□REVIEW ARTICLE □

Strongyloidiasis–Progress in Diagnosis and Treatment

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Abstract

Strongyloidiasis is an intestinal parasitic disease caused by *Strongyloides stercoralis*. Basically, detecting larvae of *S. stercoralis* in feces makes definitive diagnosis. The ordinary agar plate culture method developed at our department is much simpler to handle and much more sensitive than the conventional filter paper culture method. It is considered to be the most useful method in the diagnosis of strongyloidiasis and in evaluation of the eradicating effect. Among chemotherapeutic agents, thiabendazole representing the benzimidazole compounds is most effective. However, it has a problem in safety, since its adverse effects and liver dysfunction occur with a high incidence, and it can be severe. Regarding the effects of mebendazole, albendazole and ivermectin, a study was conducted which included many patients. A high incidence of liver dysfunction was observed with mebendazole, and eradicating effect was not sufficient with albendazole. Ivermectin is different from benzimidazole compounds in a pharmacokinetic profile. However, ivermectin showed a strong anthelmintic effect with the least toxicity. We therefore consider ivermectin is the most useful drug for the treatment of strongyloidiasis. (Internal Medicine 39: 695–700, 2000)

Key words: *Strongyloides stercoralis*, ordinary agar plate culture method, ivermectin, HTLV-I

Introduction

Strongyloidiasis is widely distributed in the tropics and subtropics, and it is estimated that there are about 56 million patients infected with *Strongyloides stercoralis* throughout the world. Okinawa Prefecture and the southwestern part of Kagoshima Prefecture in Japan, which are in a subtropical area, had been known as endemic regions. Due to improved social sanitation environment, and systematic measures for parasitic diseases after World War II, the frequency of intestinal parasitic diseases decreased sharply. However, many inhabitants are found to be still infected with *S. stercoralis*.

Okinawa Prefecture, on the other hand, has the highest infection rate of human T lymphotropic virus type-I (HTLV-I) in Japan, and many patients infected with *S. stercoralis* are HTLV-I carriers. Strongyloidiasis is a type of opportunistic infection, and it is known that the incidence of complication due to highly fatal disseminated strongyloidiasis and severe strongyloidiasis is higher in HTLV-I carriers. Therefore, highly effective and safe therapeutic drugs for this disease are few, it is an urgent need to select safer drugs and to establish a therapeutic method for strongyloidiasis.

In this review, we will introduce a new method of diagnosis and provide clinical evaluation of various therapeutic drugs. We will also discuss a therapeutic regimen with ivermectin, a highly effective and safe drug.

Life History of *Strongyloides stercoralis* in Hosts, and Pathologic State

Strongyloides stercoralis lives in warm, humid soil. Its filariform larvae infect bare feet mainly through the skin. Infecting larvae move into the lungs through the blood stream and lymphatic flow. Then, after penetrating the alveolar wall, they migrate from the respiratory tract to the esophagus and stomach, and finally reside in the mucosa of the duodenum and upper small intestine. After growing into mature females, they lay eggs. Rhabditiform larvae hatched from eggs are excreted out of the host together with feces. However, some part of them develop into filariform larvae having infecting capability, and reinfect the large intestine and the skin around the anus. This peculiar autoinfection, together the long parasitism in the duodenal mucosa, and heterotropic parasitism in the lungs and biliary tract, form the main causes of long-lasting intractable infection.

Gastrointestinal symptoms are general in this disease. The main symptoms are abdominal pain, borborygmus, swollen abdomen and loose stools, with varying degrees of severity (1). If, under such conditions, immunocompetence decreases, larvae show hyperinfection, causing malabsorption syndrome and paralytic ileus as complication. When autoinfecting larvae show further sharp increase, large numbers of larvae invade not only the digestive tract and lungs but also other organs. Moreover, a large amount of intestinal bacteria is dispersed

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through the blood stream by autoinfecting larvae, causing sepsis, pneumonia, and purulent meningitis, as fatal complications. As causative organisms, the most frequently found are *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterococcus* spp.

