Parasitology International 66 (2017) 448–452

Contents lists available at ScienceDirect

Parasitology International

journal homepage: www.elsevier.com/locate/parint

Efficacious and safe dose of praziquantel for the successful treatment of feline reservoir hosts with opisthorchiasis

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ARTICLE INFO

Article history:
Received 9 November 2015
Received in revised form 19 July 2016
Accepted 26 August 2016
Available online 26 August 2016

Keywords:
Praziquantel
Opisthorchiasis
Cat
Treatment
Reservoir host

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 Maha Sarakham 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) <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%. However, partial clearance was observed in two cats with high EPG (1502 and 1518) 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.

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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 and 37%, but in dogs prevalence was always below 4%. Since

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http://dx.doi.org/10.1016/j.parint.2016.08.005
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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 anthelminthic drug, in parallel with the treatment in human, should be performed. The current anthelminthic 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 *Clonorchiasis sinensis* in dogs. Later, Schuster et al. [9] successfully administered of 20 mg/kg PZQ to treat *O. felineus* in dogs, however, eggs of *O. felineus* 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 Maha Sarakham 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 h 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 determined 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 ($CR = 100 \times$ [number of cats with no eggs post-treatment/total number of infected cats pre-treatment] and egg reduction rate ($ERR = 100 \times [EPG_{pre\text{-}treatment} - EPG_{post\text{-}treatment}]/EPG_{pre\text{-}treatment}$) 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 to 1973 with a mean ± SD of 461 ± 494.64. The EPG median of these cats was 329 and assigned as a divider for the infection intensity. Thus cats with an EPG <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 to 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 to 1973, of which were 785.6 in the H1 subgroup and 816.3 in the H2 subgroup

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