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Research Article

Effects of Albendazole Treatment on Haematological and Biochemical Parameters in Healthy and *Toxocara canis* Infected Mice

Ender YARSAN
Ankara University, Faculty of Veterinary Medicine, Department of Pharmacology and Toxicology, Ankara - TURKEY
Çiğdem ALTINSAAT
Ankara University, Faculty of Veterinary Medicine, Department of Physiology, Ankara - TURKEY
Hasan AYÇİÇEK
Gülhane Military Medical Academy, Department of Parasitology, Ankara - TURKEY
Fatma ŞAHİNDOKUYUCU
Ankara University, Faculty of Veterinary Medicine, Department of Pharmacology and Toxicology, Ankara - TURKEY
Faruk KALKAN
SSK Ankara Hospital, Biochemistry Laboratory, Ankara - TURKEY

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Abstract: *Toxocara canis* is a nematode of the family Ascaridae. Following ingestion by dogs, the infective eggs hatch and larvae penetrate the gut wall and migrate into various tissues. There are two main clinical forms of *T. canis* infection; visceral larva migrans and ocular larva migrans. Toxocariasis is treated with antiparasitic drugs, such as diethylcarbamazine, albendazole and mebendazole. In this study, the effects of albendazole treatment on haematological and biochemical changes in healthy and *T. canis* infected mice were evaluated. Four study groups were used: Group 1 was assigned as the control, Group 2 was given infective *T. canis* eggs (as 1500 infective eggs), Group 3 was given albendazole (as 100 mg/kg b.w.) and Group 4 was given *T. canis* and albendazole. Total leukocyte counts, total eosinophil counts, differential leukocyte counts in the blood; and urea, creatine, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) activities in serum were determined on days 8, 15 and 28. The data obtained from this study show that total leukocyte counts and total eosinophil counts increased significantly in *T. canis* infected mice. These increases were observed in Group 2 in particular. Albendazole treatment in *T. canis* infected mice prevented these increases to some degree. In addition, enzyme activities in serum changed with *T. canis* infection, but these changes were not statistically significant.

Key Words: *Toxocara canis*, haematology, some biochemical parameters, albendazole, mouse

Sağlıklı ve *Toxocara canis* ile Enfekte Farelerde Albendazolun Hematolojik ve Biyokimyasal Parametrelere Etkileri

Özet: *Toxocara canis* Askaridae familyasına bağlı bir nematottur. Enfektif yumurtaların ağız yoluyla köpekler tarafından alınmasını takiben yumurtalar açılır, larvalar bağırsak duvarına penetre olur ve daha sonra çeşitli dokulara göç eder. *T. canis* enfeksiyonunun iki önemli klinik formu vardır; bunlar visseral larva migransı ve oküler larva migransıdır. *T. canis* enfeksiyonlarının sağaltımında antiparaziter ilaç olarak dietilkarbamazin, albendazol ve mebendazol kullanılır. Bu çalışma kapsamında sağlıklı ve *T. canis* ile enfekte edilen farelerde albendazol sağaltımının hematolojik ve biyokimyasal parametreler üzerine etkileri değerlendirilmiştir. Bu amaçla çalışmada 4 grup oluşturulmuştur; Grup 1 kontrol olarak tutulmuş, Grup 2'ye enfekte *T. canis* yumurtası verilmiş (1500 enfekte yumurta olacak şekilde), Grup 3'e albendazol uygulanmış (100 mg/kg canlı ağırlık dozunda), Grup 4'e ise *T. canis* ve albendazol birlikte verilmiştir. Fizyolojik ve biyokimyasal parametrelerin göstergesi olarak 8., 15. ve 28. günlerde kanda toplam lökosit sayısı, toplam eozinofil sayısı, diferensiyel lökosit sayısı ve serumda üre, kreatinin, aspartat amino transferaz (AST), alanin aminotransferaz (ALT), alkalen fosfataz (ALP) etkinlikleri saptanmıştır. Elde edilen sonuçlar *T. canis* ile enfekte farelerde toplam lökosit ve eozinofil sayılarının önemli oranda arttığını göstermiştir. Bu artışlar özellikle 2. grupta gözlenmiştir. Bununla birlikte albendazol uygulanması bu artışları farklı oranlarda olacak şekilde önlemiştir. *T. canis* enfeksiyonunda serum enzim aktivitelerinde de değişiklikler meydana gelmiştir; ancak bu değişiklikler istatistiksel olarak önemli bulunmamıştır.

