دانشگاه شیراز
Shiraz University

IJVR
ISSN: 1728-1997 (Print)
ISSN: 2252-0589 (Online)

Vol. 18 No. 3 Ser. No. 60 2017

IRANIAN JOURNAL OF VETERINARY RESEARCH

Evaluation of amprolium and toltrazuril efficacy in controlling natural intestinal rabbit coccidiosis

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(Received 20 Dec 2016; revised version 12 Mar 2017; accepted 8 Apr 2017)

Summary

This trial was undertaken with the objective to evaluate the efficacy of amprolium, toltrazuril and their combination in rabbits naturally infected with *Eimeria* species ($32 \times 10^3 \pm 4.63$ oocysts per gram (OPG) of faeces). Thirty-six rabbits (11 weeks old with average body weight (BW) 2000 ± 75 g), were randomly allocated into six groups (six kits each), namely, negative untreated and was retained as negative control (group 1), infected and kept untreated (group 2), treated with single oral dose of amprolium at 50 mg/kg BW for 5 days (group 3), received toltrazuril at 5 mg/kg BW for 2 days (group 4), treated orally with toltrazuril at 2.5 mg/kg BW, two doses with 5 day interval (group 5) and given oral doses of both amprolium and toltrazuril at 50 mg and 5 mg/kg BW (group 6), respectively. Clinical signs, mortalities, production data (feed consumption, feed conversion rate, BW, body weight gain (BWG), and performance index (PI)), OPG of faeces and the percentage of OPG reduction were recorded. The results indicated that both toltrazuril, amprolium and their concurrent use significantly ($P<0.05$) reduced OPG and effectively controlled coccidiosis related mortality, fully abolished the clinical signs, improved feed consumption, BW, weight gain and feed conversion rate. From the observations of the present study it can be concluded that the oral administration of both drugs and their combined use ameliorated the adverse impacts of intestinal coccidiosis in rabbits as therapeutic, but the concurrent use of both drugs was more superior.

Key words: Amprolium, Coccidiosis, Egypt, Rabbit, Toltrazuril

Introduction

Coccidiosis of rabbits is an ubiquitous infection caused by obligatory intracellular protozoan parasites belonging to the genus *Eimeria* and is considered as a major cause of significant morbidity and mortality (Hauptman *et al*., 2001).

In rabbit, coccidiosis control should address not only the prevention of overt disease and mortality but also mild and subclinical infections, as even minor intestinal lesions can interfere with growth and feed conversion and therefore profitability (Graat *et al*., 1998).

Amprolium is a thiamine analogue that competitively inhibits the active transport of thiamine, negatively affecting *Eimeria* species without harming the host tissues (McDougald and Reid, 1997). Whereas, toltrazuril is a broad spectrum coccidiocidal compound which is efficacious against all types of coccidiosis encountered in different avian species (Greuel and Ruhrmann, 1986) and rabbits (Peeters and Geeroms, 1986; Singla *et al*., 2000). It is active against all intracellular developmental stages including those of schizogony and gametogony (Mehlhorn *et al*., 1984) and enhances immunity against poultry coccidiosis (Grief, 2000).

The development of varying degrees of drug tolerance against in-feed coccidiostats in European countries (Peek and Landman, 2003) and the inherent side effects of ionophorous coccidiostats (Dowling, 1992), urge producers to explore other control measures. This is of particular relevance because, except for some alternative keeping systems, most rabbit production systems depend on the pharmacological control of coccidiosis (González-Redondo *et al*., 2008).

To the best of our knowledge, no report has addressed the evaluation of the anticoccidial efficacy of the concurrent administration of both amprolium and toltrazuril in controlling natural rabbit intestinal coccidiosis. Therefore, the present study was conducted taking the above view into consideration with the objective to evaluate the efficacy of amprolium, toltrazuril and their concurrent use as anticoccidial agents in controlling natural intestinal rabbit coccidiosis. The therapeutic assessment was based on the estimation of production data (live body weight (BW), body weight gain (BWG), feed consumption, feed conversion rate, performance index (PI)) and oocysts output reduction, indicating anticoccidial activity.

