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A Comparison of Xylazine, Diazepam, Chlorpromazine and Promethazine in Relation to Certain Clinical and Hematological Parameters of Indigenous Sheep (*Ovis aries*)

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Abstract: The effect of various tranquilizer and sedative agents was studied in sheep. The respiration rates, pulse rates and rectal temperature in sheep reduced significantly ($P< 0.01$) with all the tranquilizing and sedative agents except promethazine hydrochloride. The chlorpromazine hydrochloride produced longest onset and shortest duration of sedation and recovery period, while xylazine hydrochloride produced shortest onset and longest duration of sedation and recovery period. Xylazine hydrochloride and diazepam decreased the rumen motility significantly ($P< 0.01$) whereas chlorpromazine hydrochloride and promethazine hydrochloride decreased insignificantly. Hemoglobin (Hb) and packed cell volume decreased significantly ($P< 0.01$) compared with the pre-sedative control values with all the above tranquilizers and sedatives except promethazine hydrochloride. Xylazine hydrochloride reduced the PCV in a marginally significant ($P< 0.05$) level. Promethazine hydrochloride significantly ($P< 0.01$) increased the Hb but PCV insignificantly. Xylazine hydrochloride and diazepam produced good sedation in sheep but chlorpromazine hydrochloride produced moderate sedation whereas promethazine hydrochloride only tranquilizes the sheep.

Key words: Xylazine hydrochloride, diazepam and chlorpromazine hydrochloride and promethazine hydrochloride, hemoglobin, packed cell volume

Introduction

There are many surgical, obstetrical and other affections which need surgical treatment where various sedatives and tranquilizers play an important role as they act as painkiller of the animals and help in controlling the animals. These drugs are needed in veterinary practice and are indispensable as they help in overcoming resistance of the animal during examination, maintaining depth of anesthesia, reducing the amount of anaesthetic agents and increasing the margin of safety. Sedation of animals before examination, treatment of surgical interference's e.g. amputation of tail, removal of udder, dehorning, examination of rectum, uterus, vagina, abscess opening and operations under local anesthesia are also done. Their value in quieting and calming unfriendly and apprehensive animals has been beneficial in preparations of patient for neuroleptanalgesia and general anesthesia (Gross and Booth, 1995). The comparison of the effect of drugs into degrees of sedation or depression produced by many chemically unrelated and related compounds is extremely difficult. Despite this difficulty, there is some value in attempting to categorize their effects. In this experiment xylazine hydrochloride, diazepam, chlorpromazine hydrochloride and promethazine hydrochloride were used. So, the experiment was carried out to fulfill the following objectives of the mentioned tranquilizers and sedatives:

1 To determine the general effect of clinical useful doses of the sedatives and tranquilizers and to study their suitability in sheep.
2 To evaluate the potentiality of sedatives and tranquilizers in sheep.
3 To study the effect of various sedatives or tranquilizers on clinical and hematological parameters in sheep.

Materials and Methods

Ten apparently healthy indigenous sheep were used in four replications to assess various sedatives and tranquilizers on clinical and hematological parameters. The sheep were purchased from different local markets. They were of both sexes and median age was 1 year and median weight was 11 Kg. The sheep were then examined clinically to detect pathological condition.

Experimental design: The experimental sheep were divided into four (4) different groups and the following tranquilizer and sedative agents were administered.

Group 1: Xylazine hydrochloride (Roumpan, ® Bayer AG. Liverkusen) 10 ml vial, 20 mg/ml. One vial was used at the dose rate of 0.16-0.2 mg/kg, intramuscularly.

Group 2: Diazepam- (Seduxen, ®Richter, Hungary) 0.5% solution, 2 ml ampoule. 5 mg/ml. Sixteen ampoules were used at the dose of 1.43-1.55 mg/kg, intramuscularly.

Group 3: Chlorpromazine hydrochloride (Largactile, ® Rhone poulenc Rorer Bangladesh Ltd.) 2 ml ampoule, 25 mg/ml. Seventeen ampoule were used at the dose rate of 7.6-8.5mg/kg.