Anahtar Sözcükler: *Toxocara canis*, hematoloji, bazı biyokimyasal parametreler, albendazol, fare

Introduction

Toxocara canis is a nematode of the family Ascaridae, whose adult form inhabits the proximal small intestine of its mammalian definitive hosts, namely canids and felids. *T. canis* completes its life cycle in dogs, with humans acquiring the infection as accidental hosts. Following ingestion by dogs, the infective eggs hatch and larvae penetrate the gut wall and migrate into various tissues, where they encyst if the dog is older than 5 weeks. Many human infections are asymptomatic, with only eosinophilia and positive serology. The two main clinical presentations of toxocariasis are visceral larva migrans (VLM) and ocular larva migrans (OLM). In VLM, which occurs mostly in pre-school children, the larvae invade multiple tissues such as the liver, heart, lungs, brain, muscle, and cause various symptoms including fever, anorexia, weight loss, coughing, wheezing, rashes, hepatosplenomegaly and hypereosinophilia. Deaths rarely occur due to cardiac, pulmonary or neurological involvement. In OLM, the larvae produce various ophthalmologic lesions, which in some cases have been misdiagnosed as retinoblastoma, resulting in surgical enucleation. OLM often occurs in older children or young adults, with only rare eosinophilia or visceral manifestations. In this parasitic disease the diagnosis does not rest on identification of the parasite. Since the larvae do not develop into adults in humans, a stool examination would not detect any *Toxocara* eggs. However, the presence of *Ascaris* and *Trichuris* eggs in faeces, indicating faecal exposure, increases the probability of *Toxocara* in the tissues. For both VLM and OLM a presumptive diagnosis rests on clinical signs, history of exposure to puppies, laboratory findings (including eosinophilia) and the detection of antibodies to *Toxocara* (1-5).

Treatment of VLM and OLM is mostly supportive. The Medical Letter recommends diethylcarbamazine, albendazole and mebendazole as the drugs of choice. For severe symptoms or eye involvement, corticosteroids can be used in addition (6-10).

In this study we aimed to evaluate the haematological and biochemical changes in *T. canis* infected mice. Therefore, the effect of albendazole on this situation was observed. Total leukocyte counts, total eosinophil counts and differential leukocyte counts in blood and urea, creatine, aspartate aminotransferase (AST) alanine aminotransferase (ALT) and alkaline phosphatase (ALP) activities in serum were determined on days 8, 15 and 28.

Materials and Methods

Adult *T. canis* were collected from the puppies' faeces. Eggs were obtained from the uteri of adult female worms and stirred in a magnetic stirrer for 10 min with 1% sodium hypochloride. This suspension was filtered through a sieve with 150 µm pores. The filtrate was centrifuged three times at 5000 g for 3 min with 0.9% NaCl solution in order to remove the sodium hypochloride. The eggs were incubated in 0.5% formalin at 26 ºC for 4 weeks to allow embryonic development. Before the application of the embryonated egg the suspension was centrifuged at 5000 g for 3 min and washed three times in sterile distilled water to remove formalin. At the end of this process distilled water was added to the remaining sediment to reach a concentration of approximately 1500 embryonated eggs in 0.5 ml (11). Each mouse in Group 2 and Group 4 was inoculated with 0.5 ml of this egg suspension.

