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Efficacious and Safe Dose of Praziquantel for the Successful Treatment of Feline Reservoir Hosts with Opisthorchiasis

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Abstract

Opisthorchiasis caused by *Opisthorchis viverrini* is a major food-borne zoonosis in Greater Mekong sub-region. Even though campaigns discouraging the consumption of raw fish have been launched to public, the disease still remains highly endemic. The unsuccessful eradication of the disease is probably because of the persistence of the parasite in animal reservoir hosts, particularly felids. Praziquantel (PZQ) is the drug of choice for morbidity control of opisthorchiasis in humans and animals. However, there is no specific study on its dosage regimen for feline opisthorchiasis. Thus, the effective treatment dose of PZQ, as well as its adverse effects, was evaluated in *O. viverrini* infected cats. Twenty-eight infected male and female cats from the endemic area of Khon Kaen and Mahasarakham Provinces, Thailand were enrolled in this study. Physical, hematological, blood chemical and urine examinations were analyzed, as indicators of health status, on the day before and 30 days after treatment. Intensity of the infections was determined by the formalin-ethyl acetate sedimentation technique. Cats were equally allotted into the low infection group of 14 cats with egg count per gram of feces (EPG) less than 300 and the high infection group of 14 cats with EPG higher than 300. Cats in each group were equally divided into two subgroups of 7 cats; thus, there were two low infection subgroups (L1 and L2 subgroups) and two high infection subgroups (H1 and H2 subgroups). A single dose of 25 mg/kg PZQ was orally administered to each cat in the L1 and H1 subgroups and a single oral dose of 40 mg/kg PZQ was administered to the L2 and H2 subgroups. Complete clearance of *O. viverrini* eggs was found in all cats in the L1, L2 and H2 subgroups; thus, the cure rate (CR) and egg reduction rate (ERR) were 100%.

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However, partial clearance was observed in two cats with high EPG (1,502 and 1,518) in the H1 subgroup, which received 25 mg/kg PZQ. Regards, CR and ERR for these two animals was 71.4 and 99.5%. No significant difference among the 4 subgroups was seen. Almost all hematological, blood chemical and urinalysis data were within normal ranges, except for the eosinophilia and an increase of alanine aminotransferase (ALT). Hookworm infection seen in all cats would cause eosinophilia. As for drug safety, there was no side effect observed in any cats. In conclusion, this study suggested that 40 mg/kg PZQ is a highly effective and safe dosage for the treatment of feline reservoir hosts of human opisthorchiasis.

Graphical Abstract

Keywords

praziquantel; opisthorchiasis; cat; treatment; reservoir host

1. Introduction

Opisthorchiasis is a major public health problem in Greater Mekong sub-region. It is caused by *Opisthorchis viverrini*, which is the most important food-borne zoonotic trematode in this region. Infection is incurred through eating raw or undercooked cyprinid fish infected with metacercaria, the infective larva of *O. viverrini*. The adult trematode has been proven to be an important factor involving liver damage and cholangiocarcinogenesis [1]. Besides humans, the infection is also found in cats and dogs. In Thailand, *O. viverrini* infection in cats and dogs was firstly reported together in Phitsanulok and Khon Kaen provinces. The prevalence in cats of both provinces was 22.6% and in dog was 1.9% [2]. More recently, Enes et al. [3] and Aunpromma et al. [4] had surveyed the prevalence in both reservoir hosts in the endemic area of Khon Kaen Province and found that prevalence in cats ranged between 35–37%, but in dogs prevalence was always below 4%. Since prevalence in cats is always higher than in dogs, cats were considered the most important mammalian reservoir of *O. viverrini* in endemic areas. People in endemic areas usually raise cats without annual health checks or deworming. Cats roam freely around villages and defecate everywhere. It is speculated that cats get infected by eating fish caught from natural water reservoirs and fish

scraps or unattended fish sourced from village households. Infected cats are potential to disseminate the eggs in the environment, thus sustaining the trematode's life cycle.