Materials and Methods

Drugs

Amprolium HCl 20% W. S. P.® (Amprolium HCl 20%) was obtained from United Company for Chemical and Medical Preparations (UCCMA), Egypt. Each 100 g contains 20 g Amprolium HCl.

Baycox® (toltrazuril 2.5%) was obtained from Bayer Company, Bayer, Leverkusen, Germany. Each milliliter contains 25 mg toltrazuril.

Animals

Thirty naturally infected male New Zealand rabbits with intestinal coccidiosis ($32 \times 10^3 \pm 4.63$ oocyst per gram (OPG), and six coccidia free rabbits (11 weeks old with average BW 2000 ± 75 g), were used in this study. The studied rabbits were obtained from Governmental Farm, Faculty of Agriculture, South Valley University, Qena, Egypt. Prior to the study, all rabbits were proven to be coccidia free or infected by using a concentration floatation technique (Pritchard and Kruse, 1982). The coccidial species were microscopically identified following its sporulation in 2.5% w/v $K_2Cr_2O_7$ solution, by using morphological parameters (Eckert *et al*., 1995).

Housing and management

The rabbits were housed in galvanized wire cages (40 cm high × 50 cm width × 60 cm length) within the experimental animals' house, Faculty of Veterinary Medicine, South Valley University, Egypt. Fresh water was automatically available at all time. These rabbits were fed with commercial standard rabbit diet (each 100 kg of diet was formulated to contain 30% alfalfa hay, 25% ground yellow corn, 25% wheat bran, 14% soybean meal (44%), 3% cane-molasses, 1.5% lime stone, 1% sodium chloride and 0.5% vitamin and mineral premix) without any anti-parasitic or anti-coccidian drugs prior to sampling. Furthermore, all rabbits were kept under the same managerial, hygienic and environmental conditions during the study period.

Experimental design

Group 1, the coccidia free rabbits (n=6) were used as negative control group (non-infected/non-treated), while the other 30 naturally infected rabbits with different *Eimeria* species (*Eimeria media*, *Eimeria intestinalis*, *Eimeria coecicola*, *Eimeria magna*, *Eimeria exigua*, *Eimeria perforans*, *Eimeria flavescens* and *Eimeria piriformis*) were randomly grouped into five equal groups (of each sex) as follow: G2: naturally infected–non-treated group (control positive), G3: naturally infected and treated with amprolium at a dose of 50 mg/kg BW for 4 successive days in drinking water, G4: infected and treated with toltrazuril at a dose of 5 mg/kg BW for 2 successive days in drinking water, G5: naturally infected and treated with toltrazuril at a dosage rate of 2.5 mg/kg BW for 2 successive days in drinking water, two doses with 5 day interval, and G6: naturally infected and treated with amprolium at a dose of 50 mg/kg BW for 4 successive days and toltrazuril (5 mg/kg BW) for 2 successive days in the drinking water.

Assessment of therapeutic efficacy

The therapeutic efficacy was assessed on the basis of absence of oocysts in faecal samples, no clinical signs and mortality rate as well as improvement of production data {live BW, BWG, feed consumption, feed conversion rate, PI} in treated rabbits as compared to infected untreated ones. Moreover, PI (%) was calculated using the following equation:

$$PI\ (\%) = (BW\ (kg)/FCR) \times 100$$

Where,

BW: The body weight (kg) on the 10th and 17th days after the start of anticoccidial treatment, and FCR: The feed conversion rate at the same periods (North, 1984)

Oocysts output per gram of faeces

Three faecal samples were randomly collected from each group at 0 days (pretreatment), and subsequently at 1, 2, 3, 4, 5, 6 and 7 days post treatment. The samples were transferred to the laboratory in controlled cold condition. The samples were immediately analyzed by McMaster technique to estimate the number of OPG (Kruse and Pritchard, 1982). Additionally, the percentage efficacy for amprolium, toltrazuril each and then for their combination was determined (Moskey and Harwood, 1941).

