

# SINGLE-DOSE THERAPY FOR GIARDIASIS IN SCHOOL-AGE CHILDREN

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**Abstract.** A randomized controlled trial was carried out to study the efficacy of combined albendazole and praziquantel in the treatment of giardiasis in school-age children. Eighty-four children were randomly allocated to 3 groups: group 1 (n = 31) albendazole 400 mg combined with praziquantel 20 mg/kg; group 2 (n = 26) albendazole 800 mg as a single dose; group 3 (n = 27) tinidazole 50 mg/kg as a single dose. The treatment was considered curative when *Giardia* was not found in two consecutive stool samples. The parasitological cure rate was 74.2% for combined single-dose albendazole-praziquantel, 50% and 92.6% in the albendazole and tinidazole groups respectively (p = 0.0023). There was no statistically significant difference between the cure rates of the combined regimen and tinidazole (p > 0.05). This combined regimen was considered safe, with only minor side-effects being observed.

Of the single-dose regimens, tinidazole still achieves the highest parasitological cure rate for giardiasis. The albendazole-praziquantel combined regimen may be an alternative single-dose therapy for giardiasis in children, especially as this combination will eradicate common intestinal protozoa and co-existing helminths. Whether the dosage of this combination treatment should be adjusted for *G. intestinalis* remains to be established by further study.

## INTRODUCTION

Giardiasis is endemic in most areas of the world. It occurs throughout temperate and tropical regions worldwide and has the highest prevalence, 20-30%, in the developing world (Farthing, 1996). A study in the northeastern part of Thailand found that the prevalence of giardiasis in children under 7 years of age was 10.2% (Sornmani *et al*, 1973) whereas in Siriraj Hospital, Bangkok, 18.6% and 18.2% of children with and without associated symptoms respectively were reported to have giardiasis (Chavalittamrong *et al*, 1978). A study in children with chronic diarrhea in an orphanage (Phyathai Baby Home, Bangkok) showed that

85.5% of their stools were positive for *G. intestinalis* (Sabchareon *et al*, 1980); in contrast, a giardiasis prevalence of only 7.1% was reported in children aged 3-15 years in Bangkok, Thailand (Pengsaa *et al*, 1999).

It is generally accepted that patients with symptomatic *G. intestinalis* infection should receive antimicrobial therapy; the rationale of treating asymptomatic carriers is not to eradicate the organism from the environment but to reduce the number of potential reservoirs and to decrease the prevalence of *Giardia* to a point where transmission is less likely to occur. Current reviews recommend that if the parasite is found, patients should be treated.

Zaat *et al* (1997) conducted a systemic review of published randomized clinical trials and stated that metronidazole treatment for 3 days or more seems to achieve a better parasitological cure rate than other long treatment courses. Successful eradication of *G. intestinalis* has been achieved with oral metronidazole 20

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mg/kg/day for 5-10 days (Suntornpoch and Chavalittamrong, 1981; Bassily *et al*, 1987; Bulut *et al*, 1996). Side-effects and the duration of treatment are important factors affecting compliance, especially in children. The efficacy of albendazole was found to be related to the dosage given: Hall and Nahar (1993) reported that albendazole given at a daily dose of 400 mg for 5 days was as effective as metronidazole; a 3-day albendazole treatment for giardiasis gave a moderate to relatively high cure rate of 50-81% (Hall and Nahar, 1993; Pengsaa *et al*, 1999), whereas higher cure rates of 96-100% were reported in children and adults if 5-7 days of albendazole were prescribed (Hall and Nahar, 1993; Pungpak *et al*, 1996). For a single-dose therapy, tinidazole (2 g in adults) reaches a higher parasitological cure rate than other short therapies. The efficacy of a single oral dose of tinidazole or ornidazole 50 mg/kg has been reported to be 80-100% (Gazder and Banerjee, 1978; Sabchareon *et al*, 1980; Jokipii and Jokipii, 1982; Speelman, 1985), but undesirable side-effects have been reported.

