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Research Article
Ultrasonographic Evaluation of Blindness in Sheep Due to Inadvertent Closantel Overdose

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Abstract

Background and Objective: Closantel is a commonly used antiparasitic drug in sheep rearing areas. However, blindness due to its overdosage has not been evaluated by ultrasonography in the past. The objective of the study was to carry out ocular ultrasonography in sheep (10 female and 8 male) with a history of accidental closantel overdosage vis a healthy sheep. **Materials and Methods:** The clinical signs were elevated temperature and blindness manifested by bilateral mydriasis, absence of pupillary light and menace reflexes and difficulty in navigation. Ophthalmoscopy revealed an indistinct border of the optic nerve. The ocular ultrasonographic biometric parameters of the affected sheep were compared with age-matched healthy sheep, selected from the affected flocks. Six animals each (three male and three female) were selected for the age group <1 year and 1-3 years. **Results:** Ocular ultrasonographic examination of healthy sheep revealed significantly ($p<0.05$) increased anterior-posterior depth of lens, the lateromedial diameter of the lens, vitreous chamber depth and axial length in older animals (1-3 years) as compared to animals of <1 year age group. A similar trend was observed for the affected sheep. The statistical comparison of parameters between healthy and affected sheep revealed significantly ($p<0.05$) increased optic nerve sheath diameter in both the age groups of affected sheep as compared to the healthy sheep. The rest of the parameters did not differ significantly ($p<0.05$) between the healthy and affected sheep. Despite symptomatic treatment, none of the sheep regained eyesight. **Conclusion:** Closantel toxicity in sheep causes irreversible blindness due to increased optic nerve diameter.

Key words: Closantel overdose, ocular ultrasonography, optic nerve, sheep

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Gastrointestinal parasitism is one of the major health problems in sheep flocks and can negatively impact the health and production of infected animals[1]. The control of the gastrointestinal parasites is accomplished through the administration of various anthelmintic drugs[2]. Closantel is an antiparasite agent that belongs to the group of salicylanilides and is commonly used in cattle and small ruminants against different species and developmental stages of trematodes, nematodes and arthropods and can be administered via oral, intramuscular or subcutaneous routes[3]. Closantel binds strongly to plasma proteins in the blood, especially albumin and mainly interrupts oxidative phosphorylation in helminthes[3]. Intoxication with closantel has been reported in literature by Mavrot *et al.*[1].

Closantel has high anthelmintic efficacy for sheep[4,5]. However, occasional intoxication cases have been reported in literature by van der Lug and Venter[6]. Poisoning can occur when the dose is calculated considering the weight of the heaviest animal or based on the average weight, which may lead to an overdose in lighter animals[4]. Clinical signs may be observed when the dose is two to six times higher than recommended dose[6]. The common clinical signs of closantel toxicity in sheep are inappetence, paresis, ataxia, recumbency and blindness[6]. Swollen optic discs with several small papillary and peripapillary haemorrhages have been recorded in fundoscopic examination[1]. Over time, there is generalized retinal and optic disc atrophy producing irreversible blindness[1]. Widespread spongy changes of the cerebral and cerebellar white matter are regarded as consistent lesions in closantel toxicity[5]. Atrophy of the optic nerve occurs due to oedema and vacuolization. In the retina, necrosis and apoptosis of the outer retinal layers especially photoreceptive cells are recorded[6]. Although closantel toxicity has been reported in sheep, there is no published report about the utility of ultrasonography for the evaluation of closantel-induced blindness in sheep. The present study described the clinical and ultrasonographic findings of closantel toxicity in 18 sheep from three flocks.

MATERIALS AND METHODS

Study area: This study was conducted on 18 sheep suffering from closantel toxicity that were brought to the Veterinary Clinical Complex, Faculty of Veterinary Sciences and Animal Husbandry, Sher-e-Kashmir University of Agricultural Sciences and Technology of Kashmir from January, 2016 to January, 2017. The affected sheep belonged to three different sheep farms of District Ganderbal, located between 34.23°N longitude and 74.78°E latitude, Jammu and Kashmir, India. The animals were subjected to thorough clinical examination. The direct ophthalmoscopic examination was performed using Heinz hand-held ophthalmoscope. Trans corneal ultrasonographic examination was performed using a 10-18 MHz linear transducer (My Lab 40 Vet) after instilling a drop of proparacaine into the eye and application of ultrasound jelly. The ocular ultrasonographic biometric parameters of the affected sheep were compared with age-matched healthy sheep, selected from the affected flocks. Six animals each (three male and three female) were selected for the age groups <1 year and 1-3 years.