Statistical analysis

Statistical analysis was done using one-way analysis of variance (ANOVA). It was done to compare between control and other treated groups, followed by post-hoc analysis (Dunnett's test) using SPSS (statistical package for social sciences) version 17 according to Borenstein *et al*. (1997). The data were presented in form of mean±SE. The difference was considered statistically significant when $P<0.05$.

Results

Clinical signs

The coccidia infected rabbits in group G2 showed symptoms which include huddling, depression, dry fur, loss of appetite, weight loss, watery and bloody diarrhea, and dehydration. All coccidia infected and treated rabbits in groups G3, G4, G5 and G6 showed an improvement in their health conditions as compared to those in G2. This improvement was more pronounced among rabbits in the group G6.

The results concerning overall mortalities and production data (feed consumption, live BW, BWG, feed conversion rate and PI) on day 10 and 17 after the start of anticoccidial treatment were recorded in Table 1.

Overall mortality %

The overall mortalities were 33.33% and 16.66% in infected–non-treated rabbits (G2) on the 10th and 17th days post start of treatment, respectively. No mortalities were recorded in all infected treated groups except in G3 where the mortality was 16.66% on day 10.

Feed consumption

On the 10th and 17th days after the start of anticoccidial treatment, all the coccidia infected treated rabbits (G3, G4, G5 and G6) showed significant ($P<0.05$) increase in the feed consumption rate as compared to coccidia infected untreated rabbits (G2). The coccidia infected treated rabbits (G3 and G6) elicited non-significant ($P>0.05$) change as compared to

Table 1: The effect of amprolium, toltrazuril and both of them on live body weight, bodyweight gain, feed consumption, feed conversion rate, and performance index of naturally coccidia infected rabbits at day 10 and 17 from the beginning of the study. Values are means±SE (n=6)

Treatments	BW (g)			Average daily BWG (g/day)		Average daily feed consumption (g/day)		Feed conversion rate (kg/kg gain)		PI (%)*		Mortality rate			
												At (0 to 10th day)		At (10th to 17th day)	
	At (0 day)	At (10th day)	At (17th day)	At (0 to 10th day)	At (10th to 17th day)	At (0 to 10th day)	At (10th to 17th day)	At (0 to 10th day)	At (10th to 17th day)	At (0 to 10th day)	At (10th to 17th day)	No.	%	No.	%
G1	2010.17 ±7.07^{a}	2266 ±3.01^{a}	2452.80 ±1.61^{a}	25.58 ±0.54^{a}	26.69 ±0.54^{a}	82.40 ±2.08^{a}	83.2 ±1.60^{a}	3.23 ±0.07^{a}	3.12 ±0.08^{a}	70.15	78.53	0	0.00	0	0.00
G2	2008 ±4.70^{a}	2140.5 ±2.52^{e}	2231.60 ±2.38^{e}	13.25 ±0.44^{e}	13.01 ±0.47^{d}	68.5 ±0.37^{c}	69.30 ±0.50^{b}	5.19 ±0.08^{c}	5.33 ±0.28^{c}	41.24	41.84	2	33.33	1	16.66
G3	2005.6 ±4.99^{a}	2239.6 ±4.01^{c}	2376.60 ±4.03^{d}	23.40 ±0.23^{bc}	25.29 ±0.16^{b}	76.60 ±1.90^{ab}	82.70 ±0.90^{a}	3.28 ±0.03^{a}	3.27 ±0.02^{ab}	68.28	72.78	1	16.66	0	0.00
G4	2011 ±6.07^{a}	2238.67 ±3.28^{c}	2417.9 ±4.96^{b}	22.77 ±0.33^{c}	24.27 ±0.61^{b}	75.80 ±1.20^{b}	79.85 ±1.80^{a}	3.33 ±0.07^{a}	3.29 ±0.09^{ab}	67.23	72.56	0	0.00	0	0.00
G5	2015.8 ±4.21^{a}	2224 ±2.72^{d}	2388.20 ±4.36^{cd}	20.90 ±0.26^{d}	23.46 ±0.17^{c}	74.90 ±1.70^{b}	81.80 ±1.01^{a}	3.59 ±0.05^{b}	3.49 ±0.03^{b}	61.95	68.48	0	0.00	0	0.00
G6	2007 ±4.25^{a}	2254.6 ±3.20^{b}	2443.20 ±6.99^{a}	24.76 ±0.39^{a}	25.51 ±0.42^{ab}	80.30 ±2.10^{ab}	82.30 ±1.70^{a}	3.24 ±0.05^{a}	3.23 ±0.06^{a}	69.37	75.54	0	0.00	0	0.00

