# Efficacy of Benzimidazole Carbamate on an Intestinal Fluke Co-Infected with Nematodes

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*The efficacy of a single dose of benzimidazole, drugs commonly used for the treatment of Ascaris and hookworm, was evaluated against one of the tiny-sized intestinal flukes, Haplorchis sp in the endemic area where mixed infections of roundworms and flatworms existed. At day 7 after treatment, albendazole (400 mg) induced 42.5% cure rate, mebendazole (500 mg) a cure rate of 32.4%, on the other hand, praziquantel (40mg/kg) gave 94.6% cure rate and the placebo at 15.9%. At the single dose, benzimidazole could not completely expelled the haplorchid; but could reduce one third to two fifth of the infection, similar to the drugs efficacy against Trichuris infection.*

***Keywords:*** *Haplorchis sp, Treatment, Single dose, Albendazole, Mebendazole*

***J Med Assoc Thai 2005; 88(2): 233-7***
***Full text. e-Journal:*** *http://www.medassocthai.org/journal*

In endemic areas of parasitic infections, mixed infection with two or more species of parasites in the same subject occurs in high percentages, 33% in the north of Thailand[1]. Men who have mixed parasitic infections may have to take two or three anti-parasitic drugs at once. For example, a person infected with *Ascaris*, *Taenia* and *Giardia*, may have to take albenda-zole or mebendazole for treatment of *Ascaris*; prazi-quantel or niclosamide for *Taenia* infections and metronidazole for *Giardia*[2].

Trials of albendazole (400 mg) with multiple doses taken for three or seven days in opisthorchiasis patients had been conducted and the cure rates obtained were found very low from 12% to 33%[14], 43.7%[3]. Mebendazole seemed to give more satisfied results with a 96.3% (26/27) cure rate for opisthorchiasis patients with a dose of 30mg/kg taken for three or four weeks[4].

Several reports had shown that treatment of intestinal parasites required lower doses of drugs than those taken for the tissue parasites. The recommended dose of Praziquantel for opisthorchiasis is 40mg/kg single dose[5], but for intestinal fluke infections, it was found effective at only 15mg/kg[6-8]. In the present study a single dose of albendazole or mebendazole normally used to treat of intestinal-round worms was evaluated for the treatment of *Haplorchis* species.

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**Material and Method**

Fecal samples of the residents in Chalerm Prakiet District, Nan Province, North of Thailand, were collected and examined by the cellophane thick smear method. The subjects whose fecal samples contained eggs of a tiny-sized of intestinal fluke were divided into four random groups as follows: 37 subjects were treated with praziquantel (40 mg/kg) single dose, 34 subjects were given mebendazole (500 mg) single dose, 40 subjects were treated with albendazole (400 mg) single dose and 19 subjects were given placebo. At day 7 after treatment, fecal samples were collected from all subjects and examined for fluke eggs and the subjects whose fecal samples still presented with fluke eggs were given praziquantel (40 mg/kg). The subjects whose fecal samples collected after treatment with no fluke eggs found were considered to be cured. The efficacy of treatment for all drugs was compared by Chi-square Test.

It is impossible to differentiate liver fluke eggs from intestinal fluke eggs by cellophane thick

smear method. It is concluded however, that only one genus of tiny-sized intestinal fluke, *Haplorchis taichui* is present in this after identification of expelled worms (manuscript in preparation).

The present study obtained an ethical clearance from the Faculty of Tropical Medicine, Mahidol University.

## Results

Praziquantel, the drug of choice for treatment of flatworms, showed the highest efficacy against *Haplorchis* infection with cure rate of 94.6% and egg reduction rate of 99.1%. Benzimidazoles were less effective with cure rates lower than 50% for both albendazole and mebendazole. However, a single dose of albendazole (400 mg) was more effective than that of mebendazole (500 mg) for both cure rates and egg reduction rates. Lower cure rate were obtained from group receiving the placebo.

The outcome evaluated at day 7 after treatment of each drug is presented in Table 1. The Chi-square test showed there was a significant difference ($X^2 > 16.266$; df = 3, $\alpha = 0.001$) in the proportion of cure when praziquantel, albendazole, mebendazole or placebo was used to treat the subjects infected with *Haplorchis*. However, the efficacy of albendazole and mebendazole against haplorchiasis was not significantly difference ($X^2 < 20706$; df = 1, $\alpha = 0.10$). The efficacy of praziquantel was superior to both albendazole and mebendazole.

