Kafkas Univ Vet Fak Derg
21 (6): 831-836, 2015
DOI: 10.9775/kvfd.2015.13629

Kafkas Universitesi Veteriner Fakultesi Dergisi
Journal Home-Page: http://vetdergi.kafkas.edu.tr
Online Submission: http://vetdergikafkas.org

Research Article

The Effect of Xylazine HCl Used in Repeated Sedations for Sheep on Biochemical and Clinical Values [1]

Abdullah KARASU [1] Musa GENÇCELEP [1]

[1] *This study was financially supported by the Yüzüncü Yıl University Research Fund (Project No: 2012-VF-B020)*

[1] Department of Surgery, Faculty of Veterinary Medicine, University of Yuzuncu Yil, TR-65080 Van - TURKEY

Article Code: KVFD-2015-13629 Received: 22.04.2015 Accepted: 01.07.2015 Published Online: 05.08.2015

Abstract

The objective of the study is to determine the sedative effects of xylazine HCl administered to sheep in repeated fixed doses clinically and biochemically. Five Akkaraman breed rams identified to be clinically healthy were used in the study. Xylazine HCl was administered 4 times at a dose of 0.4 mg/kg intramuscular (fixed dose) with 4 day intervals to induce sedation. Rectal temperature, heart rate and respiratory rate along with rumen motility of all animals were evaluated before and after the administration. The depths of sedation and analgesia, control of reflexes along with various biochemical parameters were studied. The results showed that xylazine HCl led to change of less physiological parameters in the following administration in comparison with the first application. Whereas only moderate and deep sedation were observed in the first application on sheep; mild, moderate and deep sedation were observed in all remaining administration. The degree of analgesic effect was 0 during mild and moderate sedation periods whereas it was 1-2 during deep sedation period. It was concluded that repeated sedations of xylazine HCl administration reduce the degree of sedation in third and fourth administration in sheep.

Keywords: *Sheep, Xylazine HCl, Repeated sedation*

Koyunlarda Tekrarlanan Sedasyonlarda Kullanılan Xylazinin Biyokimyasal ve Klinik Değerlere Etkisi

Özet

Bu çalışmada ksilazinin tekrarlayan dozlarda klinik ve biyokimyasal açıdan sedatif etkilerini araştırmak amaçlanmıştır. Çalışmada klinik olarak sağlıklı olduğu belirlenen 5 adet yetişkin Akkaraman ırkı koç kullanıldı. Sedasyon oluşturmak amacıyla her uygulamada xylazin HCl 0.4 mg/kg dozunda kas içi olarak (sabit doz) 4 gün arayla 4 uygulama yapıldı. Uygulama öncesi ve uygulama sonrası rektal vücut sıcaklığı, nabız ve solunum sayısı, rumen hareketleri, takip edildi. Ayrıca sedasyon ve analjezinin derinliği, reflekslerin kontrolü ile biyokimyasal bazı parametreler araştırıldı. İlk uygulamaya göre tekrarlayan dozlarda ksilazin HCl fizyolojik parametrelerde daha az değişikliğe neden oldu. İlk ugulamada sadece orta ve ileri derecede sedasyon şekillenirken, sonraki uygulamalarda hafif, orta ve ileri derecede sedasyon şekillendi. Hafif ve orta derece sedasyonda analjezinin derecesi 0 iken, derin sedasyonda 1-2 olarak saptandı. Sonuç olarak koyunlarda tekrarlayan sedasyonlarda verilen ksilazin HCl'nin üçüncü ve dördüncü uygulamalarında sedasyonun derecesini azalttığı sonucuna varıldı.

Anahtar sözcükler: *Koyun, Ksilazin HCl, Tekrarlayan sedasyon*

INTRODUCTION

Sedation is required for the examination (endoscopy) of various surgical procedures (castration, cesarean section e.g.) in sheep and therefore α-2 adrenoreceptor agonists are used [1-4]. α-2 adrenoreceptor agonists cause respiratory distress, hypercapnia and hypoxemia. These effects may prolong the duration of sedation [5-9]. In addition they increase the amount of urine and cause hyperglycemia and hypoinsulinemia [7,10].