Means in the same column bearing different letters superscripts differ significantly (P<0.05). **G1: Control**, non-infected/non-treated group, **G2: Coccidiosis+untreated**, naturally infected–non-treated group (control positive), **G3: Coccidiosis+amprolium**, naturally infected and treated with amprolium at a dose of 50 mg/kg BW for 4 successive days in drinking water, **G4: Coccidiosis+toltrazuril**, infected and treated with toltrazuril at a dose of 5 mg/kg BW for 2 successive days in drinking water, **G5: Coccidiosis+toltrazuril 2 doses with 5 days interval**, naturally infected and treated with toltrazuril at a dosage rate of 2.5 mg/kg BW for 2 successive days in drinking water, two doses with 5 day interval, and **G6: Coccidiosis+amprolium+toltrazuril**, naturally infected and treated with amprolium at a dose of 50 mg/kg BW for 4 successive days and toltrazuril (5 mg/kg BW) for 2 successive days in the drinking water.* PI (%) = (BW (kg)/FCR) × 100

Table 2: The effect of amprolium, toltrazuril and both drugs on oocyst count ($\times10^3$)/g faeces (OPG) and % of OPG reduction (OPGR%) in naturally intestinal coccidia infected rabbits (n=6)

Treatment	Pretreatment oocyst count ($\times10^3$)	Oocyst count post treatment $\times10^3$													
		1st day		2nd day		3rd day		4th day		5th day		6th day		7th day	
		OPG	OPGR%	OPG	OPGR%	OPG	OPGR%	OPG	OPGR%	OPG	OPGR%	OPG	OPGR%	OPG	OPGR%
G2	43.3	44.2	-	45.2	-	46.1	-	47.1	-	48.1	-	49.1	-	50.1	-
G3	23.4	21.4	8.55	17.3	26.1	6.4	72.7	2	91.5	0	100	0	100	0	100
G4	24.2	22.4	7.4	18.3	24.4	10.1	58.3	3.1	87.2	1	95.9	0	100	0	100
G5	32.6	29.5	9.5	24.6	24.5	18.3	43.9	6.3	80.7	2.1	93.6	0	100	0	100
G6	39.9	35.7	10.5	28.7	28.1	8.5	79	0	100	0	100	0	100	0	100

G2: Coccidiosis+untreated, naturally infected–non-treated group, **G3: Coccidiosis+amprolium**, naturally infected and treated with amprolium at a dose of 50 mg/kg BW for 4 successive days in drinking water, **G4: Coccidiosis+toltrazuril**, infected and treated with toltrazuril at a dose of 5 mg/kg BW for 2 successive days in drinking water. **G5: Coccidiosis+toltrazuril 2 doses with 5 day interval**, naturally infected and treated with toltrazuril at a dosage rate of 2.5 mg/kg BW for 2 successive days in drinking water, two doses with 5 days interval, and **G6: Coccidiosis+amprolium+toltrazuril**, naturally infected and treated with amprolium at a dose of 50 mg/kg BW for 4 successive days and toltrazuril (5 mg/kg BW) for 2 successive days in the drinking water

non-infected/non-treated control group (G1). On the 17th day, all the coccidia infected treated rabbits (G3, G4, G5 and G6) provoked non-significant (P>0.05) change as compared to non-infected/non-treated control group (G1).