To reduce the prevalence of opisthorchiasis in endemic areas, treating the infected cats with an effective anthelmintic drug, in parallel with the treatment in human, should be performed. The current anthelmintic drug of choice for this trematode is praziquantel (PZQ), which was developed from pyrazinoisoquinolone in 1975 [5]. It is a broad-spectrum drug for the treatment of platyhelminthic infections in both humans and animals, with the exception of *Fasciola* spp. [6]. In addition, this drug has been recommended as a drug of choice for morbidity control of various trematodiasis in dogs and cats using a single oral dose of 20 mg/kg [7]. However, information regarding effective treatment of *O. viverrini* infection in cats is very limited. In 2003, Hong et al. [8] reported that a single dose of 30 mg/kg PZQ had a cure rate of 20% for the *Clonorchis sinensis* in dogs. Later, Schuster et al. [9] successfully administered of 20 mg/kg PZQ to treat *O. felinus* in dogs, however, eggs of *O. felinus* were still found in feces of the treated animals until week 10 after treatment. Lan-Anh et al. [10] administered 40 and 75 mg/kg PZQ to control small fish-borne zoonotic trematodes, but not *O. viverrini* in animal reservoir hosts in Vietnam and suggested a single dose of 40 mg/kg PZQ as the most efficacious. In this experiment, transient vomiting and loss of appetite occurred in only two cats administered 75 mg/kg PZQ. Since most studies were confined to canine opisthorchiasis, we decided to conduct a preliminary study on feline opisthorchiasis and test whether a single dose of 25 mg/kg could clear the parasite from the infected cats, especially those with high egg counts per gram. Although the effectiveness of specific doses for the treatment of feline opisthorchiasis remains unclear, a higher dose of 40 mg/kg PZQ was expected to be more effective than the recommended dose (20–25 mg/kg) without any adverse side effects. Thus, this experiment was conducted to evaluate the effectiveness of a low (25 mg/kg) and high (40 mg/kg) dose of PZQ against opisthorchiasis in cats with low and high infection intensities. In addition, adverse effects were monitored using hematology, blood chemistry and urinalysis at before and 30 days after the treatment.

2. Materials and methods

2.1 Experimental animals

A total of 28 naturally infected cats (7 males and 21 non-pregnant females), weighing 3.2 to 5.8 kg, aged over six months, were obtained from Kosumpisai District in Mahasarakham Province and Ban Phai District in Khon Kaen Province, Thailand, where are high endemic areas for human opisthorchiasis. Cats were maintained in the Experimental Animal Facility of the Faculty of Veterinary Medicine, Khon Kaen University, Thailand. Physical and general health status examinations were conducted prior to the experiment. This study was approved by the Animals Ethics Committee of Khon Kaen University, Thailand (Ethical No. AEKKU 22/2556, 5/07/2013). Since praziquantel (PZQ) is potential to cause adverse side effects, each cat was observed on an hourly basis for 24 hours for systemic (itch, fever, depression, and ataxia), gastrointestinal (vomiting and diarrhea) and respiratory symptoms (cough and nasal discharge) following PZQ administration.

2.2 Fecal, hematological and blood chemical examinations and urinalysis

All examinations were performed on the day before and 30 days after treatment. Fecal samples were collected using a rectal enema. Samples were examined by the modified formalin-ethyl acetate sedimentation technique. Number of eggs per gram of feces (EPG) was obtained to determine egg intensity as an indirect measure of infection intensity. Grading criterion was adapted from that used in humans [4]. Because the average EPG of infected cats is at a moderate level, cats were graded into low and high infection groups, using EPG median as the grouping criteria. In addition to *O. viverrini*, feces were also screened for other gastrointestinal parasites. Blood samples were collected via cephalic or jugular vein puncture. Complete blood count (CBC) and blood chemistry which reflected to liver (AST-aspartate aminotransferase, ALT-alanine aminotransferase, ALP-alkaline phosphatase, GGT-gamma glutamyl transpeptidase, TP-total protein, Alb-albumin and TB-total, DB-direct, IB-indirect bilirubins) and kidney functions (BUN-blood urea nitrogen, Cr-creatinine) were analyzed with an automatic analyzer (Olympus AU 400, Olympus Company, Germany). Prior to collecting urine, the cat was sedated with xylazine hydrochloride at a dosage of 0.1–0.2 mg/kg IM. Then, Buster cat catheter was used to collect urine at the amount of 1.5–2.0 ml directly from the urinary bladder of each cat. This practice was performed within half an hour after the sedation. Such low dose of the sedative agent and short collection time would not affect property of the urine.

