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The Effect of Oxfendazole+Oxyclozanide Paste and Tablet Formulations on Parasite Burden and Metabolic Status of Sheep

[1]V. Günes, [2]A. Inci, [3]F. Uyanik, [2]A. Yildirim, [4]N. Altug, [3]M. Eren, [1]A.C. Onmaz and [5]C.C. Gelfert
[1]Department of Internal Medicine, [2]Department of Parasitology, [3]Department of Biochemistry, Faculty of Veterinary Medicine, University of Erciyes, Kayseri, Turkey
[4]Department of Internal Medicine, Faculty of Veterinary Medicine, University of Yuzuncu Yil, Van, Turkey
[5]Clinic for Ruminants, University of Veterinary Medicine, Vienna, Austria

Abstract: The aim of the present study was to evaluate the effects of anthelmintic treatment with Oxyclozanid + Oxfendazole in different formulation (paste and tablet) on parasite load and metabolic status in sheep. Forty five sheep, infected with various gastrointestinal parasites and kept on a grazing flock, were evenly divided into 3 groups. Sheep in the control group did not receive any treatment. The sheep in the remaining groups received the same dose of Oxyclozanid (5 mg kg^{-1} body weight) and Oxfendazole (13.5 mg kg^{-1} body weight) in combination either as tablet or as paste. Faeces and blood samples were collected pre-treatment (day 0) and on day 14 post-treatment. Several gastrointestinal nematode parasites were detected in the faecal samples. Eggs Per Gram (EPG) on days 0 and 14 were 100±18 and 78±8 in CG, 96±12 and 6±3 in TG and 76±9 and 2±2 in the PG, respectively. Serum total protein and globulin concentrations increased significantly ($p<0.05$) in CG and PG on day 14 compare to pre-treatment levels. In both sampling times total protein levels did not differ whereas a slight decrease in paste group and a significant decrease in tablet group were detected concerning globulin level, but no significant difference was detected between the tablet group and paste group on day 14 post-treatment. In paste group serum albumin level increased ($p<0.05$) on day 14 compare to baseline level. Compare to control group, albumin level slightly increased in tablet group, whereas it significantly increased in paste group on day 14 post-treatment. On day 14 in paste group Pi, Mg and Cu levels were higher ($p<0.05$) than the post-treatment levels of the remaining groups. A combination of Oxyclozanid+Oxfendazole is effective to eliminate parasite burden in sheep. Drug formulation does not have any influence on the metabolic status of the sheep.

Key words: Sheep, oxyclozanid-oxfendazole, endoparasite, treatment, micro mineral

INTRODUCTION

The physiological requirement of animals for minerals is one of the major factors, which influence production parameters. Several factors including the production type, breed, age and production levels of animals, as well as the chemical structure of the elements and their interaction with other nutrients affect the mineral status of sheep (Gromadzka *et al*., 1986; Lee *et al*., 1999; Khan *et al*., 2005). Any deficiency due to increased requirements for macro and micro elements results in metabolic disorders, decreases in production yields, inhibition of growth, manifestation of clinical symptoms and in particular, suppression of the immune system (Underwood and Suttle, 1999; Gaylean *et al*., 1999; Spears, 2000).

Trace element deficiency causes poor appetite, loss of body weight, thinning, cachexia, anaemia, poor growth, pica, poor wool quality, infertility and yield losses in sheep (Hidiroglou, 1979; Herd, 1993). In the limited number of studies investigating the correlation between trace element levels and parasite burden, it has been shown that trace element deficiency may develop in the presence of internal parasites in sheep (Bal *et al*., 2004; Kozat *et al*., 2006) and therefore, the compensation of the increased requirement for trace elements has been deemed necessary in parasite infections (Lee *et al*., 1999; Saleh *et al*., 2007).

Although, the absorption of proteins, lipids, carbohydrates, vitamins and minerals is reported to be negatively influenced by endoparasitic invasions (Dakkak, 1986; Suttle and Jones, 1989; Herd, 1993; Lee *et al*., 1999; Saleh *et al*., 2007), available information on the correlation between parasitic invasions and antiparasitic treatment as well as mineral levels is scarce.

