TOLERABILITY OF IVERMECTIN IN GNATHOSTOMIASIS

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Abstract. At present, no universally-accepted effective treatment for cutaneous gnathostomiasis is available. At the Hospital for Tropical Diseases, Mahidol University, albendazole 400 mg twice a day for 14 days is commonly prescribed for patients diagnosed with cutaneous gnathostomiasis. The efficacy of albendazole to induce outward migration of the parasite was less than or around 20% in 2 studies. Research for alternative, more efficacious treatment, is needed. In this prospective open-labeled study, we assessed the safety of ivermectin in 20 Thai patients diagnosed with cutaneous gnathostomiasis. Ivermectin, one time only, at dosages of 50, 100, 150, or 200 µg/kg bodyweight, was given orally to 4 groups of patients, 5 patients each group. Adverse events were recorded and laboratory tests were obtained before and after treatment. No serious adverse events occurred in this study. Forty adverse events were possibly related to ivermectin. The adverse events were malaise (35%), myalgia (30%), drowsiness (30%), pruritus (20%), nausea/vomiting (20%), dizziness (15%), diarrhea (15%), feeling of shortness of breath (10%), feeling of palpitations (10%), constipation (5%), anorexia (5%), and headache (5%). These adverse events were self-limited and not dose-related. Laboratory abnormalities were found in 3 patients (15%). Transient microscopic hematuria, pyuria, and mildly elevated liver enzymes were found in 1 patient each. Ivermectin single dose, of 50, 100, 150, and 200 µg/kg bodyweight, is considered safe in Thai patients. Future trials of ivermectin on human gnathostomiasis may be performed using dosages up to 200 µg/kg bodyweight.

INTRODUCTION

Human cutaneous gnathostomiasis, caused by advanced third-stage larva, and in some cases young adult *Gnathostoma spinigerum*, presents as an intermittent migratory subcutaneous swelling. It is not an uncommon tissue parasitic disease in Thailand. In 1889, Levinson first described the disease when he found gnathostoma larva from an infested Thai woman (Radomyos *et al,* 1996). During the period 1933-1937, Professor Svasti Daengsvang and Professor Chalerm Prommas described the complete life cycle of the parasite (Radomyos *et al,* 1996). Humans are accidental hosts when they eat raw freshwater fish, snake, frog, chicken, reptiles, and rodents contaminated with the larval parasite (Radomyos *et al*, 1996). In the 1980s, the estimated prevalence of human gnathostomiasis in Bangkok was 4 per 1,000 humans (Suntharasamai, 1987). Currently, at the Hospital for Tropical Diseases, Out-patient Department, about 3-5 patients have been followed up each week (0-5 new cases/week). Until now, there is no universally accepted antiparasitic agent for treatment of the disease. Currently, we use albendazole 400 mg once or twice daily for 2-3 weeks. The treatment had resulted in outward migration of the parasite in 3 of 41 patients treated with albendazole 400 mg twice a day for 14 days (Suntharasamai *et al*, 1992) and 21 of 100 patients treated with either albendazole 400 mg once or twice daily for 21 days (Kraivichian *et al*, 1992). The efficacy of albendazole is not proven to be high, and the drug at a dosage of 400 mg twice daily for 14 days can also cause transient elevation of liver enzymes (Inkatanuwat *et al*, 1998).

Human gnathostomiasis can involve the eyes and rarely involves the central nervous system, causing eosinophilic myeloencephalitis or eosinophilic meningoencephalitis. Therefore, it is necessary to search for a more effective treatment.

A study of ivermectin on advanced third stage larvae of *Gnathostoma spinigerum* was

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conducted in rabbits by Anantaphruti *et al* (1992). Infected rabbits were treated with either a single dose (0.2 mg/kg) or multiple doses of ivermectin. By the 28th week after treatment, it was found that the reductions of worm load were 74.2% and 84.2% for the single-dose and multiple-dose groups, respectively. These data prompted trials of ivermectin in human gnathostomiasis.

In this study, we assessed the safety and tolerability of ivermectin in human gnathostomiasis in 20 Thai patients with serologically confirmed diagnosis of cutaneous gnathostomiasis.

MATERIALS AND METHODS

This was a prospective, open-labeled study of ivermectin in gnathostomiasis, to assess the safety and tolerability of ivermectin. The study site was at the Hospital for Tropical Diseases, Mahidol University in Bangkok. The study protocol was approved by the Ethics Committee on Clinical Research of the Faculty of Tropical Medicine, Mahidol University.

