ALBENDAZOLE STIMULATES OUTWARD MIGRATION OF *GNATHOSTOMA SPINIGERUM* TO THE DERMIS IN MAN

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Abstract. Human gnathostomiasis is characterized by space-occupying inflammatory lesions and/or hemorrhage as a result of the migration of, very often, a single larva of *Gnathostoma spinigerum*. Intermittent cutaneous migratory swellings occurring over years is the most common manifestation and the rare cerebral invasion may be fatal. There are currently no effective anthelminthics for this infection.

During a double-blind randomized placebo control trial evaluating the efficacy of albendazole in cutaneous gnathostomiasis at a dosage of 400 mg twice daily for two weeks, it was observed that gnathostome larvae tended to migrate outward as a result of the treatment so that they could be recovered by excisional biopsy or by picking with a needle. In the placebo-treated group (N = 40), no such migration was observed during the 8,470 patient-days of follow-up while in the albendazole-treated group (N = 41) there was one worm in an excisional biopsy done on day 16 and two worms were removed from the skin by the patients themselves on days 8 and 0. Assuming that the period of drug exposure of the gnathostomes was the 14 days of albendazole administration plus another washout period of 7 days (equivalent to 20 half-lives of the active detectable metabolite), the total patient-days of albendazole exposure was 830. The rate of outward migration of gnathostomes in the drug treated group (3 per 830 patient-days) was significantly ($p < 0.0001$) higher than in the placebo group (0 per 8,470 patient-days).

This study shows a unique and inexplicable effect of albendazole on parasite migration which may contribute to the general beneficial effects of albendazole in the treatment of cutaneous gnathostomiasis.

INTRODUCTION

Human gnathostomiasis is a parasitic zoonosis characterized by space-occupying inflammatory lesions and/or hemorrhage as a result of the migration of usually a single larva of *Gnathostoma* spp. (Swanson, 1971; Daengswang, 1980, 1982; Miyazaki, 1991). Intermittent migratory cutaneous swellings (IMCS) lasting over a year in many cases is the most common manifestation (Daengswang, 1980; Bunnag, 1984; Suntharasamai, 1987). Occasionally the disease can be fatal due to cerebral invasion by the parasite (Chitanondh and Rosen, 1967; Punyagupta *et al,* 1968; Bunnag *et al,* 1970; Boongird *et al,* 1977). Currently there are no effective anthelminthics for gnathostomiasis.

G. spinigerum is the most common species that infects man but infections with *G. doloresi, G. hispidum* and *G. nipponica* have also been reported. The infections are endemic in Southeast Asian countries, particularly in Thailand (Daengswang, 1980) and in Japan (Miyazaki, 1991).

Albendazole is a broad spectrum benzimidazole anthelmintic which has been shown to be effective not only in intestinal helminthiasis but also in extraintestinal helminthiasis such as opisthorchiasis (Pungpak *et al,* 1984), hydatid disease (Morris *et al,* 1985; Saimot *et al,* 1983) and cutaneous larva migrans (Sivayathorn and Kiatakrapol, 1986). It is better absorbed than mebendazole in humans and is quickly metabolized into albendazole sulphoxide which is also active therapeutically (Saimot *et al,* 1983; Morris *et al,* 1985).

The anti-gnathostome effect of albendazole has been shown in experimental infection in mice (Yingyourd *et al,* 1985). In an uncontrolled trial of ten cases of cutaneous gnathostomiasis in Thailand, the results suggested that albendazole may be an effective anthelminthic against this infection (Chitchang, 1987). Two larvae of *G. spinigerum* were removed by pinching with the patient's nails on day 7 in one case and by picking with a needle on day 8 in another case. The finding that gnathostome larvae tended to migrate to the skin and

were easily removed during the time of drug administration in 20 percent of cases appeared to be novel. In previous prospective trials with various drugs involving altogether 165 patients with follow-up periods from 3 weeks to 7 years, no such finding was recorded (Jaroonvesma and Harinasuta, 1973; Migasena *et al,* 1973; Na Songkhla, 1983; Piyayothai, 1984; Suwanprakorn, 1985). As superficial skin migration of the gnathostome larva can occasionally occur spontaneously (Swanson, 1971; Daengswang, 1980, 1982; Chitchang *et al,* 1981; Miyazaki, 1991), therefore a randomized control trial is needed to evaluate the possible outward migration effect as well as the antiparasitic effect of albendazole. This paper reports the results of a double-blind placebo controlled trial of albendazole which suggest that albendazole stimulates outward migration of the gnathostome larvae to the dermis in man.