Group 4: Promethazine hydrochloride- (Phenergan, ® Rhone poulenc Rorer Bangladesh Ltd.) 2.5% solution w/v, 2 ml ampoule, 25 mg/ml. Fifteen ampoules were used at the dose rate of 5.7-8.3 mg/kg.

Sedation: Each morning experiment was performed in the operation theater of the Department of Surgery and Obstetrics. The animals were starved of both food and water for 12 hours before sedation and then were restrained physically by an assistant and the drug was injected intramuscularly. Immediately after injection, the animals were observed for various behavioral changes i.e. change in attitude, outlook and posture and time parameters like onset time, down time and recovery time. The depth of sedation and analgesia was assessed by monitoring various ocular reflexes, pin prick reflexes, relaxation of neck, jaws, tail and anus, salivation, lacrimation, urination and grunting at 0 hr (before administration of drug) and at 15^{th}, 30^{th} minutes post administration of the drug. Respiration rate, heart rate, rectal temperature and rumen motility were also recorded.

Respiration rate: The respiration was recorded by counting the abdominal movements. Care must be taken not to excite the animal before and during monitoring.

Pulse rate: Pulse rate was recorded by auscultation with a stethoscope placed over the left side of the chest.

Rectal temperature: The rectal temperatures were taken by inserting a clinical thermometer at least 1.5-2.0 cm into the rectum

and keep it in the position for 1 minute.

Rumen motility: Rumen motility rates were measured by hearing the motility sound of rumen with the help of stethoscope.

Collection of blood samples: A total of two blood samples were collected from jugular vein of each experimental animal 15 minutes prior to administration of tranquilizers and sedatives and 15th minute after sedation and tranquilization. Immediately after collection of blood, samples were transferred to a glass vial containing Potassium EDTA (2.5 mg) as anticoagulant. The vial was gently shaken to mix the blood with the anticoagulant. The samples thus collected were subjected to following hematological tests.

Determination of hemoglobin: Sahli hemoglobinometer technique was used for determination of hemoglobin

Determination of packed cell volume (PCV): The Packed cell volume was determined by Wintrobe hematocrit tube and read by percentage (%).

Statistical analysis: The data obtained in the experiment were calculated and mean ± SD for each group was determined. The differences were analyzed using 'F' test and student paired 'T' test.

Results

General signs after administration of tranquilizers and sedatives in indigenous sheep:

Xylazine hydrochloride: Drooping of the upper eyelids, droopy head, salivation and lateral recumbency were observed in all the sheep after onset of sedation with xylazine hydrochloride at the dose rate of 0.18 mg/kg. There was milk fever like recumbency and muscle relaxation was observed. The sheep of this group showed severe drowsiness 5-10th minute after administration of xylazine hydrochloride.

Diazepam: Diazepam at the dose rate of 1.48 mg/kg produced drowsiness, walking in circle, drooping of the upper eyelids and droopy head in all the sheep. Sleepy impression, lateral deviation of the head and relaxation of the muscle were found to have good sedation.

Chlorpromazine hydrochloride: Chlorpromazine hydrochloride at the dose rate of 8 mg/kg produced drooping of the upper eyelids, droopy head and remained standing in most (nine out of ten) of the sheep. Muzzle rested on the floor, lateral deviations of the head and muscle relaxation were also found. Eight sheep out of ten of this group were found to have moderate to good sedation.

Promethazine hydrochloride: The animal became unrest, mild tremor of the hind limbs was observed in most (eight out of ten) of the sheep. In this group there was no sedation in all the sheep after administration of promethazine hydrochloride at the dose rate of 6.88 mg/kg.

Clinical parameters: The effects of xylazine hydrochloride, diazepam, chlorpromazine hydrochloride, promethazine hydrochloride sedation and/or tranquilization on the temperature, respiration rates, pulse rates and rumen motility in sheep are presented in Table 1.

