Treatment of strongyloidiasis with thiabendazole: an analysis of toxicity and effectiveness

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Summary

The effects of therapy with thiabendazole were investigated in 43 men who had been infected with *Strongyloides stercoralis* for 35 years. Side effects of drug treatment were frequent and sometimes severe; nausea was the most common symptom. Six months later, approximately one third of patients had persistent diarrhoea, recurrent urticaria or considered that their general health had not improved. Parasites were found in 7% of persons six months after treatment. Blood eosinophil counts fell dramatically but the falls in serum IgE levels and serum *Strongyloides* antibody titres were less marked. Assessment of response to treatment is difficult because of the insensitivity of parasitological techniques and the ability of this parasite to replicate. It is concluded that thiabendazole cannot always be relied upon to eradicate infection.

Introduction

Strongyloidiasis is one of the major human intestinal nematode infections. It causes chronic ill-health in an incalculable number of people, and occasionally produces an explosive, overwhelming illness in immunosuppressed persons (SCOWDEN et al., 1978). Unfortunately, it is one of the intestinal helminthiases that is least amenable to treatment with anthelmintics. Since its introduction nearly 20 years ago, thiabendazole has been the mainstay of the therapy of strongyloidiasis and is recommended in all the major textbooks.

Nevertheless, previous studies have not demonstrated with any degree of certainty that this drug always eradicates infection with *Strongyloides stercoralis*. This study examined the clinical, parasitological, haematological and serological responses six months after treatment with thiabendazole in a group of persons with strongyloidiasis who were not exposed to re-infection from the environment.

Methods

Patients: 43 Australians who had been infected with *S. stercoralis* approximately 35 years previously while prisoners-of-war in South-East Asia were studied. They were all male and ranged in age from 57 to 78 years; they have been described in detail previously (GROVE, 1980). All persons completed the study except one subject who died of carcinoma of the lung; he has been excluded from the analysis.

Drug Therapy: The first six patients were given thiabendazole (Merck, Sharpe and Dohme, Australia) 25 mg/kg twice daily orally for three days. Because many of these persons suffered severe side-effects, subsequent patients took the same total dose but spread over 4-5 days. Patients with nausea were treated with prochlorperazine 5 mg as necessary.

Clinical Assessment: Patients were interviewed and weighed before treatment, and again one and six months after therapy. Attention was paid to those symptoms which have previously been shown to be associated with strongyloidiasis; particular note was taken of the characteristic urticarial rash, diarrhoea and the patient's view of his general health.

Parasitological assessment: Faeces were examined by direct microscopy and by culture while duodenal fluid was obtained with a string wound inside an Enterotest® capsule. The diagnosis was made on the first attempt in 68% of cases, while the rest were diagnosed by either a second string test or after examination of multiple specimens of faeces (GROVE, 1980). One month after treatment with thiabendazole, faeces were examined by direct microscopy and culture. Six months after treatment, each patient was tested again with an Enterotest capsule and single specimens of faeces were examined by direct microscopy and culture.

Haematological assessment: Total white cell counts were measured with a Coulter counter and the blood eosinophil level was calculated from the differential white cell count.

Serological assessment: Total serum IgE concentrations were measured with the Phadebas PRIST kit (Pharmacia, Uppsala, Sweden). Serum antibodies against *Strongyloides* were measured as described elsewhere (GROVE & BLAIR, 1981). In brief, living infective larvae of *S. ratti* were incubated with serial dilutions of test serum, washed, then reincubated with fluorescent sheep anti-human globulin. After re-washing, the antibody titre was determined by observation of cuticular fluorescence. A titre of 1:4 has been shown to indicate infection with *S. stercoralis*; it is specific and 96% sensitive.

Results

Toxicity of Thiabendazole

89% of patients complained of one or more side-effects (Table I). Nausea was the most common symptom, affecting two thirds of patients. This usually began on the second day of treatment and varied from mild to severe in degree; vomiting occurred in 7% of persons. A group of neuropsychiatric symptoms which included sensations of disembodiment, disorientation in space, delirium, being dazed, or simply being "not all there" occurred in 23% of patients. Symptoms were so bad in three patients (7%), that each person volunteered the statement "I thought I was going to die".


Table I. Frequency and nature of side-effects in 42 men treated with thiabendazole

<table>
<thead>
<tr>
<th>Side-effects</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>nausea</td>
<td>67</td>
</tr>
<tr>
<td>smelly urine</td>
<td>26</td>
</tr>
<tr>
<td>neuropsychiatric</td>
<td>23</td>
</tr>
<tr>
<td>malaise</td>
<td>16</td>
</tr>
<tr>
<td>dizziness</td>
<td>16</td>
</tr>
<tr>
<td>anorexia</td>
<td>7</td>
</tr>
<tr>
<td>vomiting</td>
<td>7</td>
</tr>
<tr>
<td>abdominal pains</td>
<td>7</td>
</tr>
<tr>
<td>&quot;thought going to die&quot;</td>
<td>7</td>
</tr>
<tr>
<td>headache</td>
<td>5</td>
</tr>
<tr>
<td>facial flush</td>
<td>5</td>
</tr>
<tr>
<td>pruritis</td>
<td>2</td>
</tr>
<tr>
<td>paraesthesiae</td>
<td>2</td>
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<tr>
<td>sweating</td>
<td>2</td>
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<tr>
<td>flatulence</td>
<td>2</td>
</tr>
</tbody>
</table>

