Comparative studies on the efficacy of toltrazuril and diclazuril against rabbit coccidiosis

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Abstract

Coccidiosis remains one of the most important infectious disease that causes digestive disorders in fattening rabbits. It is of utmost importance to adequately prevent this disease in rational rabbit production. In this work 30 New Zealand white rabbits, clinically healthy and free from coccidiosis with the age of 29 days old were used . The rabbits were randomly divided into 6 groups of 5 rabbits each. The 1st group was non infected non treated.2nd,3rd and the 4th groups of rabbits were inoculated with 50,000 sporulated oocysts of mixed Eimeria spp./rabbit orally at the day 32nd old. One of the infected groups did not receive treatment. The other two infected groups were given toltrazuril, diclazuril respectively and the 5th and 6th (non infected) groups were given toltrazuril, diclazuril respectively at the day34th old, as prescribed by manufacturers. After infection, rabbits were examined for clinical signs, body weight gain ,feed consumption and feed conversion rate(F.C.R.) determined. Blood samples were drawn , to examine the number of erythrocytes, hemoglobin, packed cell volume (PCV).Serum albumin, alkaline phosphatase (ALP), alanine amino transferase (ALT), aspartate aminotransferase (AST), creatinine and uric acid were determined .The results of this research showed that the infection of Eimeria spp. caused weight loss, accompanied by anemia and increased of ALP activity. In the present trial, the efficacy of toltrazuril compared with a diclazuril treated and non treated control groups in an Eimeria challenge model showed that treatment with toltrazuril, diclazuril prevented coccidiosis related mortality, improved weight gain and packed cell volume and reduced fecal scoures when compared to infected untreated normal control. The main weight gain, feed conversion rate (FCR) of rabbits medicated with toltrazuril were significantly higher than diclazuril medicated rabbits, no adverse reactions were observed with applied dose regimen of both drugs. As a conclusion, although diclazuril was efficacious, toltrazuril was superior and for this it should be recommended for therapy of coccidiosis in rabbits.

Key words: *coccidiosis , Eimeria spp., rabbits , toltrazuril .*

Introduction

Coccidiosis, caused by species of intracellular protozoan parasites belonging to the genus Eimeria (E.) (Phylum: Apicomplexa). It remains one of the economically most important disease in poultry production (**Dkhil *et al*., 2011).** Rabbit coccidiosis is considered to be the most threatening factor affecting rabbit production (**Peeters *et al*., 1984 ; Gonzalez-Redondo *et al*., 2008**) as it causes severe pathological changes to infected animals leading finally to huge economic losses allover rabbit farms industry (**Baker, 2007; Taylor *et al*., 2007**). All domestic rabbits can be infected by coccidia, especially the younger populations between 1 and 4 months of age (**Pakandl *et al*., 2008).**

The morbidity and mortality in young rabbits can be as high as 90% and 60%, respectively (**Meng *et al*., 2007**).This disease occurs in two forms, hepatic and intestinal, the latter being more common than the former (**Bhat *et al*., 1996**). E. magna and E. media are the most dominant species isolated in professional rabbit husbandry today **(Coudert *et al*., 2003).** E. intestinalis and E. coecicola are generally the most predominant species in domestic rabbits in Egypt (**El-Shahawi *et al*., 2011**). Coccidiosis has a direct impact on performance but also acts in synergy with Epizootic Rabbit Enteropathy (ERE) (**Coudert *et al*., 2000**).The infection of Eimeria spp. can change the blood profiles of hosts, characterized by anemia (**Bhat *et al*., 1996; Kulisic *et al*., 2006)** and increased Alkaline phosphase (ALP) serum activity (**Hartcourt-Brown, 2003**), Renal tissues of the infected rabbits were damaged (**Metwaly *et al*., 2011**). Therefore, prevention of coccidiosis remains one of the most importance.