Xylazine hydrochloride: The mean value of respiration rates, pulse rates and rectal temperature, 15min. before xylazine hydrochloride sedation were 27.3 ± 3.37, 85.4 ± 5.66 and 103.02 ± 0.22 °F respectively. These values 15th minute of sedation were 21.9 ± 3.28, 74.7 ± 6.48 and 102.33 ± 0.33 °F. The values during 30th minute of sedation were 19.5 ± 3.34, 70.6 ± 6.72 and 102.12 ± 0.55 °F respectively. The respiration rates, pulse rates and rectal temperature were decreased significantly ($P< 0.01$) at 15th minute and also 30th minute of sedation. The mean value of rumen motility rate 15 minutes before xylazine hydrochloride administration was 1.4 ± 0.16 per minute. This value at 15th minute of xylazine hydrochloride administration was 0.56 ± 0.13. The value during 30th minute of sedation was 0.38 ± 0.15 per minute. The rumen motility rate was significantly ($P< 0.01$) reduced at 15th minute and 30th minute of xylazine hydrochloride sedation.

Diazepam: The mean value of respiration rates, pulse rates and rectal temperature, 15 minutes before diazepam sedation were 26.1 ± 78.09, 100 ± 9.07 and 103 ± 0.41°F respectively. After administration of diazepam, these mean values were 20.6 ± 7.38, 88.9 ± 10.45 and 101.96 ± 0.64 °F during 15th minute and 18.2± 5.31,85.1± 10.38 and 01.64± 0.83°F at 30th minute of sedation, respectively. The respiration rates, pulse rates and rectal temperature were significantly ($P< 0.01$) reduced at 30th minute of sedation. The mean value of rumen motility rate 15 minutes prior to diazepam administration was 1.4± 0.28 per minute. After administration of diazepam, this value was 0.62 ± 0.19 and 0.5 ± 0.17 per minute during 15th minute and 30th minute respectively. The rumen motility rate was significantly ($P< 0.01$) decreased after 15th minute and 30th minute of diazepam sedation.

Chlorpromazine hydrochloride: The mean value of respiration rates, pulse rates and rectal temperature, 15 minutes before chlorpromazine hydrochloride sedation were 29.1 ± 6.66, 95.5 ± 14.59 and 102.79 ± 0.32 °F respectively. These values reduced to 15th minute of sedation 19.5 ± 4.74,77.9 ± 11.60 and 101.72 ± 0.40 °F at 15th minute of sedation and 18.6± 4.70, 74.6 ± 8.00 and 101.44 ± 0.41°F, at 30th minute of sedation respectively. The respiration rates, pulse rates and rectal temperature were significantly ($P< 0.01$) reduced after 15th minute and 30th minute of sedation. The mean value of rumen motility rate 15 minutes before chlorpromazine hydro-chloride administration was 1.2± 0.16 per minute. This value after chlorpromazine hydrochloride administration was 1.1± 0.19 and 1.08± 0.21 per minute at 15th minute and 30th minute of sedation, respectively.

Promethazine hydrochloride: The mean value of respiration rates, pulse rates and rectal temperature, 15 minutes before promethazine hydrochloride sedation were 19.1± 5.88, 85.0 ± 9.30 and 103.24 ± 0.69°F respectively. After administration of promethazine hydrochloride, these values at 15th minute of sedation were 22.1± 10.39,101.0± 8.89 and 103.07± 0.68 °F per minute respectively. During 30th minute of sedation the values were 22.4 ± 9.11,101.8 ± 8.51 and 103.09± 0.7
7°F respectively. The respiration rates and rectal temperature were non-significantly increased but pulse rates increased significantly ($P< 0.01$) at 15th minute and 30th minute of sedation. The mean value of rumen motility rate 15th minute prior to promethazine hydrochloride administration was 1.2 ± 0.21 per minute. This value was 1.12 ± 0.21 and 1.16± 0.20 per minute at 15th and 30th minute of promethazine hydrochloride administration. The rumen motility rate was non-significantly reduced at 15th and 30th minute of sedation.