Developing a single-dose drug or drug combination which is safe and acts broadly against common intestinal parasites should be a priority. Homeida *et al* (1994) reported that the serum level of albendazole sulphoxide (the active metabolite of albendazole) increased when administered with praziquantel. If a higher level of albendazole sulphoxide is achieved when single-dose albendazole is administered simultaneously with praziquantel in the treatment of giardiasis, it would be more beneficial than a 5 day-course of albendazole alone.

We conducted this study to determine the value of the combination of albendazole and praziquantel in the treatment of giardiasis in school-age children. This study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University.

## MATERIALS AND METHODS

The children aged between seven and fifteen years from five primary school in

Bangkok metropolitan area were screened for *G. intestinalis* cysts/trophozoites from February to August 2001. Fresh stool specimens were examined by direct smear and iodine stained after ether-sedimentation concentration (Ritchie, 1948) at Faculty of Tropical Medicine, Mahidol University. Written informed consent was obtained from the parents before their children participated in the study. The children with giardiasis were enrolled and interviewed for presenting symptoms. A complete physical examination was made on the initial visit. The children were randomly allocated into 3 groups and received one of the following single-dose regimens:

- Group 1: 400 mg albendazole (Zentel®) combined with praziquantel (Biltricide®) 20 mg/kg
- Group 2: 800 mg albendazole (Zentel®)
- Group 3: 50 mg/kg (maximum 2 g) tinidazole (Fasigyn®)

Children with a history of taking any anthelmintic drug within one month, a history of drug allergy to nitroimidazole, benzimidazole and pyrazinoisoquinolone derivatives, and those with acute illnesses, were excluded.

The drugs were given after a meal as directly observed therapy (DOT) by the investigators. The children were closely observed for 60 minutes after drug administration for side-effects and then the children or their parents were asked to record the occurrence of any adverse events at home for another 3 days: a questionnaire was provided. Side-effects were considered moderate if the child asked for medication to relieve a symptom or of the side-effect interfered with normal activity. If medical intervention was needed, the side-effects were considered severe.

The efficacy of the treatment was assessed by microscopic examinations of 2 consecutive stool samples collected from each child 7-14 days after treatment, as described above. The investigators who performed the microscopy were blinded from the treatment regimens. A child was considered to be parasitologically cured when both stool examina-

Table 1  
Baseline data of the children in the three treatment groups.

	Albendazole + praziquantel	Albendazole alone	Tinidazole
Number	31	26	27
Male : Female	1.6:1	1.2:1	0.8:1
Mean age $\pm$ SD (y) <sup>a</sup>	10.0( $\pm$ 1.4)	10.1( $\pm$ 1.7)	9.9( $\pm$ 2.1)
Range 7-9 (y)	10	8	11
>9-11 (y)	16	9	8
>11-13 (y)	4	8	6
>13-15 (y)	1	1	2
Mean weight $\pm$ SD (kg) <sup>a</sup>	29.3( $\pm$ 8.2)	31.4( $\pm$ 10.7)	28.6( $\pm$ 12.4)
Mean height $\pm$ SD (cm) <sup>a</sup>	133.9( $\pm$ 8.9)	139.4( $\pm$ 9.1)	133.6( $\pm$ 13.9)

<sup>a</sup>p >0.05

tions were negative for *G. intestinalis*. In cases with persistent infection, a single dose of tinidazole was given. During and after completion of the study, all children who were found to be infected with any other intestinal parasites were appropriately treated.

#### Data analysis

Descriptive analysis was used for the baseline data. Analysis of variance (ANOVA) was used for continuous variables. Chi-squared and Fisher's exact tests were used to compare parasitological cure rates among the treatment groups. All tests were performed at a statistical significance level of  $p < 0.05$ .

## RESULTS

A total of 2,437 school children were examined. One hundred and thirty-two children (5.4%) found to have *G. intestinalis* cysts in their stool. Eighty-four children (7-15 years old) were enrolled in the study, 45 males (54%) and 39 females (46%). Age, body weight and height were not statistically significant different between groups (Table 1).

Nearly half (40/84) of the children had gastrointestinal symptoms, as shown in Table 2. Thirty-five percent (29 cases) of *Giardia*-infected children complained of infrequent mild abdominal pain except for 4 cases who experienced the symptom nearly every day but for

Table 2  
Gastrointestinal signs/symptoms of 84 children with *G. intestinalis*.