MATERIALS AND METHODS

Subject selection

Between July 1989 and February 1990 patients attending the outpatient clinic of the Hospital for Tropical Diseases with a primary diagnosis of cutaneous gnathostomiasis were eligible for inclusion in this study. Inclusion criteria included the following: age 18 years or loder; a diagnosis of suspected cutaneous gnathostomiasis; high probability of successful follow-up for at least 1 year depending mainly on residence in Bangkok and nearby vicinity and in most cases having a telephone either at home or at work. The diagnosis of IMCS was agreed upon by two attending physicians based on the actual observation of cutaneous swellings at different sites or of recurrent swelling at the same site together with eosinophilia ($> 500/mm^3$). Patients were not included in the study if it was the opinion of the attending physicians that the swelling was likely to be due to angioedema, urticaria, insect bite or other parasitic infections.

Exclusion criteria included the following: known allergy to albendazole or other benzimidazole derived drugs; treatment with any benzimidazole anthelminthics for the preceding 1 month prior to presentation; abnormal liver (SGPT > 50; alkaline phosphatase > 45) or renal (creatinine > 1.5 mg/dl) functions; history of IMCS for more than 5 years.

Data obtained at study entry included complete blood count and differential, blood urea nitrogen, creatinine, SGPT, bilirubin, alkaline phosphatase, blood sugar, urinalysis and stool examination.

Immunodiagnosis

Serum samples collected before treatment were stored at -20°C until analyzed for IgG antibody to gnathostome antigen by ELISA (Desakorn *et al,* 1990). The ELISA results were not used in the intial inclusion criteria but were used for subgroup analysis.

Randomization and treatment

Each patient was randomly assigned by means of a permuted-block scheme (Pocock, 1983) to one of two treatments: albendazole at a dosage of 400 mg (two tablets) twice daily for 14 days or placebo at the same dosage schedule.

The active drug or the placebo were pre-packaged in numbered envelops which were dispensed sequentially to eligble patients whenever they came in with the swellings at their peak or which, according to the patient had not declined to less than half of the peak size.

Follow-up

After the course of treatment, patients were given analgesic and/or antihistamine for pruritus as needed but not routinely. They were seen on days 14 and 28 and then at 4-week intervals for at least one year. Laboratory investigations done during the pre-treatment period (except stool exam) were repeated on day 14 and 28 and then at 4-week intervals until all abnormal values had returned to normal. Duration of each swelling, time interval between each swelling, symptoms and signs of the disease as well as any side effects were asked for and recorded at each visit.

End points

The primary end point in this study was the recovery of the gnathostome larvae from the skin either by spontaneous migration of the worm through the patient's skin or by minor excision. Patients were advised to attempt picking the larva from the skin by using a sterile needle whenever one was strongly suspected. Ten milliliters of 70% alcohol were given to each patient for sterilizing the skin as well as for preserving the specimen for further verification.

The denominator for calculating the rate of superficial skin migration of the parasite in the treated group was the total duration of drug administration plus 7 days. The duration was taken as the duration of drug exposure; the additional 7 days would cover about 20 half-lives of the active drug metabolites in the body (Gustafsson *et al,* 1987). For patients in whom the parasites were obtained from the skin before day 21, the duration of drug exposure was from the start of the treatment to the day of obtaining the parasite. In the placebo treated group, the duration from the beginning of chemotherapy to the time of last swelling was taken at the minimal survival time of that parasite in the host and the total of patient-days harboring the worm was used as denominator for calculating the rate of spontaneous outward skin migration without exposure to any drug.

Statistics

Comparability of various variables measured in each study group was assessed by chi-square test for qualitative data and by independent *t*-test for normally distributed data and by Mann-Whitney U test for non-normally distributed data.

