ALBENDAZOLE TREATMENT FOR *GIARDIA INTESTINALIS* INFECTIONS IN SCHOOL CHILDREN

Krisana Pengsaa[1], Chukiet Sirivichayakul[1], Chanathep Pojjaroen-anant[1], Sawat Nimnual[2] and Pataraporn Wisetsing[1]

[1]Department of Tropical Pediatrics, [2]Bangkok Hospital for Tropical Diseases, Faculty of Tropical Medicine, Bangkok, Thailand

Abstract. A randomized controlled trial, 113 school children with *Giardia intestinalis* infection were treated with albendazole or tinidazole. Albendazole 400 mg once a day x 3 days and tinidazole 50 mg/kg single dose were given orally to 62 and 51 children, respectively. Parasitological cure was documented when there were ≥ 2 times negative stool examination for *G. intestinalis* at 1-2 weeks after therapy. Thirty-one of 62 (50%) children treated with albendazole and 49 of 51 (96.1 %) children treated with tinidazole had parasitological cure ($p < 0.001$). No major side effects were observed except one case in tinidazole group had severe headache for 30 hours. Albendazole appears to be safe and produced a moderate cure rate for *G. intestinalis* infection when a 3 day anthelmintic regimen is given.

INTRODUCTION

In the succeeding decades, there are numerous clinical reports of symptomatic human infection with *Giardia intestinalis* and its place as an enteropathogen was established (Cole *et al*, 1977; Hartong *et al*, 1979). Giardiasis occurs throughout tropical and temperate zones worldwide. Prevalence rates vary from 2-5% in the industrialized world to 20-30% in the developing world (Farthing, 1996). Epidemiological study in Bangladesh showed that this infection could be acquired early within one year of age and the prevalence were high in 5-10 year-old village children (21%) and 1-5 year-old malnourished children (51%) (Gilman *et al*, 1985). In Thailand, giardiasis was diagnosed in 19% in children with unexplained chronic diarrhea, abdominal pain and failure to gain weight (Chavalittamrong *et al*, 1978) and 85% in under five-year children with chronic diarrhea from an orphanage in Bangkok (Sabchareon *et al*, 1980).

A systemic review of the treatment of giardiasis shows that metronidazole treatment more than 3 days seems to achieve a better parasitological cure rate than long treatment courses of other drug (furazolidone, mebendazole, quinacrine) while within the single-dose regimens, tinidazole (2 g for adult) reaches a higher parasitological cure rate (Zaat *et al*, 1997). Although tinidazole has a favorable antigiardial effect undesirable side effects of the drug are noted. The most frequently reported side effects were metallic taste, nausea and fatigue, these occured in 21 of 28 patients receiving the single dose of tinidazole (Jokipii and Jokipii, 1979). Vomiting immediately after taking the drug was found in 13% (Suntornpoch and Chavalittamrong, 1981).

Three studies have shown that albendazole, the benzimidazole derivatives, is active *in vitro* against *G.intestinalis* (Meloni *et al*, 1990; Edlind *et al*, 1990; Farbey *et al*, 1995). A five-day course of albendazole was reported to be as effective as a 5-day course of metronidazole (Hall and Nahar, 1993) and also a 7-day course of albendazole was effective and well tolerated in treatment for giardiasis (Pungpak *et al*, 1996). However, use of longer than 3-day course of anthelmintic as well as antiprotozoa is not applicable due to poor compliance.

There is increasing evidence to suggest that albendazole may be particularly useful in children in the developing world who harbor multiple intestinal helminths and *G.intestinalis*. Albendazole, as a single 400 mg oral dose, was highly effective against *Ascaris lumbricoides*, *Necator americanus*, *Ancylostoma duodenale* and *Trichuris trichiura* (Pene *et al*, 1982; Rossignol and Maisonneuve, 1983). Albendazole is recommended for the treatment of strongyloidiasis in a dosage of 400 mg/d for 3 days with treatment repeated one week later (Pungpak *et al*, 1987). So far there is no comparative study of albendazole and tinidazole for giardia therapy, we, therefore, studied the efficacy and safety of a 3-day course albendazole compared with a single dose tinidazole in treatment of giardiasis in school children.