Xylazine HCl is the most preferred drug among α-2 adrenoreceptor agonists and can be administered intravenously, intramuscularly and subcutaneously [8,11,12]. Xylazine HCl has analgesic effects in addition to its sedative and myorelaxant effects. However, it has been stated that xylazine HCl has a different analgesic effect among sheep species [5,9,13]. The dose of the α-2 agonists and the temperament of the animal affect the degree of sedation [9]. It is also stated that increasing drug dose results in a sedation time increase whereas no change is observed in sedation depth [14].

İletişim (Correspondence)
+90 432 2251128/4561
abdullahkarasu@hotmail.com

Pulse rate, respiratory rate, rumen motility and rectal temperature changes are observed in animals to which xylazine HCl is administered [10,11,15-17]. Various cases have been put forth especially for sheep in which clinical findings of pulmonary edema have been observed and which have ended in death [6,8,9,18].

A literature survey was carried out as a result of which no study was found in which the clinical, biochemical and sedative effects of repeated doses of xylazine HCl on sheep have been examined. The objective of our study is to determine the sedative effects of the repeated sedations of xylazine HCl from a clinical and biochemical perspective.

MATERIALS and METHODS

Animals

Five clinically healthy Akkaraman breed rams at the Yüzüncü Yıl University Research and Application Farm were used in the study. The live weights of the animals varied between 40-55 kg and their ages were between 20-24 months. The animals were subject to the same feeding program throughout the duration of the study. Consent of the Ethics Council of the University of Yüzüncü Yıl (2011/08) was taken prior to the start of the study.

Sedation Applications

The animals were not fed starting from 12 h prior to the study. Xylazine HCl (Rompun 2%, Bayer) was administered to induce sedation at a dose of 0.4 mg/kg intramuscularly (fixed dose) for 4 times with 4 day intervals.

Clinical Evaluation

Rectal temperature, pulse rate, respiration rate, pulmonary sounds and rumen activity were evaluated at times of 0 (before xylazine HCl administration -baseline) 5, 15, 30, 45, 60, 75, 90, 105 and 120 min following xylazine HCl administration. Rectal temperature was measured using a digital thermometer. Pulmonary sounds, rumen activities, pulse rate and respiration rate were measured using a stethescope. In addition, it was monitored whether oro-nasal discharge and urination started after administering xylazine HCl.

Evaluation of Reflexes

Eye movements, palpebral, corneal, pupillary, patellar and triceps brachii reflexes were controlled in all groups at times of 0 (before xylazine HCl administration-baseline) 5, 15, 30, 45, 60, 75, 90, 105 and 120 min following xylazine HCl administration.

Evaluation of Sedation

Sedation scoring was made by modifying the evaluations of Kastner et al.[19], as follows:

No sedation (before sedation-baseline): The movements, activity and standing posture of the animal are normal. The movements of the ears, neck positions and movements of the eyelids are at their physiological values.

Mild sedation: Decrease of the movements and interest of the animal towards its environment, sagging of the ear, bending of the head, uncoordinared movements of the animal while walking but not attaining a laying posture were accepted as symptoms of mild sedation.

Moderate sedation: Lying down of the animal in the sterno-abdominal position following mild sedation findings was accepted as moderate sedation.

Deep sedation: Direct lateral laying down of the animal following moderate or mild sedation conditions along with the head and extremities not moving were accepted as deep sedation.

Ending sedation: The passing of a deeply sedated animal to a sterno-abdominal or standing posture are accepted as the end of this period. Whereas this period was accepted to have ended when a moderately sedated animal attained a standing posture. Mild sedation period was accepted to have ended when the physiological behavior of a mildly sedated animal returned back to normal. Therefore, behavior of the animals was evaluted at 5 min intervals.

Evaluation of the Analgesic Effect

Analgesia was evaluated before drug administration (baseline) and at 5 min interval after drug administration until complete recovery. Onset and duration of analgesia was evaluated by applying painful stimuli with 23-gauge needle inserted through the skin and the underlying tissues in different parts of the body (perineal, left front and hind limbs interdigital and corona regions). All animal procedures were performed in the same points. Analgesic effect were measured by a single investigator throughout the experiment.

Analgesic assessment score was modified according to the evaluation of Khan et al.[11]. The grading made for no analgesic effect (normal strong reaction to painful stimuli) was 0 score, for mild analgesic effect (depressed reaction to painful stimulus) it was 1-2 score, for moderate analgesic effect (no response to needle-prick stimulation of the skin but there are response to needle-prick stimulation of the skin underlying tissue) it was 3-4 score and deep analgesic effect (no response to insertion of the needle deep into skin underlying tissue- no leg movement or contraction) was graded as 5-6 score.