Toltrazuril is anticoccidial drug, very effective against coccidiosis in rabbits, pigs, sheep and cattle (**Haberkorn and Mundt, 1988**). The first clinical trial on rabbit intestinal coccidiosis with toltrazuril indicated successful treatment with 1 ml per litter (**Zurliiski and Vladiminova, 1988**).Medication of rabbits with 25 ppm only during schizogony or gamogony 2 days treatment, (repeated after 5 days) quickly reduced clinical signs and oocyst output in hepatic and intestinal coccidiosis **(Peeters and Geeroms 1986**;**James and Campbell, 1991**). The mode of action of Toltrazuril has not yet been fully described. It is assumed that it interferes with the function of a special organelle present in Apicomplexa **(Hackstein *et al*., 1995).**

Diclazuril is a chemical substance synthesized from the benzeneacetonitrile class of compounds which is developed successfully as an anticoccidial agent for poultry, rabbits and sheep **(Hu *et al*., 2009**). Addition of Diclazuril at the dose of 5 ppm in the drinking water of naturally coccidian infected bird induced the same effect as 25 ppm of toltrazuril as a treatment for coccidiosis in chickens (**El- Banna *et al*., 2005**). Diclazuril was administered either prophylactically at 0.5, 1 or 2 mg/kg bodyweight subcutaneously two days before rabbit inoculation with 20, 000 oocysts of a mixed – species of field isolate of Eimeria or therapeutically at 1, 2 or 4 mg/kg bodyweight five days after Eimreia inoculation caused a significant reduction in oocyst shedding but the lower doses resulted in only a moderate reduction. (**Pan *et al*., 2008**). According to the anticoccidial properties of triazinones, diclazuril is active against intracellular developmental stage of coccidia, mainly during schizogony and gametogony. After diclazuril treatment, the first and second generation schizonts show its extensive degenerative changes, which are characterized by the loss of internal structure of the parasite, the appearance of many intracytoplasmic vacules and incomplete merogony. This leads to complete degeneration of schizonts and gamonts (**EFSA, 2007).**

Recently, tolerance studies in rabbits for fattening and breeding demonstrate that diclazuril was tolerated at six-fold the highest dose authorized for use in chickens and turkeys for fattening (1 mg/kg feed) **(EFSA, 2007),** diclazuril had very low acute toxicity and was not mutagenic, genotoxic, carcinogenic, embryotoxic, foetotoxic or teratogenic (**EFSA**, **2007, 2008)**.High doses of diclazuril(1280mg/kg bw per day) were teratogenic to rabbits, whereas a dose of 320 mg /kg bw per day was not teratogenic but slightly fetotoxic. (**Dom *et al*., 1997).**

A complete blood picture is a good indication of general health, as stress and numerous illness can modify haematological parameters, especially with regard to erythrocyte and lymphocyte count **(Hinton *et al*., 1982).** Infections of Eimeria spp. can change the blood profiles of hosts, characterized by anemia (decreasing of red blood cells and hemoglobin), increasing leukocytes (**Bhat *et al*., 1996** ; **Kulisic *et al*., 2006; Polijicak-Milas *et al*., 2009**), increasing packed cell volume (PCV), no change of eosinophils and decreasing lymphocytes (**Kulisic *et al*., 2006)**. The objective of this study was to

compare between Toltrazuril and Diclazuril, with regard to their effect on experimental coccidiosis of rabbits considering parasitological, haematological and clinical biochemical parameters, after inoculation with a mixed isolate of rabbit Eimeria species. The effect of treatment evaluated on the basis of body weight gain, feed consumption and faecal oocyst counts, beside the possible alterations on haematological, hepatorenal functions parameters.

Materials and Methods

Animals

A total of 30 weaned New Zealand white rabbits (29 days old) of either sexes were enrolled in the study. The rabbits were then put in a room with a natural ventilation and light, humidity (60-70%).The rabbits were placed in 35×40×40cm cages for individual animals made of stainless steel, with a wire floor. The rabbits were fed ad libitum on standard rabbit feed and were given water ad libitum via an automatic drinking trough. These rabbits had been treated with 1g/L sulfaquinoxalin in drinking water before weaning (21 to29) days of age to eliminate natural contamination with coccidia. Rabbits, were homogeneously distributed over 6 experimental treatment groups (5 rabbits each).