Swiss Albino mice weighing 30-35 g were used in this study. The mice were assigned into four groups, consisting of 21 mice each, totalling 84 mice. The mice of Group 1 were used as a control; these were fed a commercial ration, and not given *T. canis*, or albendazole. The mice in Group 2 were given infective *T. canis* eggs (1500 infective eggs in 0.5 ml) but no albendazole application. Embryonated eggs were placed in the stomach with a blunt needle. The mice in Group 3 were given albendazole (Andazol susp 2%, Biofarma Drug Corp., Istanbul, Turkey) for five consecutive days at 100 mg/kg body weight. The mice in Group 4 were previously infected with *T. canis* eggs (1500 infective eggs in 0.5 ml) and then albendazole was given for five consecutive days at 100 mg/kg body weight.

Blood samples were collected from seven mice by cardiac puncture on days 8, 15 and 28. Haematological changes were evaluated by determining the total leukocyte and eosinophil counts. Furthermore differential leukocytes counts were made on the smears stained with May Grunwald Giemsa for this evaluation in these periods (12). Biochemical changes were determined by analysing urea (mg/dl), creatine (mg/dl), AST, ALT and ALP (evaluated as U/L) activities in serum during these study periods. These analyses were performed automatically with a Shimadzu CL 770 spectrophotometer.

The data were analyzed by one-way analysis of variances (ANOVA) when significant treatment effects

were detected; Duncan's multiple range test was used to identify specific differences between treatments, with means at a probability level of 5%.

Results

Total leukocyte counts, total eosinophil counts, differential leukocytes counts and urea, creatine, AST, ALT and ALP activities were determined in blood collected from mice on post-infection days 8, 15 and 28. The total leukocytes and eosinophil counts increased dramatically in Group 2, which had only infective *T. canis* eggs. These findings regarding the total leukocyte and eosinophil counts are shown in Tables 1 and 2. The eosinophil counts increased on days 8 and 15 in Group 2 in particular compared to the control and other treatment groups. In these periods the total eosinophil counts were 3033.40 ± 2187.36 and 1322.0 ± 742.66 (eosinophil/µl), respectively. On the other hand, the total leukocyte counts were also high on days 8, 15 and 28; 122.20 ± 37.07, 139.20 ± 38.17, and 166.25 ± 67.04 ($x10^2$/µl), respectively. Therefore, changes in lymphocyte, neutrophil, eosinophil, monocyte and basophile counts were observed in *T. canis* infected mice and other treatment groups (Table 3). In addition, urea, creatine, AST, ALT and ALP activities were measured in the serum of these study groups (Table 4). According to the results, serum urea, creatine and ALP activities decreased in *T. canis* infected mice in Group 2. AST and ALT activities in serum therefore increased in this group compared to the control and other treatment groups. The levels of AST activities were (as IU/L), 248.80 ± 36.75 on day 8, 347.50 ± 56.55 on day 15 and 393.25 ± 118.34 on day 28.

Table 1. Total leukocyte counts in all study groups on days 8, 15 and 28 ($x10^2$/µl).

Groups	Day 8	Day 15	Day 28
Group 1	66.75±10.46 [a]	81.40±41.07 [a]	62.40±12.54 [a]
(n=21)	(55.0-77.0)	(46.0-147.0)	(49.0-82.0)
Group 2	122.20±37.07 [b]	139.20±38.17 [b]	166.25±67.04 [b]
(n=21)	(73.0-157.5)	(102.0-198.0)	(121.0-266.0)
Group 3	54.70±25.10 [a]	93.25±15.94 [ab]	58.40±25.34 [a]
(n=21)	(23.5-82.5)	(80.0-116.0)	(33.0-98.0)
Group 4	114.30 ±47.07 [b]	103.00±26.47 [ab]	114.50±10.40 [c]
(n=21)	(58.5-187.5)	(78.0-134.0)	(105.0-124.0)

[a,b,c] : Means within the same columns with different letters are statistically significant ($p < 0.05$).