EPG, hematology, blood chemistry and urinalysis on day 30 post-treatment were compared with that of the pre-treatment. Results were compared with reference values currently used at the Animal Hospital, Faculty of Veterinary Medicine, Khon Kaen University. Cure rate ($CR = 100 \times [\text{number of cats with no eggs post-treatment} / \text{total number of infected cats pre-treatment}]$) and egg reduction rate ($ERR = 100 \times [EPG_{\text{pre-treatment}} - EPG_{\text{post-treatment}}] / EPG_{\text{pre-treatment}}$) were used for determining the efficacy of the drug [11].

2.3 Praziquantel administration

Cats in the low and high infection groups were randomly and equally allotted into four subgroups of 7 cats; thus, there were two low (L1 and L2) and two high infection subgroups (H1 and H2). Each animal was weighed in order to calculate the accurate treatment dose. Each PZQ tablet (The Medicpharma Co. Ltd., Thailand) was trimmed and weighed to meet the designated dose for each cat. An oral dose of 25 mg/kg was given to each cat of the L1 and H1 subgroups and a 40 mg/kg to each cat of the L2 and H2 subgroups.

2.4 Statistical Analysis

Normality of the data was checked with Kolmogorov–Smirnov test (K–S test). Non-parametric statistics; the Wilcoxon Signed-Rank test was used to compare the pre- and post-treatment results and a Mann-Whitney U test was used to compare the 25 and 40 mg/kg groups, applied at the 95% confidence interval. SPSS (version 13) was used for these analyses.

3. Results

3.1 Health status, infection and treatment results

Throughout the experiment, all cats were physically healthy. Neither observable clinical symptoms nor adverse effects before or after receiving praziquantel (PZQ) were noted. This supports the conclusion that the drug is very safe for use in cats even at a high dose of 40 mg/kg.

The EPG from all 28 naturally infected cats ranged from 14–1,973 with a mean $\pm$ SD of 461 $\pm$ 494.64. The EPG median of these cats was 329 and assigned as a divider for the infection intensity. Thus cats with an EPG less than 300 were placed in the low infection group and those with an EPG higher than 300 were set in the high infection group. The EPGs of cats in the low infection group ranged from 14–212, of which 81.4% were in the L1 subgroup and 160.1 in the L2 subgroup. The EPGs of cats in the high infection group ranged from 327–1973, of which were 785.6 in the H1 subgroup and 816.3 in the H2 subgroup (Table 1). A complete clearance of *O. viverrini* eggs in the L1 subgroup with 25 mg/kg and the L2 and H2 subgroups with 40 mg/kg PZQ was obtained, resulting in a cure rate (CR) and egg reduction rate (ERR) of 100%. Partial clearance was observed in two cats of the H1 subgroup with 25 mg/kg. Both cats had very high EPGs (1,502 and 1,518). The CR and ERR of this subgroup were 71.4% and 99.5% (Table 1) and significant differences among these treatment subgroups was not seen.

Besides *O. viverrini*, hookworm (*Ancylostoma* spp.) was found in all cats with EPGs ranging from 4 to 63. Means $\pm$ SDs of EPG of the L1, L2, H1 and H2 subgroups were 23.6 $\pm$ 16.6, 8.9 $\pm$ 3.3, 8.9 $\pm$ 3.3 and 14.7 $\pm$ 21.4, respectively. Ancylostomiasis did not appear related to the intensity of *O. viverrini* infection. *Strongyloides* eggs were found only in one cat in the H2 subgroup (H2_7) with *O. viverrini* EPG of 1,973. Very low EPG of minute intestinal flukes were found only in 3 cats of the H1 subgroup (H1_2, H1_3 and H1_6) and a cat of the H2 subgroup (H2_6). According to the EPG and number of the infected cats, *Strongyloides* and minute intestinal fluke infections did not seem to affect the health of these animals.