Clinical response

Thirty-one patients had a history of rash before treatment. A recurrence of either crops of stationary urticarial wheals or pathognomonic larva currens occurred during the six months of observation in nine persons (29%). 25 patients complained of diarrhoea before treatment; six months later, 18 persons (72%) considered that this had improved while seven patients (28%) thought that the diarrhoea was unchanged. Before treatment, 24 persons had classified their general health as being poor; six months later, 16 persons (67%) thought their general health was better while eight patients (33%) considered that it had not improved.

The mean weight change in the 42 patients over the six months of observation was a gain of 1.4±2.6 (S.D.) kg; this was not significant. Although the weight gain was greater in patients in whom diarrhoea had improved (2.1±2.7 kg versus 1.1±3.5 kg) and whose general health had improved (2.2±2.8 kg versus 1.1±2.5 kg), this gain was not statistically significant. There was, however, a significantly greater weight gain (P<0.05, "t" test) in the 22 patients whose rash had not recurred (2.4±2.8 kg) compared with the weight change in nine patients in whom the rash had recurred (−0.1±2.1 kg).

Parasitological response

Parasites were found in three of 42 persons (7%) six months after treatment; larvae were found in the stools of two persons and in the duodenal fluid of one person. Altogether, parasites were recovered, diarrhoea persisted, or rash recurred in 14 of 42 persons (33%).

Blood eosinophil response

The geometric mean blood eosinophil level of the 42 patients before treatment was 411 (range 92 to 1850) μl. This fell dramatically to 91 (6 to 1380) after one month and 75 (7 to 806) after six months (P<0.005, paired "t" test). The value at six months was not significantly different from the level of 52 (10 to 501) eosinophils/ml in 44 uninfected control subjects. There was no significant difference between the

14 patients in whom parasites, diarrhoea or rash persisted and the remainder, the percentage falls over six months being 87% and 78%, respectively. The blood eosinophil levels before and six months after treatment in the 43% of patients who had an initial blood eosinophil level above the normal range (10 to 501) are shown in Fig. 1.

Serum IgE response

The geometric mean serum IgE level of the 42 patients before treatment was 323 (range 24 to 4430) units/ml. This fell slightly to 269 (21 to 3420) after one month and 231 (16 to 3280) after six months (P<0.005, paired "t" test). The value at six months was significantly higher than the level of 64 (17 to 245) units/ml in 44 uninfected control subjects (P<0.005, "t" test). There was no significant difference between the 14 patients in whom parasites, diarrhoea or rash persisted and the remainder, the percentage falls over six months being 36% and 26%, respectively.

The serum IgE levels before and six months after treatment in the 64% of patients who had an initial
difficult parasitological diagnosis with other parasites, diarrhoea. The Sennz Strongyloides antibody to control months after Fig. 3). to of shown serum lntients Fig. 116 THIABENDAZOLE TREATMENT c T r E

Assessment The mean serum antibody titre against Strongyloides of the 42 patients before treatment was 1:41 (range 4 to 425). There was a moderate fall to 1:23 (2 to 255) after one month and a further substantial fall after six months to 1:5 (0.3 to 91) (P<0.001, paired “t” test, Fig. 3). Serum antibody titres were still elevated above normal six months after treatment, 24 of 42 patients had a serum antibody titre ≤1:4 c.f. one of 44 control subjects (P<0.001, χ² with Yates correction). The percentage fall of 78% (from 1:37, range 3 to 456, to 1:8, range 0.3 to 187) in the 14 patients in whom parasites, diarrhoea or rash persisted was significantly less (P<0.05, paired “t” test) than the 91% fall in the other 28 patients (from 1:43, range 4 to 426 to 1:4, range 0.3 to 59).

Discussion

Assessment of the response to treatment in patients with strongyloidiasis is hard for two reasons. Firstly, parasitological diagnosis of this infection may be very difficult as the worm burden is frequently low and multiple specimens of faeces and duodenal contents often need to be examined (GROVE, 1980). Secondly, since S. stercoralis has the ability to multiply, the administration of a partially effective drug may so reduce worm numbers that they are no longer detectable but subsequent replication of the few remaining worms will allow autoinfection and persistent disease. In this study, therefore, patients were re-assessed six months after treatment in the hope that this may have allowed sufficient time for any remaining worms to increase to demonstrable levels. In addition, changes in clinical, haematological and serological parameters were followed in an attempt to gain an indirect measure of responsiveness.

Thiabendazole is an important advance on its predecessors. Gentian violet, the traditional remedy, was probably no better than a placebo. Dithiazanine iodoide appeared to have some anthelmintic effect, but was withdrawn after a patient died from a toxic reaction (STEMMERMAN & NAKASONE, 1960). After thiabendazole was noted to be effective against Strongyloides in sheep, this compound was investigated in human strongyloidiasis. Initial results were encouraging, and since then this drug has enjoyed widespread use.