The difference in the rate of superficial cutaneous migration, expressed as number of events per patient-day, were evaluated by the chi-square test for comparing two rates (Smith and Morrow, 1991). All analyses were performed according to intention to treat. Level of significance were represented by p values derived from two-sided tests.

RESULTS

Eighty-one patients were enrolled in the trial: 40 in the placebo-treated group and 41 in the albendazole-treated group. The two groups were similar in age, weight, sex ratio, duration of intermittent migratory cutaneous swelling (IMCS) and peripheral blood eosinophilia before enrolment (Table 1).

Table 2 shows the sites of swelling when treatment was started in each patient. Peripheral parts of the upper extremities (arm, wrist, hand or fingers) were the more common sites for the lesions.

Incidence of outward migration of gnathostome larvae

Table 1

Clinical features of patients in the placebo-treated and in the albendazole-treated groups.

Variable	Placebo (N = 40)	Albendazole (N = 41)
Age (years)	32.8 ± 8.7*	33.2 ± 7.5
Weight (kg)	59.4 ± 10.2	56.6 ± 8.3
% male	42.5	31.7
Duration on IMCS before treatment (days)	300 (7-1825)#	365 (7-1825)
Duration of last swelling (days)	5.5 (1-30)	5 (1-17)
Eosinophils per mm^3	1028 (67-6966)	728 (0-4182)
%	12 (1-61)	9 (0-34)
Number of case with positive ELISA	36	33

* mean ± SD # median (range)

No outward migration of worms occurred in the placebo-treated group while in the albendazole treated group, there were three such events. In the first case with a history of IMCS for 7 months, the swelling at the lateral aspect of the right wrist subsided on day 7 of treatment; 2 days later it recurred in the same area as a small nodule that persisted until the follow-up visit on day 14. The patient agreed to have surgical excision on day 16 with successful removal of parasite.

Table 2

Site of swelling at the beginning of treatment.

Sites of swelling	Placebo	Albendazole
Face, head or neck	9	5
Trunk	1	4
Arm	8	8
Wrist, hand or finger	17	18
Leg, knee or thigh	4	2
Ankle, foot or toe	1	4
Total	40	41

In the other two patients the larvae were removed using a needle by the patients themselves on days 8 and 9. In the second patient with a history of IMCS for 20 months, the original swelling on the back of the right hand subsided on day 2, while a swelling on the thenar aspect of the hand persisted until day 9 when the patient observed a thin red line over the swelling. After manual manipulation, the larva protruded and was removed.

In the third patient with a history of IMCS for one month the swelling occurred on the posterior of the left thenar area when the treatment was started; on day 8 the patient noted a small and painful red pimple at the junction of wrist and the thenar eminence. The worm was successfully removedafter two attempts at picking with a needle.

The difference between the two rates of outward skin migration that led to successful recovery of the gnathostomes were highly significant ($p < 0.0001$, chi-square = 20.4).

When the ELISA results were used for confirmation of the diagnosis, there were 39 cases in the placebo treated group and 33 cases in the albendazole-treated group who were seropositive. The 3 cases with outward migration of the worm were all ELISA positive. The rate of outward migration became 3 per 630 patient-days in the albendazole-treated group and 0 per 7,929 patient-days in the placebo treated group. The difference of the two rates remained statistically significant ($p < 0.0001$; chi-square = 24.1).

All of the three worms removed from the albendazole treated patients were identified as third stage larvae of *Gnathostoma spinigerum.*

Side effects

Following treatment with albendazole, elevated levels of SGPT (> 50 U) were observed in five patients on day 14 and in another four patients on day 28. Mild and transient side effects including nausea and dizziness occurred in one placebo-treated patient and dizziness and somnolence in two albendazole-treated patients (Table 3). The abnormalities reverted to normal within 4 to 12 weeks.

DISCUSSION

Infestation with gnathostomes is pathogenic (Rhithibaed and Daengswang, 1937; Chitanondh and Rosen, 1967; Punyagupta *et al,* 1968; Bunnag *et al,* 1970; Boongird *et al* 1977); therefore ways and means of removing the worms should be sought. The conventional approach is to search for an anthelmintic that can kill the parasite in the human host. However there is a theoretical risk that the dead parasite might induce a space-occupying inflammatory reaction that is occasionally harmful to the host particularly when it occurs in a critical area such as the brain stem. Surgical excision of the tissue and sometimes a part of an organ containing the parasite has been another approach in trying to terminate the infestation. This method may also result in disturbance or loss of organ function or in disfiguration.