Corresponding Author: Vehbi Gunes, Department of Internal Medicine, University of Erciyes, Mevlana Cd. No:1 Kocasinan, Kayseri, Turkey

Possible alterations in trace element and mineral levels resulting from the reduction of parasite burden by antiparasitic active substances have been reported (Sahin and Akgul, 2006; Yuksek *et al*., 2007). To the authors' knowledge, however, there is no study investigating the effects of the paste formulation of the oxyclozanid-oxfendazole combination on the metabolic status of the animals. Therefore, the present study was initiated to investigate the possible effects of 2 different drug formulations (paste and tablet) containing the same active substances (Oxyclozanid+Oxfendazole) in the same concentration on serum proteins glucose and mineral levels of sheep with varying numbers of parasite eggs in the gastrointestinal tract.

MATERIALS AND METHODS

Animals, experimental design and sample collection: The present study was performed between October and November 2006, on a farm with 400 sheep, located in the Tuzhisar area of Bunyan district, Kayseri province, Turkey.

One hundred and forty 2, clinically healthy, Akkaraman sheep aged three years were selected randomly and included in to the study. They were vaccinated against certain viral and bacterial infections (enterotoxemia, brucellosis, sheep pox) and free from ectoparasites, before starting the study no antihelminthic treatment was performed. Approximately 10 g of faeces was collected from each of the 142 sheep for parasitological examination.

After confirming the existence of an infection with gastrointestinal parasites, 45 out of 142 sheep were randomly allocated to three groups according to the EPG (eggs per gram of faeces) values determined. The first group kept as control (CG) and no therapy was administered. All sheep in the other two groups were treated with a single combined dose of 5 mg kg^{-1} Body Weight (BW) Oxfendazole and 13.5 mg kg^{-1} BW Oxyclozanid. In group 2 (Tablet group TG), the drugs were given as tablet (Oksavet®, Vilsan, Istanbul, Turkey), in group 3 (Paste group PG), all sheep received the drugs as a paste (Pasthelmin®, Alke, Istanbul, Turkey). In order to determine the drug doses to be administered to the groups, the body weights of the animals were measured at the beginning of the trial. Body weights of the animals in the control, tablet and paste groups were 71±6.6 kg, 68.7±8.2 kg and 65.5±8.5 kg, respectively. Following this single-dose treatment, the current feeding management was continued by grazing all animals on pasture. No mineral supplement was offered to the animals at any before and during the study.

Before the treatment and fourteen days after the treatment, blood samples were collected from the jugular vein of each animal using tube without any anticoagulant. After clotting, the blood samples were centrifuged at 1300 g for 10 min to separate the serum.

Parasitological examination: Prior to the establishment of the trial groups, faecal samples collected from 142 sheep were examined for eggs of gastrointestinal nematodes, using the zinc sulphate flotation method (Kassai, 1999). The numbers of nematode Eggs Per Gram of faeces (EPG) were determined with the zinc sulphate McMaster egg counting technique (Kassai, 1999). Faecal samples determined to be positive were further cultured and third-stage larvae were identified using current identification keys (Soulsby, 1986).

Biochemical analyses: The concentrations of total protein, albumin, glucose, Calcium (Ca), inorganic Phosphorus (Pi) and Magnesium (Mg) were measured spectrophotometrically (Shimadzu 1208 UV/Visible model spectrophotometer) with commercially available kits (Biolabo, France). Globulin levels were calculated with substraction of albumin levels from total protein levels. The concentrations of iron (Fe), cobalt (Co), manganese (Mn), copper (Cu) and zinc (Zn) was determined using an atomic absorption spectrophotometer (SOLAAR® Termo, UK). Trace element analyses were performed in the Scientific Application and Research Centre, University of Yuzuncu Yıl, Van, Turkey.