Biochemical Evaluation

Blood samples were taken from jugular vein of all animals in all administrations prior to sedation, during

sedation (on the 45th min after xylazine HCl administration) and after sedation (on the 120th min after xylazine HCl administration). The obtained blood samples were centrifuged at 5.000 rpm to remove the serums which were then frozen at -18°C and were stored until the day of the analyses. The serums were then thawed after which their glucose, total bilirubin, BUN, AST, ALT, ALP, Ca, Na, K and Cl values were measured using an analyzer (Roche - Hitachi, Germany).

Statistical Evaluation

The comparison of the numerical values obtained during the applications was carried out via SPSS (Statistical Package for the Social Sciences Program) for Windows, ver. 21.0 statistical package software using Student-t test. A value of P<0.05 was considered as statistically significant.

RESULTS

Clinical Evalation Results

Oro-nasal discharge and urination started earliest on the 5th min after injection in all administrations and continued until at most the 90th min with various intervals. At most 2 urinations occured in all animals during the time period of 120 min. Penis prolapse was observed in only one animal during all the administrations. No pathological pulmonary sound was determined in any animal during sedation.

Rectal temperature increased in all administrations following xylazine HCl administration and even though it decreased below the control values after a certain period of time (15-60 min) it remained within physiological limits.

Respiratory rate increased in all administrations until the 45th min in comparison with the control values, after which it started to decrease below the pre-sedation values and remained at a low level until the 120th min.

Rumen activity decreased in all groups until the 30th min in comparison with the control values after which it increased until the 120th min however it could not reach the control values.

The changes in rectal temperature, respiration rate and rumen activity were statistically significant for the 1st aplication (P<0.05) and statistically insignificant for the other three applications (P>0.05) *(Table 1)*.

Pulse rate remained at a low level in all applications for 120 min. This decrease was statistically significant for the 2st, 3st and 4st applications (P>0.05) and statistically insignificant for the first application (P<0.05) *(Table 2)*.

Reflex Evaluation Results

Reflexes (eye movements, palpebral, corneal, pupillary, patellar and triceps brachii reflexes) were not lost during the sedation periods.

Table 1. *Average rectal temperature, respiration rate and rumen activity values according to 1st application periods.*

Tablo 1. *1. Uygulamada ortalama rektal ısı, solunum sayısı ve rumen sayısı değerleri*

Time (min)	Rectal Temperature (°C)	Respiration Rate (breaths/min)	Ruminal Contraction (Contractions/5 min)
0	39.68±0.39^{x}	51.80±16.31^{xyz}	5.20±2.59^{x}
5	39.72±0.40^{x}	73.00±28.23^{xy}	1.40±1.67^{yz}
15	39.60±0.35^{x}	70.20±26.25^{xy}	1.00±1.00^{z}
30	39.12±0.38^{xy}	79.80±32.15^{x}	1.00±1.00^{z}
45	38.62±0.26^{y}	54.80±18.75^{xyz}	1.20±1.09^{yx}
60	38.56±0.18^{y}	35.60±20.20^{yz}	2.20±0.84^{xyz}
75	38.52±0.26^{y}	27.00±10.22^{z}	3.20±1.30^{xyz}
90	38.52±0.26^{y}	26.00±7.58^{z}	3.20±0.84^{xyz}
120	38.78±0.41^{y}	2.500±4.00^{z}	4.20±1.79^{xy}
p	*	*	*

^{x,y} *the difference between the averages on the same column is statistically significant (P<0.05)*

Sedation Evaluation Results

The first animal: Mild sedation started on the 5th min after injection in the first application. The animal attained a sterno-abdominal laying posture on the 10th min of mild sedation. The animal attained a standing posture 30 min later and the animal was out of sedation completely after the 35th min.

Mild sedation started on the 10th min after injection in the 2nd application. On the 50th min of this period the animal attained a sterno-abdominal laying posture and attained a standing posture 17 min later. The animal was out of mild sedation after 20 min.

A mild sedation started on the 8th and 12th min during the 3rd and 4th applications. The mild sedation occurred after 75 and 85 min.

