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Full Length Research Paper

Comparison of ivermectin and thiabendazole in the treatment of uncomplicated human *Strongyloides stercoralis* infection

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Ivermectin is the drug of choice in the treatment of onchocerciasis, and has been proven to be highly effective against *Strongyloides stercoralis*. This study compares ivermectin's efficacy and safety with that of thiabendazole, an established drug of choice for strongyloidiasis, in 252 confirmed cases of uncomplicated human intestinal strongyloidiasis. Subjects were administered orally with ivermectin (200 μg/kg) in a single dose or thiabendazole, 25 mg/kg, twice daily (50mg/kg/day) for 3 consecutive days. Stools were parasitologically examined 7, 21 and 30 days after treatment. Only 18 of 113 and 22 of 103 ivermectin- and thiabendazole-treated subjects, respectively, had stools positive for larvae 30 days post-treatment. This indicates parasitological cure rates of 84.07% and 78.64% for ivermectin and thiabendazole, respectively. Ivermectin was not significantly more effective than thiabendazole ($P < 0.05$). There was considerable reduction in parasite output in parasitologically uncured subjects with mean of 81% in ivermectin-treated and 75% in thiabendazole-treated groups, respectively. Clinical adverse reactions were mild and transient in subjects treated with ivermectin, while they varied from mild to severe in those treated with thiabendazole. Single-dose ivermectin provides efficacy comparable with standard, multiple-dose thiabendazole, with a much reduced incidence of adverse effects and consequently better patient compliance.

Key words: Ivermectin, thiabendazole, *Strongyloides stercoralis,* strongyloidiasis.

INTRODUCTION

Strongyloides stercoralis is an intestinal nematode parasite found chiefly in tropical and subtropical regions of the world, although endemic regions abound in southeast USA, Japan and south Europe (Datry et al., 1994). Infections with this parasite are usually of a chronic nature primarily due to the auto infective ability of the parasite (Grove, 1982). According to Genta (1989), severe disseminated disease may occur in immunocompromised and untreated individuals.

Chemotherapy is advocated and considered an effective control measure for the reduction of morbidity resulting from intestinal nematode infection (Savioli et al., 1992; Warren et al., 1993). The current drug of choice for strongyloidiasis is the benzimidazole compound, thiabendazole, introduced into human medicine three decades ago. Therapy with this drug is however, fraught

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with a number of disadvantages. It is not always curative (Most, 1984) and some investigators have suggested that it merely reduces larval production (Grove, 1982). Treatment often requires multiple doses (at least 3 consecutive days of treatment) and is frequently associated with considerable adverse effects, particularly in the gastro-intestinal and neuropsychiatric systems (Grove, 1982, 1989; Most, 1984), thus reducing compliance.

Ivermectin, a semi-synthetic macrocyclic lactone derivative of Avermectin B, has gained wide acceptability as the drug of choice in the treatment of human onchocerciasis. Single oral doses of ivermectin have been found to be highly effective and well tolerated (Greene et al., 1985; Richard-Lenoble, 1998). It has also been reported to have a wide spectrum of activity against many nematodes and ectoparasites of man and domestic animals, including *Strongyloides westeri* and *Strongylus vulgaris* (Goldsmith, 1988; Campbell, 1989). Data from non-comparative (Freedman et al., 1989; Scaglia et al., 1990; Testa et al., 1990) and comparative studies with other drugs (Datry et al., 1994; Gann et al., 1994; Marti et al., 1996) indicate that the drug is well tolerated and highly effective in the treatment of *S. stercoralis* infections in man. The results presented here are those of a study comparing the efficacy and safety of single-dose ivermectin with that of a standard 3-day course thiabendazole.

MATERIALS AND METHODS

Study population and Choice of subjects

The study was carried out in collaboration with the Primary Health Care Unit of the Yewa South Local Government area of Ogun State, Nigeria. The study population comprised 274 subjects, aged 5 to 66 years, with uncomplicated intestinal strongyloidiasis and whose stools were positive for *S. stercoralis* larvae during a larger survey on intestinal helminths (unpublished data). Prior to participation, a full medical history was taken from each subject, while a physical examination was conducted by the physician (A.O. Adenusi).