3.2 Hematological, blood chemical and urine analyses

All hematological data of cats receiving 25 and 40 mg/kg PZQ were in normal range, except for a single cat displaying eosinophilia. The eosinophilic condition was higher than reference values before and after treatment (Table 2). However, there was no significant difference between the pre- and post-treatment either with 25 or 40 mg/kg PZQ treatment.

The blood chemical data regarding liver function test (AST, ALT, ALP, GGT, TP, Alb, TB, DB and IB) and kidney function test (BUN and Cr) between the pre- and post-treatments with 25 and 40 mg/kg PZQ are shown in Table 3. Almost all data were in the normal range, except alanine aminotransferase (ALT) and total protein (TP). The pre- and post-treated ALT enzyme (67.78 and 109.64 U/L in the 25 mg/kg PZQ group and 61.92 and 77.21 U/L in the 40 mg/kg PZQ group) was higher than the reference value (10–60 U/L). However the Mann-Whitney U Test at a 95% confidence interval did not show any significant difference among these data. These hematology and blood chemistry results implied that these cats were

infected without showing any serious clinical symptoms of opisthorchiasis. Moreover, urinalysis did not reveal any deviation from the reference values (Table 4).

4. Discussion

Opisthorchiasis is a major community health problem in Southeast Asia and is one of the most important food-borne causes of trematodiasis in Thailand [12]. Despite local, national and regional campaigns against eating raw or uncooked fish and fish products and mass anthelmintic drug administration in infected communities, the disease still remains. Unsuccessful eradication of the disease is related to the persistence of the parasite in the environment, as infected humans and animals shed eggs with feces into the environment. In humans, good sanitation and defecation in functional latrines can prevent such shedding. However, it is more difficult to prevent shedding in the infected animals, especially feral and wild cats. Since prevalence in cats in endemic areas is always higher than in the other animals [2,3,4], cats are considered the major animal reservoir host of *O. viverrini*.

Anthelmintic drug administration to infected cats may be an effective and practical approach to reducing the number of parasites in the environment. Praziquantel (PZQ) has become a major candidate for this purpose due to its effectiveness and wide safety margin. Absorption of the orally administered PZQ occurs in the gastrointestinal tract. The drug reaches maximum serum concentration within one hour and most is excreted with urine within 24 hours. In the rat, 15% of the oral dose is eliminated with bile within 7 hours [13]. Once taken by the worm, the rapid increase of permeability of its tegumental cells leads to the loss of the intracellular calcium homeostasis that further decreases the release of lactose, glycogen and ATP [14]. The worm dies with massive contractions and rapidly muscular paralysis. Moreover, pathological vacuolization of the tegumental cells causes leakage of sugars and amino acids and cell breakage [5,15,16,17]. With these precise effects on the worm tegument, a single oral dose at 25 or 40 mg/kg PZQ is likely effective in eliminating the worm. Although the treatment dosage of 25 mg/kg t.i.d. in human gives effective result, the applying 3 repeated administrations is not practical in cats. Regarding, a single dose of treatment is more appropriate. However, total clearance may not be completed with a dose of 25 mg/kg in cats with very heavy infection (EPG >1500). In this case, a higher dose at 40 mg/kg is required. Thus, regardless of EPG intensity, a dose at 40 mg/kg is recommended.