Hematological parameters:

Xylazine hydrochloride: The mean volume of Hb and PCV 15 minutes before xylazine hydrochloride sedation were 8.8 ± 0.52gm% and 35.4 ± 9.03% respectively. The mean value of hemoglobin and PCV at 15th minute of administration were 8.42± 0.55 gm % and 33.7± 9.89% respectively. The mean value of Hb significantly ($P< 0.01$) reduced and PCV also significantly ($P< 0.05$) decreased (Table 2).

Diazepam: The mean value of hemoglobin (Hb) and packed cell volume (PCV) 15 minutes before sedation were 8.86 ± 0.38gm% and 32.7 ± 9.42% respectively. Fifteen minutes after sedation the mean value of Hb and PCV were 8.54± 0.30gm% and 31.2± 8.31% respectively. The mean values of both Hb and PCV reduced significantly ($P< 0.01$).

Chlorpromazine hydrochloride: The mean value of Hb and PCV 15 minutes before sedation were 8.58 ± 0.50 and 35.6 ± 9.00g %

Table 1: Effects of xylazine hydrochloride, diazepam, chlorpromazine hydrochloride and promethazine hydrochloride on respiration rates, pulse rates, rectal temperature and rumen motility in indigenous Sheep (*Ovis aries*)

Treatment and Parameters		15min. before sedation (mean ± SD)	15 min. after sedation (mean ± SD)	30min. after sedation (mean ± SD)	P values
Xylazine hydrochloride					
	Respiration rates	27.3± 3.37	21.9± 3.28	19.5± 3.34	P< 0.01
	Pulse rates	85.4± 5.66	74.7± 6.48	70.6± 6.72	P< 0.01
	Rectal temperature	103.02± 0.22	102.33± 0.33	102.12± 0.55	P< 0.01
	Rumen motility	1.4± 0.16	0.56± 0.13	0.38± 0.15	P< 0.01
Diazepam					
	Respiration rates	26.1± 7.09	20.6± 7.38	18.2± 5.31	P< 0.05
	Pulse rates	100.0± 9.07	88.9± 10.45	85.1± 10.38	P< 0.01
	Rectal temperature	103.0± 0.41	101.96± 0.64	101.64± 0.83	P< 0.01
	Rumen motility	1.4± 0.28	0.62± 0.19	0.5± 0.17	P< 0.01
Chlorpromazine hydrochloride					
	Respiration rates	29.1± 6.66	19.5± 4.74	18.6± 4.70	P< 0.01
	Pulse rates	95.5± 14.59	77.9± 11.60	74.6± 8	P< 0.01
	Rectal temperature	102.79± 0.32	101.72± 0.4	101.44± 0.41	P< 0.01
	Rumen motility	1.21± 0.16	1.1± 0.19	1.08± 0.21	P> 0.05
Promethazine hydrochloride					
	Respiration rates	19.1± 5.88	22.1± 10.39	22.4± 9.11	P> 0.05
	Pulse rates	85.0± 9.30	101.0± 8.89	101.8± 8.51	P< 0.01
	Rectal temperature	103.24± 0.69	103.07± 0.68	103.09± 0.77	P> 0.05
	Rumen motility	1.2± 0.21	1.12± 0.21	1.16± 0.20	P> 0.05

Table 2: Effects of xylazine hydrochloride, diazepam, chlorpromazine hydrochloride and promethazine hydrochloride on hemoglobin (Hb) and packed cell volume (PCV) in indigenous sheep (*Ovis aries*)