Subjects

Twenty patients, aged 20-65 years, who presented with active symptoms of recurrent migratory swelling, having the diagnosis of gnathostomiasis confirmed by Western blot analysis for serum antibodies against the 24 kDa somatic antigen of the 3rd stage larvae of *G. spinigerum*, were enrolled with their consent. Pregnant or nursing women, patients who had used any antiparasitic agents within the past 14 days, or patients with underlying diseases, such as pulmonary diseases (especially asthma), renal diseases (especially hematuria), history of seizure, liver diseases including elevated abnormal liver function tests (above maximum normal range), cardiac diseases (especially tachycardia with heart rate >100/minute.), or blood disorders [anemic (Hct <25%), or leukopenia (WBC <3,500/mm^3)], or thrombocytopenia (platelet < 100,000/mm^3), or hypotension (blood pressure < 90/60 mmHg) were not eligible for this study.

Drugs and doses

The dosage of ivermectin used in this study was given at increments of 50 µg/kg bodyweight single dose. Dosages ranged from 50 µg/kg bodyweight to a maximum dose of 200 µg/kg, which is the maximum dose used in humans in the literature. Each dose was given to 5 consecutive patients.

Monitoring and evaluations

Safety and tolerability were assessed and recorded. Each patient was observed for immediate adverse reactions at the Out-patient Department for 30 minutes. Other symptoms were recorded for 7 days in a diary card given to the patient. The severity of a symptom was classified as mild, moderate, or severe. Mild symptom meant that it was self-limited without any treatment. Moderate symptom meant that the symptom was relieved with medication or an outpatient visit was required. Severe symptom meant that the patient needed hospitalization. Laboratory tests (CBC, AST, ALT, BUN, creatinine, and urine examination) were obtained at baseline and on the 7th day to assess any immediate laboratory adverse events that may have occurred. If an abnormality occurred, the laboratory test was repeated periodically until it returned to normal. A complete physical examination was performed at baseline, on the 7th day, and on the 28th day.

Since there was not enough information to definitely determine whether the causality of adverse events was related to ivermectin, we categorized adverse events into 2 groups: possibly-related to and not-related to ivermectin. Any adverse events that might be equally caused by ivermectin or other causes were called 'possibly related', while adverse events that were definitely related to other causes than ivermectin were called 'not related'.

After treatment with ivermectin, any patient who developed recurrent subcutaneous migratory swelling after 7 days of treatment initiation, and within 6 months, would be considered a treatment failure. These patients were evaluated for the need of further antiparasitic treatment (albendazole 400 mg twice daily for 14 days).

RESULTS

Twenty-one patients were enrolled. One patient withdrew consent prior to treatment initiation. There were 14 females and 6 males. Their

mean age was 32.3 ± 9.35 years. Their mean bodyweight in kilograms was 57.26 ± 7.17. Sixteen patients resided in Bangkok and it vicinities. Two patients were from the central region and one patient each was from the western and northeastern regions.

Of the 20 patients, 2 were lost to follow-up before the 7th day visit, four patients had no adverse events, and the other 14 patients reported adverse events. Three patients had only 1 adverse event. The other 11 patients had more than one adverse event. A total of 48 adverse events were reported. No severe adverse events occurred during the study. Five adverse events were of moderate severity, but none required an out-patient visit. Forty and eight adverse events were considered 'possibly–related' and 'not-related' to ivermectin, respectively. Malaise (7/20), myalgia (6/20), drowsiness (6/20), pruritus (location not specified) (4/20), nausea/vomiting (4/20), dizziness (3/20), diarrhea (3/20), feeling of breathing discomfort (2/20), feeling of palpitations (2/20), constipation (1/20), anorexia (1/20), and headache (1/20) were possibly related to ivermectin (Table 1). Adverse events that were not related to ivermectin were localized rash (3/20), common cold (3/20), localized pruritus (1/20), and feeling of palpitations (1/20). All of these symptoms were transient. They lasted for 24-96 hours (Table 2).

Three patients reported palpitations. Two of them were in the 50 µg/kg group and 1 was taking ivermectin at a dosage of 200 µg/kg. One patient complained of palpitations during the 30 minute observation period. On physical examination, the heart rate and rhythm were regular. The other 2 patients had symptoms at home. These 3 patients also reported multiple other symptoms during the first 7 days.

Two patients stated that they had a feeling of breathing discomfort, which occurred on the first and second days after administration of ivermectin. The symptoms were mild and self-limited and did not occur within the 30-minutes observation period.

Three patients reported mild dizziness, which occurred during the first 3 days, and lasted for 24-48 hours.