The drug toxicity is a major concern in both human and veterinary medicine. Nonetheless, PZQ is considered a very safe drug against opisthorchiasis. For example, LD50 of PZQ is not less than 2 g/kg in murine species. The acute toxicity in mouse and rat is 2,454 and 2,249 mg/kg via oral route [18]. Rats can tolerate the daily oral dose of 1,000 mg/kg PZQ for 4 weeks and 180 mg/kg in dog for 13 weeks without having any structural damage [19]. The incidence of adverse effects by the oral administration in cats is very rare and mild. The clinical signs included salivation, vomiting, diarrhea, lethargy, anorexia and pain at the injection site. Lan-Anh et al. [10] reported a few adverse effects, including vomiting and transient anorexia in two cats after receiving an oral dose of 75 mg/kg PZQ. Greater toxicity could be seen in cats administered injectable doses of PZQ, in which a parenteral dose of 200 mg/kg could be lethal. Since this experiment gave only a single oral dose at 25 and 40 mg/kg; it does not get close to reported toxicity levels. It is apparent that the drug's adverse

effects did not occur in our study. After a dose of 25 or 40 mg/kg PZQ was administered to each cat, no clinical symptom or allergic reaction to the drug was detectable. These results are consistent with the study of Chai [20] stating that PZQ is a highly efficacious and safe anthelmintic drug against trematode and cestode infections for uses in both humans and animals. This drug can be used safely even at high dose (75 mg/kg) to which temporary vomiting and loss of appetite were merely detected on the first day of the drug administration [10]. This would be a temporary salivation reaction to bitter substances or improper restraint of the cats. Thus, this drug is the best candidate even at high doses for the control of feline opisthorchiasis.

All naturally infected cats being used in this experiment were caught in a human endemic area of opisthorchiasis. The pre-treated physical examination, hematology and blood chemistry data showed that these cats were healthy. No single clinical symptom of feline opisthorchiasis was observable despite having low or heavy infection. An egg count per gram of feces (EPG) was used as an indicator of the severity of the *O. viverrini* infection. The egg intensities ranged from light to very-heavy, while the average intensity was moderate. The high EPG levels reflect the high number of adult worms in the bile apparatus of the host which are able to shed high egg numbers into bile and feces with further release into the environment. Theoretically, heavy *O. viverrini* infection should affect body functions, through changes in health status, hematology, blood chemistry and urinalysis. Severe cases may exhibit the clinical symptoms of opisthorchiasis, but since this study could not detect significant changes in these cats, it would imply that they do not have any clinical symptoms that cause the changes in these laboratory data. Since development of clinical signs of opisthorchiasis is usually chronic in nature, one would not expect to observe these in young cats with recent infection being used in this experiment. Thus, the ailments should be more pronounced in older cats with chronic infection. Although all experimental cats were healthy and their hematological data were generally in normal range, eosinophilia in both 25 and 40 mg/kg groups was the only hematological abnormality detected, likely attributed to hookworm infection.

Alanine aminotransferase (ALT) is an enzyme that leaks from injured hepatocytes into the blood stream. Therefore, increases of serum ALT could indicate hepatocellular damage. Liver cell damage, necrosis, and inflammation or lipidosis can be found in cases with liver fluke infection [21] and additionally egg-induced granulomas may also incite inflammatory reactions that can lead to the damage of the liver cells [22]. In our study, almost all blood chemical data were within normal range, except ALT. Increase in ALT indicates a certain degree of liver damage in these infected cats. Other potential causes of increase in ALT activity could be influenced by hepatic injuries, such as necrosis and inflammation [21]. Nonetheless, the level of ALT was not significantly high as those observed in hepatic disease. However, the infection would probably be in the early infection period since the clinical symptoms and other laboratory results were unchanged. In conclusion, a single oral dose of 40 mg/kg praziquantel is safe and efficacious for the treatment of feline opisthorchiasis.

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Research Highlights

- Efficacious dose of PZQ for the treatment of opisthorchiasis in feline reservoir host is proven.
- No clinical symptoms such as jaundice, vomit or diarrhea were apparently exhibited.
- Hematology and blood chemistry were generally in normal range.
- Urinalysis profiles of Ov infected cats were in normal range.