Group A : non infected non treated(negative) control group (NINT)
Group B : infected non treated (positive control) group (INT)
Group C : infected + toltrazuril treated group (I Toltra)
Group D : infected + diclazuril treated group (I Dicla)
Group E ; non infected + toltrazuril group (NI Toltra)
Group F: non infected + diclazuril group (NI Dicla)

Parasites

The gut contents and scrapings of naturally infected rabbits were mixed and soaked overnight in 2, 5% potassium dichromate solution. The suspension was filtered through a fine sieve and filtrate was centrifuged (1500 rpm) for 2-3 minutes. The supernatant was discarded and the sediment was re-suspended in saturated solution of sodium chloride and centrifuged. The top layer was pipetted out, mixed with water, kept overnight and supernatant was discarded. The sediment containing oocysts was re-suspended in 2.5% potassium dichromate solution. The solution containing oocysts was poured into petri dishes and kept at 30 cº for 24 -72 hours with forced aeration and humidity. Latter oocysts were washed out by centrifugation with distilled water to remove the residues of potassium dichromate, after which the oocysts were counted using haemocytometer and diluted with distilled water for obtaining 50, 000 of sporulated oocysts per 2 ml of inoculum. **(Hodgson, 1970; Long *et al*., 1976)** to inoculate rabbits by oral gavaging (each rabbit with 50, 000 sporulated oocysts of mixed Eimeria spp).

Drugs and administration

Toltrazuril oral solution (Herricox® 2.5%, product of Herris Group, USA).
Diclazuril water soluble formulation (Diclasol® 1%, Pharma Swede – Egypt)
Group A &B (Control groups) received 1 ml of tap water /rabbit for 2 days
Group C&E (Toltra group) was treated with 2.5 % toltrazuril (2.5% at 25 ppm in drinking water for 2dpi) and group D &F (Dicla group) was treated with diclazuril(1% at 5ppm 2 dpi).
Toltra and Dicla were administered orally following the commercially available suspensions.

Rabbits were clinically observed once daily during the entire study period and mortality and morbidity was noted. Once every 24 hour, fresh faecal pellets were collected and weighed for each rabbit from day 0 -10 post-treatment. Faecal pellets were homogenized in tap water, and then 2 g of the mixture was put into 60 ml of saturated salt solution (**Velkers *et al*., 2010)**.The suspension was then emptied into a modified McMaster chamber **(Coudert *et al*. 1995)**.Five minutes later the oocysts float to the top of the solution.The oocysts within the

chamber were counted under the microscope and the oocyst per gram (OPG) was calculated.

Individual body weights were measured weekly at days 29th, 36th, 43rd, 50th and 57th, feed consumption, feed conversion rate (FCR) for each group was also recorded.

Two blood samples were drained from the vena marginalis of each rabbit at 0, 7th and 14th days post treatment. The first sample was taken with anticoagulant (EDTA) for hematologic analysis of (RBCs count, Hb. Content and PCV%) according to **Jain, (1986).**The second sample was collected without anticoagulant for the preparation of clear non-hemolysed serum. were analyzed for serum clinical biochemistry. Variables parameters included serum albumin **(Doumas 1971),** alanine aminotransferase (ALT), aspartate amino transferase(AST) according to **Reitman and Frankel, (1957**), alkaline phosphatase(ALP) according to **Belfield and Goldberg, (1971),** creatinine (**Bartels 1971)** and serum uric acid **(Trinder 1969)**.The therapeutic efficacy was assessed on the basis of weight gain, feed consumption, number of ooccysts in the faecal samples and clinical signs in treated infected rabbits as compared to infected untreated rabbits, all groups compared with normal (negative)control.

Results

Weight gain and feed consumption: Due to the coccidial challenge, weight gain was significantly lower in the INT rabbits during the 10 days period following the inoculation ($P \leq 0.01$) (Table 1). During 36- 43days, the weight gain of the INT, and Dicla rabbits was significantly lower than the NINT rabbits ($P \leq 0.001$) and ($P \leq 0.01$)respectively, for the total period there were continous significantly lower weight gain in the INT rabbits compared to the other groups($P \leq 0.05$), ($P \leq 0.01$). Toltra treated rabbits had the highest numerical weight gain compared to the NINT and Dicla treated rabbits also these differences were not statistically significant. Weight gain was significantly lower for INT($P \leq 0.001$) and significantly higher for INT toltra, INT dicla, NI toltra.