The second animal: Mild sedation started on the 4th min after injection in the first application. The animal attained a sterno-abdominal laying posture 8 min later and attained a standing posture 7 min later. The animal attained a sterno-abdominal laying posture again 10 min later and stood up completely after 11 min. The animal was out of mild sedation after 35th min.

It was identified in the 2nd application that mild sedation started at the 5th min after injection. On the 5th min of this period, the animal attained a sterno-abdominal laying position and stood up 14 min later. 6 min later the animal attained a lateral laying position and stood up 25 min later. The animal was out of mild sedation after 30 min.

It was determined in the 3rd application that mild sedation started 3 min after injection and 4 min later the

Table 2. *Average pulse rate according to application periods*
Tablo 2. *Uygulama peryodu dönemlerinde ortalama nabız sayısı*

Time (min)	Pulse Rate (beats/min)			
	1st application	2nd application	3rd application	4th application
0	80.20±25.26	74.80±9.36^{x}	76.40 ± 7.09^{x}	75.80 ± 13.31^{x}
5	75.20±15.00	55.40±7.67^{y}	69.00 ± 8.89^{yz}	60.00 ± 4.89^{xy}
15	69.80±8.95	62.20±4.66^{xy}	70.20±6.94^{yz}	61.00±7.81^{xy}
30	72.00±16.75	58.60±2.88^{y}	66.40±5.41^{yz}	62.20±10.47^{xy}
45	60.60±5.78	57.20±68.0^{y}	62.60±6.46^{z}	59.00±10.07^{y}
60	65.60±9.21	58.40±5.55^{y}	67.00±3.39^{yz}	57.00±1.87^{y}
75	62.60±84.4	60.60±9.32^{xy}	74.80±7.36^{yz}	58.20±4.02^{y}
90	67.00±13.00	62.80±11.52^{xy}	69.80±11.05^{yz}	58.20±2.28^{y}
120	69.80±8.81	63.40±6.56^{xy}	71.60±16.83^{xy}	58.60±8.96^{y}
p	-	*	*	*

^{x,y,z} *the difference between the averages on the same column is statistically significant (P<0.05)*

animal attained a sterno-abdominal laying position and 2 min after that attained a lateral position and stood up after staying in the same position for 20 min. It was decided that mild sedation symptoms disappeared 40 min after that.

In the last application, mild sedation started in the 3rd min after injection and 5 min later the animal attained a sterno-abdominal laying position and after staying in the same position for 55 min, it stood up. The mild sedation ended 15 min later.

The third animal: Mild sedation started on the 6th min after injection in the first application. The animal attained a lateral laying posture after 5 min and stood up after staying in the same position for 25 min. It was decided that mild sedation symptoms disappeared after 45 min.

Mild sedation started at the 8 min after injection in the second administration. The animal attained a sterno-abdominal laying posture after 6 minutes and attained a lateral laying posture after 20 min. It again attained a sterno-abdominal position after staying in the same position for 7 min and stood up 13 min later. It was decided that mild sedation symptoms disappeared 45 min after that.

Mild sedation started 5 min after injection in the third application. The animal attained a sterno-abdominal laying posture after 4 min and attained a lateral laying posture after 24 min. It stood up after staying in the same position for 11 min. The animal was out of mild sedation after 35th min.

Sedation started 6 min after injection in the fourth application. The animal attained a sterno-abdominal laying posture after 10 min and 25 min later it attained a lateral laying posture. It attained a sterno-abdominal position after staying in the same position for 30 min and stood up 20 min later. It was decided that mild sedation ended 10 min after that.

The fourth animal: Sedation started 5 min after injection in the first application. The animal attained a sterno-abdominal laying posture after 10 min and stood up 15 min later. It was decided that the animal was out of sedation 40 min after that.

Only mild sedation started in the 2nd, 3rd and 4th applications. The sedation times were determined as 60, 75 and 70 min respectively.

The fifth animal: Sedation started 10 min after injection in the first administration. The animal attained a sterno-abdominal laying posture after 10 min and attained a lateral laying posture15 min later. It again attained a sterno-abdominal position after staying in the same position for 20 min and stood up 10 min later. The mild sedation ended 35 min after that.

Sedation started 8 min after injection in the second administration. The animal attained a sterno-abdominal laying posture after 15 min and attained a lateral position 10 min later. It again attained a sterno-abdominal position after staying in the same position for 8 min. It stood up after staying in the sterno-abdominal position for 12 min. The mild sedation symptoms disappeared 40 min after that.

