

COMPARATIVE STUDIES ON THE EFFICACY OF THREE ANTHELMINTHICS ON TREATMENT OF HUMAN STRONGYLOIDIASIS IN OKINAWA, JAPAN

Hiromu Toma¹, Yoshiya Sato^{1,2}, Yoshiyuki Shiroma³, Jun Kobayashi¹, Isao Shimabukuro¹ and Masahiro Takara⁴

¹Department of Parasitology and ²Okinawa-Asia Research Center of Medical Sciences, Faculty of Medicine, University of the Ryukyus, 207 Uehara, Nishihara, Okinawa 903-0215, Japan; ³Izumizaki Hospital, 1-11-12 Izumizaki, Naha, Okinawa 900-8556, Japan; ⁴Kumejima Family Clinic, 1134 Nakadomari, Gushikawa, Okinawa 901-3124, Japan

Abstract. A study was undertaken to compare the efficacy of three drugs in the treatment of uncomplicated strongyloidiasis in Okinawa, Japan. Two hundred and eleven patients with confirmed *Strongyloides stercoralis* infection were given either ivermectin, 6 mg in a single dose, albendazole, 400 mg/day for 3 days or pyrinium pamoate, 5 mg/kg/day for 3 days. For each treatment, the same regimen was repeated once 2 weeks later. Efficacy was evaluated at 2 weeks, 6 months and 12 months after the second course of treatment. Each follow-up examination included a parasitological examination of stool specimens, using the agar-plate culture method. Coprological cure was obtained in 65 of the 67 patients treated with ivermectin (97.0%), in 65 of the 84 patients treated with albendazole (77.4%) and only in 14 of the 60 patients who were given pyrinium pamoate (23.3%). The cure rates were lower in males and in the patients with concurrent HTLV-1 infection. An epidemiological feature of *Strongyloides* infection in recent Okinawa might allow workers to evaluate the exact efficacy of the treatment for an extended period, over a year, without the possibility of reinfection from the environment.

INTRODUCTION

Strongyloidiasis is a parasitic disease resulting from an infection caused by the nematode *Strongyloides stercoralis*, which is relatively common in tropical and subtropical areas. The nematode has unique characteristics, including its ability to replicate in the host. This ability permits cycles of internal autoinfection and a tendency to maintain the infection for several decades. The great majority of patients have a chronic infection with no symptoms clearly attributable to the infection. The infection, however, often progresses to the fatal hyperinfected state, due to the internal autoinfection under immunosuppressive conditions (Scowden *et al*, 1978). Autoinfection is also considered to be responsible for obstinacy of the parasitic disease against anthelmintic treatment. Additionally, once the hyperinfected state is established, it becomes difficult to treat (Dwork *et al*, 1975; Scowden *et al*, 1978; Igra-Siegamn *et al*, 1981; Grove, 1989). Therefore, effective treatment at the stage of chronic infection is essentially

important to prevent such a severe infection.

The treatment of strongyloidiasis has been tried by many workers using various anthelmintics (Grove, 1989). The efficacy of these treatments, however, has been inconsistent even when the same drug was used in a similar regimen. Several reasons are considered for the inconsistency of effectiveness. One of the reasons may be the different sensitivity of the methods applied to assess the efficacy of treatment. Different time periods between treatments and follow-up examinations can also be given as another explanation, since the parasitic infection incompletely treated has been known to relapse frequently after treatment. Therefore, the follow-up examination for a long period, using a sensitive diagnostic method is essential to estimate complete cure after treatment. An epidemiological reason, such as re-infection from the environment, may also be a factor limiting assessment of exact therapeutic efficacy, when the efficacy is monitored for an extended period in endemic areas.

The present study was designed to evaluate the efficacy of three anthelmintics in treatment of chronic strongyloidiasis in Okinawa where the opportunity to acquire re-infection from the environment does not occur under the improved sanitary conditions.

Correspondence: Dr Hiromu Toma, Department of Parasitology, Faculty of Medicine, University of the Ryukyus, 207 Uehara, Nishihara, Okinawa 903-0215, Japan.
Tel: +81-98-895 1129; Fax: +81-98-895 1409; E-mail: htoma@med.u-ryukyu.ac.jp

MATERIALS AND METHODS

Patients

As seen in Table 1, the trials were carried out on a total of 211 patients, all harboring *Strongyloides stercoralis*, whose ages ranged from 38 to 86 years (mean years: 66.4±8.7). The number of male subjects was about two times that of females. Among the subjects, the positive rate of HTLV-1 (human T-lymphotropic virus type 1) infection was 29.4% (62/211).