Signs/Symptoms	Number (%)
Abdominal pain	29 (34.5)
Loose stool	21 (25)
Abdominal distention	9 (10.7)
Poor appetite	4 (4.8)

whom no medication was required. Loose stool was the second most common symptom (25%): it too did not interfere with school activity. Nine cases had mild to moderate abdominal distention and 4 cases complained of poor appetite.

The degree of malnutrition, according to the standard curve for Thai children, is shown in Table 3. Among 40 cases of symptomatic giardiasis, 68% (27 cases) were well-nourished and 32% (13 cases) were malnourished. Fifty-nine percent of well-nourished (including 6 cases of obesity) and 41% of malnourished children were in the asymptomatic group. No statistically significant difference was observed in nutritional status related to gastrointestinal symptoms.

Parasitological cure was achieved in 74.2% with combined albendazole-praziquantel, compared with 50% and 92.6% with albendazole and tinidazole respectively (Table 4). The cure

Table 3  
Nutritional status in symptomatic and asymptomatic giardiasis.

Nutritional status <sup>a</sup>	Symptomatic children Number (%)	Asymptomatic children Number (%)
Normal	27 (68)	26 (59)
Malnutrition	13 (32)	18 (41)
- First degree	10	12
- Second degree	2	5
- Third degree	1	1

<sup>a</sup>p > 0.05

Table 4  
Parasitological cure rate of single-dose albendazole plus praziquantel compared with albendazole and tinidazole.

	Cases treated	No. cured	<sup>a</sup> Cure rate (%)
Albendazole-praziquantel	31	23	74.2
Albendazole	26	13	50
Tinidazole	27	25	92.6

<sup>a</sup>p < 0.01

Table 5  
Adverse effects observed in the 3 studied groups.

Adverse effects	Albendazole -praziquantel	Albendazole	Tinidazole
Headache	4	3	3
Dizziness	2	2	2
Drowsiness	1	0	2
Abdominal pain	5 <sup>a</sup>	0	2
Nausea	2	1	1
Vomiting	0	0	2
Metallic taste	1	0	4
Total	15	6	16

<sup>a</sup>Two cases needed treatment.

rates of the three groups showed statistically significant differences ( $p < 0.01$ ). A single dose of tinidazole was more effective than a single dose of 800 mg albendazole ( $p < 0.01$ ). There was no significant difference between the cure rate of combined albendazole-praziquantel and 800 mg albendazole ( $p > 0.05$ ). Though the highest cure rate of 92.6% was in the tinidazole group, a statistically significant difference with the combined regimen was not demonstrated

( $p > 0.05$ ).

The side-effects of the combined albendazole-praziquantel regimen were mild to moderate. Systemic symptoms that were self-limited included one case of drowsiness, 2 cases of dizziness and 4 cases of headache. Regarding gastrointestinal side-effects, there were 5 cases of abdominal pain: among these, one case with dizziness and one case with nausea required medication. There were 3 cases

of headache, 2 cases of dizziness and one case of nausea in the group to whom 800 mg albendazole was given; all of these cases were mild and no medication was needed. Mild to moderate neurological symptoms were also reported in the tinidazole group, including 2 cases who vomited within 30 minutes after medication and 4 cases who complained of a metallic taste (Table 5).

Other intestinal parasites found included hookworm (2 cases), *Trichuris trichiura* (3 cases), *Hymenolepis nana* (4 cases) and *Blastocystis hominis* (9 cases).

## DISCUSSION

*In vitro*, albendazole inhibits the growth of the trophozoites of *G. intestinalis*, impedes their adhesion to cultured intestinal epithelial cells, and disrupts the activity of the microtubules and microribbons in the trophozoite's adhesive disk (Liu and Weller, 1996). A 4.5-fold increase in the area under curves and maximum concentration of albendazole sulphoxide were reported when albendazole was concomitantly administered with praziquantel (Homeida *et al*, 1994).