Table 1

Clearance of *O. viverrini* (OV) eggs from the infected cats having low (<300) and high (>300) eggs per gram (EPG) on day 30 after receiving an oral dose of 25 (L1 and H1 subgroups) or 40 mg/kg (L2 and H2 subgroups) of praziquantel (PZQ). Only egg reduction rate (ERR) and cure rate (CR) of the H1 subgroup were not 100%. All cats were found to have *Ancylostoma* spp. infection (F=female, M=male).

PZQ	Cat sub-group No.	Gender	Body Weight (kg)	<i>Ancylostoma</i> spp.			ERR (%)	CR (%)
				Pre-treated OV	Post-treated OV	EPG		
25 mg/kg	L1_1	M	4	16	0	14	100	
	L1_2	M	3.4	30	0	16	100	
	L1_3	F	3.6	55	0	37	100	
	L1_4	F	3.2	10	0	50	100	
	L1_5	F	3.7	11	0	124	100	
	L1_6	F	3.4	32	0	143	100	
	L1_7	F	3.4	11	0	186	100	
	Mean±SD	2M, 5F	3.5	23.6±16.6	0	81.4±68.1	100	7/7 (100)
	H1_1	F	3	11	0	327	100	
	H1_2	F	3.8	7	0	331	100	
	H1_3	M	5.8	12	0	496	100	
	H1_4	F	4.2	9	0	585	100	
	H1_5	M	3.8	7	0	740	100	
	H1_6	F	3.6	35	12	1502	99.2	
	H1_7	M	4.2	43	14	1518	99.1	
40 mg/kg	Mean±SD	3M, 4F	4.1	17.7±14.8	3.7±6.4	785.6±15.2	99.76	5/7 (71.4)
	L2_1	M	3.6	13	0	16	100	
	L2_2	F	3.8	8	0	149	100	
	L2_3	F	3.4	14	0	166	100	
	L2_4	M	4	5	0	182	100	
	L2_5	F	3.4	8	0	190	100	
	L2_6	F	4.2	7	0	206	100	
	L2_7	F	3.4	7	0	212	100	

PZQ	Cat sub-group No.	Gender	Body Weight (kg)	<i>Ancylostoma spp.</i>			ERR (%)	CR (%)
				EPG		Post-treated OV		
				Pre-treated OV				
	Mean±SD	2M, 5F	3.7	8.9±3.3	160.1±67.2	0	100	7/7 (100)
	H2_1	F	4.6	11	384	0	100	
	H2_2	F	4	7	443	0	100	
	H2_3	F	3	6	701	0	100	
	H2_4	F	3.8	7	724	0	100	
	H2_5	F	3.6	4	742	0	100	
	H2_6	F	3.4	5	747	0	100	
	H2_7	F	3.2	63	1973	0	100	
	Mean±SD	0M, 7F	3.7	14.7±21.4	816.3±531.7	0	100	7/7 (100)

Table 2

Hematological data of the *O. viverrini* infected cats before and after receiving 25 and 40 mg/kg praziquantel (PZQ).