Laboratory abnormalities were found in 3 patients. Transient microscopic hematuria and pyuria were found on the 7th day follow-up visit in 1 patient each. The patient with transient microscopic hematuria (10-15 cells/hpf) and the one with transient pyuria (5-20 cells/hpf) were taking ivermectin 200 and 100 µg/kg, respectively. The abnormal findings became normal by the 28th day follow-up visit. Transient elevation of liver enzymes (AST=44, ALT = 66) was found in 1 patient taking ivermectin 150 µg/kg on the 7th day follow-up visit. There was no evidence of other concomitant medication or alcohol use in this patient. The liver enzymes returned to nor-

Table 1
Adverse events possibly related to ivermectin.

Adverse events	50 µg/kg	100 µg/kg	150 µg/kg	200 µg/kg	Total patients
Malaise	4	0	1	2	7
Myalgia	2	1	1	2	6
Drowsiness	2	0	3	1	6
Pruritus	4	0	0	0	4
Nausea/vomiting	2	0	0	2	4
Dizziness	0	2	0	1	3
Diarrhea	3	0	0	0	3
Feel shortness of breath	1	0	0	1	2
Feel palpitations	2	0	0	0	2
Constipation	1	0	0	0	1
Anorexia	1	0	0	0	1
Headache	0	0	1	0	1
Total	22	3	6	9	40

Table 2
Onset and duration of adverse events after administration of ivermectin.

Symptoms	Onset less than 3 days (No. of patients)	Onset after 3 days (No. of patients)	Duration of symptoms (hours)	Total patients
Malaise	7	0	24-96	7
Myalgia	6	0	24-48	6
Drowsiness	6	0	24-96	6
Pruritus	2	3	24-96	5
Nausea/vomiting	3	1	24-48	4
Dizziness	3	0	24-48	3
Diarrhea	1	2	Less than 24	3
Feel shortness of breath	2	0	Less than 24	2
Feel palpitations	3	0	Less than 24- 96	3
Constipation	1	0	Less than 24	1
Anorexia	1	0	Less than 24	1
Headache	1	0	Less than 24	1
Localized rash	0	3	24-96	3
Common cold	1	2	48-96	3

mal values on the 28th day follow-up visit. This patient remained healthy throughout the 6-month follow-up.

During 6 months of follow-up, we found that 3 patients most likely had idiopathic urticaria/ localized angioedema rather than gnathostomiasis. Of these 3 patients, 2 had facial swelling about once a month, while another developed generalized urticaria by the 7th day follow-up visit.

Seventeen patients with a clinically and serologically confirmed diagnosis of cutaneous gnathostomiasis, had been actively symptomatic for months to over 1 year prior to enrollment. Ten patients had been symptomatic for less than 3 months, while the other 7 patients had recurrent subcutaneous swelling for over 1 year. They had subcutaneous swelling located on the upper extremities (n=10), head and neck (n=4), and feet (n=1), respectively. The other 2 patients had no recorded swelling locations.

After treatment, 6 patients experienced recurrent subcutaneous swelling at the previous location, occurring within 7 days. These swellings were mild and self-limited, lasting from 1-6 days (mean=3.8 days). Nine patients had no recurrent subcutaneous swelling during the first 7 days. Two patients did not have the 7th day follow-up visit.

DISCUSSION

Ivermectin was discovered in 1975 by Merck Research Laboratory in New Jersey, USA. Ivermectin, a derivative of avermectins, is a potent macrocyclic lactone with antiparasitic activity. It causes paralysis in many nematodes and arthropods through an influx of chloride ions across the cell membrane. The chloride influx is mediated through the GABA receptors (Ottesen and Campbell, 1994).

Due to broad antiparasitic activity for both ecto- and endoparasites in cattle, swine, horses, and companion animals, and acceptable toxicological features, ivermectin was introduced to the veterinary market in 1981. In 1995, ivermectin was the world's largest-selling animal health product, with more than 5 billion doses sold worldwide (Merck, 1995).

Ivermectin use in humans started in 1978, after Campbell and colleagues at Merck & Co, Inc observed its macrofilaricidal effect on *Onchocerca cervicalis* in horses. The first clinical trial of ivermectin in humans began in 1981 in Senegal (Aziz *et al*, 1982). That study of 32 patients started with a very low ivermectin dose of

5 µg/kg bodyweight and increased in small increments until it reached 50 µg/kg bodyweight. The second study was done in Paris, France on 12 West African immigrants (Coulard *et al*, 1983). Both studies showed that a single oral administration of ivermectin with a dose range to a maximum of 200 µg/kg bodyweight was well tolerated. No serious adverse events were observed during these initial 2 studies.