Flisser *et al* (1995) reported the statistical significance of unexpected reductions of *Entamoeba histolytica* and *G. intestinalis* in the residents of two rural communities after a single dose of praziquantel 5 mg/kg, given as part of a *Taenia solium* cysticercosis intervention. The result suggested that praziquantel might have a direct effect on these organisms or, alternatively, the drug might affect intestinal microorganisms that, by changing environmental conditions, favor expulsion of the protozoan parasites. A significant increase in echinococcosis patients with nonviable protoscoleces was observed in the group treated with albendazole plus praziquantel 25 mg/kg/d, compared with those treated with albendazole alone, at doses of both 10 mg/kg/d ( $p = 0.004$ ) and 20 mg/kg/d ( $p = 0.03$ ) (Cobo *et al*, 1998).

On the other hand, in concurrent administration of albendazole and praziquantel in

schoolchildren with schistosomiasis and geohelminths, neither drug interfered with the cure rate of the other and this drug combination produced no appreciable side-effects (Olds *et al*, 1999). Praziquantel was not shown to have synergistic or antagonistic effects with albendazole in the treatment of *Trichuris trichiura* infection (Sirivichayakul *et al*, 2001).

The fair cure rate of 74.2% produced by the combined regimen in this study may be due to the fact that praziquantel 20 mg/kg did not increase the blood level of albendazole sulphoxide or that a high blood level of albendazole sulphoxide, if it occurred, did not completely disrupt or inhibit the trophozoite's activity. A pharmacokinetic study of albendazole combined with praziquantel in Thai children is needed to clarify this issue. Though not the most effective regimen, a synergistic effect on albendazole was achieved by praziquantel. However, from the fairly high cure rate (74.2%) produced by the combined albendazole-praziquantel regimen, when compared to the lower cure rate (50%) given by albendazole alone, it may be extrapolated that *G. intestinalis* really needs a high dose if only a single dose is to be prescribed. The potential activity of praziquantel on the body surface of the protozoa should be fully investigated.

The cure rate (50%) of single-dose 800 mg albendazole in this study is lower than that reported in the study by Hall and Nahar (1993), and confirmed that albendazole was less effective at all dosages, except at 400 mg for 5 days. It has been accepted that the reinfection rate is very high in places where sanitation is inadequate; because a typing system is not available, it is not possible to determine if prolonged excretion is caused by persistent or new infection.

Though several episodes of side-effects were observed in the albendazole-praziquantel regimen in our study, they were mild, except for two cases of abdominal pain and nausea/dizziness that needed medication. The observed side-effects were acceptable and support the previous report that praziquantel can be safely administered with albendazole to eliminate

nematodes, cestodes, trematodes and some protozoa (Cobo *et al*, 1998; Olds *et al*, 1998; Sirivichayakul *et al*, 2001).

Single-dose treatments have important advantages: they not only result in excellent compliance, but also provide a chance to decrease drug resistance which may easily occur during long periods of drug exposure. Though tinidazole elicited the highest cure rate for the treatment of *G. intestinalis* in our study, a fairly high rate of adverse effects was seen, as in previous studies (Suntornpoch and Chavalittamrong, 1981; Bassily *et al*, 1987; Pengsaa *et al*, 1999). Secnidazole, the long half-life single-dose nitroimidazole yields high parasitological cure rates with good tolerance in children infected with *G. intestinalis* (Gillis and Wiseman, 1996; Di Prisco *et al*, 2000); it seems to be a promising treatment for giardiasis, but unfortunately it is not available in Thailand.

The prevalence of *G. intestinalis* in our study was not high. Nutritional deficiency may be an additional risk factor for the acquisition of giardiasis (Sullivan *et al*, 1990). Although we did not find any correlation between symptomatic giardiasis and malnutrition, nearly half of the children had gastrointestinal symptoms and 32% of them were malnourished. The most beneficial drug in the treatment of common intestinal parasitic infections and also health education should be promoted as a matter of urgency. Further studies for the development of appropriate drugs for the treatment of common intestinal parasitic infections, in order to promote better health of children in developing countries, are needed.

In conclusion, the single dose of combined albendazole-praziquantel may be an alternative in the treatment of giardiasis in school-age children. A regimen that encourages better compliance with fewer side-effects should be encouraged.

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