower (P< 0.05) from 0.5 to 2 h with xylazine as compared to detomidine, and from 0.5 to 1.5 h with medetomidine as compared to detomidine. No difference was observed for blood glucose level between xylazine and medetomidine. Previous studies have shown hyperglycaemic effects of xylazine (Marais *et al*., 1991; Kijavdekar *et al*., 2000), detomidine (Singh *et al*., 1994; Kumar *et al*., 1997) and medetomidine (Raekallio *et al*., 1994; Kijavdekar *et al*., 2000) in small ruminants.

CONCLUSION

It can be concluded from the present study that the intravenous administration of xylazine, detomidine and medetomidine decreased heart rate and respiratory rate, and increased blood glucose level in sheep.

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(Accepted: November 11, 2014)