Efficacy of Ivermectin against *Strongyloides Stercoralis* in Humans

Koushin SHIKIYA, Nagisa KINJO, Takeshi UEHARA, Hiroyuki UECHI, Junichi OHSHIRO, Tamiki ARAKAKI, Fukunori KINJO, Atsushi SAITO, Mamoru IJU and Kazumine KOBARI*

Okinawa Prefecture is an endemic area of *Strongyloides stercoralis* infection. Since treatment of this infection remains unsatisfactory, we evaluated the efficacy of ivermectin. Twenty-three patients were treated with a single oral dose of ivermectin (mean $\pm$ SD, 105.5 $\pm$ 20.8 mcg/kg of body weight), followed by a second dose two weeks later. The rate of cure was 85.7% at 2 weeks after the first treatment, and 90.5% at 2 weeks after the second treatment. Side effects occurred in 2 patients (8.7%), but they were mild and transient. The results indicate that ivermectin might be useful and relatively safe for the therapy of *Strongyloides stercoralis* infection as an alternative to thiabendazole or mebendazole. (Internal Medicine 31: 310–312, 1992)

Key words: *Strongyloides stercoralis*, ivermectin

Introduction

Although the incidence of *Strongyloides stercoralis* (*S. stercoralis*) infection in Okinawa Prefecture was found to be less than 2% of the population when determined by traditional methods, it was proven to be 6.2% by a new technique, the agar plate method (1–3). Thiabendazole is strongly active in eradicating the organism, but it is well known that the rate of severe side effects is extremely high (4–6). Mebendazole is also active against *S. stercoralis* (7, 8), but a high incidence of liver disfunction was shown in our previous studies (9, 10). Ivermectin (IVM) has recently been found to be safe and effective for treatment of human onchocerciasis (11–14) and lymphatic filariasis (15), but there are only two published reports concerning the efficacy of IVM against *S. stercoralis* in humans (16, 17). We therefore attempted to evaluate the efficacy of IVM against *S. stercoralis* infection.

Materials and Methods

Study Subjects

Twenty-three patients, 16 males and 7 females, with a positive *S. stercoralis* stool culture were included in this study. They ranged in age from 47 to 77 years with a mean age of 62 years.

Treatment Protocol

IVM (Merck Sharp & Dohme Research Laboratories, New Jersey, USA) was given in a single dose of 6 mg one hour before breakfast and this treatment was repeated 2 weeks later. The dosages of IVM ranged from 68.4 to 160.0 mcg/kg of body weight.

Parasitological Examination

Fresh fecal samples, obtained before treatment, 2 weeks after the first treatment and 2 weeks after the second treatment, were examined using the agar plate method.

Clinical Examination

Clinical examination was done before treatment, 2 weeks after the initial treatment and 2 weeks after the second treatment. The examinations included a clinical history, a complete blood count, serum-chemistry studies, serological studies and urinalysis.

Results

Pretreatment Evaluation

Of the 23 patients, 9 patients (39.1%) had no complaints before the treatment. Fourteen patients complained of some symptoms, including abdominal pain or borborygmus (n = 9 patients), heartburn (n = 4), blurred vision (n = 3), arthralgia or lumbago (n = 3), headache (n = 2), urinary frequency (n = 2), diarrhea

From the First Department of Internal Medicine, Faculty of Medicine, University of the Ryukyus, Okinawa and * Ohama First Hospital, Okinawa

Received for publication February 6, 1991; Accepted for publication August 7, 1991

Reprint requests should be addressed to Koushin Shikiya, M.D., the First Department of Internal Medicine, Faculty of Medicine, University of the Ryukyus, 207 Uehara, Nishihara Town, Okinawa 903–01, Japan

(n = 2), and constipation (n = 2).

There were no abnormal laboratory data except eosinophilia and elevation of IgE. The former occurred in 34.8% of the patients, and the latter was detected in 39.1% of the patients.

Antiparasitic Effect

The parasitological eradication rate at 2 weeks after the initial treatment was 85.7% (18 of 21 patients) and 2 weeks after the second course was 90.5% (19 of 21 patients). Three patients were uncured, their dosages of IVM were 133.3, 78.9 and 113.2 mcg/kg of body wt.

Side Effects

Twenty-one patients (91.3%) experienced no side effects. One patient complained of borborygmus after the second treatment. Another patient complained of nausea, anorexia, dizziness or vertigo, blurred vision, and malaise after the first treatment, and itching after the second treatment. All symptoms were mild and required no treatment and subsided in a few days. None complained of severe dizziness or orthostatic hypotension. No abnormal laboratory findings were obtained in the hematological, serum chemistry or serological values after the treatment.

Discussion

Parasitological diagnosis is sometimes difficult because *S. stercoralis* larvae in the stool may be very few and inconsistently present. However, the new method, the agar plate method, is more efficient than the traditional methods (direct stool smear method, filter paper culture method and formalin-ether concentration method) (1–3).

S. stercoralis infection is usually asymptomatic and limited to the intestine. However, severe systemic disease due to *S. stercoralis* may develop in patients suffering from wasting diseases or malnutrition, or who are receiving immunosuppressive therapy or corticosteroids. Therefore, *S. stercoralis* infection should be treated with an effective and active drug. Although thiabendazole is effective against *S. stercoralis*, severe side effects occur (4–6).

We recently treated 24 patients with 100 mg of mebendazole twice a day for 28 days in accordance with the reports of successful treatment of *S. stercoralis*, those reports also indicated only mild and infrequent side effects of the drug (7, 8). Although the eradication rate for our patients was 83.3%, the incidence of liver dysfunction was 71.4% of the patients (9). We then treated 47 patients for 5 day periods, repeating the treatment at 1, 3 and 4 weeks following the initial 5 day treatment. The eradication rate was 100%, but liver dysfunction still occurred in 48.9% of the patients (10).

