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Zaat J, Mank TH, Assendelft WJJ

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[Intervention Review]

Drugs for treating giardiasis

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ABSTRACT

Background

There can be a high rate of recurrence of disease after initial drug treatment for giardiasis. These drugs also have a range of adverse effects.

Objectives

The objective of this review was to assess the effects of drug treatments for giardiasis.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL, MEDLINE, EMBASE, Current Contents, and reference lists of articles.

Selection criteria

Randomised and quasi-randomised trials of drug therapy for giardiasis compared with placebo or another drug.

Data collection and analysis

Two reviewers independently assessed trial quality and extracted data.

Main results

Thirty-four trials were included. Only one trial was without serious methodological flaws. Compared with placebo, drug treatment was associated with an improved cure rate (odds ratio 11.51, 95% confidence interval 2.29 to 57.98). Metronidazole treatment longer than three days had a better parasitological cure rate than other long treatment courses (odds ratio 2.41, 95% confidence interval 1.31 to 4.44), but there was significant heterogeneity between the trials. Available evidence has not detected a difference in cure between single dose therapy and longer treatment courses (odds ratio 0.33, 95% confidence interval 0.08 to 1.34). Within the single dose regimens, the available evidence did not demonstrate a difference in parasitological cure rate between tinidazole and other short therapies (odds ratio 3.39, 95% confidence interval 0.95 to 12.04), but had a higher clinical cure rate (odds ratio 5.33, 95% 2.66 to 10.67).

Authors' conclusions

A single dose of tinidazole appears to give the highest clinical cure rate for giardiasis with relatively few adverse effects.

PLAIN LANGUAGE SUMMARY

Drugs for treating giardiasis (Review)

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BACKGROUND

Giardiasis is a common parasitic disease with a worldwide distribution (Sullivan 1988; Guerrant 1990; Kaminsky 1991; Flannagan 1992; Mitchell 1993; Thompson 1994b; Mank 1995a). The potential of the parasite *Giardia lamblia* to cause diarrhoea and abdominal pain is without doubt (Rendtdorff 1954; Nash 1987). Whereas some people have only a mild self-limiting illness, others develop a chronic illness lasting for several months. People may be infected and have no symptoms, and it has even been suggested that some children benefit from the carrier state (Ish-Horowicz 1989). Due to the variable presentation of the disease and the common nature of the symptoms the parasitic nature of the complaints often goes undetected.

A definitive diagnosis can be made by examining stool samples or duodenal aspirate. However, detecting the organism through stool tests is not straightforward and many tests lack sensitivity (Gilman 1985; Shepherd 1989). Establishing that a patient has been cured can be difficult, as the number of cysts excreted varies among patients and over time. Some patients constantly excrete relatively large numbers of cysts, while others excrete large numbers of cysts over short periods alternating with long periods with very few cysts (Danciger 1975). Less sensitive laboratory techniques may, therefore, result in patients who still have a parasitic infection being declared cured. The laboratory techniques used varies between countries and laboratories. For example, in the UK and the European mainland most laboratories use direct microscopy (saline, eosine or iodine staining) and different (formol) concentration techniques with unpreserved stools. In the USA, trichrome staining of preserved stools is more commonly used. Sophisticated laboratory techniques (such as haematoxylin-Kinyoun or trichrome staining of preserved stools (Palmer 1991) and enzyme linked immunological assays (Isaac-Renton 1991; Mank 1997) seem to be more sensitive and to reveal more cases of giardiasis in patients with chronic or intermittent diarrhoea (Mank 1995b; Stazzone 1996).

Current reviews and textbooks recommend that if the parasite is found patients should be treated (Davidson 1984; Wolfe 1992; Thompson 1993; Boreham 1994; Freeman 1997), some even advise treating asymptomatic patients (Addiss 1991). Therapy in highly endemic areas is, however, often disappointing as high recurrence rates of up to 90% are seen (Gilman 1985; Gilman 1988; Sullivan 1988). Treatment preference varies among doctors and between countries. Treatments include metronidazole and other nitro-imidazole derivatives, furazolidone, quinacrine, albendazole

and paromomycin. Some treatments are taken as a single dose (such as tinidazole) whilst others, such as metronidazole, are generally prescribed to be taken up to four times a day over a period of two weeks. Treatments have side effects, such as nausea, a metallic taste in the mouth, yellow colouring of the skin (quinacrine), increment of liver enzymes (albendazole) and nausea when taken with alcohol (the disulfiram-like effect of metronidazole).