The amount of feed consumped by rabbits of each individual cage was measured at days 29, 36, 43, 50 and 57and the results are represented in (Table 2). Feed consumped for the period was defined as the cumulative weight of feed introduced to the cage, minus the weight of unconsumped feed in the feed bin received immediately before making the assessment. Thus feed usage included wasted as well as consumed feed. INT rabbits had a significantly lower feed intake compared with NINT and Toltra and Dicla treated rabbits, which was most pronounced between d36 and d43of age ($P \leq 0.001$).Infected and non infected toltra treated groups had a significantly higher feed intake and feed conversion ratio(FCR)($P \leq 0.05$) ($P \leq 0.01$) respectively compared with NINT group.

Oocyst excretion: The rabbits of group B infected unmedicated showed high oocyst output ($P \leq 0.001$)by the 2nd day and lasted to maximum during the days 2-10 as compared by the rabbits of group A (non infected non treated).Total OPG in the Toltra group was significantly lower ($P \leq 0.001$) by the 5th day post treatment and in Dicla group ($P \leq 001$)by the 7th day post treatment followed by a complet decline of oocyst count (Table 3).

Haematological indicators : The measured values of the erythrocyte count, the haemoglobin concentration, packed cell volume (PCV), are illustrated in (Table 4).

A significant decrease of total erythrocytic count and haemoglobin concentration in INT group ($P \leq 0.001$) at day 0 ($P \leq 0.01$), at day 7 ($P \leq 0.05$), at day 14 post treatment compared to the control group. The erythrocytic count, Hb value and PCV percentage of the infected treated rabbits were significantly lower than the normal control group at the day 0 and 7 post treatment.

Biochemical indicators : Liver function parameters showed a significant increase in serum AST ($P \leq 0.001$), ALT ($P \leq 0.05$) ALP ($P \leq 0.001$) and a significant decrease in serum albumin ($P \leq 0.001$) in rabbits with coccidiosis

compared to normal control (Table 5).The results of treatment of rabbit coccidiosis with toltra or dicla had a good response changed parameters that it could returned to early normal values within two weeks post treatment as there was no significant difference in these parameters between control and treated groups except serum ALP activity that it was still very significant increased (P≤0.001). Serum uric acid level was significantly elevated (P≤ 0.001) in infected non treated group compared to non infected non treated group (Table 6). Both creatinine and uric acid levels were within normal levels in both infected and non infected treated groups.

Table (1). Effect of toltrazuril and diclazuril medication on body weight gain in rabbits experimentally infected with Eimeria species (n =5)

	Control non infected non treated	Infected non treated	Infected Toltra treated	Infected Dicla treated	Non infected Toltra treated	Non Infected Dicla treated
Start weight (gm/rabbit)	680± 5.48	688± 2, 70	698± 2.17	698± 2.17	692± 1, 41	698± 2.21
d29-d36 (gm/day/rabbit)	48±2.09	41±1.18*	44±1.00	46±1.049	49±1.18	48±1.516
d36-d43(gm/day/rabbit)	50±0.707	25.2±0.47***	49+-0.89	42±.0.948**	48±0.84	48±0.548
d43-d50(gm/day/rabbit)	48±0.95	44±0.707*	49.8±0.66	47±1.00	49±0.63	47±0.89
d50-d57(gm/day/rabbit)	50±1.14	48±1.05	52±0.95	52±0.707	50±0.836	52±0.707
Weight gain d-29-d57 n (gm / rabbit }	1374±5.83	1100.4±5.22***	1363.6±8.36	1309±11.40**	1472±2.59***	1365±4.18
End weight(gm / rabbit)	2054± 2.28	1795.4±2.32***	2061.6±3.24	2007±3.86***	2164±1.58***	2063±3.30

Table (2). Effect toltrazuril and diclazuril medication on feed consumption and feed conversion rate (FCR)in rabbits experimentally infected with Eimeria species.(n=5) Values are Mean± standard error