Sedation started 6 min after injection in the third application. The animal attained a sterno-abdominal laying posture after 18 min and stood up 14 min after that. After 35 min the mild sedation ended.

Sedation started 12 min after injection in the final application. The animal attained a sterno-abdominal laying posture after 28 min and stood up 11 min after that. After 25 min the mild sedation ended *(Table 3)*.

Analgesic Effect Evaluation Results

As a result of the applied pain tests, the analgesic effect score was 0 (normal strong reaction to painful stimuli)

Table 3. *Sedation level of sheep in the application periods, number of sheep and rations*
Tablo 3. *Uygulama peryodu dönemlerinde koyunların sedasyon dereceleri, koyun sayısı ve oranları*

Applications	Mild Sedation (No recumbency)		Moderate Sedation (Sterno-abdominal recumbency)		Deep Sedation (Lateral recumbency)	
1	-	(0%)	3[n]	(60%)	2[n]	(40%)
2	1[n]	(20%)	1[n]	(20%)	3[n]	(60%)
3	2[n]	(40%)	1[n]	(20%)	2[n]	(40%)
4	2[n]	(40%)	2[n]	(40%)	1[n]	(20%)

during mild and moderate sedation periods and 1-2 score (depressed reaction to painful stimulus) during deep sedation period.

The onset of analgesia occured betwen 10 and 40 min after xylazine HCl administration in sheep during deep sedation period. The duration of analgesia was determined between 10 and 30 min.

Biochemical Evluation Results

It was observed as a result of the examination of biochemical parameters that xylazine HCl caused hyperglycemia ($P<0.01$). Even though some of the other parameters (total bilirubin, BUN, AST, ALT, ALP, Ca, Na, K and Cl) were statistically insignificant, they were within the physiological values ($P>0.01$).

DISCUSSION

It is stated in literature that xylazine HCl can cause oro-nasal discharge and urination [7,11,16,20,21]. In our study, it was observed that oro-nasal discharge started as early as 5 min after injection and continued at various intervals until at most the 90th min. Urination was observed at most twice in the animals during the 5th and 30th min after injection. In addition, penis prolapse was observed only in one animal in all applications.

Rams which are administered with xylazine HCl at a dose of 0.3 mg/kg intramuscularly [22] and 0.2 mg/kg intramuscularly [11] laid down 15 min after injection. In our study, sheep attained a laying posture between the 3rd and 12th min after the first drug was administered in all applications.

Sheep in sedation have remained in a laying posture for 55 min [22], whereas Khan et al.[11] have stated that it was between 90 and 105 min. In our study, animals in moderate sedation laid down for 11-55 min whereas animals in deep sedation laid down for 7-30 min. The shortest sedation time in all groups was 60 min whereas the longest sedation time was 95.

Some animals are mildly sedated until the 15th min after injection and the sedation deepens on the 45th min after which 60% of the animals continue to do so on the 60th min and they are completely out of sedation 120 min later [11].

In our study, sedation time for animals which were only mildly sedated varied between 20 and 85 min. Whereas the sedation times of animals in moderate sedation varied between 11 and 55 min. Sedation times of animals in deep sedation were observed to be between 7 and 30 min.

It has been observed in more recent studies [11,16,17] that rectal temperature decreases for a short period of time for sheep to which xylazine HCl is administered. The initial increase of rectal temperature in all applications after xylazine HCl is injected and its decrease afterwards is in accordance with the statement of Dart [23], saying that hypothermia or hyperthermia can occur in animals due to the depression of the thermoregulation center by α-2 agonists.

Some investigators [11,15-17] stated that pulse rate has decreased. Pulse rates decreased in all applications in this study for a period of 120 min after xylazine HCl is administered.

Respiratory rate decreased in animals to which xylazine HCl has been administered [11,15,16]. In contrast, Ismaila et al.[17] have reported an increase in respiration rate. Whereas some researchers put forth that α-2 agonists cause tachypnea in sheep and bradypnea in other ruminants. In addition, they also state that α-2 receptor agonists have different effects on different sheep species and that there are even individual differences among the species [10]. The increase of respiration rate in the first 45 minutes and the decrease that started after the 45th minute to values below the pre-sedation values as well as the low values for 120 min is in accordance with the aforementioned references.

