A COMPARATIVE TRIAL OF ALBENDAZOLE ALONE *VERSUS* COMBINATION OF ALBENDAZOLE AND PRAZIQUANTEL FOR TREATMENT OF *TRICHURIS TRICHIURA* INFECTION

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Abstract. A randomized clinical trial was conducted to compare the effectiveness of albendazole alone and albendazole combined with praziquantel in the treatment of *Trichuris trichiura* infection. The drug regimens consisted of single dose of albendazole 400 mg (A1, n=34), 3 days of albendazole 400 mg daily (A3, n=34), 5 days of albendazole 400 mg daily (A5, n=35), single dose of albendazole 400 mg plus praziquantel 40 mg/kg (A1P1, n=34), and 3 days of albendazole 400 mg plus praziquantel 40 mg/kg daily (A3P3, n=36). It was found that treatment with 3 or more consecutive days of albendazole with or without praziquantel resulted in a significant reduction in density of *Trichuris* eggs in stools while a single dose of such drug did not. Praziquantel was not shown to have synergistic or antagonistic effects with albendazole. A regimen of 400 mg of albendazole daily for 3 days was found to be the most suitable therapy for *Trichuris* infection.

INTRODUCTION

Trichuris infection is prevalent worldwide, especially in warm, humid climates of tropical countries. Although the adult worms usually do not cause significant illnesses, it may cause some degree of anemia, abdominal pain, or dysentery-like symptoms in heavily infected patients (Miyazaki, 1991). In addition, there have been many studies suggesting that this infection could cause impairment in growth and mental function (Stephenson *et al*, 1989; Nokes *et al*, 1992; Simeon *et al*, 1994). Therefore it is recommended to treat all patients irrespective of the presence of symptoms. Mebendazole and albendazole are considered the safest and most effective drugs for the treatment of trichuriasis (Tracy and Webster, 1996). Single dose treatment with either drug, however, does not produce impressive results (Jackson *et al*, 1998) and 3 consecutive days of treatment with albendazole was shown to produce better results (Hall and Nahar, 1994). However, there has been no data to show whether or not further increasing duration of treatment (*ie* to 5 days) will have additive effects on the outcome.

As we know that *Trichuris* sucks blood and tissue fluid for its living, it is interesting whether increasing the blood level of albendazole sulphoxide (the active metabolite of albendazole) will increase the effectiveness of treatment. Homeida *et al* (1994) studied pharmacokinetic interaction between praziquantel and albendazole and reported that the area under curves as well as maximum concentration of albendazole sulphoxide increased significantly when administered with praziquantel.

We therefore designed this study to clarify the effect of co-administration of praziquantel with albendazole and the effect of duration of treatment on the therapeutic outcome of *Trichuris* infection.

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MATERIALS AND METHODS

This was an open randomized clinical trial. A stool examination was done to detect *Trichuris* infected patients in communities. All children and adults who were infected with *T. trichiura* and met the following criteria were recruited: age more than 4 years; no history of allergic reaction to albendazole or praziquantel; no history of cysticercosis; no concurrent pregnancy, active liver or renal diseases, on other serious infectious illnesses. Informed consent was obtained from the patients or guardians. Pre-treatment stool examination using a modified Kato Katz technique (Martin and Beaver, 1969) was done to detect the density of *Trichuris* eggs in the stools. Pre-treatment intensity of *Trichuris* infection was graded according to the density of egg in stool: grade 1, *Trichuris* eggs <100 eggs per gram of stool (epg); grade 2, *Trichuris* eggs 100-<1,000 epg; grade 3, *Trichuris* eggs 1,000-<10,000 epg; and grade 4, *Trichuris* eggs ≥10,000 epg. The patients were then stratified randomly into 5 treatment groups (A1, A3, A5, A1P1, A3P3) depending on to the pre-treatment intensity of infection. The treatment regimens were as follows: A1, single dose of albendazole 400 mg; A3, 3 consecutive days of albendazole 400 mg daily; A5, 5 consecutive days of albendazole 400 mg daily; A1P1, single dose of albendazole 400 mg plus praziquantel 40 mg/kg; A3P3, 3 consecutive days of albendazole 400 mg plus praziquantel 40 mg/kg daily. All drugs were administered orally as a single daily dose with breakfast. Both albendazole and praziquantel were produced by the Thai Government Pharmaceutical Organization. The patients were asked to report pre-treatment and post-treatment symptoms. Physical examination was done on day 0 and day 7 and whenever it was indicated by the presence of abnormal symptoms. The occurrence of post-treatment symptoms that were not present or that were more severe than that in the pre-treatment period was considered as side effects. Three consecutive stool examinations using a modified Kato Katz technique were performed 2-3 weeks after the last dose of treatment to assess the effectiveness of each regimen. This was done by investigators who were unaware of the treatment regimens. Cure was defined as no *Trichuris* eggs in all of the three post-treatment stool samples.