Period	Control non Infected Non treated	Infected Non treated	Infected Toltra treated	Infected Dicla treated	Non Infected Toltra treated	Non Infected Dicla treated
D29-d36 (gm/week/rabbit)	654±4.30	600±1.96***	648±3.39	645±2.91	650±3.56	658±2.73
D36-d43 (gm/ week/rabbit)	904±5.10	600±2.36***	650±2.55***	644±2.55***	650±3.54***	658±2.55***
D43-d50 (gm/ week/rabbit)	902±3.39	966±4.00***	986±5.09***	966±4.00***	960±3.54***	938±5.83**
D50-d57 (gm/ week/rabbit)	1034±2.92	994±4.30***	1090±2.24***	1074±2.92***	1100±5.35***	1036±3.31
Total period d-29 -d57(gm/rabbit)	3494±4, 60	3160±8.36***	3374±4.6***	3329±3.29***	3360±7.07***	3290±5.48***
F.C.R.	2.52±0.02	2.89±0.02***	2.42±0.03*	2.54±0.01	2.33±0.04**	2.45±0.02

Values are means ± standard error, * Significantly different at P≤0.05 compared with control, **Significantly different at P≤0.01compared with control, ***Significantly different at P≤0.001 compared with control

Table (3). Effect of toltrazuril and diclazuril medication on daily oocysts count/gram of faeces in rabbits experimentally infected with Eimeria species

Days post treat.	Control non inf.non treated	Inf. non treated	Inf. toltra treated	Inf. dicla treated	Non inf. Toltra treat.	Non inf. Dicla treat.
0	$2.03x10^3$±0.18	$2.33x10^3$±0.18	$2.05x10^3$±0.05	$2.09x10^3$±0.04	$1.8x10^3$±0.04	$1.6x10^3$±0.07
1	$2.0x10^3$±0.58	$2.83x10^3$±0.12	$1.73x10^3$±0.09*	$1.87x10^3$±0.09	$1.16x10^3$±0.09**	$1.3x10^3$±0.12
2	$2.06x10^3$±0.12	$1.5x10^4$±0.12***	$1.4x10^3$±0.12**	$1.8x10^3$±0.12	$0.8x10^3$±0.12***	$0.87x10^3$±0.09***
3	$2.2x10^3$±0.14	$1.7x10^4$±0.07***	$0.8x10^3$±0.06***	$1.76x10^3$±0.03*	$0.73x10^3$±0.04***	$0.85x10^3$±0.12***
4	$2.7x10^3$±0.05	$2.5x10^4$±0.29***	$0.68x10^3$±0.04***	$1.75x10^3$±0.04***	$0.68x10^3$±0.04***	$0.73x10^3$±0.09***
5	$2.5x10^3$±0.14	$2.86x10^4$±0.05***	$0.53x10^3$±0.09***	$1.73x10^3$±0.06**	$0.47x10^3$±0.007***	$0.56x10^3$±0.03***
6	$2.53x10^3$±0.18	$2.9x10^4$±0.06***	Nil	$1.27x10^3$±0.09***	Nil	$0.5x10^3$±0.58***
7	$2.6x10^3$±0.12	2.8710^4±0.11***	Nil	$1.2x10^3$±0.12***	Nil	Nil
8	$2.33x10^3$±0.18	$2.9x10^4$±0.58***	Nil	Nil	Nil	Nil
9	$2.43x10^3$±0.13	$1.8x10^4$±0.08***	Nil	NIL	Nil	Nil
10	$2.3x10^3$±0.12	$1.4x10^4$±0.08***	Nil	Nil	Nil	Nil

Table (4). Mean values of some haematological parameters in treated rabbits with toltrazuril and diclazuril.