MATERIALS AND METHODS

All together 1,876 school children aged between 3 and 15 years were participated for stool

examinations. Those with stool positive for *G. intestinalis* were enrolled in the study. Written consent forms were obtained from all the children's parents. The study was approved by the Ethical Review Committee of the Faculty of Tropical Medicine, Mahidol University, Thailand. None of the children who entered into the study received antiparasitic treatment during four weeks preceding the study. Age, gender, body weight, height and clinical symptoms of the studied children were recorded. Assessment of the children nutritional status was performed by measuring of weight for height using standard curve for Thai children (Chavalittamrong and Tantiwongse, 1987). Each stool was examined microscopically within 6 hours of collection using both direct smear in 0.9% saline and ether sedimentation method (Ritchie, 1948). Children infected with *G. intestinalis* were randomly allocated into 2 groups to receive either albendazole (Zentel®) 400 mg once daily for 3 days (group 1) or tinidazole (Fasigyn®) 50 mg/kg single dose (maximum 2g) (group 2). Both drugs were given orally by one of the investigators. Each child was observed closely for immediate side effects for at least 30 minutes after drug administration. Every morning until 3 days after treatment, each child was asked if any pre-listed possible side-effects occurred after taking the drug.

Treatment success was defined as absence of *G. intestinalis* cyst by at least 2 successive stool examinations done at 1-2 weeks after completion of the treatment. Twenty-one children were excluded from efficacy analysis; one girl in group 1 had not completed course of albendazole, one boy in group 2 was given albendazole by mistake instead of tinidazole, one girl died from accident, one boy moved to other school outside Bangkok and 17 children whose stools could not be obtained for at least 2 times after therapy (5 in albendazole group and 12 in tinidazole group). Data collected from 113 children were included in the assessment of the therapeutic efficacy. Side-effects were analysed from 131 children who have taken the drugs (68 in albendazole group and 63 in tinidazole group).

Statistical analysis for qualitative variables, χ^2 and Fisher's exact test were used while Student's *t*-test was used for comparison of quantitative variables with the level of confidence at 95%.

RESULTS

Among 1,876 school children whose stool examinations were performed, stool samples from 309 (16.5%) children were positive for intestinal protozoa and helminths. *G. intestinalis* cysts were found in 134 children, thus the prevalence of giardiasis in this group was 7.1%. Sixteen children had concomitant intestinal protozoa which included *Entamoeba coli*, *Entamoeba histolytica* and *Endolimax nana* cysts and also vacuolated form of *Blastocystis hominis*. Hookworm ova and *Trichuris trichiura* ova were also found in two children and one child, respectively. Other 175 (9.3%) children habored many kinds of protozoa and helminths which included Hookworm, *T. trichiura* and *S. stercoralis*. Twenty-four percent (42 cases) of these children had more than one kind of intestinal parasites (Table 1).

A total of 134 children with giardiasis in this study, consisted of 71 (52.9%) boys and 63 (47.1%) girls with the most prevalence age between 7 and 12

Table 1
Prevalence of intestinal parasites in 1,876 Thai school children.

	Case (%)
Positive stool examination	309 (16.5)
Positive for *G. intestinalis* with and without other parasites	134 (7.1)
• *G. intestinalis* only	118 (6.3)
• *G. intestinalis* with other parasites	16 (0.9)
- *E. histolytica* cyst	2 (0.1)
- *E. coli* cyst	9 (0.5)
- *E. nana* cyst	4 (0.2)
- *B. hominis* vacuolated form	2 (0.1)
- Hook worm ova	2 (0.1)
- *Trichuris trichiura* ova	1 (0.05)
Positive for other parasites without *G. intestinalis*	175 (9.3)

years (82%). Most of the children were well nourished. Twenty-one children (15.7%) had protein energy malnutrition (PEM) which 11.2% (15 cases) were first degree PEM, only 6 cases were second degree PEM. One-third of the infected children (45/133 cases) were asymptomatic. Characteristics of 113 children who were included in this efficacy analysis are shown in Table 2. In 88 symptomatic cases, approximately 22% (19/88 cases) had moderate abdominal pain and moderate loose stools (7 cases in albendazole group and 12 cases in tinidazole group). The rest had nonspecific gastrointestinal symptoms which were not disturbed daily activities (Table 3).