Unfortunately, the side-effects of thiabendazole are frequent and sometimes severe, particularly in those given a dose of 50 mg/kg or more per day (FRANZ, 1963; DOMART et al., 1967, COUNCIL ON DRUGS, 1968). The toxicity of thiabendazole was underlined in the present study with many patients vowing that they would never take the drug again. Symptoms were prevalent despite a reduction in dosage to 33 mg/kg per day. The patients treated were elderly,
however, and it is possible that their age may have accentuated the frequency and severity of toxic reactions.

Earlier investigators have claimed cure rates of between 55 and 100% after thiabendazole treatment; satisfactory responses were closer to 100% in those persons given larger doses (FRANZ, 1963; AZIZ, 1969; MOST et al., 1965). The significance of these findings is difficult to determine, however, for these investigators assessed their patients only for short periods, ranging between one and five weeks after treatment. There have been few reports of long-term follow-up of treated patients. DOMART et al. (1967) treated 100 patients with thiabendazole in a single dose of 50 mg/kg and observed their patients for varying periods after therapy. For example, 64 persons were examined one month after treatment and 13% were noted to have persistent infections, while 14% of 38 patients reviewed after six months were infected. NAUENBERG et al. (1970) treated 25 patients with 20-35 mg/kg of thiabendazole on two successive days and claimed at 96% cure rate. 20% of these patients were re-examined 12 or more months after treatment, but larvae were not found in any subjects.

The likelihood of finding larvae after treatment depends not only upon the interval between treatment and assessment, but also upon the determination and assiduity with which parasites are sought. In the present study, examination of the faces and duodenal contents six months after treatment was performed on once only. Parasites were found in three (7%) of these subjects. One of these subjects had been treated with thiabendazole 25 mg/kg b.d. for three days while the others received the modified regimen. It is likely that if parasites had been sought on more occasions, or if patients were followed for longer, that further patients would be proved to harbour persistent infection. Indeed, larvae have been found nine months after treatment in one such patient who complained of recurrent larval currens.

Clinical assessment is necessarily subjective, but approximately one third of patients thought that their general health had not improved and admitted to persistent diarrhoea or urticaria. Some validation of these histories may be provided by the objective observation that weight gain was greater in persons whose symptoms had improved. It seems likely that persistent urticaria indicates continuing infection and recurrent larval currens almost certainly does. There are other possible explanations for diarrhoea, however. It may be the result of an entirely unrelated cause, e.g., 16% of uninfected control subjects had diarrhoea (GROVE, 1980). Alternatively, persistent diarrhoea may be due to a post-infectious irritable bowel syndrome.

A number of laboratory parameters were assessed in an attempt to test the view that some patients had persistent occult infections. The mean blood eosinophil level dropped sharply by six months after treatment. A similar fall has been noted after treatment of hookworm infection, and presumably reflects a lessened stimulus to eosinophils after elimination or reduction of the worm burden (GROVE et al., 1974). The mean serum IgE level also fell, but less markedly. This may indicate either that there is persistent antigenic stimulation of a reaginic response, or that insufficient time has elapsed for those serum IgE levels which were elevated to return to normal. This latter possibility seems less likely, however, as the serum IgE level returned to within the normal range six months after the onset of trichinosis (ROSENBERG et al., 1971). Unfortunately, the serum IgE level is an imperfect guide to the presence or absence of infection, as levels may be normal in many persons with strongyloidiasis (GILL et al., 1979; GROVE, 1980).

Similarly, levels of antibodies specific for Strongyloides are difficult to interpret. Nevertheless, it would seem reasonable that antibody titres reflect, at least in part, the antigenic stimulus and the worm burden. Thus, the less marked fall in titres in patients with continued diarrhoea or urticaria may indicate a continuing infection, albeit diminished in numbers.

Thiabendazole is no panacea. Firstly, it has a high incidence of unpleasant side-effects. Secondly, it does not always eradicate infection, both in persons with uncomplicated strongyloidiasis as reported here, and in patients with immunosuppression and disseminated strongyloidiasis (CUNLIFFE & SILVA, 1968; RIVERA et al., 1970; MELTZER et al., 1979). On the other hand, it has been life-saving in some patients with severe strongyloidiasis (SCOWDEN et al., 1978; SCHUMAKER et al., 1978; HARRIS et al., 1980). There is an urgent need to develop less toxic and more effective agents for the treatment of strongyloidiasis.

Two other benzimidazoles, mebendazole, and cambendazole, are available in a number of countries. Mebendazole is poorly absorbed and its effectiveness in this condition in which systemic migration of larvae occurs is uncertain (KEYSTONE & MURDOCH, 1979). There has been little experience with cambendazole, but a recent report has claimed no toxicity and a success rate of 100% (RODRIGUES et al., 1977). This study must be interpreted with caution, however, as patients were assessed for only several weeks after infection.

Until other drug regimens have been proved to be effective, the use of thiabendazole is mandatory in patients at risk from systemic strongyloidiasis. Its value in relatively asymptomatic patients with uncomplicated strongyloidiasis is less certain, although such persons deserve the chance of cure.

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References


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