Body weight and body weight gain

On the 10th and 17th days after the start of anticoccidial treatment, all the coccidia infected treated rabbits (G3, G4, G5 and G6) showed significant (P<0.05) increase in the live BW and daily BWG as compared to coccidia infected untreated rabbits (G2). The coccidia infected treated rabbits of G6 group revealed significant (P<0.05) increase as compared to infected treated groups (G3, G4 and G5), meanwhile non-significant decrease was recorded as compared to non-infected/non-treated control group (G1).

Feed conversion ratio

On the 10th and 17th day after the start of anticoccidial treatment, all the coccidia infected treated rabbits (G3, G4, G5 and G6) showed significantly (P<0.05) decreased the feed conversion rate as compared to coccidia infected untreated rabbits (G2). Meanwhile, non-significant (P>0.05) change as compared to non-infected/non-treated control group (G1).

Performance index

On the 10th and 17th days after the start of anticoccidial treatment, all the coccidia infected treated rabbits in groups G3, G4, G5 and G6 showed a higher PI as compared to coccidia infected untreated rabbits (G2).

Oocysts output per gram of faeces

The results concerning the OPG and the percentage of reduction in OPG in faeces are shown in Table 2. All infected treated groups (G3, G4, G5 and G6) showed significant ($P<0.05$) reduction in OPG in faeces as compared to infected untreated group (G2). The OPG reach zero (00±00) on the 4th day post treatment in G6, 5th day in G3 and 6th day in both G4 and G5. Based on criteria of percentage of reduction in the OPG in faeces, it was observed that the concurrent administration of both amprolium and toltrazuril (G6) was superior (74%), followed by amprolium (G3) 71%, then toltrazuril 5 mg/kg BW (G5) 67.6% and finally toltrazuril 2.5 mg/kg BW at two doses with 5 day interval (G5) 64.6%.

Discussion

Rabbit coccidiosis is a common and widespread protozoan infection in commercial operations and is responsible for major pathogenicity in the definitive host (Al-Quraishy, 2012).