Among 62 children in the albendazole treated group, 31 children had successful treatment (50%) compared to 49/51 (96.1%) in the tinidazole treated group ($p < 0.001$). In the 131 children who had taken the drug, 14 of 68 children (20.6%) in albendazole- and 24 of 63 children (38.1%) in tinidazole-treated groups reported side effects ($p < 0.05$). Common side-effects were headache and abdominal pain. Nausea, vomiting, dizziness and loose stool were also observed. These symptoms were mild except three children in albendazole group who developed moderate headache for approximately 6 hours and only one dose of paracetamol was required for each. In tinidazole group, one case had severe headache which lasted for 30 hours and needed 6 doses of paracetamol, another case developed moderate nausea and vomiting. Dizziness was observed significantly more frequent in tinidazole-treated group ($p < 0.05$), the frequency of other side effects in both groups were not significantly different (Table 4). No other serious side effects were observed.

Table 2
Characteristics of the children in both groups.

	Albendazole (n = 62)	Tinidazole (n = 51)	p-value
Gender			0.76
Male	31	24	
Female	31	27	
Mean weight ± SD (kg)	27.89 ± 8.39	29.02 ± 8.95	0.49
Age distribution			0.95
3-6 years	5	4	
7-12 years	52	42	
> 12 years	5	5	
Malnourished children	10	8	0.95
First degree	7	6	
Second degree	3	2	

Table 3
Presenting symptoms in 88 children with *G. intestinalis* infection.

	Mild (%)	Moderate to severe (%)
Abdominal pain	45 (51.1)	10 (11.4)
Loose stool	34 (38.6)	9 (10.2)
Anorexia	16 (18.2)	2 (2.3)
Malaise	14 (15.9)	1 (1.1)
Abdominal distension	12 (13.6)	4 (4.5)

Mild, symptoms did not disturb daily activity; Moderate, symptoms disturbed daily activity; Severe, symptoms prevented daily activity.

Table 4
Side effects of 3-day albendazole and single dose tinidazole treatments in 131 children.

	Albendazole (n = 68) No. of side effect (%)	Tinidazole (n = 63) No. of side effect (%)
Headache[a]	8 (11.8)	15 (23.8)
Abdominal pain	11 (16.2)	15 (23.8)
Nausea[b]	3 (4.4)	7 (11.1)
Loose stool	3 (4.4)	2 (3.2)
Dizziness[c]	2 (2.9)	8 (12.7)
Metallic taste	1 (1.5)	3 (4.8)
Vomiting	-	3 (4.8)
Total	28 (41.2)	53 (84)

[a] three cases with moderate headache in albendazole group and one case with severe headache in tinidazole group.
[b] one case in tinidazole group had moderate nausea and dizziness.
[c] $p < 0.05$

DISCUSSION

Prevalence of giardiasis has been reported to vary greatly depending on the methods used and the population studied. The prevalence is greater in areas of poor sanitation, overcrowding and in children. Previous reports in Thailand showed the prevalence of 10.5% in children below 12 years in northeast of Thailand (Sornmani *et al*, 1973) and 18.2% in asymptomatic children attending an out-patient department, Siriraj Hospital. (Chavalittamrong *et al*, 1978). The prevalence of giardiasis in this study (7.1%) was lower than the previous studies in Thailand, may be because of the method used or probable due to the fact that these school children were rather healthy. Examination of a single stool specimen may detect up to 73% of cases of giardiasis, rising to 85% after examination of three separate specimens passed on different days because cyst excretion varies in intensity from day to day (Goka *et al*, 1990).

A comparative trial of 2.4 g of metronidazole either once or on two successive days with 2.0 g of tinidazole once in adult patients with giardiasis produced the cure rates of 50%, 77% and 100% respectively. The average serum half life of biologically active metronidazole was 9.5 hours while that of tinidazole was 13 hours. The slower elimination of tinidazole was regarded as one possible explanation for its greater antigiardia efficacy (Jokipii and Jokipii, 1979). Tinidazole and ornidazole in a single dose were reported to have effectiveness as high as 86-100%. The single dose regimen is more convenient but its side effects, dizziness and vomiting were oftenly observed (Sabchareon *et al*, 1980; Suntornpoch and Chavalittamrong, 1981; Jokipii and Jokipii, 1982; Speelman, 1985; Bassily *et al*, 1987; Bulut *et al*, 1996).