Table 2. Total eosinophil counts in all study groups on days 8, 15 and 28 (eosinophil/µl).

Groups	Day 8	Day 15	Day 28
Group 1	433.0±180.12 a	266.40±152.88 [a]	325.0±234.89 [ab]
(n=21)	(270.0-687.0)	(100.0-485.0)	(100.0-670.0)
Group 2	3033.40±2187.36 [b]	1322.0±742.66 [b]	790.0±655.14 [b]
(n=21)	(370.0-5810.0)	(705.0-2610.0)	(320.0-1935.0)
Group 3	691.0±391.84 a	201.25±130.02 [a]	152.20±48.67 [a]
(n=21)	(350.0-12000.0)	(80.0-335.0)	(85.0-215.0)
Group 4	1070.0±462.23 [a]	852.60±199.37 [a]	636.60±352.79 [ab]
(n=21)	(540.0-1600.0)	(608.0-1165.0)	(250.0-1093.0)

[a,b] : Means within the same columns with different letters are statistically significant ($p < 0.05$).

Table 3. Differential leukocyte counts in all study groups on days 8, 15 and 28 (%).

Days		Group 1 (n=21)	Group 2 (n=21)	Group 3 (n=21)	Group 4 (n=21)
Day 8	Lymphocytes	59.40±16.04 a (33.0-76.0)	38.60±5.63 b (32.0-46.0)	54.25±14.00 ab (34.0-66.0)	45.60±15.96 ab (26.0-61.0)
	Neutrophils	25.40±15.89 (57.0-74.0)	26.40±8.17 (35.0-67.0)	27.50±11.84 (51.0-75.0)	28.00±8.45 (36.0-73.0)
	Eosinophils	6.4±2.96 a (3.0-10.0)	28.8±13.23 c (10.0-45.0)	9.75±7.13 ab (1.0-18.0)	21.60±11.26 bc (6.0-36.0)
	Monocytes	8.80±1.92 b (6.0-11.0)	7.2±1.92 ab (5.0-10.0)	6.5±3.0 ab (4.0-10.0)	4.6±3.2 a (1.0-9.0)
	Basophiles	-	0.60±0.54 (0.0-1.0)	0.2±0.44 (0.0-1.0)	0.20±0.44 (0.0-1.0)
Day 15	Lymphocytes	66.60±14.48 a (50.0-88.0)	50.8±8.13 ab (39.0-59.0)	52.50±18.71 ab (34.0-74.0)	46.20±12.02 b (33.0-62.0)
	Neutrophils	25.60±13.48 (11.0-43.0)	33.00±12.62 (20.0-53.0)	25.75±11.08 (13.0-40.0)	27.60±8.04 (19.0-36.0)
	Eosinophils	4.20±2.04 a (2.0-6.0)	17.75±4.19 b (12.0-22.0)	4.0±3.0 a (1.0-7.0)	14.40±7.36 b (8.0-27.0)
	Monocytes	5.60±2.30 a (2.0-8.0)	5.60±2.88 a (2.0-8.0)	14.25±8.26 b (8.0-26.0)	7.20±3.27 b (3.0-12.0)
	Basophiles	-	-	-	-
Day 15	Lymphocytes	64.60±6.10 (57.0-74.0)	56.00±12.32 (35.0-67.0)	58.00±9.84 (51.0-75.0)	56.20±13.47 (36.0-73.0)
	Neutrophils	16.80±8.70 (5.0-24.0)	23.40±8.20 (19.0-38.0)	22.80±6.53 (13.0-30.0)	22.20±11.43 (9.0-40.0)
	Eosinophils	8.4±4.2 ab (3.0-14.0)	13.75±0.95 b (13.0-15.0)	5.40±1.14 a (4.0-7.0)	12.80±6.01 b (5.0-19.0)
	Monocytes	10.20±4.7 (6.0-18.0) -	12.20±3.4 (9.0-18.0) -	7.2±1.30 (5.0-8.0) -	8.60±4.61 (5.0-16.0) -

a,b,c. Means within the same row with different letters are statistically significant ($p < 0.05$).

