ALBENDAZOLE IN THE TREATMENT OF OPISTHORCHIASIS AND CONCOMITANT INTESTINAL HELMINTHIC INFECTIONS

SWANGJAI PUNGPARK, DANAI BUNNAG and TRANAKCHIT HARINASUTA

Department of Clinical Tropical Medicine and Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

INTRODUCTION

In Thailand 54.6% of the rural population are found to be infected with one or more intestinal helminths. In Northeastern Thailand, multiparasitism is common especially with hookworm and *Opisthorchis viverrini*. The prevalence of hookworm and *O. viverrini* infections reported were 41% and 35% respectively (Preuksaraj *et al.*, 1982). Although a few broad spectrum anthelmintic drugs are available, they are not equally effective against *Trichuris* and hookworm.

Albendazole (Zentel ®) has been found to be effective in soil transmitted helminthiasis (Chitchang *et al.*, 1983; Pene *et al.*, 1982; Viravan *et al.*, 1982) as well as in liver fluke infection (Theodorides *et al.*, 1976). Therefore, a clinical trial of albendazole was carried out on patients with *O. viverrini* infection with or without other helminthic infections.

MATERIALS AND METHODS

The study was carried out at the Hospital for Tropical Diseases, Bangkok, Thailand from January to June 1983. Fifty-five patients with *Opisthorchis viverrini* infection with or without other helminthic infections but with no other serious diseases who attended the Out-patient Department were invited to participate in this trial as in-patients. Their ages ranged from 14 to 69 years (average of 34.8). There were 43 males and 12 non pregnant females. All of them came from Northeastern Thailand. Clinical evaluation was performed on each patient before treatment, during treatment and on day 29 or 30 after starting treatment.

Laboratory values were monitored on days-3 to 0^+, 1, 3, 5, 7 and 29 or 30. The investigations were carried out according to conventional methods. The haematological parameters consisted of haemoglobin, packed cell volume, white blood count, differential white blood count, red cell morphology, estimation of platelets, reticulocyte counts and sedimentation rate. The blood chemistry tests included serum bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, serum cholesterol, serum albumin and globulin ratio, blood urea nitrogen, serum creatinine and blood sugar. Urinalysis was also performed on the same day. The radiological examination of the chest was done on pretreatment day and electrocardiograms were performed on days-3 to 0^+, 3, 7 and if needed on day 29 or 30.

Faecal examinations and egg counts were carried out during pretreatment period, on days 6 to 15 and 29, 30. Two specimens were collected prior to treatment, and from each specimen two aliquots were quantified (Stoll, 1921). The egg count per gramme (EPG) was recorded and geometrical mean (GM) was calculated on the four EPG values. On days 29 and 30, stool specimens were also collected and two examinations made by a concentration method (Ritchie, 1948). If eggs were not found Stoll counts were omitted. Egg counts from daily faecal specimens. were performed from days 6 to 15 to observe reduction in egg out put. The expelled worms were retrieved from every stool on days 0 to 7

by sedimentation. Species of worms found were identified.

Symptoms and signs were recorded; side effects and toxic effect were monitored daily during drug administration and throughout the observation period.

Blood samples for pharmacokinetic study were collected from seven patients from each group and the results will be reported elsewhere.

The patients were randomized and divided into group I and group II of 26 and 29 patients respectively. Four hundred mg of albendazole was given orally after morning and evening meals for three days in group I and for seven days in group II.

RESULTS

In group I, 25 patients and in group II, 27 patients had completed the follow-up period of 30 days. The age, weight, height and concomitant helminthic infections of the two groups were comparable (Table 1).

Table 1

Background data and parasitism in the 2 groups of patients.

Patient characteristics	Group I	Group II
No. of patients	25	27
Age years	46.9 (14-65)	36.7 (18-69)
Weight kg	52.9 (30-72)	48 (42-65)
Height cm	159.6 (140-170)	159 (154-168)
No. of patients with:		
Single infection	8	3
Double infection	11	16
Triple infection	6	7
Multiple infection	0	1

Range in parenthesis.

Effects of the two regimens of albendazole on the egg output of *O. viverrini* on day 14 and day 30 are shown in Table 2. In all patients of both groups marked egg reduction was observed during the second week of treatment; 88% in group I and 85% in group II reached the lowest value, however in about half of these patients the egg output subsequently increased a little. Thus, the cure rates on day 14 were higher than on day 30 in both groups.

Table 2

The efficacy of albendazole in opisthorchiasis viverrini.