Statistical analyses: Data were analysed with SPSS 15.0 (SPPS Inc, Chicago, Illinois USA). Differences between the three treatment groups were analysed using one-way Analysis of Variance (ANOVA) and when the F value was significant Duncan's multiple range test was performed. For analysing the changes over time, the t-test was used. The level of significance was set at $p<0.05$.

RESULTS

The EPG values at day 0 and percentages of reduction of EPG at day 14 in the three groups are given in Table 1. They did not differ significantly between the groups ($p=0.365$). Third-stage larvae obtained from faecal culture in the pre-treatment sampling were identified. *Ostertagia* was the most common species, followed by *Nematodirus* sp., *Haemonchus* sp., *Trichostrongylus* sp., *Oesophagostomum/Chabertia* sp. and *Cooperia* sp. (Table 2).

Table 1: Prevalence of gastrointestinal parasite eggs (EPG) in faeces of sheep treated with or left untreated and the changes of prevalence over time

	Control group		Tablet group		Paste group	
Day	EPG[1]	Change to day 0 (%)	EPG	Change to day 0 (%)	EPG	Change to day 0 (%)
0	100.0±18		96±12		76±9	
14	77.8±7.5	-22.2	6±3	-93.75	2±2	-97.37

1: average egg per gram faeces of 15 sheep/group

Table 2: Distribution of gastrointestinal nematode species in the sheep included in the three trial groups

	Number of sheep infected		
Nematod species	Control group	Tablet group	Paste group
Ostertagia sp.	20	19	22
Nematodirus sp.	14	16	13
Haemonchus sp.	5	7	4
Trichostrongylus sp.	10	12	11
Oesophagostomum/ Chabertia sp.	2	1	1
Cooperia sp.	1	NF	NF

NF: not found

Table 3: Pre-and post-treatment concentrations of serum protein and glucose in sheep infected with gastrointestinal parasites

		Groups		
Parameters	Days	Control group x±SE (n=15)	Tablet group x±SE (n=15)	Paste group x±SE (n=15)
Total protein (g L^{-1})	0	84.1±1.5^{A}	85.3±1.0	80.6±1.9^{A}
	14	94.5±2.8^{B}	86.7±1.5	91.4±2.8^{B}
Albumin (g L^{-1})	0	40.9±0.8	42.2±0.8	39.7±0.7^{A}
	14	38.9±0.5^{b}	41.2±0.8^{ab}	42.7±0.9^{B,a}
Globulin (g L^{-1})	0	47.2±1.8^{A,a}	46.9±1.7^{a}	40.9±2.2^{A,b}
	14	55.5±2.5^{B,a}	45.5±1.8^{b}	48.7±2.7^{B,ab}
Glucose (mmol L^{-1})	0	4.58±0.12	4.78±0.07	4.69±0.12
	14	4.07±0.07	4.14±0.08	4.24±0.07

^{A,B}Mean values differed significantly between day zero and day 14 within one group (p<0.05), $^{a,b:}$ Mean values differed significantly between the groups at the same day (p<0.05), SE: Standart Error

Table 4: Pre-and post-treatment concentrations of serum minerals in sheep infected with gastrointestinal parasites

		Groups		
Parameters	Days	Control group x±SE (n=15)	Tablet group x±SE (n=15)	Paste group x±SE (n=15)
Calcium (mmol L^{-1})	0	2.85±0.09	3.16±0.16	2.91±0.11
	14	2.87±0.06	2.94±0.09	3.1±0.12
Phosphate (mmol L^{-1})	0	1.69±0.04	1.68±0.02	1.63±0.02
	14	1.66±0.02^{b}	1.68±0.01^{b}	1.75±0.02^{a}
Magnesium (mmol L^{-1})	0	0.99±0.005	0.99±0.005	1.01±0.005
	14	0.99±0.005^{b}	0.97±0.005^{b}	1.02±0.01^{a}
Copper (µmol L^{-1})	0	11.38±0.27	11.84±0.68	11.62±0.82^{A}
	14	11.51±0.34^{b}	11.33±0.54^{b}	13.87±0.84^{B,a}
Manganese (µmol^{-1} L)	0	0.60±0.04^{A}	0.53±0.04^{A}	0.66±0.05^{A}
	14	0.89±0.04^{B}	0.91±0.04^{B}	0.89±0.06^{B}
Zinc (µmol L^{-1})	0	7.02±0.30^{b}	8.05±0.25^{a}	6.79±0.28^{b}
	14	6.82±0.17	7.44±0.20	6.90±0.34
Cobalt (µmol L^{-1})	0	0.83±0.10	0.95±0.12	1.15±0.13
	14	0.81±0.05	0.95±0.08	0.88±0.04
Iron (µmol L^{-1})	0	37.36±2.42	37.92±3.51^{A}	39.98±3.76
	14	41.78±3.15	57.81±8.88^{B}	47.32±7.38