Present Situation of Strongyloidiasis in Japan

Intestinal parasitic disease decreased sharply in Okinawa Prefecture after World War II, and the infection rate of strongyloidiasis has been considered to be maintained at 0.5–1.5%. However, according to an investigation using ordinary agar plate culture method at various places in Okinawa Prefecture after 1988, the infection rate was found to be over 10% (2). The patients infected with *S. stercoralis* are frequently older, with more than 95% being over 50 years. Few or no infected persons were observed in the young stratum. This is presumably due to improved social sanitation environment and modernization of lifestyle, which make infection from outside difficult. The above findings also indicate that once infected, the carrying state of *S. stercoralis* lasts for a long time.

The Kyushu region in Japan has a high incidence of adult T-cell leukemia (ATL), and in particular there are many patients with ATL in Okinawa prefecture. According to our investigation of inpatients, the *S. stercoralis* positive rate in HTLV-I carriers was 17.5% (43/246), which was significantly higher than the 6.7% (73/1,082) in HTLV-I negative patients (Fig. 1). In our recent survey of *S. stercoralis* severe cases, 76.5% (13/17) developed in HTLV-I carriers, or ATL. Such patients with HTLV-I infection are considered to be at the highest risk of aggravating the strongyloidiasis.

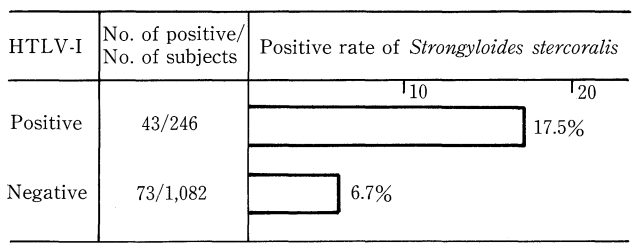

Figure 1. Relationship between HTLV-I carriers and rate of infection with *Strongyloides stercoralis*.

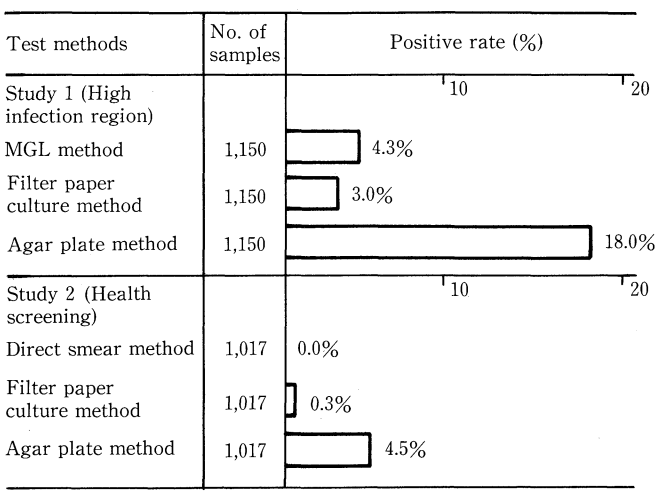

Figure 2. Comparison of agar plate culture method and conventional methods.

New Method of Diagnosis of Strongyloidiasis (Ordinary Agar Plate Culture Method)

Since larvae of *S. stercoralis* are generally excreted in the stools in far less abundance than are ova of other parasites, such conventional methods as direct smear method, formalin ether concentration method, and filter paper culture method cannot produce sufficient sensivity. The ordinary agar plate culture method is one in which larvae are detected by tracing crawling marks on the agar medium (3). As shown in Fig. 2, this method shows excellent sensitivity. The details of the method are described below.