A reliable summary of the evidence is needed to inform decisions on who to treat and what to treat with. We therefore conducted this systematic review of all randomised clinical trials of treatment for giardiasis.

OBJECTIVES

To estimate the effect of various drug treatments for giardiasis on the presence and severity of symptoms, and on the excretion of *Giardia* cysts or trophozoites in the stool.

The following hypotheses are tested:

1. Treatment shortens the symptomatic illness and the period of excretion of cysts or trophozoites.
2. All antiparasitic therapies are equally effective in reducing symptoms or eliminating evidence of infection in stool or duodenal aspirates.

METHODS

Criteria for considering studies for this review

Types of studies

Any trial which attempted a randomised comparison between drug treatments for giardiasis and placebo, or comparison between different drugs or treatment regimens. Pseudo-randomised trials (alternation of any kind) were also included.

We excluded all reports of open studies, case studies, double publications, congress abstracts and studies with comparisons of treatment but no mention of an attempt to randomise allocation of treatment.

Types of participants

Adults or children with positive parasitological laboratory tests for giardiasis (cysts or trophozoites) in stool samples or duodenal aspirate. Symptomatic and asymptomatic patients are analysed separately.

Types of interventions

Drug therapy aimed at eradication of *Giardia* cysts and/or trophozoites, such as nitro-imidazole derivatives, furazolidine, mebendazole, albendazole, paromomycine and quinacrine.

Types of outcome measures

Clinical measures sought from trials in symptomatic patients were diarrhoea, abdominal pain, flatulence/loose stools or other symptoms at the end of follow-up.

The reported duration of diarrhoea was extracted where possible. Parasitological measures sought from all trials were the presence of cysts/trophozoites in stools or duodenal aspirate at the end of therapy. Results from stool samples taken 15 to 28 days after the start of treatment were preferred above other days.

The reported duration of excretion of cysts/trophozoites was extracted where possible.

The outcome 'clinical cure' was defined as both absence of symptoms and negative stools at the end of follow-up.

Search methods for identification of studies

MEDLINE from 1966 to July 2005 was searched using the following search terms: giardiasis (MeSH) and treatment (MeSH), giardiasis and albendazole, furazolidone, metronidazole, ornidazole, quinacrine, tinidazole, secnidazole, albendazole or paromomycin (textwords).

EMBASE was searched from 1980 to July 2005 using 'giardiasis' as the search term.

Current Contents was searched (term: giardiasis) to cover publications from the end 1997 to March 1998.

Trials were also identified through existing literature reviews (Gilman 1985; Davidson 1984; Wolfe 1992; Thompson 1993; Boreham 1994) and checking the references of the included and excluded trials, patient series and case reports. The Infectious Diseases Group trials register was used to check coverage. Current researchers in the field were also contacted to help ensure all possible trials had been identified. Authors of reports published after

1985 were approached for clarification of methods and data where necessary.

Data collection and analysis

All identified trials were entered in a trial register. The inclusion criteria were then applied to all possible trials separately by two of the reviewers (ThM, WA). When they disagreed, the third reviewer (JZ) was asked for an opinion and, if possible, a consensus reached among the three parties.

All included trials were examined by two investigators and scored on a pre-defined list of methodological aspects (see Cochrane Infectious Diseases Group Editorial Information).

We assessed the quality of the laboratory examinations using a scoring system to summarise the description of the technique, the adequacy of the technique, whether repeat examinations were made and whether inter-observer variation was considered (details in Zaat 1997).

The following pre-specified characteristics of the included trials were extracted and tabulated:

- Methods: randomisation procedure; concealment of allocation; whether patients were blind to treatment; diagnostic procedure used; length of follow-up (if available).
- Participants and setting: whether symptomatic, asymptomatic or a mixture; age; the country; primary care or hospital/out-patient clinic.
- Comparison groups: drugs and dose used, duration of therapy.
- Outcome measures: parasitological cure, symptoms, clinical cure, side effects.
- Notes: community prevalence of giardiasis; other parasitoses to inform about background morbidity.