^{A,B}Mean values differed significantly between day zero and day 14 within one group (p<0.05), ^{a,b}Mean values differed significantly between the groups at the same day (p<0.05)

The treatment with OXY/OFZ reduced the infection rate noticeably in TG and PG. After 14 days, EPG was reduced of 94.2% in TG and 97.37% in PG (Table 1).

No significant differences in reduction rate between the 2 drug formulations was found (p>0.05).

The concentrations of serum total protein (Table 3) increased significantly (p<0.05) in CG and PG overtime but did not show significant differences between the three groups on days zero and 14. The globulin concentrations were significantly higher in CG before the treatment compared to PG and TG, Compare to the pre-treatment values, globulin levels in CG and PG increased on day 14 post-treatment (p<0.05). The albumin concentration was significantly higher in PG at day 14 compared to day zero and compared to CG. Serum Mg and Pi concentrations increased in PG compared to both CG and TG (p<0.05). No significant differences were detectable in concentrations of calcium or glucose (Table 3).

In all groups, post-treatment concentrations of Mn were significantly higher (p<0.05), but there was no difference between groups (p>0.05) at day 14. The Cu level in PG was significantly (p<0.05) higher than in CG and TG (Table 4). The concentrations of Fe showed only a remarkable increase in TG on day 14 post-treatment (p<0.05). None of the treatments had any effects on Co and Zn levels.

DISCUSSION

Oxfendazole and Oxyclozanide combination against subclinical gastrointestinal nematode infections have been commonly used in sheep (Dinc and Kanbur, 2002; Coles *et al*., 2006; Mottier *et al*., 2006). Himonas and Theodorides (1986) found that the efficacy of Oxfendazole was 100% against *Haemonchus contortus*, *Ostertagia circumcincta*, *Trichostrongylus axei*, *T. colubriformis* and *Chabertia ovina*. In another study, the efficacy of oxfendazole alone was 77.5% and that of the combination of oxfendazole and levamisole was 100% on day 11 after treatment in sheep infected with benzimidazole resisted *H. contortus* and *Ostertagia* sp. (Andrews, 2000). In the present study, according to the EPG values obtained on day 14 post-treatment, the paste and tablet formulations were effective at rates of 97.5 and 94.2%, respectively. These findings were consistent with the results of previous studies (Himonas and Theodorides, 1986; Waruiru *et al*., 1996; Andrews, 2000). In this study, these two rates were closely similar and it can be concluded that the efficacy rates for both treatment groups did not differ.

In all groups, concentrations of total protein as well as albumin and globulin concentrations were elevated at day 0, exceeding the physiological ranges for sheep (Uyanik, 2001; Ozyurtlu *et al*., 2007). Similar values were found in another study (Ayaz *et al*., 2006). Sahin and Akgul (2006) described a reduction of total protein and albumin concentrations with increasing amount of EPG. The mean EPG in their study, however, was much higher than the mean EPG of the present study. In a study of Kozat *et al*. (2006), concentrations of albumin, globulin and total protein were significantly lower in pregnant ewes, infected with gastro-intestinal parasites. Unfortunately there is no information about EPG. Therefore, their results are not comparable to the results of the present study. It seems that the dimension of the parasite burden influence the protein metabolism. A very high parasite burden will decrease the amount of protein available which will lead to a decrease of albumin followed by a decrease of total protein. Low albumin levels were found in sheep infected with *Moniezia* sp. (Yuksek *et al*., 2007).