Group	0 days post treatment			7 days post treatment			14 days post treatment		
	RBCS 10^6/ul	H.b. g/dl	P.C.V. %	RBCS 10^6/ul	H.b. g/dl	P.C.V. %	RBCS 10^6/ul	H.b. g/dl	P.C.v %
Control non inf. non treated	4.83 ±0.10	9.5 ±0.08	28.5 ±0.17	4.47 ±0.09	9.17 ±0.34	28.67 ±0.24	5.0 ±0.58	9.5 ±0.58	28.67 ±0.35
Inf. non treated	3.33 ±0.18 ***	7.33 ±0.08 ***	28.23 ±0.19	3.13 ±0.3 **	6.60± 0.87 *	29.0 ±0.12	3.27 ±0.12*	6.60± 0.87*	29.0 ±0.12
Infected toltra treated	3.83 ±0.09 ***	9.5 ±0.58	29, 0 ±0.29	3.66 ±0.18 *	7.73 ±0.12 *	23.0 ±0.35 ***	4.16 ±0.09	9.00±0.31	28.33 ±0.18
Inf. dicla treated	3.8 ±0.06 ***	8.52 ±0.18 **	28.65 ±0.26	3.66 ±0.08 **	7.5 ±0.23 **	22.0 ±0.46 ***	4.1 ±0.15	9.00±0.52	28.66 ±0.18
Non inf. toltra treatrd	4.5 ±0.17	8.3 ±0.59	28.33 ±0.09	4.5 ±0.17	8.26 ±0.18	28, 66 ±0.18	4.7 ±0.12	9.33 ±0.09	28.93 ±0.23
Non inf. dicla treated	4.7 ±0.58	8.70 ±0.60	28.5 ±0.26	4.6 ±0.06	8.5 ±0.58	29.16 ±0.71	4.9 ±0.58	8.66 ±0.2	28.97 ±0.15

Values are means ± standard error, * Significantly different at P≤0.05 compared with control, **Significantly different at P≤0.01compared with control, ***Significantly different at P≤0.001 compared with control

Table (5). Mean values of some serum liver function parameters in treated rabbits with toltrazuril and diclazuril.

Group	0 day post treatment				7 days post treatment				14 days post treatment			
	AST U/L	ALT U/L	ALP U/L	Albumin g/dl	AST U/L	ALT U/L	ALP U/L	Albumin g/dl	AST U/L	ALT U/L	ALP U/L	Albumin g/dl
Control non Inf. non treated	36.00 ±1.15	34.00 ±2.31	22.00 ±1.15	4.20 ±0.12	42.33 ± 0.27	39.67 ±3.18	25.66 ± 1.2	4.00 ± 0.12	38.00 ± 1.15	35.00 ± 1.73	27.67 ± 1.45	4.30 ± 0.06
Inf. Non treated	65.00 ±1.15***	41.00 ±0.58*	290.00 ±5.77***	3.00 ±0.06***	72.00 ±1.63 ***	43. 00 ± 0.58	314.67 ± 2.4***	2.80 ± 0.12***	70.00 ± 2, 89***	40.00 ± 2.89	306.67 ± 8.82***	2.50 ± 0-06 ***
Inf. treat. toltra	30.00 ± 1.77 *	45.00 ±2.88 *	300.0 ±5.77***	3.37 ± 0.09 **	68.00 ±0.58***	104.00 ± 0.58 ***	396.00 ±1.15***	3.60 ± 0.09*	53.33 ± 1.76**	90.0 0 ± 2.89***	311.67 ± 4.41***	4.03 ± 0.09
Inf. treated dicla	28.00 ±1.10 **	26.00 ±2.28	270.0 ±5.77***	3.5 ± 0.06 **	29.0 ±0.58***	51.0 ±0.58*	234.00 ± 1.15***	3.70 ± 0.12	32.67 ± 2.4	47.67 ± 1.45**	220.0 ± 5.77***	3.9 ± 0.06 **
Non inf. treated toltra	39.00 ± 4.28	40.00 ± 3.46	12.25 ±1.7 **	3.50 ±0.06**	37.67 ±0.88 **	40.33 ± 4.33	27.66 ±1.45	3.40 ± 0.21	36.30 ± 0.58	44.00 ± 1.15**	27.66 ± 0.89	4.20 ± 0.12
Non inf. dicla treat.	20.00± 1.84 ***	29.00±1. 84	17.00±2. 02	3.3±0.06 **	26.67±0. 88 ***	25.33±0. 33	28.0±1.1 5	3.7±0.004	25.0±0.5 8 ***	24.0±0.5 8 **	30.0±1.1	3.57±0.09

Table (6). Mean values of some serum kidney function parameters in the serum of rabbits treated with toltrazuril and diclazuril.

