**DETERMINATION OF THE MINIMUM EFFECTIVE DOSAGES OF PRAZIQUANTEL, ALBENDAZOLE, AND MEBENDAZOLE AGAINST CLONORCHIS SINENSIS INFECTION IN RATS**

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In order to determine the minimum effective dosages of praziquantel, albendazole, and mebendazole against *Clonorchis sinensis* infection in Sprague-Dawley rats, each rat was infected with 30 metacercariae and treated with one of three drugs. The rats were killed and examined 25 days after praziquantel treatment or 11 days after albendazole or mebendazole treatment. The minimum effective dosages were a single dose of praziquantel 375 mg/kg, albendazole 150 mg/kg, and mebendazole 150 mg/kg. Trials are required to determine whether these dosages are useful in the treatment of human clonorchiasis.

Key Words: albendazole, *Clonorchis sinensis*, mebendazole, minimum effective dosage, praziquantel


**Materials and Methods**

**Drugs**

Praziquantel (2-cylohexycarbonyl-4-one) is a type of acylated isoquinoline pyrazine. It has high activity against both cestode and trematode parasites in human and animal subjects [16].

Albendazole (Zentel; GSK, Kingdom Pharmaceutical Co., Taipei, Taiwan), methyl-5-propylthio-1 H-benimidazole-2-yl carbamate, is a benzimidazole derivative. It causes degenerative changes in the intestine and tegumental cells of helminths. This effect has been attributed to the interaction with cytoplasmic microtubules [17].

Mebendazole (Vermox; SK&F, Paris la Defense, France), methyl 5(6)-benzol-2-benzimidazole carbamate, clonorchiasis patients were treated successfully with albendazole 600 mg t.i.d. for 2 or 3 consecutive days [15]. Mebendazole is another broad-spectrum anthelmintic used against intestinal nematode infections. Its minimum effective dosage in the treatment of clonorchiasis remains unknown.

The present study was conducted to determine the minimum effective dosages of these three drugs against clonorchiasis in Sprague-Dawley (SD) rats.

*Clonorchis sinensis* is an important human parasite in East Asia. This parasite is widely distributed in China, Japan, Korea, Taiwan and Vietnam [1]. Previous reports note that the highest *C. sinensis* infection rate in Taiwan was 50% among the inhabitants of Meinung Area, Kaohsiung County, Sun-Moon Lake Region, Nantou County, and government workers in the Miaoli County [2–7]. Infection rates among the local people in part of Pingtung and Miaoli Counties were 10–13% [8–10].

Praziquantel is reported to be an effective and safe drug in the treatment of clonorchiasis [11,12]. At 75 mg/kg body weight in three doses 4–6 hours apart, there were no failures among 46 patients and the side effects were mild [13]. Moreover, 34 patients who received 14 mg/kg t.i.d. for 5 consecutive days were cured and the passage of the flukes in the feces began as early as 10 hours after the first dose [14].

Albendazole is a broad-spectrum anthelmintic with high activity against intestinal nematode, cestode and trematode infections. Rim et al reported that several

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is a synthetic broad-spectrum anthelminthic with high efficacy against common nematode parasites. Pharmacologically, mebendazole is very stable. It irreversibly blocks glucose uptake in the parasite but has no effect on the blood glucose level of the host [17].

**Experimental infection**

Metacercariae of C. sinensis were collected from Pseudorasbora parva caught in Chengching Lake, Kaohsiung County, Taiwan. Each of the 111 male SD rats (mean weight, 200 g) was inoculated with 30 metacercariae using a long needle (No. 18) with a small tin bulb at the tip. The needle was attached to a 1 mL plastic syringe. Metacercariae were inoculated directly into the stomach with this needle.

**Drug administration**

Each dose of each drug was administered to one group of three rats. On the 35th day post-infection, all rats were infected, as shown by stool examination. They received a single dose of drug suspension in physiologic saline using the above needle 2 days after the infection was confirmed. For praziquantel, 14 dosages were used: 600, 575, 550, 525, 500, 475, 450, 425, 400, 375, 350, 325, 300, and 275 mg/kg. For albendazole, 12 dosages were used: 600, 500, 400, 350, 300, 250, 200, 150, 100, 50, 25, and 12 mg/kg. For mebendazole, eight dosages were used: 300, 250, 200, 150, 100, 50, 25, and 12 mg/kg. For each drug, a control group received saline only. Three treated rats or three controls in each group were then kept in a metal cage (30 × 20 × 16 cm) and given a regular diet.

**Post-treatment examination**

All the rats were killed by ether overdose, 25 days after praziquantel treatment or 11 days after albendazole or mebendazole treatment. The liver was removed and visually examined for the presence of adult C. sinensis.