The elevated concentrations of total protein are mainly effected by the increased level of globulin. High globulin levels in sheep infected with parasites were described in other studies (Mousa *et al*., 1998; Dhanalakshmi *et al*., 2002). Significant increases were also reported in the total protein, albumin and globulin levels of the sheep treated with ivomec and doramectin compare to untreated animals (Bal *et al*., 2003; Mostafa *et al*., 2005). This can be interpreted as an activated immune response due to the parasite infection (Ayaz *et al*., 2006). The globulin concentrations, therefore, were still elevated in CG and had increased. The still ongoing of the parasite infection maintain the high level of globulin concentrations in the sheep. In both treatment groups, the globulin concentrations were still elevated; however, they were lower than in CG. In the study of Sahin and Akgul (2006), globulin concentrations were still elevated in sheep, being treated against gastro-intestinal parasites one month before and found free of parasites at the day of blood sampling. The globulin levels remained elevated although no actual infection occurred. The results of the present study confirm the result of Sahin and Akgul (2006).

Little information only is available about the mineral levels of sheep treated with antiparasitic drugs. In the present study, concentrations of calcium, phosphorus and magnesium were in physiological ranges remained nearly unchanged in all groups despite the fact that some differences were statistically significant. These significant changes in Mg and Pi concentrations were very small and probably did not have any clinical relevance. No clinical signs of any macro mineral deficiency occurred during the study. Ayaz *et al*. (2007) also did not find significant differences in the concentrations of Mg and Pi when they compared healthy sheep and sheep infected with trichostrongylids. Yuksek *et al*. (2006) did not found reduced calcium concentrations in sheep infected with *Moenezia* sp. and *Dicrocoelium dendriticum*.

In all sheep, blood zinc concentrations were below physiological values (Yur *et al*., 2002; Seyrek *et al*., 2004) indicating a slight zinc deficiency. After treatment, however, the zinc concentrations did not show any improvement. In the study of Yuksek *et al*. (2007), the zinc concentrations of infected sheep were also decreased. Fourteen days after treatment, they were still reduced and increased noticeably not before the third week after treatment. Therefore, an increase of zinc concentration after treatment might not be expected in the present study due to the time point of blood sampling.

The concentrations of the other micro elements measured did not show any deficiency. Kozat *et al*. (2006) reported lower serum Fe and serum Cu levels in parasite infected pregnant ewes compared to the values obtained from the uninfected group. Iron concentrations, however, were below physiological ranges in both groups and copper concentrations were normal in that study. Bal *et al*. (2004) also found a significant decrease of serum Cu levels in sheep. In the study of Sahin and Akgul (2006) even the treated animals had lower concentrations of iron than the sheep of CG of the present study. These fact shows that the results of the different study are not comparable due to the different feeding condition, the different parasites found in the animals and the use of sheep in different stage of lactation. Gastrointestinal parasite infections may aggravate trace element deficiency in sheep and trace elements may be supplemented in parasite infections (Saleh *et al*., 2007). In the present study, the slight parasite burden might be the reason for the lack of general deficiency of micro elements. For the concentrations of copper were in physiological ranges (Seyrek *et al*., 2004) in all groups at both sampling times, the significant changes found in PG are difficult to interpret. Before postulating any influence of the drug formulation, more research has to be done. The results of the present study and those of the previous study also show that the feeding management and feed quality probably has a greater impact on the mineral status of sheep than parasite infection.

CONCLUSION

In conclusion, the result of the present study shows that the administration of an oxyclozanid-oxfendazole combination to grazing sheep reduces the parasite burden nearly completely. According to the results the drug formulation does not have any influence on the metabolic status of the sheep. Further research is needed, to elucidate the impact of parasite infection on mineral metabolism and the use of blood samples for a proper diagnosis of micro element deficiency in sheep.

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