To prevent the *S. stercoralis* from getting out of the Petri dish, the dish is equipped with double walls (outer diameter 10 cm, inner diameter 8.0 cm, depth 2.4 cm). First, about 10 ml of ordinary agar treated with autoclave is put into the sterilized dish so that the thickness of the agar is 2–3 mm. Next, about 3 g of feces is placed at the center of the agar medium, which is then cultured for 24–48 hours at 28°C. To prevent the larvae from crawling out of the dish, about 7 ml of a 25% solution of glycerin is poured into the space between the outer wall and inner wall. When there is a lapse in time after collection of feces or feces are refrigerated, the larvae are liable to die, with a resultant decrease in the detection rate. Therefore, fresh feces must be used. When feces are hard, add a small amount of water beforehand to make the feces soft, which helps to obtain a high detection rate. When disinfecting solution is used in place of glycerin, the detection rate decreases. In the case of *S. stercoralis*-positive, bacteria in feces are dispersed over the culture medium by larvae. As a result, bacterial colonies are formed with a lapse of time (Fig. 3). Observation is made under a low magnification microscope, and the presence of larvae can be confirmed from the first day of culture when crawling marks are traced (Fig. 4). When larvae are collected by a suction device, identification can be made. Thus, it is useful for early diagnosis (Fig. 5). In some cases, free-living adult male or females, larvae, and eggs are observed on the culture (Fig. 6). Even when larvae are not found, if such peculiar crawling marks and bacterial colonies are observed, it can be concluded that the patients are *S. stercoralis*-positive, judging from the results of many tests made to date in Okinawa Prefecture (4, 5). This method can also be used for duodenal fluid, trachea washings, and sputum.

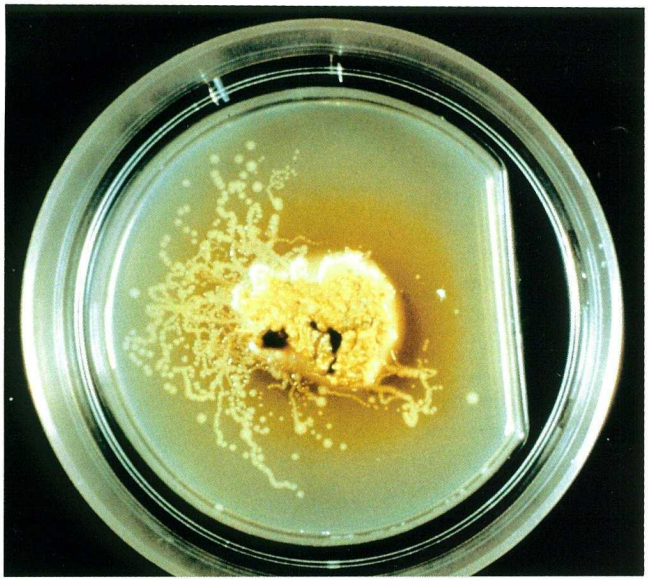

Figure 3. After 24–48 hour, bacterial colonies due to crawling of *Strongyloides stercoralis* larvae are found around the stool.

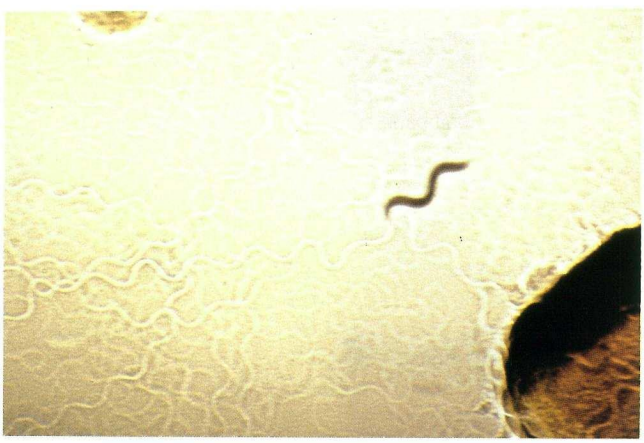

Figure 4. Free moving *Strongyloides stercoralis* larva can be seen under the microscope (×40).

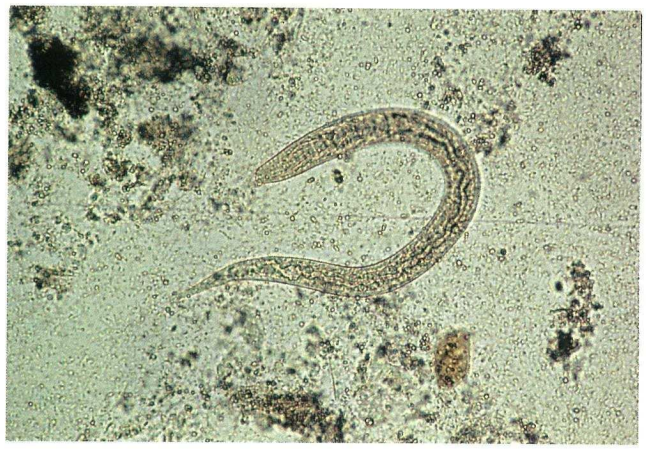

Figure 5. Rhabditiform larva of *Strongyloides stercoralis* (×100).