**Table 1.** Efficacies of albendazole 400 mg and mebendazole 500 mg, single dose against haplorchiasis patients comparing to praziquantel and placebo

| Drug | No. treated | Cure rate (%) | Egg reduction rate | 95% confidence intervals (%) |
|---|---|---|---|---|
| Praziquantel | 37 | 94.6 | 99.9 | 99.6-100 |
| Albendazole | 40 | 42.5 | 71.6 | 68.2-75.0 |
| Mebendazole | 34 | 32.4 | 15.1 | 10.4-19.8 |
| Placebo | 19 | 15.9 | 36.3 | 28.7-43.9 |

Most of the *Haplorchis* infected subjects in the present study (76.5%) had fecal egg counts below 1,200 eggs per gram (epg) and only 6.8% had fecal egg counts above 4,000 epg (Fig. 1). The number of curable subjects was equally distributed in all fecal egg count groups.

## Discussion

The evaluations of treatment in the present study were done at one week post treatment which is similar to previous studies commonly conducted at one week to one month after treatment[9,10]. Heterophyids are small flukes in which metacercarial stage is fully developed with all reproductive organs present. It needs only a short period of time to become a fully mature adult. Eggs can be observed in the uterus of worms three days after infection, however, it requires 9-13 days before eggs can be found in host's feces[11].

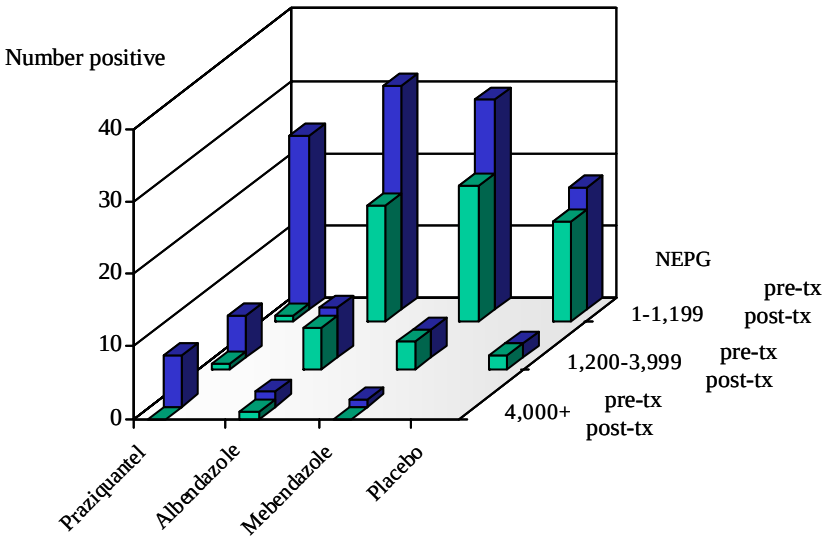


**Fig. 1** Number of Haplorchis taichui infected subjects before and after treatment with three anthelminthic drugs and placebo classified in three classes of egg counts

Previous study reported a decrease of number of Trichuris eggs which nearly disappeared in 5-7 days after taking mebendazole[12]. It was subsequently decided that day 7 after treatment would be the optimal period to observe the curable condition. It was believed that in the present study of eggs should not appear in the fecal sample of curable subjects and it would be too early to have eggs in fecal samples from new infection.

Benzimidazole inhibits cell division and glucose absorption in the digestive tract of the worms. This action results in the expulsion of the worm by peristalsis movement of the intestines. This will be highly effective to nematodes but not so effective for flatworms which can absorb food through the teguments as well as the digestive tracts. The treatment of flukes with benzimidazole for a single dose is therefore less effective. The potency of benzimidazole anthelmintics is enlarged by prolonging the duration of exposure of the parasite to the compound or its active metabolites. Consequently, repeated low doses can be equally or more effective than a single high dose[13]. In the present study, the drug administration period was only one day like in the treatment of general intestinal nematodes; if it had been extended to a longer period the cure rate may have been higher. In a previous study, albendazole at a dosage of 400 mg twice daily for 3 days and 7 days was found to have an effect on opisthorchiasis viverrini[14]. While in the present study it was slightly lower than one third to two fifth of the cure rate obtained with praziquantel now considered effective for the treatment of most trematodes[2]. However, it is still ineffective in *Fasciola hepatica* infection[15-17] and has no effect on nematodes seen in multiple intestinal helminthic infections. The 42.5% and 32.4% of cure rates by albendazole and mebendazole were higher than the rates obtained by the drugs against trichuriasis[18]. For small intestinal fluke infections, multiple dose regimens should be applied in order to have a complete cure. No small intestinal flukes were found in mice treated with albendazole syrup given in two divided doses[19]. Albendazole has produced a higher cure rate than mebendazole for these small fluke infections. In comparative trials with mebendazole, the efficacy of a single dose was similar in the treatment of *A. lumbricoides*, *Trichuris trichiura*, hookworm. The treatment using multiple doses 100 mg twice a day for three days of mebendazole is highly effective against the soil-transmitted helminths[20]. It seems mebendazole requiring administration over an extended period is effective in treatment. The drug was found to be effective when given in dosages of 30 mg/kg body weight for 3 to 4 weeks, only a few Opisthorchis eggs being found in the stool of one of 27 persons at 3 or 4 weeks post-treatment with 89-94% cure rates[4]. Undoubtedly, the most effective of the broad-spectrum anthelminthic agents is albendazole, which as a result of rapid absorption from the small-intestinal lumen achieves a high tissue concentration when administered at relatively low dosage. Although in the present study the cure rate was not so high, marked egg reduction was observed at the end of the week after treatment (94.1%) indicating that only few flukes survived. This was also supported by a number of flukes expelled. The two major colorectal nematode infections, *Trichuris trichiura* and *Enterobius vermicularis*, and the two major small-intestinal nematode infections, hookworm and *Ascaris lumbricoides* infections also respond to the benzimidazoles. At present, benzimidazoles can increase water solubility and thus can be used against systemic infections. Anyway, benzimidazoles are more frequently used for intestinal parasites and particularly in veterinary practice because of their broad spectrum and low toxicity. The effect on small intestinal flukes is a great advantage when treating soil-transmitted helminthiasis co-infection. The cure rate could be increased as the period of treatment is extended, however there was no significant difference between albendazole and mebendazole.