Pre-treatment and post-treatment *Trichuris* eggs counts in each group were calculated as geometric mean eggs per gram of stool. To make calculation possible, the value of 0 epg was replaced by the value of 1. Paired *t*-test was used to compare pre-and post-treatment geometric mean eggs within the same group. The baseline and outcome data from different groups were compared and analyzed by analysis of variance (ANOVA) (continuous variables) for quantitative data and chi-square test or Fisher exact test for qualitative data whichever was appropriate. This study was approved by the Ethics Committee, Faculty of Tropical Medicine, Mahidol University, Bangkok.

RESULTS

One hundred and seventy-three patients were recruited into the study. Thirty-four, 34, 35, 34 and 36 patients were in the A1, A3, A5, A1P1 and A3P3 treatment group respectively. Twenty-four (13.9%) patients were female and 149 (86.1%) were male. Their age ranged from 9 to 42 [mean (SD) 18.7(5.3)] years old and weight ranged from 22 to 63 [mean (SD) 36(11)] kg. The pre-treatment *Trichuris* eggs density in stools ranged from 23 to 46,000 (geometric mean 677.95) epg. Thirty (17.3%), 75(43.3%), 54(31.2%) and 14(8.1%) patients had intensity of infection of grades 1, 2, 3 and 4 respectively. The pre-treatment symptoms are shown in Table 1. All of the symptoms were mild, *ie* the patients were aware of the symptoms but easily tolerated. There was no difference in baseline characteristics of the patients in different treatment groups (Table 2).

The *Trichuris* eggs density in stool was significantly reduced in the patients who were

treated with 3 and 5 days of albendazole alone and 3 days of albendazole plus praziquantel (Table 3). Post-treatment geometric mean eggs in these 3 treatment groups were also less than that in the other 2 groups (p=0.004 by ANOVA). There was no different in the post-treatment geometric mean eggs among the A3, A5 and A3P3 treatment groups as well as between the A1 and A1P1 treatment groups. The cure rate was also higher in patients who were in A3, A5 and A3P3 treatment groups but there was no statistical significance (Table 4).

All of the treatment regimens were well tolerated. All of the reported symptoms were mild and physical examination revealed no detectable abnormality. Although these side effects were not different between treatment groups, it was noted that more patients in A1P1 and A3P3 treatment groups had fatigue (Table 5).

Table 1
Pre-treatment symptoms of studied patients.

Symptom	No. of patients (%)
Headache	13 (7.5)
Dizziness	9 (5.2)
Anorexia	12 (6.9)
Diarrhea	13 (7.5)
Fatigue	15 (8.7)
Dyspepsia	10 (5.8)
Pruritus ani	16 (9.2)
Vomiting	1 (0.6)

DISCUSSION

Although single dose of 400 mg albendazole was found to be highly effective against *Ascaris* and hookworm infection, it's effectiveness against *Trichuris* infection was low (Ramalingam *et al*, 1983; Jongsuksuntigul *et al*, 1993; Albonico *et al*, 1994; Norhayati *et al*, 1997; Jackson *et al*, 1998). The cure rate for *Trichuris* infection varied from 5.5

Table 2
Baseline characteristics of the studied patients.

	A1 (n=34)	A3 (n=34)	A5 (n=35)	A1P1 (n=34)	A3P3 (n=36)
Mean (SD) age (year)	18.2 (5.1)	18.6 (4.8)	19.2 (5.7)	19.2 (6.2)	18.1 (4.9)
Gender [n(%)]					
Male	30 (88.2)	29 (85.3)	31 (88.6)	29 (85.3)	30 (83.3)
Female	4 (11.8)	5 (14.7)	4 (11.4)	5 (14.7)	6 (16.7)
Mean (SD) weight (kg)	37.1 (13.1)	34.1 (11.7)	36.7 (9.4)	38.2 (11.6)	34.1 (8.7)
Trichuris eggs count (epg[a])					
Range	23-46,000	23-28,060	46-22,540	23-13,041	46-34,040
Arithmetic mean (SD)	3,796 (10,215)	2,674 (5,508)	3,122 (5,436)	2,130 (3,475)	2,995 (6,499)
Geometric mean	622.6	651.5	838.7	660.4	636.1
Intensity of infection[b] [n(%)]					
Grade 1	7 (20.6)	6 (17.6)	5 (14.3)	6 (17.6)	6 (16.7)
Grade 2	15 (44.1)	14 (41.2)	15 (42.9)	15 (44.1)	16 (44.4)
Grade 3	10 (29.4)	11 (32.4)	12 (34.3)	10 (29.4)	11 (30.6)
Grade 4	2 (5.9)	3 (8.8)	3 (8.6)	3 (8.8)	3 (8.3)

[a]epg = eggs per gram of stool
[b]Intensity of infection:
Grade 1 = *Trichuris* eggs count <100 epg, Grade 2 = *Trichuris* eggs count 100 - <1,000 epg, Grade 3 = *Trichuris* eggs count 1,000 - <10,000 epg, Grade 4 = *Trichuris* eggs count ≥ 10,000 epg.