Statistical analysis: The qualitative data were presented as frequency. The quantitative data were presented as Mean±SEM. The ocular biometric parameters of healthy and affected sheep were compared by independent t-test. The significance level was set at $p<0.05$ for all the statistical procedures.

RESULTS

All the affected sheep had a history of oral administration of closantel, 3-6 days before the development of the clinical signs (Table 1). Out of 18 sheep, 8 were male and 10 were females. Half of the affected animals were below one year of age. All the sheep were presented for evaluation because of blindness and anorexia. The clinical examination findings were mydriasis, absence of pupillary light reflex and absence of menace reflex. The dose of closantel administered was 3-6 times higher than the recommended dosage (10 mg kg^{-1} b.wt.). Development of full-blown clinical signs took 3-6 days.

Vital parameters of the animals were within the normal reference range, except for elevated rectal temperature. Ophthalmologic examination revealed bilateral irresponsive mydriasis, absence of pupillary light and menace reflexes and absence of visual perception manifested by difficulty in navigation and hitting objects while moving around. Spinal reflexes were normal. The sheep appeared hurdled together in a group and refused to move easily when stimulated. In addition to these clinical signs, frequent micturition was observed in animals of the flock 3. Ophthalmoscopic examination revealed no inflammatory changes in the anterior aspect of the eye. However, an indistinct border of the optic nerve was observed in all the affected sheep.

Table 1: Various parameters recorded in closantel-affected sheep

Particulars	Flock 1	Flock 2	Flock 3	Total
Total flock strength	72	10	100	182
Number of affected animals	6	2	10	18
Sex				
Male	3	1	4	8
Female	3	1	6	10
Age				
Upto1 year	6	2	1	9
>1 year	0	0	9	9
Dosage exceeded	3 times	3 times	6 times	3-6 times
Development of clinical signs	4-5 days	5 days	3-6 days	3-6 days
Clinical symptoms				
Bilateral mydriasis	6	2	10	18
Absence of pupillary light reflex	6	2	10	18
Absence of menace reflex	6	2	10	18
Elevated temperature	6	2	10	18

Table 2: Ultrasonographic biometric measurements (Mean±SEM) of ocular structures in normal and affected sheep

Age (years)	Groups	Central corneal thickness (mm)	Anterior chamber depth (mm)	Anterior-posterior depth of lens (mm)	Lateromedial diameter of the lens (mm)	Vitreous chamber depth (mm)	Axial length (mm)	Optic nerve sheath diameter (mm)
<1	Healthy	0.8±0.07	2.22±0.4	7.6±0.6^{a}	11.1±0.29^{a}	9.6±0.1^{a}	20.3±0.12^{a}	3.76±0.56
	Affected	0.81±0.06	2.24±0.3	7.64±0.5^{a}	11.0±0.21^{a}	9.5±0.4^{a}	20.7±0.2^{a}	5.2±0.62*
1-3	Healthy	0.85±0.06	2.73±0.2	8.6±0.7^{b}	12.6±0.21^{b}	10.8±0.4^{b}	23.5±0.41^{b}	3.89±0.36
	Affected	0.88±0.03	2.81±0.5	8.5±0.8^{b}	12.7±0.31^{b}	10.75±0.5^{b}	23.7±0.27^{b}	5.86±0.64*

*Differ significantly ($p<0.05$) between normal and affected sheep. For each age group, corresponding values in a column with different superscripts differ significantly between the same age groups of normal and affected sheep

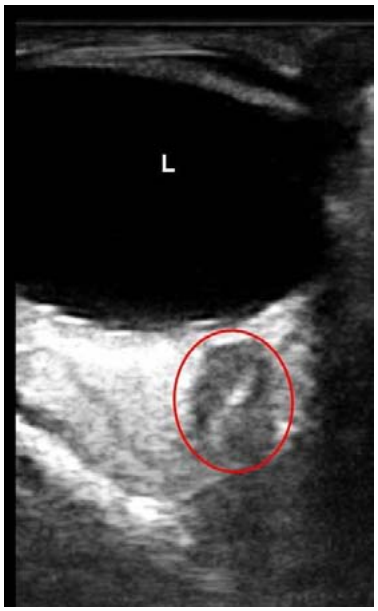

Fig. 1: Ocular ultrasonogram showing thickening of the optic nerve, prominent acoustic shadow (red circle)