Stool examination

The stool examinations were performed by a fecal concentration (the formalin-ether concentration), the Harada-Mori fecal culture using a filter paper strip and the agar plate fecal culture. In the last method, recently developed in Okinawa, in which fecal samples (approximately 3 g) were placed on the primary agar plate for bacterial culture and incubated at 28°C for 3 days (Arakaki *et al*, 1988). After incubation, the surface of the agar plate was examined under a microscope to find motile larvae that emerged from the fecal mass on the agar plate. With this method, the unique alignment of bacterial colonies, which formed along the tracks of wandering larvae on the surface of the agar, were an indicator of the presence of the larvae. In such cases, a careful search for larvae on the agar surface was performed. When found, the larvae were transferred to a glass slide and identified morphologically, differing as they do from larvae of hookworm and free-living *Rhabditis*. If colony alignment and larval tracks were observed but no larvae were found on the agar surface, the presence of larvae was assumed and further appropriate examinations (*ie* a fecal concentration and/or the Harada-Mori fecal culture) were repeated for a correct diagnosis. The

above stool examinations were repeated for two stool samples collected on different days for each subject. The agar plate culture method has been known to be the most effective for diagnosis of chronic, low-level infection among the conventional methods (Kaminsky, 1993; Salazar *et al*, 1995; Sato *et al*, 1995).

Treatment

Treatments were performed with pyrvinium pamoate on 60 patients, with albendazole on 84 patients and with ivermectin on the remaining 67 patients, respectively (Table 1).

Pyrvinium pamoate was given in the form of a Poquil suspension (Waner Lambert) in a daily dosage of 5 mg per kilogram of body weight on 3 successive days. For albendazole treatment, the patients were given the drug (Zentel; Tianjin Smithkline and French Laboratories Ltd) in a daily dosage of 400 mg (2 tablets) for 3 successive days. Ivermectin (Mectizan; Merck USA) was administered once in a single dose of 6 mg (1 tablet) to each patient. The above treatments were repeated 2 weeks later, and the follow-up examinations were performed at 2 weeks, 6 months and 1 year after the final treatment, respectively, by fecal examinations.

When the subjects were found to be not effectively treated by the above initial treatment, they received further treatment with drugs different from that in the initial treatment; albendazole treatment for pyrvinium pamoate-resistant subjects and ivermectin treatment for albendazole-resistant subjects.

Detection of antibodies to HTLV-1

Individuals having anti-HTLV-1 antibody have been known to harbor HTLV-1 infection (Gotoh *et al*, 1982). The sera of the subjects were ex-

Table 1
Subjects treated with anthelmintics.

Treatment	No.treated	Mean age(range)	Sex	HTLV-1 positive rate	
Pyrvinium pamoate	60	67.8±8.1(50-86)	Male	35	16(45.7)
			Female	25	11(44.0)
Albendazole	84	66.8±8.5(38-82)	Male	54	11(2.04)
			Female	30	8(26.7)
Ivermectin	67	65.6±9.2(46-85)	Male	48	11(22.9)
			Female	19	5(26.3)

Table 2
Results of treatment of strongyloidiasis with three anthelmintics.

Treatment	No.cured/No.treated(Cure rate%)			
	Male	Female	Total	
Pyrrvinium pamoate	4/35(11.4)	10/25(40.0)*	14/60(23.3)	p<0.001
Albendazole	38/54(70.4)	27/30(90.0)	65/84(77.4)	
Ivermectin	47/48(97.9)	18/19(94.7)	65/67(97.0)	p<0.001

*p<0.01 (males vs females)

Table 3
Effect of HTLV-1 infection on treatment of strongyloidiasis.

Treatment	HTLV-1	No.cured/No.treated(Cure rate%)	
Pyrrvinium pamoate	positive	3/27(11.1)	p<0.05
	negative	11/33(33.3)	
Albendazole	positive	12/19(63.2)	p<0.02
	negative	53/65(81.5)	
Ivermectin	positive	14/16(87.5)	p<0.002
	negative	51/51(100)	

amined for anti-HTLV-1 antibodies using an indirect agglutination test kit (SERODIA-HTLV; Fujirebio Inc, Tokyo, Japan)(Ikeda *et al*, 1984).

Statistics

The data were analyzed by the χ^2 (chi-square) test to determine significance level among the subject groups, using StatView computer program (Abacus Concepts, Inc, Berkeley, USA). A p-value of more than 0.05 was considered to be not significant.

RESULTS

The results of the treatments with the three anthelmintics are summarized in Table 2. Ivermectin was the most effective among the drugs examined. Albendazole was also effective for strongyloidiasis, but pyrrvinium pamoate was the least effective, showing only about a 20% curative rate. The efficacies of pyrrvinium pamoate and albendazole were markedly lower in male subjects than females. In Table 3, the effect of concurrent HTLV-1 infection on the efficacy of treatment is

shown. The cure rates were significantly lower in the subjects with concurrent HTLV-1 infection.

A total of 63 subjects, who were treated with pyrrvinium pamoate or albendazole, were not cured. The subjects whose infections were resistant to the drug treatment were further treated with different drugs. Table 4 shows the results of the additional treatment. The cure rates were consistently lower than those of the subjects who received initial treatment with each drug. The positive rate of HTLV-1 among the subjects with resistant infections, however, was significantly higher than that of subjects who did not receive preceding treatment, indicating that the infections in subjects with concurrent HTLV-1 infection were significantly more resistant in the previous treatments.