Treatments	Parameters	15min. before sedation (mean± SD)	15 min. after sedation (mean± SD)	P values
Xylazine hydrochloride	Hb (gm%)	8.8± 0.52	8.42± 0.55	P< 0.01
	PCV (%)	35.4± 9.03	33.7± 9.89	P< 0.05
Diazepam	Hb (gm%)	8.86± 0.38	8.54± 0.30	P< 0.01
	PCV (%)	32.7± 9.42	31.2± 8.31	P< 0.01
Chlorpromazine hydrochloride	Hb (gm%)	9.12± 0.41	8.1± 0.39	P< 0.01
	PCV (%)	34.3± 6.04	33.0± 6.28	P< 0.01
Promethazine hydrochloride	Hb (gm%)	8.58± 0.50	9.14± 0.45	P< 0.01
	PCV (%)	35.6± 9.0	36.0± 9.73	P> 0.05

respectively. Fifteen minutes after sedation the mean values of Hb and PCV were 9.14± 0.45gm% and 36± 9.73gm% respectively. The mean value of Hb increased significantly (P< 0.01) but PCV non-significantly.

Discussion

In the experiment xylazine hydrochloride was used at the dose rate of 0.18 mg/kg of body weight intramuscularly as a good sedative in all of the animals which correlate with the findings of Shorky *et al.* (1976) and Raptopoulos (1990). They get sedative effect by the drug at dose rate of 0.20 mg/kg body weight. Drooping of the upper eyelids, droopy head, salivation, milk fever like recumbency, severe drowsiness and muscle relaxation appeared in all of the animals within 5 to 10 minutes after the administration of xylazine hydrochloride, which was correlated with the findings of Hoque *et al.* (1994) and Naylor *et al.* (1997). They reported that xylazine produced adequate sedation, muscle relaxation and narcosis in cattle and sheep. They also observed salivation, mild depressed palpebral and swallowing reflex. Limbs, tail, abdominal musculature and prenuptial sheath were moderately relaxed. The copious secretion of saliva after xylazine administration might be due to its parasympathomimetic like action.

Diazepam was used at the dose rate of 1.48 mg/kg body weight as a good sedative in all of the experimental animals. Drowsiness, round walking, drooping of the upper eyelids and droopy head were observed in all the sheep. Sleepy impression, lateral deviation of the head and relaxation of the muscle were also observed which correspond with the findings of Kumar *et al.* (1999); Pratap *et al.* (1997). They postulated that diazepam produced slight relaxation of jaw, sluggish pedal relax, reduced response to pin prick, decreased response to noise, slight incoordination and muscle relaxation in goats; vacant look, standing motionless with head lowered, stumbling and slight swaying in yaks.

After using chlorpromazine hydrochloride it was found in most sheep that they remained in standing position. Drooping of the upper eyelids, droopy head, muzzle rested on the floor, lateral deviation of the head and muscle relaxation were common at a dose rate of 8 -mg/kg body weight. These signs were correlated to those observed by Kumar and Singh (1977); Pathan (1982). Additionally, they found stopped bleating, chewing and licking habit in case of goats after a dose rate of 3.48 mg/kg.

In this experiment promethazine hydrochloride produced restlessness, mild tremor of the hind limbs and no sedation in sheep. These symptoms were similar to those observed by Jones (1957) and Pathan (1982). They reported that promethazine hydrochloride produced confusion, dizziness, incoordination, hyper excitability, tremor and no sedative effect in goats.

Effects on clinical parameters

Respiratory rate: The respiration rate significantly reduced with all the sedative agents except promethazine hydrochloride in indigenous sheep. These observations correspond with the findings of Lele and Bhokre (1985); Doherty *et al.* (1986); Pandey and Sharma (1986); Shahriari (1988); Dehghani *et al.* (1991); Mohammad *et al.* (1996); Celly *et al.* (1997); Scholtysik *et al.* (1998) and Kumar *et al.* (1999). These reductions in respiration

rate resulted from direct depression effect of sedative or premedicant on the central nervous system (Peshin and Kumar, 1979 and Haskins *et al.,* 1986). Intramuscular administration of promethazine hydrochloride at a dose rate of 6.88 mg/kg caused insignificant increase in the respiratory rate. Although, chlorpromazine is a phenothiazine drug but it did not increase respiratory rate rather it decreased the rate; however, the intensity of action of chlorpromazine may be possible for this effect.