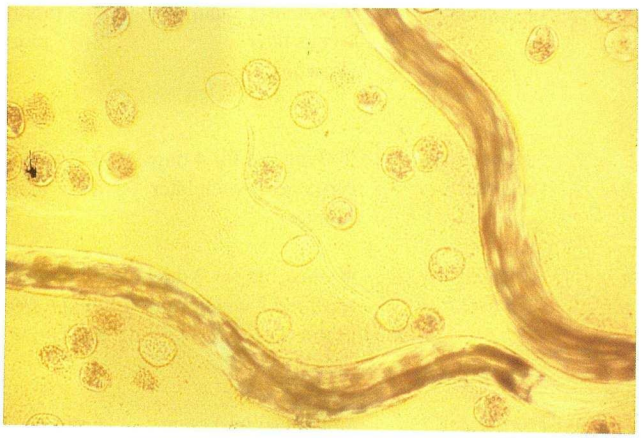

Figure 6. After three-five days, free-living adult females, larva, and eggs are observed on the culture (×40).

Clinical Evaluation of Therapeutic Drugs for *Strongyloides stercoralis*

Historically drugs such as gentian violet, basic bismuth carbonate, dithiazanine iodide, and pyrvinium pamoate have been used. Essentially however, drugs other than pyrvinium pamoate are not considered to have an eradicating effect.

Pyrvinium pamoate

With pyrvinium pamoate, the incidence of adverse effects is low. To date many studies have been conducted. In a therapeutic method with administration of 5 mg/kg for 5 consecutive days as a course, an 85% eradication rate was observed one month after the treatment. However, 70% of treated patients turned out to be positive later, resulting in little difference as compared with the control group. This might be due to the low sensitivity of the fecal examination at that time. It can be supposed that as a result of the decreased number of *S. stercoralis*, undetectable cases were taken as eradication. After introduction of an ordinary agar culture method, a study was conducted with a 3-course treatment, which showed approximately 30% eradication. The manufacture of this drug was discontinued in 1989, and consequently further study was impossible.

Thiabendazole

Thiabendazole is the only drug approved for treatment of strongyloidiasis under the health insurance in Japan. For a total of 162 patients, who were *S. stercoralis*-positive in a health examination, thiabendazole (500 mg tablet) was given 3 times

Table 1. Administration Methods, Anthelmintic Effects and Adverse Effects of Various Therapeutic Agents

	Regimen	Period after treatment/Rate of eradication	Adverse effects		Liver dysfunction
Thiabendazole (162 cases)	1,500 mg tid for 5 days, repeated 3–4 courses every 2 weeks (Tablet)	7 days/100.0% 6 months/100.0% 12 months/100.0%	General fatigue Dizziness Nausea Appetite loss Head ache Overall	24.5% 23.8% 22.5% 21.2% 15.9% 67.5%	33.8%
Mebendazole (33 cases)	200 mg bid for 28 days (Powder)	2–24 days/81.8% 3–7 months/77.3% 8–15 months/85.0% 24 momths/93.8%	Head ache Constipation General fatigue Abdominal pain Overall	11.1% 11.1% 7.4% 7.4% 40.7%	71.4%
Mebendazole (47 cases)	200 mg bid for 5 days, repeated 1, 3 and 4 weeks later (Powder)	2–24 days/100.0% 3–7 months/80.0% 8–15 months/87.1%	Diarrhea Abdominal pain Dizziness Appetite loss Overall	10.6% 6.4% 6.4% 4.3% 34.0%	51.1%
Mebendazole (16 cases)	200 mg bid for 4 days, repeated 1 week later (Tablet)	2–24 days/93.8% 8–15 months/69.2%	Diarrhea Head ache Overall	6.3% 6.3% 12.5%	12.5%
Albendazole (27 cases)	400 mg bid for 3 days, repeated 2 weeks later (Tablet)	14 days/70.4% 28 days/66.7% 14 days/91.6%	Abdominal pain Head ache Nausea Overall	14.8% 7.4% 3.7% 25.9%	33.3%
Ivermectin (125 cases)	1 tablet (6 mg) once, repeated 2 weeks later	6 months/96.5% 12 months/98.2% 24 months/97.3%	Dizziness Diarrhea Nausea Borborygmus General fatigue Overall	2.4% 1.6% 1.6% 0.8% 0.8% 7.2%	13.6%