Subjects qualified for participation in the study if they had not received any form of anti-filarial therapy and any other anthelmintic treatment in the 6 months and 72 h respectively, preceding the study. Only subjects with no allergic diatheses, disseminated strongyloidiasis, severe renal, hepatic, haematological (haemoglobin level under 5 g/dL) or cardiovascular functions participated in the study. Potentially childbearing women not using contraceptives and subjects in which the parasite was detected in stool samples more than 30 days before commencement of the study were excluded. Subjects were educated on the objectives of the study and the attendant benefits to them. Only those who gave informed oral consent (parents, if subjects were children) participated in the study.

Parasitology

Following informed oral consent and before treatment, each participant (subject) was given an empty wide-mouth, screw-top plastic container and asked to bring a fresh stool sample the following day (pre-treatment stool sample). Each stool sample was parasitologically examined quantitatively in the laboratory for the larvae of *S. stercoralis*, using the modified Baermann concentration technique (WHO, 1981). The immediate examination of the freshly passed stool samples enabled detection of the rhabditiform larvae of *S. stercoralis*, which were recognised by their characteristically short buccal cavity (WHO, 1981).

Treatments

Subjects were assigned to either ivermectin- or thiabendazole-treatment group using a randomised list for the sequential allocation of the drugs, prepared in advance. They were weighed and those in the former group administered with single dose, 200 μg/kg body weight ivermectin (Mectizan, M.S.D.). They had fasted for 6 h before and were also asked to fast for 2 h after drug intake, so as to ensure satisfactory absorption. Thiabendazole (Mintezol, M.S.D.) was administered as a twice-daily oral dose (each 25 mg/kg body weight) with meals for 3 consecutive days, up to a maximum daily dose of 3 g for patients over 60 kg. Drug intake was under personal supervision. All treated subjects were instructed to report any new signs and symptoms (adverse effects), following drug administration to medical assistants.

Evaluation of drug safety

Clinical adverse effects of either drug were investigated through voluntary spontaneous complaints by subjects and also by interviews conducted using a standard questionnaire based on the common adverse effects of either drug reported in the literature. All these were done within 7 days post-treatment.

Evaluation of drug efficacy

Drug efficacy was evaluated on days 7, 21 and 30 post-treatment when follow-up stool samples were collected and examined, using the same procedures as in the pre-treatment. Each subject served as his or her own control as both pre- and post-treatment stool sample parasite counts were compared in each subject. In this study, a subject was considered parasitologically cured, if all 3 post-treatment stool samples tested negative for larvae of *S. stercoralis*. All subjects who did not provide all 3 follow-up stool samples (on days 7, 21 and 30 post-treatment) were excluded from the analysis of drug efficacy. Analysis of drug efficacy was carried out using the chi-square test while the reduction in mean parasite output (in parasitologically uncured subjects) was analysed using the t-test (Sokal and Rohlf, 1981).

RESULTS

Of the 274 subjects with *S. stercoralis* larvae in their stool samples, only 252 were eligible for participation in the trial, 22 having been excluded for medical reasons. Of the 252, 21 had incomplete treatments, while 15 had incomplete follow-ups (i.e. did not submit all 3 post-treatment stool samples). Only the 216 subjects with complete treatment and follow-ups were used for evaluation of drug efficacy (i.e. calculation of cure rates and parasite load reduction). Of these, 113 were of the ivermectin group, while 103 were treated with

Table 1. Demographics (A) and treatment groups (B) of subjects before and after treatments.

A.

	Males	Females	Totals
Number positive for *S. stercoralis* larvae	141	133	274
Number excluded from study	12	10	22
Number eligible for participation	129	123	252

B.

	Treatment group		
	Ivermectin	Thiabendazole	Total
No. eligible for participation in trial	126	126	252
No. with incomplete treatment	4	17	21
No. evaluated for adverse effects of drug	122	109	231
No. evaluated for drug efficacy	113	103	216
Males	59	55	114
Females	54	48	102

Table 2. Results by treatment group of follow-up stool examinations, using the Baermann technique.