Discussion

Worldwide, several hundred million domestic dogs are infected with the parasitic nematode *T. canis*. The adult worms reside in the gastrointestinal tract and produce eggs which are subsequently covered with faeces and extruded into the environment. One *T. canis* adult female can produce 20,000 eggs per day, and since intestinal parasite burdens range from one to several hundred worms, infective animals contaminate the environment with millions of eggs every day (1,2,5). Toxocariasis is treated with antiparasitic drugs, such as diethylcarbamazine, albendazole and mebendazole, and these are usually combined with anti-inflammatory medications (6-10).

In this study, we aimed to evaluate the haematological and biochemical changes in *T. canis* infected mice. Therefore, the effects of drug treatment on *T. canis* infection were also evaluated. In many helminth-infected hosts, the number of eosinophils in particular increases dramatically, often without any concurrent increases in the number of other leukocytes, so that eosinophil becomes the dominant cell type (13-19). Many experimental investigations have revealed this. Takamoto et al. (18) studied eosinophilia, IgE production and cytokine production by lung T cells in surface CD4–deficient mutant mice infected with *T. canis*. The results show that eosinophil counts reached a peak on day 10 in *T. canis* infected mice. In another study, Takamoto

Table 4. Enzymes activities in serum all study groups on days 8, 15 and 28.

Days	Days	Group 1 (n=21)	Group 2 (n=21)	Group 3 (n=21)	Group 4 (n=21)
Day 8	Urea (mg/dl)	66.20±14.61 a (51.0-85.0)	62.00±11.33 a (48.0-79.0)	99.25±25.69 b (65.0-119.0)	57.00±16.23 a (43.0-80.0)
	Creatine (mg/dl)	0.56±8.94 a (0.50-0.70)	0.48±4.47 ba (0.4-0.5)	0.47±5.00 ba (0.4-0.5)	0.447±5.47 b (0.4-0.5)
	AST (U/L)	188.25±100.53 (78.0-275.0)	248.80±36.75 (211.0-303.0)	267.33±27.53 (239.0-294.0)	217.40±47.65 (160.0-284.0)
	ALT (U/L)	29.00±4.54 (25.0-35.0)	43.00±17.95 (31.0-74.0)	40.75±4.5 (37.0-47.0)	31.40±7.5 (23.0-41.0)
	ALP (U/L)	86.20±30.62 (55.0-136.0)	83.20±27.50 (52.0-120.0)	121.50±27.48 (96.0-160.0)	92.60±43.02 (65.0-169.0)
Day 15	Urea (mg/dl)	60.20±10.55 (48.0-74.0)	55.40±6.76 (44.0-62.0)	63.66±16.25 (51.0-82.0)	67.00 ±8.62 (51.0-75.0)
	Creatine (mg/dl)	0.52±4.4 ab (0.50-0.60)	0.46±5.4 a (0.40-0.50)	0.70±0.10 bc (0.60-0.80)	0.83±0.24 c (0.40-1.10)
	AST (U/L)	293.25±139 .62 (150.0-476.0)	347.50±56.55 (284.0-419.0)	334.33±29.77 (300.0-353.0)	294.00±120.03 (169.0-484.0)
	ALT (U/L)	54.00±44.93 (25.0-132.0)	43.20±10.80 (35.0-62.0)	47.00±18.00 (29.0-65.0)	45.83±12.51 (31.0-58.0)
	ALP (U/L)	147.00±51.0 ab (70.0-203.0)	87.00±33.66 a (60.0-140.0)	196.66±86.3 b (115.0-287.0)	106.83±28.50 a (78.0-153.0)
Day 15	Urea (mg/dl)	52.40±5.72 a (44.0-57.0)	61.50±4.04 a (56.0-65.0)	80.00±10.43 b (66.0-97.0)	79.66±16.77 b (65.0-107.0)
	Creatine (mg/dl)	0.60±0.23 (0.40-1.0)	0.40±1.8 (0.40-0.40)	0.46±5.16 (0.4-0.5)	0.58±0.21 (0.4-1.0)
	AST (U/L)	331.80±179.60 (200.0-648.0)	393.25±118.34 (296.0-559.0)	255.66±99.07 (166.0-432.0)	234.00±115.55 (89.0-377.0)
	ALT (U/L)	53.00±19.81 (38.0-81.0)	45.5±14.47 (29.0-60.0)	49.00±3.464 (44.0-53.0)	41.16±12.46 (24.0-52.0)
	ALP (U/L)	136.6±31.02 ab (100.0-170.0)	147.0±51.98 ab (88.0-200.0)	203.5±75.28 b (89.0-286.0)	109.66±33.05 a (55.0-140.0)