Table 3
Geometric mean *Trichuris* eggs count (epg[a]) before and after treatment with different anthelmintic regimens.

Anthelmintic regimen	*Trichuris* egg count		p-value
	Pre-treatment	Post-treatment	
A1 (n=34)	622.6	791.8	0.580
A3 (n=34)	651.5	119.7	0.002[b]
A5 (n=35)	838.7	111.0	<0.001[b]
A1P1 (n=34)	660.4	423.9	0.168
A3P3 (n=36)	636.1	124.8	0.001[b]

[a]eggs per gram of stool
[b]statistical significance ($p<0.05$)

Table 4
Cure rate after treatment with different anthelmintic regimens.

Anthelmintic regimen	Outcome		Cure rate (%)
	Cure	Not cure	
A1 (n=34)	1	33	2.9
A3 (n=34)	6	28	17.6
A5 (n=35)	7	28	20.0
A1P1 (n=34)	1	33	2.9
A3P3 (n=36)	6	30	16.7

to 67.4% and egg reduction rate varied from 39.2 to 87%. Our study did not only confirm the low effectiveness of single dose of albendazole in the treatment of *Trichuris* infection but showed no beneficial effect from the single dose of albendazole. The exact cause of this difference is not known. It may be due to different study design, variation in pharmaceutical production, variation in pharmacokinetics of the patients, different intensity of infection and strain of *Trichuris*, or induction of drug resistance after long term use of albendazole in the community.

Our study also confirmed a previous report that 3 consecutive daily doses of 400 mg albendazole was more effective in the treatment of *Trichuris* infection (Hall and Nahar, 1994) although, again, the effectiveness was poorer in our study. Increasing duration of the treatment from 3 days to 5 days did not show a significantly better result. However, this should be confirmed by further studies.

Although praziquantel was shown to increase the blood level of albendazole sulphoxide (Homeida *et al*, 1994), addition of praziquantel showed neither synergistic nor antagonistic effect to albendazole in the treatment of *Trichuris* infection. It may be because the effectiveness of treatment does not depend on the blood level of albendazole sulphoxide or because praziquantel did not

Table 5
Number (%) of episodes of side effects according to the treatment group.

Side effect	A1 (n=34)	A3 (n=34)	A5 (n=35)	A1P1 (n=34)	A3P3 (n=36)
Headache	1 (2.9)	1 (2.9)	0	2 (5.9)	0
Dizziness	0	0	1 (2.9)	2 (5.9)	1 (2.8)
Anorexia	1 (2.9)	0	1 (2.9)	0	0
Diarrhea	1 (2.9)	0	1 (2.9)	1 (2.9)	0
Dyspepsia	3 (8.8)	1 (2.9)	0	3 (8.8)	1 (2.8)
Fatigue	3 (8.8)	1 (2.9)	2 (5.7)	9 (26.5)	4 (11.1)
Vomiting	0	0	1 (2.9)	3 (8.8)	0
Somnolence	0	0	0	1 (2.9)	0
Insomnia	0	0	0	0	1 (2.8)
Pruritus ani	0	1 (2.9)	3 (8.6)	2 (5.9)	0
Generalized pruritus	1 (2.9)	0	0	0	0

increase the blood level of albendazole sulphoxide in our patients. Unfortunately, we did not detect the blood level of albendazole sulphoxide in this study. However, the finding that the co-administration of albendazole and praziquantel did not show antagonistic therapeutic effects or synergistic adverse effects encourages the use of this combination in patients who have mixed infections with nematodes and cestodes or trematodes. The more frequent occurrence of fatigue in the patients of A1P1 and A3P3 treatment groups was most likely due to the sedative effect of praziquantel per se and should not discourage the use of this drugs combination.

In conclusion, a regimen of 400 mg albendazole daily for 3 days was found to be the most suitable therapy for *Trichuris* infection. Combination of praziquantel and albendazole was not found to be better or worse than albendazole alone for the treatment of *Trichuris* infection.

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