Studies carried out [16,17,20,24-26] indicate that xylazine HCl decreases ruminal activity in sheep and causes tympani. In this study, rumen activity decreased until the 30th min in all applications after which it increased until the 120th min; however failing to reach the control values.

The animals did not give any reaction to various stimuli on the 45th min during the evaluation of reflexes; such responses started after the 60th min and all responses were observed on the 90th min [11]. It was observed in our study that all reflexes were observed during all sedation periods.

The analgesia level with xylazine HCl in sheep was determined by Khan et al.[11] with the score of between

4-6 was determined. Whereas Grant and Upton [12] Grant et al.[27] states that a complete analgesic effect does not occur in sheep when xylazine HCl is administered in an intramuscular way. The analgesic effect of xylazine HCl differs among sheep species [28]. In this study the degree of analgesia was determined as 1-2 score during deep sedation period. We think that xylazine HCl has a mild analgesic effect on sheep during deep sedation period.

It has been put forth in various studies in literature [7,10] that xylazine HCl causes hyperglycemia. In this study, hyperglycemia was observed in all animals during and after sedation.

It was concluded that even though biochemical parameters started changing after the first application, repeating sedations did not change enzyme and mineral levels since normal limits were not exceeded.

It was decided that repeating sedations can be carried out since xylazine HCl application changed the respiration rate, rectal temperature and rumen activity number less in the following applications in comparison with the first application.

The results of this study indicate that repeated fixed doses of xylazine HCl in sheep as first application caused moderate and deep sedation while mild sedation did not occur. However, the sedation depth decreased significantly in third and fourth applications. We suggest that this should be taken into account during repeated sedations in sheep.

Acknowledgments

This study is supported by the Scientific Research Project Directory of the University of Yüzüncü Yıl (Project No. 2012-VF-B020). We would like to thank them for their support.

REFERENCES

1. Brounts SH, Hawkins JF, Baird AN, Glickman LT: Outcome and subsequent fertility of sheep and goats undergoing cesarean section because of dystocia: 110 cases (1981-2001). *J Am Vet Med Assoc,* 224, 275-281, 2004. DOI: 10.2460/javma.2004.224.275

2. Stierschneider M, Franz S, Baumgartner W: Endoscopic examination of the upper respiratory tract and oesophagus in small ruminants: Technique and normal appearance. *Vet J,* 173, 101-108, 2007. DOI: 10.1016/j.tvjl.2005.09.002

3. Melches S, Mellema SC, Doherr MG, Wechsler B, Steiner A: A castration of lambs: A welfare comparison of different castration techniques in lambs over 10 weeks of age. *Vet J*, 173, 554-563, 2007. DOI: 10.1016/j.tvjl.2006.01.006

4. Stafford K: Castrating older lambs: What are the issues? *Vet J*, 173, 477, 2007.

5. Taylor PM: Anesthesia in sheep and goats. *In Pract,* 13, 31-36, 1991.

6. Celly CS, Mc Donell WN, Young SS, Black WD: The comparative hypoxaemic effect of four alpha-2 adrenoceptor agonists (xylazine, romifidine, detomidine and medetomidine) in sheep. *J Vet Pharmacol Ther,* 20, 464-471, 1997. DOI: 10.1046/j.1365-2885.1997.00097.x

7. Carroll GL, Hartsfield SM, Champney TH, Geller SC, Martinez EA, Haley EL: Effect of medetomidine and its antagonism with atipamezole on stress-related hormones, metabolites, physiologic responses, sedation, and mechanical threshold in goats. *Vet Anaesth Analg,* 32, 147-157, 2005. DOI: 10.1111/j.1467-2995.2005.00187.x

8. Kästner SBR: A_2-agonists in sheep: A review. *Vet Anaesth Analg,* 33, 79-96, 2006. DOI: 10.1111/j.1467-2995.2005.00243.x

9. Riebold TW: Ruminants. **In,** Tranquilli WJ, Thurmon JC, Grimm KA (Eds): Lumb & Jones' Veterinary Anesthesia and Analgesia. 731-746, Wiley-Blackwell, Ames, IA, 2007.