30-day-follow-up	Group I	Group II
Dosage 400 mg b.i.d.	3 days	7 days
No. of pt.	25	27
Pre treatment Geometrical mean EPG	15540 (3438-50594)	16326 (2834-121011)
Concentration method:		
Egg negative		
D14	16 %	57 %
D30	12 %	33 %
Mean egg reduction		
D14	96 %	99 %
D30	94 %	95 %
Stoll method		
Egg negative		
D14	60 %	96 %
D30	40 %	63 %
Mean egg reduction		
D14	91 %	92 %
D30	92 %	92 %

Range in parenthesis.

O. viverrini were expelled in the stools. The flukes recovered from day 0 to day 7 are shown in Table 3; 96% and 99% were on day 1 to day 4. The highest number of 3,418 flukes recovered was from a patient in group II; he had 22,006 EPG and the worms retrieved were 1;3317; 97;3 on days 1, 2, 3 and 4 respectively. All the flukes recovered appeared morphologically normal.

The effect of Albendazole on concomitant intestinal helminths is shown in Table 4. Twenty six patients with hookworm and 9 patients with *Strongyloides stercolaris* infections were cured.

Intestinal nematodes, cestodes and trematodes were found in stools in both groups. Almost all worms recovered were on day 1 to day 3 of treatment.

Side effects were observed in 69% and 62% in group I and group II respectively. They occurred on the first 3 days of drug administration (Table 5). They were mild and subsided within 1-2 days. The symptoms recorded were diarrhoea, insomnia, dizziness, epigastric pain, headache, lassitude, "hot sensation", myalgia, nausea, sleepiness, low back pain, constipation and itching. The itch of palms and skin all over the body began one hour after the first dose lasting 10 minutes and recurred several times for nine days with no rash observed; eosinophilia varied from 15 to 32%; this patient was in group I and had no past history of the symptom.

As expected, before treatment there was eosinophilia of 10-40% in 76% and 90% of group I and group II respectively; after treatment on day 30 there was some reduction in most of the cases, however the absolute count was still higher than normal.

There was no evidence of toxicity from the results of laboratory tests carried out on the patients. The electrocardiograph monitoring were essentially normal; however sinus bradycardia was observed in a few patients. This may not be due to the drug as it is commonly found in patients admitted into this hospital as well as in healthy individuals.

Clinical improvement was observed in all except one person in each group. The main symptom was dull aching pain, in group I in

Table 3

Number of *Opisthorchis viverrini* retrieved from stools daily.

Day	Group I (26 patients)			Group II (29 patients)		
	No. pt. with flukes	Range and No. flukes recovered	Total flukes	No. pt. with flukes	Range and No. flukes recovered	Total flukes
0	1	107	107	3	1,1,2	4
1	13	1-610	1,504	13	1-2044	7,027
2	19	2-735	1,614	24	1-3317	8,207
3	15	1-160	466	14	1-97	483
4	12	1-35	122	17	1-91	235
5	4	1-25	31	7	1-28	79
6	2	1,3	4	9	1-28	67
7	2	1,6	7	2	1,3	4
Total	25	1-735	3,855	29	1-3317	16,106

Table 4

Effect of albendazole on intestinal helminths.

Helminth Species	Group	No. pt. with egg/larvae in stools	Egg/larvae per gramme (range)	Cure rate on day 30	Worms recovered	No.pt. with worms expelled in stools
Hookworm*	I	11	1500 (400-3600)	100	*N.amer.* 247 (131 ♂ 116 ♀)	15
	II	15	1642 (400-5200)	100	*N.amer.* 186 (79 ♂ 107 ♀)	12
					A.duo. 8 (2 ♂ 6 ♀)	3
					A.cey. 4 (2 ♂ 2 ♀)	2
S. stercolaris	I	4	400	100	-	-
	II	5	1080 (400-2000)	100	-	-
E. vermicularis	I	-	-	-	85 (37 ♂ 48 ♀)	5
	II	-	-	-	111 (11 ♂ 100 ♀)	9
T. saginata	I	-	-	-	segments	2
	II	-	-	-	segments 1.2 m-5 m	5
Echinostoma sp.	I	1	600	100	*E. ilocanum* 1	1
	II	2	400	100	*E. malayanum* 2 *E. ilocanum* 1	2

**N. amer. = Necator americanus; A. duo = Ancylostoma duodenale; A. cey = Ancylostoma ceylanicum.*

the right hypochondrium and in group II in the epigastrium. Most of the patients of both groups felt better by therapy and were discharged as cured.

DISCUSSION

Albendazole at a dosage of 400 mg twice daily for 3 days and 7 days was found to have an effect on opisthorchiasis viverrini. Using the concentration method for evaluation, the cure rates on day 30 were 12% and 33% and the percentages of egg reduction were 94 and 95 in group I and group II respectively. Using the Stoll method the cure rate were 40% and 63% and the percentage egg reduction were 92 and 92 in group I and group II respectively. The cure rate increased as the period of treatment was extended, however there was no significant difference between groups.