Pulse rates: The tranquilizers and sedatives influenced the activity of the cardiovascular system. The heart rate decreased significantly ($P< 0.01$) with all the tranquilizers and sedatives except promethazine hydrochloride. After administration of xylazine hydrochloride the heart rate decreased significantly ($P< 0.01$) in indigenous sheep during 15th 30th minute of sedation. Similar results have been reported in sheep by other investigators (Dehghani *et al.,* 1991; Mohammad *et al.,* 1996). Xylazine produces bradycardia and hypotension due to central and peripheral suppression of sympathetic nervous system and as a result reduction of pulse rate occurs (Lacuata and Flores, 1972). Heart rate decreased significantly ($P< 0.01$) with diazepam and chlorpromazine hydrochloride in sheep. These results correspond with the findings of Pathan (1982); Pratap *et al.* (1997); Kariman *et al.* (1998) and Chitale *et al.* (1998). The heart rate is reduced by preventing the stimulant effect of epinephrine and norepinephrine upon the heart (Adams, 1995). When using promethazine hydrochloride a significant increase in heart rate was recorded which is in agreement with the findings of Pathan (1982).

Rectal temperature: In this study rectal temperature reduced significantly ($P< 0.01$) with all the sedatives and tranquilizers with the exception of promethazine hydrochloride. The reduction of rectal temperature with xylazine hydrochloride, diazepam, chlorpromazine hydrochloride are agreeable with the earlier reports (Pathan, 1982; Robertson *et al.,* 1990; Amarpal *et al.,* 1995 and Chitale *et al.,* 1998). It might result from depression of thermoregulatory center in the hypothalamus (Kumar *et al.*, 1979; Kumar and Thurmon, 1979). Kumar *et al.* (1990) suggested that reduction of body temperature is due to attribution of inhibitory effects of these agents on metabolism and dissipation.

Rumen motility rate: A significant reduction in rumen motility rate with xylazine hydrochloride, diazepam were observed in this investigation like others (Brikas *et al.*, 1986; Dehghani *et al.,* 1991 and Mohammad *et al.*, 1996). It is postulated that xylazine decreases sympathetic discharge and reduces release of norepinephrine and ultimately reduces the rumen motility (Gross and Booth, 1995). Rumen motility reduced insignificantly after the administration of chlorpromazine hydrochloride in sheep. These findings correspond to the previous report (Souza *et al.,* 1974).

Hematological parameters: In indigenous sheep hemoglobin and packed cell volume reduced significantly ($P< 0.01$ and $P< 0.05$) with all the tranquilizers and sedatives during the maximum depth of sedation excerpt promethazine hydrochloride, where it significantly ($P< 0.01$) increased the Hb but PCV insignificantly. These correlate the findings of Hossain and Shahriari (1989); Dehghani *et al.* (1991); Dilipkumar *et al.* (1997); Chitale *et al.* (1998) and Bhattacharya and Samanta (1998).

Packed cell volume is correlated with the size and number of erythrocyte per unit volume of blood (Schalm *et al.,* 1975). The reduction of hemoglobin and packed cell volume might be attributed to the combined effect of these drugs (Kumar and Singh, 1990). The pooling of erythrocytes and leukocytes in the spleen might in decrease of PCV and Hb (Nara *et al.,* 1978). Similar observations have also been reported by other workers (Peshin and Kumar, 1979; Sanger *et al.,* 1958).

Conclusion: Xylazine hydrochloride, diazepam, chlorpromazine hydrochloride at the dose rate of 0.18 mg/kg, 1.48 mg/kg and 8 mg/kg body weight respectively are suitable for sedation /tranquilization and/or premedication in indigenous sheep, because these sedatives and tranquilizers produce short induction and long duration of action with sufficient muscle relaxation.

Promethazine hydrochloride did not produced sedation but acted as a good tranquilizer.

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