10. Valverde A, Doherty TJ: Anesthesia and analgesia of ruminants. **In,** Fish RE, Brown MJ, Danneman PJ, Karas AZ (Eds): Anesthesia and Analgesia in Laboratory Animals. 285-411, Academic Press, London, UK, 2008.

11. Khan MA, Ashraf M, Pervez K, Rashid HB, Mahmood AK, Chaudhry M: Comparative effects of detomidineand xylazine as sedative and analgesic agents in small ruminants. *Pak Vet J,* 24, 62-69, 2004.

12. Grant C, Upton RN: Comparison of the analgesic effects of xylazine in sheep via three different administration routes. *Aust Vet J,* 82, 304-307, 2004. DOI: 10.1111/j.1751-0813.2004.tb12712.x

13. Carroll GL, Hartsfield SM: General anaesthetic techniques in ruminants. *Vet Clin North Am: Food Anim Pract,* 12, 627-661, 1996.

14. Dugdale A: Veterinary Anaesthesia Principles to Practice. 255, Wiley-Blackwell Malaysia, 2010.

15. Doherty TJ, Pascoe PJ, Mc Donell WN, Monteith G: Cardiopulmonary effects of xylazine and yohimbine in laterally recumbent sheep. *Can J Vet Res,* 50, 517-521, 1986.

16. Habib S, Das BC, Islam MN, Hossain MK, Ahmed MF: A Comparison of xylazine, diazepam, chlorpromazine and promethazine in relation to certain clinical and hematological parameters of indigenous sheep *(Ovis aries). Pak J Biol Sci,* 5, 484-488, 2002.

17. Ismaila MS, Onifade KI, Agaie BM, Elsa AT, Chafe UM: The influence of environmental temperature on physiological parameters in xylazine sedated sheep. *Int J Anim Veter Adv,* 2, 37-42, 2010.

18. Hall LW, Clarke KW, Trim CM: Anaesthesia of sheep, goats and other herbivores **In,** Hall LW, Clarke KW, Trim CM (Eds): Veterinary Anaesthesia. 341-366, WB Saunders, London, UK, 2001.

19. Kästner SBR, Wapf P, Feige K, Demuth D, Bettschart-Wolfensberger R, Akens MK, Huntinen M: Pharmacokinetics and sedative effects of intramuscular medetomidine in domestic sheep. *J Vet Pharmacol Ther,* 26, 271-276, 2003. DOI: 10.1046/j.1365-2885.2003.00492.x

20. Powell JD, Denhart JW, Lloyd WE: Effectiveness of tolazoline in reversing xylazine-induced sedation in calves. *J Am Vet Med Assoc,* 212, 90-92, 1998.

21. Galatos AD: Anesthesia and analgesia in sheep and goats. *Vet Clin North Am: Food Anim Pract,* 27, 47-59, 2011. DOI: 10.1016/j.cvfa.2010.10.007

22. Shokry M, Morad HM, Khalil IA: Studies on the effect of rompun in sheep. *Vet Med Rev,* 2, 237-243, 1976.

23. Dart CM: Advantages and disadvantages of using alpha-2 agonists in veterinary practice. *Aust Vet J,* 77, 720-721, 1999. DOI: 10.1111/j.1751-0813.1999.tb12907.x

24. Toutain PL, Zingoni MR, Ruckbush Y: Assessment of alpha-2 adrenergic antagonists on the central nervous system using reticular contraction in sheep as a model. *J Pharmacol Exp Ther,* 223, 215-218, 1992.

25. Deghani S, Behbodikhah A, Khorsand N: Clinical, haematological and biochemical effects of xylazine, ketamine and their combination in cattle and sheep. *Proceedings of the 4th International Congress of Veterinary Anaesthesia,* 123-128, Utrecht, The Netherlands, 1991.

26. Mohammad FK, Wahed RA, Dabbagh BK: Stimulation of food intake by xylazine in sheep. *Zentralbl Veterinarmed A,* 43, 387-391, 1996. DOI: 10.1111/j.1439-0442.1996.tb00466.x

27. Grant C, Summersides GE, Kuchel TR: A xylazine infusion regimen to provide analgesia in sheep. *Lab Anim,* 35, 277-281, 2001. DOI: 10.1258/0023677011911606

28. Ley S, Waterman A, Livingston A: Variation in the analgesic effects of xylazine in different breeds of sheep. *Vet Rec,* 26, 508, 1990. DOI:10.1136/vr.126.20.508