Treatment group	Days post-treatment			Cure	% reduction of mean parasite output (range)
	7	21	30		
Ivermectin	107/122	98/116	95/113	84.07	81 (77-86)
Thiabendazole	85/109	81/105	81/103	78.64	75 (69-81)

Note:
- data shown are no. of subjects negative for larvae/no. of subjects tested.
- declines in no. of samples tested with days reflect loss of subjects due to follow-up.
- declines in no. of samples negative for larvae with days reflect treatment failure and loss of subjects due to follow-up.

thiabendazole for 3 consecutive days (Table 1). Both treatment groups were comparable in parasite/worm burdens, age and sex.

Table 2 shows cure rates and percent larval reduction following treatment with either ivermectin or thiabendazole. Of the 113 ivermectin-treated subjects, there was parasitological cure in 84.07%, while 78.64% of the thiabendazole-treated subjects were parasitologically cured, 30 days after treatment. The observed higher cure rate with ivermectin was however, not significant ($P < 0.05$). Treatment failures were detected in 13 of the 18 parasitologically uncured ivermectin-treated subjects on day 7 post-treatment, and in another 5 on day 21. Out of the 22 parasitologically uncured thiabendazole-treated subjects, treatment failures were detected in 19 on day 7 post-treatment and in 3 on day 21. Mean parasite (larval) counts in parasitologically uncured subjects declined by 81% (range, 77 to 86%) among the 18 parasitologically uncured ivermectin-treated subjects, while it declined by 75% (range, 69 to 81%) in the thiabendazole group. The difference in mean reductions between the two groups was also not significant ($P < 0.05$).

At baseline (before treatment), signs and symptoms such as epigastric pain, urticaria and diarrhoea were recorded in subjects. They were possibly associated with strongyloidiasis as there were significant declines in all these symptoms, 21 days after treatment, even in parasitologically uncured subjects. There was no difference in the resolution of symptoms for the two treatment regimens.

Of the 231 subjects evaluated for adverse effects of drug treatments, 48.48% experienced one or more side effects of either medication, 31.15% in the ivermectin-

treated subjects and 67.89% in the thiabendazole-treated group (difference significant). Over 95% of the adverse effects were reported within 3 days after treatment.

Constipation and fever were reported only after ivermectin treatment, while malaise, anorexia, abdominal pain and disorientation were reported only with thiabendazole medication. Nausea, fatigue and dizziness were recorded significantly more often after thiabendazole medication (Table 3).

Most of the adverse reactions after medication with ivermectin were considered mild and transient, as the subjects though aware of these reactions easily tolerated them and did not last for more than 24 to 48 h. Adverse reactions varied from mild to severe and lasted 1 to 7 days in those treated with thiabendazole. Twenty two of the subjects treated with thiabendazole, including all 16 with disorientation were sufficiently incapacitated to be unable to perform normal daily activities.

Table 3. Number of subjects developing one or more new signs and symptoms within 7 days after treatment (adverse effects).

Symptoms	Thiabendazole (n =109)	Ivermectin (n =122)
Constipation	0	7*
Nausea	49*	5
Fatigue	54*	16
Malaise	21*	0
Dizziness	28*	6
Anorexia	39*	0
Abdominal pain	6*	0
Fever	0	8*
Headache	7	11
Disorientation	16*	0

n = number of subjects evaluated for adverse effects after treatment.
*indicates significant difference ($P < 0.05$), using the t-test.

DISCUSSION

At present, the therapeutic arsenal available for the treatment of strongyloidiasis includes thiabendazole and its alternative, albendazole. The unsatisfactory efficacy of these two drugs and the frequent and considerable adverse reactions associated with thiabendazole therapy have however, prompted the need for better therapeutic alternatives.