a day for a 5-day course. Three or 4 courses were given with intervals of 2 weeks (Table 1). After one course of treatment, some adverse effects, such as general fatigue, dizziness, nausea, anorexia and headache, were observed in 67.5% of the patients. Consequently, 45.1% of the patients dropped out in the course of treatment, and a dose decrease had to be made in 32.1%. Finally it was only 22.8% (37 patients) for which a full course could be given. In the case of treated more than 3 course, the eradicating rate after 2 weeks and 6 months and one year was 100% respectively. Liver dysfunction was observed in 33.8%, and the incidence increased with increased dose, and the severity also intensified. As shown above, the eradicating effect of this drug is excellent. However, since it has a high incidence of such adverse effects as general fatigue, dizziness, nausea, appetite loss, and liver dysfunction, thiabendazole is not suitable as a therapeutic drug for strongyloidiasis (6).

Mebendazole

In Japan, mebendazole is indicated for trichuriasis. In Europe and America, it is being used for strongyloidiasis as well. There is a report that even when this drug is used for the treatment of hydatidosis, adverse effects and liver dysfunction are few. Meanwhile, the life cycle of *S. stercoralis* is about 28 days. Taking this into consideration, we set the administration period at 28 days. However, liver dysfunction occurred more than anticipated. That was considered to be a toxic hepatic disorder. We therefore decreased the dose, and changed the dosage form from powder to tablet. However, liver dysfunction still occurred. Finally, two courses of 4-day administration were given at an interval of 2 weeks. Then, although the incidence of liver dysfunction decreased, the eradicating effect also decreased (7).

Albendazole

In Japan, Albendazole is indicated for hydatidosis. It is also

being tried worldwide for strongyloidiasis. We gave two courses of 3-day administration at an interval of 2 weeks. Although the degree of liver dysfunction was low, the eradicating rate was not satisfactory (8).

Ivermectin as a Therapeutic Drug for *Strongyloides stercoralis*

Reason for study

As already mentioned, the adverse effects of thiabendazole are very strong. Our department therefore studied mebendazole and albendazole. However, the former had a high incidence of liver dysfunction, and the latter did not have a satisfactory eradicating effect. In view of the fact that there are reports that ivermectin is effective for human strongyloidiasis (9–11) and that this drug is being clinically used widely for the treatment of human onchocerciasis with WHO as the guiding organization, we imported this drug directly from Merck & Co., Inc., New Jersey, USA, and started our study. The results were far better than expected, and from 1990, we were able to participate in the Ministry of Health and Welfare's project of developing new drugs as a member of the Team for Development of Drugs for Tropical Diseases, and for Treatment of such Diseases. Thus, we were able to study many patients.

Background of the development of ivermectin

In 1979, as a result of a joint study by Omura Research Office, of Kitasato Research Institute, and Merck, USA, avermectins, with a high eradicating activity, were discovered in culture solution of *Streptomyces avermitilis* isolated from the soil in Kawana, Ito City, Shizuoka Prefecture, Japan. It is known that there are 8 types in avermectin. Ivermectin was induced and semisynthesized from among them so that efficacy and safety could be secured. It shows strong activity against nematodes and ticks, and its marketing in Japan was started in 1981 as an animal drug. In the world market, Merck supplied it free of charge in 1987 through WHO for onchocerciasis, and at present, it is being used by 33 million patients.