Group	0 day post treatment		7 days post treatment		14 days post treatment	
	Creatinine Mg/dL	Uric acid Mg/dL	Creatinine Mg/dL	Uric acid Mg/dL	Creatinin Mg/dL	Uric acid Mg/dL
Control non inf. non treated	0.78±0.04	1, 06±0.05	0.55±0.08	0.97±0.09	0.53±0.12	0.84±0.05
Inf. non treated	0.62±0.06	1.8±0.03***	0.67±0.09	1.77±0.09**	0.64±0.05	1.72±0.07***
Inf. treat. Toltra	0.74±0.05	1.0±0.07	0.65±0.03	0.86±0.05	0.52±0.06	0.84±0.05
Inf. treat. Dicla	0.78±0.04	0.84±0.02**	0.8±0.03*	0.8±0.12	0.52±0.06	0.7±0.05
Non inf. treat. Toltra	0.58±0.04*	0.62±0.06**	0.53±0.08	0.87±0.09	0.42±0.06	0.84±0.05
Non inf. treat. Dicla	0.6±0.05*	1.0±0.07	0.57±0.12	0.67+-0.18	0.42±0.06	0.52±0.05**

Values are means ± standard error, * Significantly different at P≤0.05 compared with control, **Significantly different at P≤0.01compared with control, ***Significantly different at P≤0.001 compared with control

Discussion

Coccidiosis in post-weaned rabbit cause loss of body weight significantly, the loss of body weight was probably caused by the disruption of metabolism in the small intestine which resulted in the lack of sugar and consequently weight loss as reported by (**Zulpo *et al*., 2007).**The loss of body weight has been reported in cows, goats, horse, sheep, dogs and chickens infected with Eimeria spp. **(Soulsby, 1986**) Our results indicate that toltrazuril was more effective in improving mean weight gain when compared to the unmedicated and infected group B. In addition, toltrazuril was also more efficacious than diclazuril in improving mean weight gain, feed conversion rate.The results of this study was agreed with those of **Ramadan *et al*., (1997)** who showed that the

addition of toltrazuril to the drinking water of broiler chickens improved body weight gain.

In a controlled, randomized, blinded experimental study, the effects of treatment with Toltrazuril (two applications), Diclazuril (two application) in the pre-patent stage of coccidia infections were compared with regard to their influence on oocyst excretion. Toltrazuril reduced significantly both the duration and the amount of oocyst excretion and the overall of cumulative excretion prevalences, while Diclazuril exhibited no such effect. The dose of 25 ppm of toltrazuril for two consecutive days was found to be highly effective in coccidian infected rabbits which is in agreement with the previous report of **Zurliiski and Vladiminova (1988).** This dose resulted into zero OPG while **James and Campbell (1991)** reported that two 48 hour treatments with 25 ppm of toltrazuril in water, 5 days apart reduced output to zero approximately 40 days in hepatic and intestinal mixed infection, and in hepatic coccidiosis **(Singla *et al*., 2000)**. Zero OPG on day, 6 post treatment with toltrazuril indicated an indirect effect on the free living stages due to severe suppression of or the killing effect on the proceeding stages.Thus it is concluded that toltrazuril given at 25 ppm for two days was an effective method of reducing oocysts due to intestinal coccidiosis to nil.

Infection of Eimeria spp. caused significant decrease of erythrocytes and haemoglobin concentrations ($P \leq 0.001$) compared to the normal control group. This data showed that rabbits infected with Eimeria spp. suffered from anemia. Anemia was probably due to the damage of the intestinal mucosal epithelium and blood vessels by Eimeria spp. A decrease in the number of erythrocytes and hemoglobin, with a form of anemia as reported in dogs and sheep suffering from coccidiosis (**Sahinduran *et al*., 2006**; **Kaymaz *et al*., 1999**). At day 7 post treatment, the experimental infection resulted in anemia. Anemia occured due to intestinal destruction resulting in blood loss as a consistent finding in Eimeria species infection in chickens **(McDougald and Reid, 1997).** There was no significant difference in PCV between the infected non treated rabbits and the control normal group, this result is similar with **Kaymaz *et al*., (1999)** they reported that coccidiosis in dogs showed no change in PCV**.**The significant decreased of red blood cells (RBC) and hemoglobin (Hb) of the infected rabbits relative to the control normal group is an indicator of anemic animal.