a,b,c. Means within the same row with different letters are statistically significant ($p < 0.05$).

et al. (17) investigated, eosinophilia, parasite burden and lung damage in *T. canis* infection in C57B1/6 mice genetically deficient in IL-5 was examined. At the end of the study, it was revealed that eosinophil counts increased markedly in their peripheral blood. Another study, by Sugane et al. (16), looked at eosinophilia, IL-5 levels and the recovery of larvae in IL-5 transgenic mice infected with *T. canis*. In that study, the investigators established high eosinophil counts of peripheral blood on days 11 and 7 of infection in C3H/HeN mice. Oto et al. (14) studied eosinophilia meningo-encephalo-myelitis due to *T. canis*. At the end of the study, small numbers of leukocytes with an increased rate of eosinophil (23.2%) were present. In another study, Schaffer et al. (15) studied the development and characterization of a model of eosinophilia-mediated cardiomyopathy in rats infected with *T. canis*. It was shown that *T. canis* develop marked hypereosinophilia, with peak blood eosinophil levels of approximately 3.500 eosinophil/µl whole blood, observed approximately 14 days post-infection.

In our study results, eosinophil counts in particular increased in whole blood in *T. canis* infected mice in Group 2. These increases were observed in three sampling periods, on days 8, 15 and 28; 30.33 ± 2187.36, 1322.0 ± 742.66, and 790 ± 655.14, respectively. In addition, eosinophil levels increased in Group 4, with both infective *T. canis* eggs and albendazole given. However, these increases were not as large as in Group 2. In this respect our findings agree with those of Schaffer et al. (15) in particular and those of other investigators.

Therefore, after ingestion of infective *T. canis* eggs, these hatch and larvae penetrate the gut wall and migrate into various tissues, where they encyst. Humans are accidental hosts who become infected by ingesting infective eggs in contaminated soil. After ingestion, the eggs hatch and larvae penetrate the intestinal wall and are carried by the circulation to a wide variety of tissues, such as the liver, heart, lungs, brain, muscle and eyes. They also cause severe local reactions that are the basis of toxocariasis (1-3). With this in mind we examined biochemical enzyme activities in serum. According to our results, serum urea, creatine and ALP activities decreased slightly in *T. canis* infected mice in Group 2, and AST and ALT activities in serum also increased in this group. Serum AST activities in Group 2 were determined on days 8, 15 and 28 as follows; 248.80 ± 36.75, 347.50 ± 56.55 and 393.25 ± 118.34, respectively. Serum ALT activities in these periods were 43.00 ± 17.95, 43.20 ± 10.80 and 45.5 ± 14.47, respectively. These changes, which were particularly observed in Group 2, as high serum AST activities, can be evaluated as the effects of *T. canis* infection on the liver.

The findings obtained from this study showed that total eosinophil counts in particular, and also total leukocyte counts increased significantly in *T. canis* infected mice. Although albendazole treatment prevented the eosinophilia and leukocytosis to some degree, the levels did not decrease compared to the control group levels.

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