Mode of action and pharmacokinetics of ivermectin in humans

Ivermectin is a neurotransmission system inhibitor with an entirely different mode of action than benzimidazole compound. Ivermectin inhibits signal transmission from the ventral cord interneurons to the excitatory motor neurons in nematodes by stimulating the release of the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA) from pre-synaptic nerve terminals. In arthropods, it inhibits neurotransmission by the same mode of action. In mammals, however, ivermectin does not readily penetrate into the central nervous system, and consequently, it does not inhibit GABA-dependent neurotransmission. With single oral administration 12 mg tablet, the maximum plasma concentration in 4 hours is 46.6 (±21.9) ng/ml, and half-life is about 12 hours. Ivermectin and/or its metabolites are excreted almost exclusively in the feces over an estimated 12 days with less than 1% of the administered dose being excreted in the urine.

Dose and administration method

In the literature, administration of 140–200 μg/kg is given only once. At our department, however, we gave one tablet (6 mg), and then another tablet at an interval of 2 weeks. The reason for this method of administration is that we thought this drug would be ineffective for larvae and eggs in body tissues, and that it takes 2 weeks for the *S. stercoralis* from percutaneous infection to discharge in feces, and its cycle is completed in 3–4 weeks. The eradicating effect described here is based on administration of 2 tablet (6 mg) at an interval of 2 weeks regardless of the body weight.

Clinical effect

In our study of 125 subjects, the eradicating rate was 91.6% (109/119) after 2 weeks, 98.2% (54/55) after one year, and 97.3% (36/37) after 2 years. Thus, the results were satisfactory. In the treatment-resistant group, 80% were HTLV-I carriers, and peripheral eosinophil count and serum IgE were lower than in the worm-eradicated group. Regarding adverse effects, only dizziness (2.4%), nausea (1.6%) and diarrhea (1.6%) were observed after administration of one tablet. Each of these was mild and transient, and none required any particular treatment. Liver dysfunction was observed in 13.6%, and the severity of liver dysfunction was mild in almost all patients as compared with those observed with benzimidazole compound, and none required any particular treatment (12).

In our clinical use of ivermectin, we covered more than 350 patients. There were only 2 patients for whom the administration was discontinued due to liver dysfunction. Scarcely any subjective symptoms were observed that would present clinical problems. Thus, the eradicating effect of ivermectin was excellent, and the incidences of adverse effects and liver dysfunction were low, and their severity was mild.

Care to be Taken in the Treatment of Strongyloidiasis and Evaluation of Effect

Spontaneous cure of strongyloidiasis can not be expected. Once it has become severe, complete eradication becomes difficult. Even in the asymptomatic state, strongyloidiasis must be treated because of the potential for fatal hyperinfection. Especially for patients requiring the use of immunosuppressant, and for those scheduled to undergo surgery of the digestive tract or other major surgery, diagnosis and treatment should be given at an early stage. As a principle in treatment, the peculiar life cycle of *S. stercoralis* should be taken into consideration, and a 2-course treatment at an interval of 2 weeks is the most effective. For disseminated strongyloidiasis, an antibacterial drug should be given concomitantly with anthelmintic. In case of complication with HTLV-I, the capability of eradication decreases. In such a case, fecal examination may be often false-negative. In making an evaluation of the therapeutic effect, it is necessary to make the evaluation carefully after a sufficient term.

Conclusions

We have discussed the ordinary agar plate culture method and the clinical effect of various therapeutic drugs. Since strongyloidiasis has peculiar autoinfection, it is difficult to attain complete eradication. With conventional test methods, it becomes difficult to detect larvae when excreted number of larvae is decrease. Consequently, a wrong evaluation can be made by thinking that *S. stercoralis* has been eradicated. Therefore, especially in evaluating the eradicating effect, a method with sharp sensitivity should be used, and careful test should be made repeatedly. Fortunately, this method is simple, and it is already being used widely in Okinawa Prefecture. With a view to obtaining approval for treatment with ivermectin, we are proceeding with clinical trial at 200 μg/kg (12 mg when the body weight is 60 kg). With administration by this method, a high eradicating effect and safety are being confirmed. At present, we can get a supply of ivermectin from the person in charge of storage of rare drugs, of the Development Research Team of Drugs for Tropical Diseases, of the Ministry of Health and Welfare. [In Japan, ivermectin will be distributed, if a request is made to the Department of Tropical Medicine, Jikei Medical School, or to the First Dept. of Internal Medicine, University of the Ryukyus.]

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