Regarding liver and kidney function parameters, there was a significant increase in serum AST, ALT, ALP in rabbits infected with coccidiosis. The alteration of liver enzymes suggested that the liver might be adversely affected by coccidiosis. In rabbits, ALP is found in all tissues, mostly in the epithelial cells of intestine, tubulus renalis, osteoblast, liver and placenta, infection of Eimeria magna destroyed the epithelial cell of intestine. The inflammatory reaction caused an increasing cell activity and change in cell permeability; consequently, the ALP was released into the plasma and body liquid **(Hartcourt-Brown, 2003).** Our results revealed a significant increased in serum ALP level in the coccidian infected rabbits, this results was nearly similar to those observed by **Hana, *et al*., (2011).** The decrease in serum albumin could be attributed to the disruption of lysosomal membranes under the effect of various toxicants leading to liberation of their hydrolytic enzymes lysis and dissolution of the target material (**Ebaid *et al*., 2007**). Intestinal eimerian infection can alter and affect other organs than their final sites of multiplication, in lambs suffering from intestinal coccidiosis a membrane proliferative glomerulonephritis was reported(**Majid and Winter, 1986**). Malfunction in the glomerular filtration results in the retention of substances including uric acid, and this may be responsible for their high serum level in the infected group (**Metwaly, *et al*., 2011).**

Conclusion : The results of this work concluded that the infection of Eimeria spp. in rabbits caused weight loss, accompanied by anemia, and increasing of ALP activities. There were correlations between clinical symptoms, and blood profile of rabbits infected with Eimeria spp. for seven days. These findings were useful

to have a better understanding of pathophysiology of Eimeria spp. infection in rabbits Treatment of coccidiosis in rabbits is possible with oral toltrazuril or diclazuril. Toltrazuril had a more efficacy in controlling rabbit coccidiosis infestation than diclazuril.

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دراسة مقارنه لتأثيرات مركبي التولترازوريل و الديكلازوريل على طفيل الكوكسيديا في الأرانب

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الملخص العربى

تهدف هذه الدراسة الى تقييم كفائه استخدام كل من التولترازوريل والدايكلازوريل في ارانب نيوزيلاندى معديه تجريبيا بطفيل الايميريا المعوية - اجريت التجربه على 30 ارنب عمر 29 يوم- قسمت الى سته مجموعات متساويه-المجموعه الاولى اعتبرت مجموعه ضابطه(غير معالجه و غير معديه).-المجموعه الثانيه مجموعه ضابطه معديه تجريبيا بجرعه50000 حويصله كوكسيديا معويه وغير معالجه- مجموعه مصابه تجريبيا بطفيل الكوكسيدبا وتعالج بمركب التولترازوريل(25 جزء في المليون لمده يومان فى ماء الشرب)- مجموعه مصابه تجريبيا بطفيل الكوكسيديا وتعالج بمركب الديكلازوريل(5 جزء في المليون لمده يومان في ماء الشرب)- مجموعه غير مصابه وتعالج بمركب التولترازوريل والمجموعه الاخيره غير مصابه وتعا لج بمركب الديكلازوريل- تم سحب عينات دم وسيرم للفحص الهيماتولجى- كيمياء السيرم- تم تقييم كفائه المركبين في علاج المرض وذلك بالاعتماد على حساب الوزن المكتسب،معدل استهلاك العلف, معامل التحويل الغذائى وعدد الحويصلات في البراز بالاضافه إلى التحليل الكيميائي الحيوي لبعض مكونات الدم وبعض عناصر السيرم (الالبيومين وإنزيم الاللأنين امينوترانسفيرز والاسبرتيت امينوترانسفيرز و الأكالين فوسفاتيز والكرياتينين وحمض اليوريك. بالنسبة للمجموعة المصابة والتى تم إعطائها دواء التولترازوريل فقد سجل نقص في عدد الحويصلات في البراز إما بالنسبة لعقار الدايكلازوريل فقد أعطى نتائج متشابه في مدد اطول. وقد وجدت زيادة معنوية في الوزن المكتسب ومعامل التحويل الغذائى في الأرانب التي أعطيت التولترازوريل عن الأرانب التي أعطيت الدايكلازوريل- وقد خلصت الدراسة إلى كفائه كل من التولترازوريل واليكلاروزوريل في علاج الكوكسيديا في الارانب ولكن مركب التولترازوريل كان اكثر فاعليه من العلاج بمركب الدايكلازوريل.