It is clear from the present study that benzimidazoles has expulsion effect against small intestinal flukes but the result that an optimal dosage and duration of treatment have not been achieved. So far there is no report on worm burden and eggs count of *Haplorchis* or related species and no accurate information concerning worms density and symptom of the infection. To be able to evaluate the efficacy of drugs correctly, intensity of infection must be clearly determined. Egg porduction had known to be inversed proportion to worm burden.

**Conclusion**

The benzimidazole are important broad-spectrum drugs for the control of helminth parasites in mammals. The ideal agent with broad-spectrum activity needs to be effective against all intestinal and systemic nematodes (and other helminthes) including 100% efficiency when given as a single dose. The present study showed evidence that benzimidazoles have an effect upon *Haplorchis*. It seems most likely that they will be widely used in practice for small

intestinal flukes for they are more frequently used for intestinal nematodes because of their broad spectrum and low toxicity. The use of almost all benzimidazoles in high dosages are contraindicated during pregnancy because of potential embryotoxic and teratogenic actisvities as shown experimentally in rats and rabbits. In human clinical practice, only two benzimidazole compounds, albendazole and mebendazole, are currently in use. It should be noted that albendazole and mebendazole are effictive against all the major soil-transmitted helminthiasis. These have been shown to be highly effective and safe for the treatment of the majority of intestinal helminth infections and to be useful for both selective and mass treatment. Their limited absorption and rapid metabolism has meant only high and prolonged doses are effective in the treatment of human systemic infection including the small liver flukes.

**Acknowledgements**

This study was supported in part by Mahidol University Research Grants. The authors wish to thank Nan Provincial Health Office for their technical assistance.

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## *ประสิทธิผลของยากลุ่มเบนซิมิดาโซลคาร์บาเมทที่มีต่อพยาธิใบไม้ลำไส้นอกจากที่ใช้รักษาพยาธิตัวกลม*

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*ประสิทธิผลของยากลุ่มเบนซิมิดาโซลที่รับประทานครั้งเดียว ซึ่งปกติใช้ในการรักษาพยาธิไส้เดือน และพยาธิปากขอ จะถูกประเมินในการใช้รักษาพยาธิใบไม้ลำไส้ขนาดเล็กด้วยคือ พยาธิแฮพพลอคิส ในท้องที่ที่มีความชุกชุมของพยาธิมักมีการติดเชื้อร่วมกันของพยาธิตัวกลม และพยาธิใบไม้ หลังจากให้การรักษาจนถึงวันที่ 7 พบว่ายาอัลเบนดาโซล (400 มก) ให้ผลการรักษาพยาธิใบไม้ลำไส้ขนาดเล็ก 42.5% ส่วนยามีเบนดาโซล (500 มก) ให้ผลการรักษา 32.4% ในขณะที่ยาพลาซิควันเทล (40 มก/กก) ให้ผลการรักษา 94.6% และยาหลอก ให้ผลการรักษาเพียง 15.9% จากการศึกษาพบว่า การรับประทานยากลุ่มเบนซิมิดาโซลครั้งเดียวไม่สามารถให้ผลการรักษาขับตัวพยาธิใบไม้ลำไส้แฮพพลอคิส แต่สามารถลดภาวะการติดเชื้อของพยาธิลงได้ 1/3-2/5 ซึ่งใกล้เคียงกับประสิทธิผลของยาต่อการรักษาการติดเชื้อพยาธิแส้ม้า*