DATA ANALYSIS

The data to be extracted and comparisons to be made were pre-specified.

The primary analysis focussed on the comparison between any drug therapy and placebo.

Further analyses were conducted comparing:

Standard dose metronidazole versus other longer therapies,

Single dose versus longer therapy with imidazoles

Standard short course (tinidazole) versus other short therapies.

Because of the increasing popularity of albendazole, in this updated version of the review we analyzed the efficacy of albendazole versus metronidazole.

Subgroup analysis of symptomatic and asymptomatic patients was included where applicable.

Odds ratio was used for dichotomous data (using a random effect model where results were heterogeneous). Although in most systematic reviews 'events' are defined as unfavourable outcomes,

such as morbidity or mortality, in this review we have defined events as beneficial outcomes. The reason is that in treating diseases like infectious diarrhoea clinicians think in terms of cure rates and not in terms of therapy failure. Consequently in this review an odds ratio >1 represents a better outcome with the 'experimental' regimen.

Heterogeneity between trials was investigated and explanations were looked for (Thompson 1994b).

As an additional analysis we investigated the dose-response relationship between metronidazole and parasitological cure rate. The total dose per kg during the treatment period was calculated. We made the following assumptions:

- all patients were 100% compliant with their prescribed regimen
- the bioavailability of all drugs used was the same
- where trials did not report patient weight, we recalculated the dose to mg/kg. In children we took assumed body weights from the median of normal distribution curves of weight for age. In adults we assumed a standard weight of 60kg. We did a regression analysis of the total dose in mg/kg and the cure rate.

RESULTS

Description of studies

Forty-nine trials were included in our trial register; 17 trials were excluded because they were not randomised comparisons or their outcome criteria were not clear (see Characteristics of excluded studies) or they were duplicate publications of included trials. Thirty-two published trials were included. Two of these reported two independent trials - two different treatment regimes tested at different times in the same population (Hall 1993, further reported as Hall 1993a and Hall 1993b), or in different populations (Speelman 1995, further reported as Speelman 1985a and Speelman 1985b). So, 34 independent trials were included altogether.

Twenty-nine trials were conducted in developing countries (including both double trials) and five in industrialised countries (one in Spain, two in Finland, one in the USA and one in Israel). Eight trials were conducted between 1970 and 1980, thirteen between 1981 and 1990, and 13 between 1991 and 1994. Sixteen trials included only symptomatic patients or described the results of the symptomatic patients separately.

In six trials the source population is not clear. Seven trials were conducted in open populations (slums, kibbutz), five trials in hospitals and all other trials in out-patient or traveler clinics (see Table of characteristics of included studies).

Twelve different drugs were investigated. In 32 trials a nitro-imidazole derivative was used in one of the treatment groups. Various different dose schedules were used. In the 28 trials where metronidazole was given to one (or more) of the treatment groups, 27

different dose regimens were identified. The total dose varied between 33 and 500mg/kg (recalculated over the total treatment period). Data from 28 studied groups in 26 trials were available for dose-response analysis.

Most studies did not measure symptoms by a clearly stated method. The proportion of study participants who had symptoms varied. For example, diarrhoea at the start of therapy was reported in 8% of participants in the study by Romero-Cabello (1995) compared to all participants in the study by Murphy (1983). Abdominal pain was reported by 30% of the patients in the study by Gazder (1977) and in 95% of the patients in the study by Gupta (1989).

The period of follow-up varied between seven days and four weeks. Loss to follow-up was considerable in some trials (see Table of characteristics of included studies).