Although the cure rate was not high, the mean percentage egg reduction was very high indicating that only few flukes survived. This was also supported by a great number of flukes expelled. Albendazole therefore is effective against *O. viverrini.*

It is interesting to note that the cure rate on day 14 of both groups and by both methods (concentration and Stoll) were higher than those on day 30. The flukes were affected by albendazole as most of them were dead and were expelled but some were injured and

Table 5

Percentage distribution of side effects on day 0-4 and day 4-7 in group I (26 pt.) and group II (29 pt.).

Symptoms	Day 0-4		Day 4-7	
	Group I	Group II	Group I	Group II
Patients with symptoms	69	62	12	10
Diarrhoea	31	21	0	0
Insomnia	12	17	0	0
Dizziness	12	7	0	0
Epigastric pain	12	7	0	0
Headache	12	0	0	0
Lassitude	8	14	0	3
Hot sensation	8	7	8	0
Myalgia	8	4	0	0
Nausea	8	3	0	0
Sleepiness	4	7	0	0
Low back pain	4	0	4	7
Itching	4	0	0	0
Constipation	0	7	0	0

ceased laying eggs, later they recovered, and egg production was restored. It is therefore recommended that evaluation should not be made at 2 weeks.

Jaroonvesama *et al.*, (1981) reported mebendazole another benzimidazole derivative in the treatment of opisthorchiasis at dosages of 20 mg per kilogram body weight for 4 weeks, 30 mg/kg for 4 weeks and 3 weeks yielded cure rates of 70%, 89% and 94% respectively. In our study the drug administration period was only 3 and 7 days; if it had been extended to a longer period the cure rate may have been higher.

Praziquantel has been shown to be the most effective drug in treating trematode and cestode infections. The cure rates of opisthorchiasis using 6 doses of 25 mg/kg for two days, 3 doses of 25 mg/kg for one day, 2 doses of 25 mg/kg, for one day and a single dose of 40 mg/kg were 100%, 100%, 88% and 91% effective respectively (Bunnag and Harinasuta, 1980, 1981; Supanvanich *et al.*, 1981). Praziquantel on the other hand has no effect on nematodes which commonly accompany opisthorchiasis. The patients in the two groups are representative of the rural populations in Thailand which harbour multiple intestinal helminths.

The recovery of *O. viverrini*, *Necator americanus*, *Ancylostoma duodenale*, *A. ceylanicum*, *Enterobius vermicularis*, *Echinstoma malayanum*, *E. ilocanum* and segments of *Taenia saginata* in stools confirms the effect of albendazole on trematode, cestode, as well as on nematode infections.

Viravan *et al.*, (1982) reported slight rises in alkaline phosphatase in 3 patients out of 22 patients who received a single dose of albendazole for hookworm infection, but in the present study the alkaline phosphatase levels remained within normal limits throughout the study period in all patients. The patients treated by Viravan *et al.*, (1982) had malaria and were treated with antimalarial drug 4-5 weeks earlier; the rise in alkaline phosphatase is probably due to some interaction between albendazole, malaria and antimalaria drugs. This remains to be clarified.

In both groups, side effects occurred on Day 1 to 3 and coincided with expulsion of worms. In group II side effects subsided despite continuation of drug therapy. This suggests that side effects may result from some toxic product of dead or dying worms.

This study demonstrates a definite therapeutic effect of albendazole against *O. viverrini*, but the results suggest that an optimal

dosage and duration of treatment have not yet been achieved.

SUMMARY

A total of 52 adult patients with opisthorchiasis with or without concomitant intestinal helminthic infections were treated with albendazole at dosage regimens of 400 mg twice daily for 3 days (group I with 25 patients) and 7 days (group II 27 patients). By concentration method with four examinations from two faecal specimens of each patient the cure rates and percentage egg reduction on day 30 in group I and group II were 12% and 33%, 94 and 95 respectively; by Stoll method the cure rates and percentage egg reduction were 40% and 63%, 92 and 92 in group I and group II, respectively. There were no statistically significant differences between the results of the two regimens. Twenty six patients with hookworm and 9 patients with *S. stercolaris* infections were cured. *Opisthorchis viverrini*, *N. americanus*, *A. duodenale*, *A. ceylanicum*, *E. malayanum*, *E. ilocanum*, *S. stercolaris*, *E. vermicularis*, and *T. saginata* segments were expelled in stools, mostly on days 1 to 4. Most of the patients felt relieved from symptoms of pain in the right hypochondrium and epigastrium.

The side effects were mild and transient. There were no evidence of toxic effects on the bone marrow, heart, liver or kidneys.

Albendazole was shown to be effective against *Opisthorchis viverrini* infection as well as other concomitant intestinal helminthic infections; but the optimal dosage and duration of treatment have not yet been achieved.

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