Parameters	References	PZQ 25mg		PZQ 40mg	
		Before (Mean±SD)	After (Mean±SD)	Before (Mean±SD)	After (Mean±SD)
Red Blood Cell Count ($\times 10^6/\text{mm}^3$)	5.5–10	6.19±1.52	6.76±1.08	6.62±1.25	6.36±1.23
Hemoglobin (g%)	8–14	9.53±2.12	10.05±1.29	10.26±1.86	9.57±1.71
Hematocrit (%)	24–45	27.25±5.91	30.27±3.39	30.15±5.98	28.91±5.32
Mean Corpuscular Volume (fL)	40–55	44.52±3.52	45.24±4.22	45.63±3.63	45.61±2.81
Mean Corpuscular Hemoglobin (pg)	13–17	15.52±0.96	14.95±0.89	15.55±0.91	15.08±0.69
Mean Corpuscular Hemoglobin Conc. (g%)	31–35	34.95±1.71	33.20±1.73	34.15±1.38	33.13±1.55
Platelet Count ($\times 10^3/\text{mm}^3$)	300–600	167.35±110.81	214.50±120.82	177.00±110.14	219.42±82.92
White Blood Cell Count ($\times 10^3/\text{mm}^3$)	5.5–19.5	13.69±6.81	14.02±5.91	14.80±3.75	13.57±6.18
Neutrophil ($\times 10^3/\text{mm}^3$)	2.5–12.5	8.52±5.59	7.72±3.20	8.86±3.55	6.96±3.38
Lymphocyte ($\times 10^3/\text{mm}^3$)	1.5–7.0	3.78±1.73	4.22±1.84	4.10±1.68	4.45±1.95
Monocyte ($\times 10^3/\text{mm}^3$)	0–0.9	0.25±0.12	0.31±0.06	0.26±0.14	0.28±0.23
Eosinophil ($\times 10^3/\text{mm}^3$)	0–0.8	1.13±0.76	1.34±0.99	1.59±0.93	1.85±2.19
Basophil ($\times 10^3/\text{mm}^3$)	0–0.2	0.0007±0.008	0.016±0.011	0.0009±0.006	0.013±0.014

Blood chemical data of *O. viverrini* infected cats before and after receiving 25 and 40 mg/kg praziquantel (PZQ).

Table 3

Parameters	Refer ences	PZQ 25 mg		PZQ 40 mg		
		Before (Mean± SD)	After (Mean± SD)	Before (Mean ±SD)	After (Mean ±SD)	P- valu e
Blood Urea Nitrogen (mg%)	13–33	23.75±2 .95	24.95±7 .91	22.02± 3.63	21.02± 3.92	0.51 0
Creatinine (mg%)	0.5– 1.9	1.23±0. 26	1.37±0. 22	1.44±0. .22	1.32±0. 26	0.32 4
Aspartate aminotransferase (U/L)	10–60	57.57±1 4.86	46.14±1 8.05	0.0 44.57± 19.85	52.35± 11.81	0.18 7
Alanine aminotransferase (U/L)	10–60	67.78±3 4.32	109.64± 97.17	0.1 61.92± 46.79	77.21± 31.45	0.08 4
Alkaline phosphatase (U/L)	10–80	28.42±1 0.83	35.14±8 .14	0.0 33.21± 10.66	33.50± 15.85	0.61 5
Gamma glutamyltranspeptidase (U/L)	< 5	< 5	< 5	< 5	< 5	
Total protein (g%)	5.4– 7.8	7.75±0. 60	7.18±0. 74	0.1 7.16±0 .44	7.40±0. 88	0.32 7
Albumin (g%)	2.1– 3.3	2.82±0. 38	2.92±0. 19	0.3 2.98±0 .21	2.72±0. 43	0.05 4
Total bilirubin (mg%)	0–1	0.15±0. 08	0.22±0. 11	0.1 0.16±0 .06	0.17±0. 13	0.94 2
Direct bilirubin (mg%)	0–0.5	0.02±0. 04	0.03±0. 08	1.0 0.03±0 .04	0.02±0. 05	0.52 7
Indirect bilirubin (mg%)	0–0.5	0.12±0. 10	0.17±0. 06	0.2 0.12± 0.07	0.15±0. 94	0.24 7

Table 4

Urinalysis of the cats in the four subgroups (L1, L2, H1 and H2). The pre- and post-treatment urine protein to urine creatinine ratio (UP:UC), protein, creatinine and pH from the urinalysis of any sub-group appeared within the reference ranges.

Parameter	References	L1		L2		H1		H2	
		Pre-	Post-	Pre-	Post-	Pre-	Post-	Pre-	Post-
UP:UC ratio	<0.5	0.1	0.36	0.5	0.17	0.31	0.23	0.17	0.26
Protein	5–150	21	98.1	77	46.12	52.14	55.7	43.57	65.91
Creatinine	110–250	200.7	269.82	155.34	270.74	169.12	46.12	253.35	256.91
pH	6–7	6.7	6.5	6.21	6.21	6.21	65.91	6.0	6.21