Ocular ultrasonographic examination of healthy sheep revealed significantly ($p<0.05$) increased anterior-posterior depth of the lens (7.6±0.6 vs. 8.6±0.7 mm), the lateromedial diameter of the lens (11.1±0.29 vs. 12.6±0.21 mm), vitreous chamber depth (9.6±0.1 vs. 10.8±0.4 mm) and axial length (20.3±0.12 vs. 23.5±0.41 mm) in older animals (1-3 years) as compared to animals of <1 year age group (Table 2). A similar trend was observed for the affected sheep. The other ultrasonographic biometric parameters did not differ significantly ($p<0.05$) between the two age groups of healthy or affected sheep. The statistical comparison of ultrasonographic biometric parameters between healthy and affected sheep revealed significantly ($p<0.05$) differences concerning optic nerve sheath diameter only. The optic nerve sheath diameter was significantly ($p<0.05$) increased in affected sheep than in the healthy sheep for both the age groups (5.2±0.62 vs. 3.76±0.56 mm in young animals and 5.86±0.64 vs. 3.89±0.36 mm in older animals) as shown in Table 2. The rest of the biometric parameters did not differ significantly between the healthy and affected sheep. The increased optic nerve sheath diameter cast a prominent acoustic shadow in Fig. 1.

All the affected sheep were treated symptomatically but none of them regained their eyesight, although their appetite improved.

DISCUSSION

Although optic neuropathy has been reported in sheep associated with overdosage of closantel[4]. To the author's knowledge, this is the first study to describe ocular

ultrasonographic changes of closantel toxicity in sheep. In sheep, closantel is commonly used for the control of *Haemonchus* spp., *Fasciola* spp. and *Oestrus ovis*[7], has a narrow margin of safety, sometimes resulting in its toxicosis with ocular manifestations due to its overdosage. A two-fold (moderate) overdosage may result in blindness, ataxia depression and recumbency while higher levels of overdosage may result in the death of animals[8].

In this study, the sheep developed clinical signs of toxicosis 3-6 days after the oral administration of 3-6 times higher doses of closantel. The period for the development of clinical signs of closantel toxicity is reported to be variable by different studies. The onset of toxicity signs in goats[9] and sheep[6] have been recorded 18-120 hrs after closantel dosing. Higher levels of overdose may result in a more rapid onset of clinical signs, especially the young animals. This may be attributed to higher dosage in young animals, as the body weight may have been easily overestimated. But this is just over assumption and may be confirmed in an experimental study. Interestingly, Ecco *et al.*[9] reported the overdosage of 8-10 fold. Other scientists have reported the development of clinical signs with overdosage of 1.6-5 fold[6,8].

Clinical signs of closantel toxicity manifest in the form of inappetence, teeth grinding, depression, muscle tremors, opisthotonus, an extension of the limbs, hyperaesthesia and periodic tonic-clonic convulsions head pressing, incoordination, ataxia, paresis, recumbency, blindness, circling, depression of the palpebral and pupillary reflexes, nystagmus and dilated pupils, frothy salivation and recumbency[5,7]. Death can occur due to higher levels of overdose[8]. Clinical signs other than blindness are reported in animals receiving higher closantel overdose, however, these signs usually disappear leaving only irreversible blind animals[9].

In this study, the affected sheep improved in terms of feed intake but the blindness was irreversible and was attributed to increased optic nerve diameter, which was confirmed on ocular ultrasonography.

The blindness observed in previous studies has been attributed to lesions in the retina and optic nerve. The irresponsive mydriasis with the absence of photo motor reflex differentiates these cases from those of cerebrocortical necrosis that can also occur in sheep. The proposed mechanism for toxicity is the disruption of cells with tightly packed layers of the cell membrane e.g., photoreceptors causing retinopathy, Schwann cells leading to myelinic oedema and oligodendrocytes producing white matter vacuolation. In the retina, closantel toxicity leads to the necrosis and apoptosis of the outer layers especially the photoreceptive cells[10] and retinal separation in the tapetal and non-tapetal areas[8]. Optic nerve lesions are characterized by intramyelinic oedema characterized by necrosis, foamy macrophage infiltration and intracanalicular nerve fibrosis with loss of ganglion cells[4].

An indistinct border of optic nerve suggestive of the papilledema was observed upon indirect ophthalmoscopic examination. Previous researchers have described acute retinal degeneration and papilledema as well as narrowing of retinal blood vessels on ophthalmoscopic examination[8,9].