The cure rate recorded for ivermectin in the present study is within the range reported by previous workers using ivermectin in similar dosages, either in non-comparative studies (Freedman et al*.,* 1989; Naquira et al*,* 1989) or in comparative studies with other drugs (Datry et al*.,* 1994; Gann et al., 1994; Marti et al., 1996) in the treatment of uncomplicated, human strongyloidiasis. Similarly, the cure rate recorded for thiabendazole in the present study fall within those reported by previous workers (Nauenberg et al*.,* 1970; Grove, 1982), although the drug has been reported not to be curative (Most, 1984). Although ivermectin recorded a higher cure rate than thiabendazole in the present study, this difference was not significant. Gann et al. (1994) found ivermectin to be at least as effective as thiabendazole in the treatment of uncomplicated strongyloidiasis.

Inspite of the failure of either drug to cure infection (18 subjects in ivermectin- and 22 subjects in thiabendazole-treated groups), there was still some level of reduction in parasite counts after treatment. The failure of either drug to completely eradicate the parasite in some of these subjects is surprising as some of them, even had lesser parasite counts before treatment than some parasitologically cured patients. Thus, non-cure in these patients could not be attributed to heavy worm burden (parasite counts). These treatment failures notwithstanding, the results of the present study are reliably ensured by the one-month follow-up of patients and the effective use of the Baermann concentrations.

The clinical signs and symptoms recorded at baseline (at the start of the trial and before drug treatments) have been reported previously as being associated with strongyloidiasis (Grove, 1989; Gann et al., 1994). The resolution of these signs and symptoms after either medication, even in parasitologically uncured subjects, indicates that they were associated with infection; this decline perhaps due to a decrease in worm burdens.

Clinical adverse reactions encountered in the present study were as reported in previous studies where similar dosage regimens of ivermectin (Freedman et al*.,* 1989; Naquira et al., 1989; Datry et al*.,* 1994) or thiabendazole (Grove, 1982, 1989; Gann et al., 1994) were employed. Treatment with thiabendazole was associated with a significantly higher rate of adverse effects than was with ivermectin, which appeared to be better tolerated. Severe side effects including disorientation, which interfered with the normal daily activities of the subjects, were reported only after thiabendazole medication.

The results of this study have further demonstrated and confirmed previous reports on the efficacy and relatively good safety of ivermectin in the treatment of uncomplicated strongyloidiasis in man (Freedman et al*.,* 1989; Naquira et al*.,* 1989; Scaglia et al*.,* 1990; Datry et al., 1994).

Ivermectin is effective against both larval and adult stages of *S. stercoralis* (Liu and Weller, 1993). Observations in previous studies of ivermectin use in humans indicate that the drug can be effective in patients who have not responded to repeated courses of thiabendazole (Wijesundera and Sanmuganathan, 1992; Adenusi, 1997).

Ideally, a very good anthelmintic for the treatment of gastrointestinal helminthiasis and in particular strongyloidiasis should be very effective in single dose regimens. Treatment of *S. stercoralis* infection with thiabendazole normally requires multiple doses in order to achieve optimum results, which is often associated with mild to severe toxicity. Due to the close monitoring of subjects, compliance with medication in the present study was believed to be excellent. In clinical practice however, many patients would be unwilling to complete the prescribed 3-day course of thiabendazole. The potency and safety of single-dose regimen of ivermectin against *S. stercoralis* infection as reported here as well as in previous studies renders more aggressive, multiple dose regimens as in the case with thiabendazole unnecessary. Campbell et al. (1983) have reported a wide margin of safety for ivermectin in cattle and dogs, as there were no toxicities associated with the administration of 10 to 30 times the dose employed in this study.

The presently reported efficacy of ivermectin, the advantage of a single-dose treatment and given the low frequency of mild adverse effects observed with ivermectin compared with thiabendazole, we conclude that single-dose (200 μg/kg body weight) ivermectin is a better treatment regimen and should become the treatment of choice for uncomplicated strongyloidiasis, especially in a developing country including Nigeria, where patient compliance with the multiple-dose/day regimen of thiabendazole is difficult and where concurrent onchocerciasis may also be endemic. Our results open the opportunity to evaluate in large-scale studies, whether ivermectin has any potential value in the treatment of chronic, gastrointestinal strongyloidiasis as well as complicated hyperinvasive strongyloidiasis in immunocompromised individuals. This is with a view to determining its potentiality as a recommended treatment of choice in all cases of human strongyloidiasis.

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