The coccidia infected un-medicated rabbits (G2) showed symptoms which include huddling, depression, dry fur, loss of appetite, weight loss, watery and bloody diarrhea, and dehydration. Similar findings were in accordance with that mentioned by (Paklandl, 2009; Oncel *et al*., 2011; Shameem *et al*., 2011). All coccidia infected and treated rabbits in groups G3, G4, G5, and G6 showed an improvement in their health conditions as compared to those in G2. This improvement was more pronounced among rabbits in the group G6. Needless to say, one would expect amprolium and toltrazuril to be effective at blocking the multiplication of coccidia. This is in line with previous studies that reported continuous administration of 10-15 p.p.m. of toltrazuril in the drinking water was highly effective in reducing oocysts output and in preventing clinical signs and macroscopic lesions in rabbits experimentally infected with *E. flavescens*, *E. intestinalis*, *E. magna*, *E. perforans* and *Eimeria stiedae* (Peeters and Geeroms, 1986). On the other hand, the oral administration of amprolium was highly efficacious against intestinal coccidiosis in Ambararow ewes (Abakar *et al*., 2005). The more pronounced improvement in G6 could be attributed to the augmented effect of both toltrazuril which is effective against all developmental stages of coccidia within the cells of an infected animal and amprolium which is effective against early developmental stages (Balicka-Ramisz, 1999). The overall mortalities were 33.33% and 16.66% in infected non-treated rabbits (G2) on the 10th and 17th days after the start of anticoccidial treatment, respectively. No mortalities were recorded in all infected treated groups except in G3 where the mortality was 16.66% on the 10th day post start anticoccidial treatment. The mortalities in intestinal coccidiosis may be owing to the disturbances in water and electrolyte balance occur in the parasitized part of the intestine before the appearance of the macroscopic lesions and are essentially characterized by a loss of water and sodium. The loss of sodium is compensated by the exchange of potassium from the blood, thereby leading to hypokalemia and causing death of the animal (Jithendran and Bhat, 1996). Amprolium and toltrazuril could reduce mortalities in coccidia infected treated groups; this coincided with a previous report (Mukiibi-Muka *et al*., 2001). On the 10th and 17th days after the start of anticoccidial treatment, the coccidia infected untreated rabbits (G2) showed significant ($P<0.05$) decrease in the feed consumption rate, live BW and daily BWG as compared to uninfected untreated rabbit control group (G1). Because diarrhea hinders the absorption of food from coccidia-induced damaged intestinal mucosa, this diarrhea can lead to weight loss and emaciation (Svensson, 1998). Moreover, the anorectic effects of coccidiosis coupled with depressed intestinal absorption would markedly reduce feed efficiency in rabbits. Eimerian infections cause many structural and functional changes to their hosts and have a negative impact on animal growth and food utilization (Grèes *et al*., 2003), as they induce nutrition imbalance and disturbance in food digestion and absorption (Taylor *et al*., 2007). The loss of BW was probably caused by disturbance of the metabolism of the small intestine due to infection of *E. magna* which resulted in the lack of sugar (Zulpo *et al*., 2007). In the present study, differences in weight gain of treated and untreated rabbits showed the potential economic losses inferred by coccidiosis. On the 10th and 17th days after the start of anticoccidial treatment, all the coccidia infected treated rabbits in groups G3, G4, G5 and G6 showed significant ($P<0.05$) increase in the feed consumption rate, live BW and daily BWG as compared to coccidia infected untreated rabbits (G2). High gains in the weight of treated animals may be attributed to high feed intake and accelerated feed conversion ratio (Morand-Fehr *et al*., 2002). Similar findings were also confirmed based on previous studies (Abakar *et al*., 2005; Iqbal *et al*., 2013). All the infected treated groups (G3, G4, G5 and G6) showed significant ($P<0.05$) reduction in OPG in faeces as compared to infected unmediated group (G2). Based on criteria of percentage of reduction in the OPG in faeces, it was observed that the concurrent administration of both amprolium and toltrazuril (G6) was superior (74%), followed by amprolium (G3) 71%, then toltrazuril 5 mg/kg BW (G5) 67.6% and finally toltrazuril 2.5 mg/kg BW in two doses with 5 day intervals (G6), 64.6%. Generally speaking, based on criteria of percentage of reduction in the OPG in faeces, amprolium, toltrazuril and their concurrent use were effective in reducing the coccidial oocysts excretion in natural intestinal coccidia infected rabbits. One would expect amprolium and/or toltrazuril to be able to control the infection in infected treated rabbits (G3, G4, G5 and G6). This was demonstrated by weight gain and final weights, which were comparable with the uninfected-untreated control rabbits and significantly higher than the infected-untreated control group. These results were in accordance with those previously mentioned studies (Mundt *et al*., 2003). Moreover, these findings were also confirmed by Redrobe *et al*. (2010). The superiority of the G6 which had received both amprolium and toltrazuril is due to the augmented effect of toltrazuril which is effective against all developmental stages of coccidia within the cells of an infected animal and amprolium which is effective against early developmental stages (Abakar *et al*., 2005).

From data in this study, it could be concluded that the use of amprolium, toltrazuril alone and in combination was able to control natural intestinal coccidial infection in rabbits. The combined use of both drugs can be proven to better manage the infection adequately due to the augmented effect of both drugs.

Acknowledgements

We thank the reviewers for their time to carefully review our manuscript. We believe that their positive comments substantially improved this article.

Conflict of interest

The authors declare that there are no conflicts of interest.

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