In humans, ultrasonographic measurement of the optic nerve sheath diameter is regarded as the quick, non-invasive method of identification of high intracranial pressure. The optic nerve extends towards the orbit wrapped in a sheath derived from meninges[11]. In the present study, there was a significant increase in most of the ultrasonographic biometric parameters of the eye in healthy sheep with an increase in age. So, assumed that the significant difference between the two age groups of the affected sheep was not due to closantel toxicity but was age-related. However, the optic nerve diameter did not differ significantly between the two age groups of healthy or affected sheep but optic nerve diameter was significantly increased in both age groups of affected sheep as compared to healthy sheep. So, we conclude that enlarged optic nerve diameter was a true and consistent finding on ultrasonography in the affected sheep.

There were a few limitations of this study. First, the eyes from the affected animals could not be harvested so the optic nerve diameter could not be measured physically. Second, the changes in the eye and adjacent structures could not be confirmed on histopathology.

CONCLUSION

Closantel overdosage is dangerous because of its ocular and neural effects and that special attention must be paid to young animals because their body weight can be easily overestimated leading to overdosage with closantel which possesses a narrow margin of safety. Ocular ultrasonography proved to be a useful non-invasive tool to evaluate the cause of irreversible blindness associated with closantel toxicity. The true and consistent finding on the ocular ultrasonography was an increase in optic nerve diameter.

SIGNIFICANCE STATEMENT

This study discovered the use of ultrasonography in detecting the changes in optic nerve diameter in sheep suffering from the closantel overdosage and therefore should provide an easy, quick and non-invasive method of the evaluation of blind sheep.

REFERENCES

1. Mavrot, F., H. Hertzberg and P. Torgerson, 2015. Effect of gastro-intestinal nematode infection on sheep performance: A systematic review and meta-analysis. Parasites Vectors, Vol. 8. 10.1186/s13071-015-1164-z.
2. Seyoum, Z., Y. Demessie, B. Bogale and A. Melaku, 2017. Field evaluation of the efficacy of common anthelmintics used in the control of gastrointestinal nematodes of sheep in Dabat District, Northwest Ethiopia. Ir. Vet. J., Vol. 70. 10.1186/s13620-017-0097-6.
3. Hanna, R.E.B., C. McMahon, S. Ellison, H.W. Edgar and P.E. Kajugu *et al*., 2015. *Fasciola hepatica*: A comparative survey of adult fluke resistance to triclabendazole, nitroxynil and closantel on selected upland and lowland sheep farms in Northern Ireland using faecal egg counting, coproantigen ELISA testing and fluke histology. Vet. Parasitol., 207: 34-43.
4. Dixit, A.K., G. Das, P. Dixit and R.L. Sharma, 2019. Efficacy of herbal extracts and closantel against fenbendazole-resistant *Haemonchus contortus*. J. Helminthol., 93: 529-532.
5. Barlow, A.M., J.A.E. Sharpe and E.A. Kincaid, 2002. Blindness in lambs due to inadvertent closantel overdose. VetRecord, 151: 25-26.
6. van der Lug, J.J. and I. Venter, 2007. Myelin vacuolation, optic neuropathy and retinal degeneration after closantel overdosage in sheep and in a goat. J. Comp. Pathol., 136: 87-95.
7. Sakhaee, E. and A. Derakhshanfa, 2010. Polioencephalomalacia associated with closantel overdosage in a goat. J. South Afr. Vet. Assoc., 81: 116-117.
8. Ghods, S., E.K. Pour, H. Riazi-Esfahani, H. Faghihi and B. Inanloo, 2021. Closantel retinal toxicity: Case report and literature review. Case Rep. Ophthalmol. Med., Vol. 2021. 10.1155/2021/4832965.
9. Ecco, R., C.S.L. de Barros, D.L. Graça and A. Gava, 2006. Closantel toxicosis in kid goats. Vet. Rec., 159: 564-566.
10. Cheraghmakani, H., R. Jafari, E. Karimpour-Razkenari and M. Ghazaeian, 2021. Reversible blindness after erroneous prescription of closantel: A case report. Clin. Case Rep., Vol. 9. 10.1002/ccr3.5157.
11. Wang, L., L. Feng, Y. Yao, Y. Wang, Y. Chen, J. Feng and Y. Xing, 2015. Optimal optic nerve sheath diameter threshold for the identification of elevated opening pressure on lumbar puncture in a chinese population. PLoS ONE, Vol. 10. 10.1371/journal.pone.0117939.