IVM is a semisynthetic macrocyclic lactone (a fermentation product of an actinomycete, *Streptomyces*

avermitilis). Although it has been found to be micro-filaricidal in clinical trials in humans, its precise action mechanism is unknown (18, 19). A series of clinical trials of IVM showed that a dose of 150 mcg/kg was safe and effective for onchocerciasis therapy (20).

There are only two reports concerning the efficacy of IVM against *S. stercoralis* in humans. Freedman and his colleagues (16) reported that IVM was 100% effective against strongyloidiasis (3 patients, with dosages of IVM ranging from 140 to 200 mcg/kg). Naquira and colleagues (17) described results in which the cure rate at 30 days after treatment averaged 88% (101 patients, dosages of IVM were 50, 100, 150, 200, 100 × 2, 200 × 2 mcg/kg). Although the cure rates were significantly higher in recipients of doses >150 mcg/kg, there was no significant variance above that dose. In this study all patients were given 6 mg of IVM and the dosage of uncured patients was <150 mcg/kg. Therefore, it would have been possible to eradicate the infection if those patients had received a higher dose of the drug.

We conclude that IVM is an effective drug for the treatment of *S. stercoralis* and that it also causes minimal side effects.

Acknowledgments: This study was supported by the Drug Research of Tropical Diseases Grant from the Ministry of Public Welfare, 1990, Japan and the 16th Oyama Health Foundation Grant, 1990, Japan.

References

- 1) Arakaki T, Hasegawa H, Asato R, et al. A new method to detect *Strongyloides stercoralis* from human stool. *Japan J Trop Med Hyg* 16: 11, 1988.
- 2) Arakaki T, Iwanaga M, Kinjo F, et al. Efficacy of agarplate culture in detection of *Strongyloides stercoralis* infection. *J Parasitol* 76: 425, 1990.
- 3) Asato R, Nakasone T, Arakaki T, Ikeshiro T. Prevalence of *S. stercoralis* infection among inhabitants of Okinawa by agar-plate method and evaluation of the methods for detection. *Ann Rep Okinawa Prefec Inst Publ Hlth* 23: 66, 1989 (in Japanese).
- 4) Grove DI. Treatment of strongyloidiasis with thiabendazole: an analysis of toxicity and effectiveness. *Trans R Soc Trop Med Hyg* 76: 114, 1982.
- 5) Pelletier LL. Chronic strongyloidiasis in World War 2 Far East ex-prisoners of war. *Am J Trop Med Hyg* 33: 55, 1984.
- 6) Oyakawa T, Kuniyoshi T, Arakaki T, et al. New trial with thiabendazole for treatment of human strongyloidiasis. *J J A Inf D* 65: 304, 1991 (in Japanese).
- 7) Goldsmid JM. The use of mebendazole as a broad-spectrum anthelmintic in Rhodesia. *S Afr Med* 48: 2265, 1974.
- 8) Musgrave IA, Hawes RB, Jameson JL, Sloane RA, Quayle PA. Mebendazole: evaluation of a new anthelmintic for trichuriasis, hookworm, and strongyloidiasis. *Med J Aust* 1: 404, 1979.
- 9) Shikiya K, Kuniyoshi T, Uechi H, et al. Treatment of strongyloidiasis with mebendazole and its combination with thiabendazole. *J J A Inf D* 64: 1408, 1990 (in Japanese).
- 10) Shikiya K, Kuniyoshi T, Uechi H, et al. Treatment of strongyloidiasis with mebendazole – long term eradication and new trials –. *J J A Inf D* 65: 433, 1991 (in Japanese).
- 11) Albiez EJ, Walter G, Kaiser A, et al. Histological examination of onchocercosmata after therapy with ivermectin. *Trop Med Parasit* 39: 93, 1988.

- 12) Greene BM, Taylor HR, Cupp EW, et al. Comparison of ivermectin and diethylcarbamazine in the treatment of onchocerciasis. *N Engl J Med* **313**: 133, 1985.
 - 13) Pacque M, Munoz B, Greene BM, et al. Safety of and compliance with community-based ivermectin therapy. *Lancet* **335**: 1377, 1990.
 - 14) Sole GD, Dadzie KY, Giese J, Remme J. Lack of adverse reactions in ivermectin treatment of onchocerciasis. *Lancet* **335**: 1106, 1990.
 - 15) Ottesen EA, Vijayasekaran V, Kumaraswami V, et al. A controlled trial of ivermectin and diethylcarbamazine in lymphatic filariasis. *N Engl J Med* **322**: 1113, 1990.
 - 16) Freedman DO, Zierdt WS, Lujan A, Nutman TB. The efficacy of ivermectin in the chemotherapy of gastrointestinal helminthiasis in humans. *J Inf D* **159**: 1151, 1989.
 - 17) Naquira C, Jimenez G, Guerra JG, et al. Ivermectin for human strongyloidiasis and other intestinal helminths. *Am J Trop Med Hyg* **40**: 304, 1989.
 - 18) Campbell WC, Fisher MH, Atapley EO, Albers-Schonberg G, Jacob TA. Ivermectin: a potent new antiparasitic agent. *Science* **221**: 823, 1983.
 - 19) Ette EI, Thomas WOA, Achumba JJ. Ivermectin: a longacting microfilaricidal agent. *DICP, Ann Pharmacother* **24**: 426, 1990.
 - 20) Taylor HR, Greene BM. The status of ivermectin in the treatment of human onchocerciasis. *Am J Trop Med Hy* **41**: 460, 1989.
-