In this double-blind study, the results showed that after the administration of albendazole, the infesting gnathostomes tended to migrate outward to the skin of the human host and were subsequently easily removed by picking with a needle or, in Chitchang's (1987) series, by just a scratch with the patient's nail.

Table 3

Frequency and rates of outward migration of gnathostome in patients treated with placebo and albendazole.

	Placebo	Albendazole
Number of cases	40	41
Number of cases with outward migration of gnathostome	0	3
Duration of follow-up (days)	485 (56-883)#	406 (23-719)
Duration of exposure to treatment in each patient (patient-days)	118 (21-519)	21 (8-21)
Total duration of exposure to treatment in all patients in each group (patient-days)	8470	830
Rate of outward migration@ per 1,000 patient-days of exposure	0*	3.6*
Rate of outward migration per 100 patients treated	0	7.3

@ $\text{Rate} = \frac{\text{number of case with outward migration}}{\text{total duration of exposure to treatment}} \times 1000$

median (range)

* Significant difference ($p < 0.001$), by method of Smith and Morrow (1991)

Table 4

Frequency of side effects in patients treated with placebo and albendazole.

Side effects	Placebo (n = 40)	Albendazole (n = 41)
SGPT (>50 U)		
Day 14	0	5
Day 28	0	4
Nausea and dizziness	1	0
Dizziness	0	1
Somnolence	0	1

The incidence of outward migration that led to parasite elimination appeared to be lower in this study than in that of Chitchang (1987). This may be due to chance variation, differences in patient population, compliance, bioavailbility of drug and difference in parasite strains.

Whether prognosis is related to the location of the swelling cannot be answered from the available data. In our series, patients were predominantly affected in the peripheral parts of the upper extremities and so were all of the three swellings that yielded the migrating worms.

It is not known why and how the drug induces the worms to migrate to the skin surface. If may be just an increase in random motility or it may represent a directional movement of the parasite toward the surface because of some gradients of

physical factors such as temperature, resistance of certain tissues or as yet unknown chemical factors.

Migration to the skin is not the natural route of migration of this nematode in its definitive feline and canine hosts. However in dracontiasis where such migration is an esential part of its life cycle, incidence of spontaneous extrusion of the parasite was higher in the niridazole-treated group (59%) than in the control group (11%) (Kothari *et al,* 1969). Padonu (1973) also reported that another drug-metronidazole reduced the expulsion time of guinea-worms from three to one week.

Side effects in term of symptoms and signs were almost negligible in this study. However, abnormality of liver functions known to occur particularly when high dose and prolonged therapy with albendazole was given (Morris *et al,* 1985; Morris and Smith, 1987; Pungpak *et al,* 1987; De Rosa and Teggi, 1990), was noted in this study during treatment in five patients and at two weeks after treatment in another four patients. As the abnormalities were not severe and were entirely reversible, the schedule of treatment and laboratory monitoring need not be changed but patients should be advised to avoid hepatotoxic agents such as alcohol and should be examined at 2-to 4-week interval. Nevertheless liver function tests should be performed before albendazole treatment and the daily dose of 800 mg should not be exceeded.

In conclusion, the study shows a unique and inexplicable effect of albendazole on parasite migration which my contribute to the general beneficial effects of albendazole in the treatment of cutaneous gnathostomiasis. The antiparasitic effects other than the outward migration of worms are currently being analysed.

ADDENDUM

After the end of the double-blind study, from March 1990 to February 1992 we had recruited another 273 cases of cutaneous gnathostomiasis for albendazole treatment at the same dosage with the same selection criteria. Seventeen cases of outward migration of *G. spinigerum* larvae on days 2 to 14 of treatment were recorded. The duration of illness in these patients ranged from 1 months to 8 years. The proportion of success in patients treated with albendazole in this uncontrolled trial was 0.062 which was not significantly different from the result of 0.073 in the controlled trial above.

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