DISCUSSION

In the present study, it was demonstrated again that ivermectin was the most effective for treatment of strongyloidiasis (Freedman *et al*, 1989; Naquira *et al*, 1989; Shikiya *et al*, 1992; Datry *et al*, 1994; Marti *et al*, 1996). Albendazole was also found to be highly effective for treatment of chronic

Table 4

Comparison of efficacy of treatment between the subjects who received initial treatment and those who were unsuccessfully treated in previous treatment.

Anthelmintic	Previous treatment	No.cured/No.treated(Cure rate)			HTLV-1 rate
		Male	Female	Total	
Albendazole	None	38/54(70.4)	27/30(90.0)	65/84(77.4)	19/84(22.6)
	Unsuccessful	9/18(50.0)	7/12(58.3)*	16/30(53.3)*	16/30(53.3)**
Ivermectin	None	47/48(97.9)	18/19(94.7)	65/67(97.0)	16/67(23.9)
	Unsuccessful	15/16(93.8)	6/7(85.7)	21/23(91.3)	10/23(43.5)

*p<0.05, **p<0.005

infection, although the cure rates with the drug varied from 17% to 100% in previous reports (Grove, 1989). The efficacy of pyrvinium pamoate, however, was quite doubtful as a complete cure of the infection. The efficacy of treatments was significantly affected by the gender of patients and concurrent HTLV-1 infection in the present study, as has already been reported by the authors (Takara *et al*, 1992; Sato *et al*, 1992; Kobayashi *et al*, 1996).

Drug treatment of strongyloidiasis seems to be one of the difficult problems in treatment of helminth infections. One of the significant points of the present therapeutic study is that the efficacy of treatment was assessed for an extended period, over a year, with no possibility of reinfection during the follow-up period. It is essential for the exact evaluation of therapeutic efficacy with any anthelmintic to do a follow-up examination of the subjects for an extended period after treatment, since *Strongyloides* infection has been known to relapse frequently after incomplete treatment. In such cases, the worm numbers that decreased to undetectable levels after treatment may recover to a diagnostic level several months after treatment. Okinawa prefecture, Japan, has been an endemic area for strongyloidiasis and it is the only parasitic infection that currently remains among the inhabitants. The average prevalence rate seems to be about 10% (Asato *et al*, 1992) but almost all patients (more than 90%) were over 40 years old (Sato, 1986). From the significant age relationship of the parasitic infection, it has been supposed that present-day Okinawa provides a unique field where new infection from the environment is now almost negligible because of improved sanitary conditions. This epidemiological feature in Okinawa may permit a long-term assessment of exact therapeutic efficacy unaffected by reinfection from the

environment after treatment.

Another important point for estimation of therapeutic efficacy may be the sensitivity of the fecal examination method applied. Strongyloidiasis is usually diagnosed by demonstrating the larvae in stools. A false-negative result, however, may sometimes be encountered among patients with chronic infection because of the periodic excretion of larvae and the small numbers of larvae in their stools. It has been our experience that the reconfirmation rate of fecal larvae, when 123 persons with chronic *Strongyloides* infection was followed for several months without any treatment, was <25% when a stool examination was performed only once, and <50% even when examinations were repeated for 3 successive days (Sato *et al*, 1995). By such fecal examinations, it also seems to be difficult to prove complete eradication or lack of effectiveness of treatment. Although relatively few studies have followed patients for an extended period to estimate relapse after treatment, it is generally considered that the inability to detect fecal larvae in follow-up examination is not always proof of successful treatment. In a previous survey, we used albendazole to treat 40 patients and followed them over a year. The cure rate was 88.9% in the first follow-up examination performed at 2 weeks after the treatment. The cure rate, however, decreased to 62.5% in the subsequent examinations at 6 and 12 months after the treatment, suggesting that there were many false-negative results at the first follow-up examination and relapses during the period before the next follow-up examination (Toma *et al*, 1993). For a number of parasitic infections, drug therapy that reduces the worm burden below the clinical level is usually adequate; however, drug therapy of strongyloidiasis requires complete eradication of the parasite to remove the danger of potentially serious dis-

ease. Therefore, we need a highly sensitive diagnostic test for the follow-up examinations. In the present study, the follow-up examination was performed using the agar plate fecal culture. This method is known to be 2-3 times more sensitive in detecting low-level infection than other conventional methods, such as the Harada-Mori fecal culture (Sato *et al.*, 1995). There have been no other reports evaluating the therapeutic effect of anthelmintics on strongyloidiasis using such a sensitive test. On the basis of the above consideration, the results in the present study seem to reflect the efficacy of anthelmintic treatment for chronic strongyloidiasis.

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