Recently benzimidazole derivatives, which are widely used as anthelmintic drugs has been shown to have *in vitro* activity against *Giardia* (Meloni *et al*, 1990; Edlind *et al*, 1990; Farbey *et al*, 1995). Albendazole, a benzimidazole derivative is thought to act by binding to parasite β-tubulin, inhibiting its polymerization and impairing glucose uptake (Venkatesan, 1998). Findings of apparent irreversible binding of albendazole to *Giardia* tubulin, shown by continued activity after removal of the drug compared to a reversible effect of the nitroimidazoles, may explain the necessity for large and/or multiple doses of the latter *in vivo* (Meloni *et al*, 1990). The drug is relatively insoluble and poorly absorbed from the gut thus maximizing contact with intestinal parasites (Botero, 1986).

Albendazole 400 mg given for 5 days was highly effective against giardia infections (Hall and Nahar, 1993; Reynoldson *et al*, 1998). The cure rates for giardiasis after albendazole administration of 400 mg for 7 days were 96% in children and 100% in adult which were significantly better than those after the 1- or 2-day regimens. The lower cure rate of *G. intestinalis* infection after 3-day albendazole treatment in this study (50%) than that reported by Hall and Nahar in 1993 (81%) may be due to the difference in stool examination methods and the suscep-

tibility pattern of different strain of parasites. There is evidence of variable drug sensitivity between strains of *Giardia* (Mc Intyre *et al*, 1986; Gordts *et al*, 1987). However, many factors including infectious status, frequency and time interval of stool examination may also affect results.

In this study, 400 mg albendazole daily for 3 days apparently cure only 50% of *Giardia* infection compares to 96.1% after a single dose of tinidazole. Single dose tinidazole produced the high cure rate for giardiasis but has no anthelmintic effects and is shown by our three cases with persisted hookworm and *T. trichiura* infections following tinidazole treatment. In addition, the side effects were reported to be significantly higher in tinidazole group ($p < 0.05$). Apart of very safe and good anthelmintic activity of albendazole (Pene *et al*, 1982; Rossignol and Maisonneuve, 1983) this study showed that the drug is fairy good for *G. intestinalis* infection. In addition, 3-day course of albendazole is relatively cheaper than a single dose tinidazole (2 US$ dollars *vs* 3 US$ dollars).

A longitudinal study in Gambian children suggested that giardiasis reduced weight velocity, which was related to the duration and severity of giardiasis (Cole and Parkin, 1977). In more severe manifestations of chronic giardiasis in children, the weight and height velocity can be impaired (Farthing *et al*, 1986). A study in Gambian children with chronic diarrhea and malnutrition showed that 45% had giardiasis compared with only 12% of healthy age-matched and sex-matched control children (Sullivan *et al*, 1991). The study suggested that nutritional insufficiency may be an additional risk factor for the acquisition of giardiasis. Study of children who were usually asymptomatic, have not found evidence of growth failure and there was no association between *Giardia* and the occurrence of diarrhea (Pickering *et al*, 1984). From a study of 300 children aged less than five years in Khartoum, Sudan which comprised of 9.4% malnourished children, giardiasis was the commonest infestation (21.1%) among all parasites and *G. intestinalis* significantly affected the undernourished group (Karrar and Rahim, 1995).

The rationale of treating the asymptomatic carrier is not to eradicate the organism from the environment but to identify and reduce the number of potential reservoirs and to decrease the prevalence of *Giardia* to a point where transmission, and therefore diarrhea, is less likely to occur (Addiss *et al*, 1991). Albendazole should be particularly useful for children in developing countries when treatment for intestinal helminths and *Giardia* is oftenly needed. Drug resistance has been convincingly demonstrated for *Giardia* (Mc Intyre *et al*, 1986) so, safe, single dose drug or drug combination which act against common intestinal parasites should be an important focus in the developing countries.

ACKNOWLEDGEMENTS

The authors wish to thank the volunteer children from Chonpratarn Songkrao School, Wat Chong Non Sri School and Rajvithi Girl School, Thailand and laboratory staffs from School of Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Thailand for their kind co-operation. We also thank Pfizer Laboratories Ltd, and Smith Kline Beecham Pharma, Thailand, for the supply of tinidazole and albendazole, respectively. The authors wish to give sincere thanks to Prof Arunee Sabchareon for reviewing the manuscript.

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