Two previous community-based open-labeled studies on ivermectin and onchocerciasis involved approximately 59,000 participants. Most were age 5-55 years old, in West Africa (De sole *et al,* 1989; Pacque *et al,* 1989). The study subjects were given ivermectin at a single dose of 100-200 µg/kg bodyweight. Monitoring of self-reported adverse events was conducted under an active surveillance system for at least 72 hours, and certain groups of the study subjects were followed for 4 weeks. About 9% of 31,260 patients and 1.3% of 7,699 patients, in these 2 separate studies, respectively, reported adverse events. The most common adverse events were various pain conditions (6.3%), pruritus and rash (3.7%), fever (3.3%), subcutaneous swelling (3%), painful lymphadenopathy (1.5%), headache (<1%), dizziness (<1%), nausea (<1%), weakness (<1%), and diarrhea (<1%). Severe adverse events occurred in 0.24%. These reactions included severe symptomatic postural hypotension (inability of a patient to stand for at least 2 minutes owing to severe dizziness or weakness attributable to a marked drop in blood pressure) (0.147%), high fever (0.090%), and severe dyspnea (0.009%).

Severe symptomatic postural hypotension mostly occurred during the first day. It was not dose related. Although the symptoms, which occurred in a total of 49 patients, were transient and self-limited, 9 patients required intravenous injections of hydrocortisone.

For severe dyspnea, the relationship with ivermectin treatment was uncertain. Two patients had a history of asthma, but were in remission at the time of treatment. One had active pre-existing respiratory symptoms prior to the severe episode of laryngeal edema.

Since then, ivermectin has been considered a beneficial antiparasitic agent for onchocerciasis. It has been used as a drug of choice for onchocerciasis in millions of humans since 1987. It has also been used for loiasis, other lymphatic filariases, some intestinal nematodes, and scabies, for years without any report of serious adverse effects (Kumaraswami *et al,* 1988; Shikiya *et al*, 1992; Coutinho *et al,* 1994; Meinking *et al,* 1995; Bockarie *et al,* 1998; Huffam and Currie, 1998; Kombila *et al,* 1998;). Several community-based trials showed that ivermectin was largely well-accepted. It could be administered in mass treatment programs with minimum medical supervision (De Sole *et al*, 1989; Pacque *et al*, 1989). Previous studies demonstrated that a single dose of ivermectin (200 µg/kg body weight) was more effective, with fewer side effects, in treating strongyloidiasis than thiabendazole (Darty *et al*, 1994).

A study by Pacque and colleagues (1990) showed no major effect on pregnancy outcomes after inadvertent ivermectin treatment of 203 unnoticeably pregnant women during community-based distribution.

In our current study, 65% of patients reported adverse events within 7 days after a single dose of ivermectin. This high number of adverse events included events both possibly, and not, related to ivermectin. In addition, the diary-card containing specific questions whether the symptoms were present or absent might increase adverse event detection compared to the monitoring of self-reported adverse events under an active surveillance system in previous studies.

In this study, adverse events possibly related to ivermectin were malaise (35%), myalgia (30%), drowsiness (30%), pruritus (20%) nausea/vomiting (20%), dizziness (15%), diarrhea (15%), feeling of breathing discomfort (10%), feeling of palpitations (10%), constipation (5%), anorexia (5%), and headache (5%). These events were mild, self-limited, and not dose related.

There were reports of tachycardia, orthostatic hypotension, worsening of bronchial asthma, hematuria, abnormal complete blood counts (CBC), elevated liver enzymes (AST and ALT) which were transient and occurred uncommonly (less than 3.5%)(Njoo *et al,* 1993). Various pain conditions and fever that were common adverse events in previous studies did not

present in this study. We found one patient (5%) with transient microscopic hematuria, one patient (5%) with transient microscopic pyuria, and one patient (5%) with transient mildly-elevated liver enzymes. We were not able to confirm that these laboratory abnormalities were due to causes other than ivermectin.

We observed recurrent subcutaneous swelling within 7 days of a single-dose ivermectin in 6 patients (30%). This reaction may have been a parasite-ivermectin interaction, but was not an indication of treatment success, as 2 of these 6 patients had recurrent migratory subcutaneous swelling during the 6-month follow-up.

In summary, ivermectin is considered safe for further trials in human gnathostomiasis in the Thai population. Nevertheless, more clinical trials are needed to confirm safety and to assess efficacy.

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