**Results**

**Praziquantel**

No worms were found in the first 10 groups, giving a cure rate of 100% with dosages of 375–600 mg/kg. The cure rate was 67% in the 350, 325, and 300 mg/kg groups and 33% in the 275 mg/kg group. The total number of worms recovered from the 350, 325, 300, and 275 mg/kg and control groups were two (from 1 rat), three (from 1 rat), five (from 1 rat), seven (from 2 rats), and 21 (from 3 rats), respectively. Therefore, the minimum effective dosage of praziquantel against clonorchiasis in SD rats was 375 mg/kg.

**Albendazole**

No worms were found in the first eight groups, giving a cure rate of 100% with dosages of 150–600 mg/kg. The cure rate in the 100 mg/kg group was 67%, in the 50 and 25 mg/kg groups was 33%, and in the 12 mg/kg group was 0%. The total number of worms recovered from the 100, 50, 25, and 12 mg/kg and control groups were one (from 1 rat), seven (from 2 rats), 10 (from 2 rats), 39 (from 3 rats), and 61 (from 3 rats), respectively. Therefore, the minimum effective dosage of albendazole against clonorchiasis in SD rats was 150 mg/kg.

**Mebendazole**

No worms were found in the first five groups, giving a cure rate of 100% with dosages of 150–300 mg/kg. The cure rate in the 100 mg/kg group was 67%, in the 50 and 25 mg/kg group was 33%, and in the 12 mg/kg group was 0%. The total number of worms recovered from the 100, 50, 25, and 12 mg/kg and control groups were two (from 1 rat), six (from 2 rats), six (from 2 rats), 11 (from 3 rats), and 28 (from 3 rats), respectively. Therefore, the minimum effective dosage of mebendazole against clonorchiasis in SD rats was 150 mg/kg.

**Discussion**

In the study by Rim, 283 cases infected with C. sinensis were administered different dosages of praziquantel for 1 or 2 days [18]. Two months after therapy, the egg reduction rate ranged from 82.6% to 100% and the cure rate from 6.7% to 100%. The group treated with a single dose of 20 mg/kg body weight for 2 days showed an 82.6% egg reduction rate and a 6.7% cure rate. At a dose of 25 mg/kg t.i.d. for 2 days, the egg count fell to zero and the cure rate became 100%. These results indicate that the therapeutic effect was proportional to the praziquantel dose. In an unpublished experiment, we recovered 84 degenerated worms of C. sinensis from six rats with negative stool examination. Therefore, a zero egg count may not correspond to complete worm eradication in humans and a total dose of 150 mg/kg may not be an effective dose.

In another study, Rim et al used praziquantel on experimentally infected rats and observed the anthelminthic effects at various developmental stages of C. sinensis, in association with dose [16]. Dosages of 1 × 100 mg/kg for
3 days, 3 × 100 mg/kg for 1 day, and 3 × 100 mg/kg for 2 days were tested. In the group receiving 3 × 100 mg/kg for 2 days (total dose, 600 mg/kg), all developmental stages of *C. sinensis* were completely eradicated. In the present study, we found that only 375 mg/kg or more of praziquantel completely cured clonorchiasis in rats. Therefore, this is the minimum effective dosage of this drug against clonorchiasis in rats, which is higher than that obtained in man. This may be due to the physiologic differences between humans and rats. Praziquantel at a single dose of 600 mg/kg has also been shown to have a larvicidal effect against this parasite [19].

Rim et al also reported that several clonorchiasis patients were successfully treated with albendazole at a dose of 600 mg t.i.d. for 2 or 3 consecutive days [15]. In the present study, the minimum effective dosage against clonorchiasis in rats was 150 mg/kg, much lower than that in humans, as reported by Rim et al [15]. It is necessary to conduct chemotherapeutic trials to determine the minimum effective dosage of this drug in the treatment of human clonorchiasis.

In the present study, we also used mebendazole to treat rats experimentally infected with *C. sinensis*. This is the first time this drug has been used in the treatment of *C. sinensis* infection. Our results demonstrated that the minimum effective dosage of mebendazole against clonorchiasis in SD rats was 150 mg/kg. Further study is required to confirm whether mebendazole is effective in the treatment of human clonorchiasis.

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測定吡喹酮、阿苯達唑及甲苯達唑治療大白鼠中華肝吸蟲感染最低有效劑量

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應用不同劑量吡喹酮、阿苯達唑及甲苯達唑治療 SD 大白鼠感染中華肝吸蟲病之最低有效劑量。每一 SD 大白鼠實驗感染 30 個囊狀幼蟲。感染後 25 天用吡喹酮治療或感染後 11 天用阿苯達唑及甲苯達唑治療，而後犧牲大鼠檢查蟲量。吡喹酮、阿苯達唑及甲苯達唑治療測定之最低有效劑量分別為每公斤 375 毫克、150毫克及 150 毫克。上述劑量是否可用於治療人體感染中華肝吸蟲病尚待確定。

關鍵詞：阿苯達唑，中華肝吸蟲，甲苯達唑，最低有效劑量，吡喹酮
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