Risk of bias in included studies

Internal validity

Only the two trials of Hall (1993) had an adequate concealment and generation of allocation procedure. Five trials were inadequately concealed and used some kind of alternation procedure (Jokipii 1982; Kavousi 1979; Speelman 1985a; Speelman 1985b; Suntornpoch 1981). Seven trials described concealment procedures open to bias such as open random number lists (Gascon 1990; Miyares 1988; Murphy 1983; Nigam 1991; Oren 1991; Dutta 1994) and the other trials did not give a clear description of the concealment and randomisation procedures (see Table of characteristics of included studies). The follow-up period varied between 7 days and 4 weeks. Loss to follow-up was considerable in some trials. In four trials the possibility of bias through loss to follow-up was minimised by hospitalizing patients (Bassily 1970; Gazder 1977; Gupta 1989; Misra 1995a). Only 12 trials had at least one blinded outcome measurement (Al-Waili 1992; Bakshi 1978; Bulut 1996; Cimerman 1988; Gupta 1989; Hall 1993a/b; Jokipii 1982; Kalayci 1995; Leary 1974; Ockhuysen 1989; Palomino 1970; Speelman 1985a/b).

Laboratory parasitological examination

The mean score on our parasitological quality index was 4.8 (range 0-8) out of a maximum possible of 15 indicating a relatively low quality (see table 2). Eleven trials scored 7 or 8 points (Andrews 1995; Bassily 1970; Chacon 1991; Hall 1993a/b; Jokipii 1982; Kavousi 1979; Kyronseppa 1981; Palomino 1970; Romero-Cabello 1995; Speelman 1985a/b; Vinaychandran 1979), mainly due to the relatively great weight of the item 'repeated examinations at the follow up'.

Only Ockhuysen 1989 used permanent stained smears of preserved stool samples. Five trials did not mention their technique at all (Al-Waili 1992; Gascon 1990; Gazder 1977; Leary 1974; Quiros Buelna 1989), in two trials the technique is not clearly stated (Bulut 1996; Kalayci 1995). Inter-observer varia-

tion was not described in any trial. Fourteen trials used repeated examinations at follow-up, e.g. 3 stool specimens at day 19, 20 and 21 to increase the sensitivity of the examinations (Andrews 1995; Bassily 1970; Bulut 1996; Chacon 1991; Garg 1972; Hall 1993a/b; Jokipii 1982; Kalayci 1995; Kavousi 1979; Kyronseppa 1981; Palomino 1970; Quiros Buelna 1989; Speelman 1985a/b; Vinaychandran 1979).

Data were difficult to extract from some trials. The side effects were sometimes presented as numbers of patients, but in reality were numbers of events. When symptoms were described, only information per single symptom (diarrhoea, pain) was given and the number of patients with more than one symptom was always missing. Mean duration of symptoms was seldom described. The two trials of Hall have raised some special issues: they described the effect of different doses of albendazole and metronidazole, but the researchers made a distinction between first infections and reinfections in the same patients. We decided to include only the results for the first infections in our comparisons.

Effects of interventions

ANY DRUG THERAPY VERSUS PLACEBO

Parasitological cure

Four trials compared therapy with a placebo (Bassily 1970; Leary 1974; Palomino 1970; Ockhuysen 1989). The first three used only parasitological cure as the outcome. In the three studies 297 patients were actively treated and 85 patients received a placebo. There seems to be a considerable effect in cure rate in favour of therapy (OR 11.51, 95% CI 2.29 to 57.98, random effects model), but there was significant heterogeneity among the trials ($p < 0.01$). All the studies were seriously flawed: Leary (1974) did not mention his parasitological technique, used a low dose of metronidazole (1 gram single dose and 1 gram on two consecutive days versus placebo) and the follow-up periods differed between the treatment groups. Palomino (1970) used broxiquiline/brobenzoxaldine as one of his therapeutic regimens. The cure rate in this subgroup was comparable to the placebo group, reducing the effect in the therapeutic group as a whole. The description of the allocation procedure in the study of Bassily (1970) is unclear: "Patients were allotted at random to three different treatment regimens, a fourth group was given no treatment and used as control." So, serious bias in the allocation of patients to the control group is not excluded in this study. In addition, the lack of spontaneous remission in any of the 20 patients in the control group is unexpected given the natural history of giardiasis and, therefore, results from this study need to be interpreted with caution.

Duration of symptoms

Ockhuysen (1989) conducted the only study in which the duration of diarrhoea was an outcome measure. A dichotomous outcome measure was not available for whether a patient was cured or not. In Ockhuysen's study, the mean duration of diarrhoea in the treatment group was 39 hours versus 66 in the placebo group.

However, the sample size is small (only six children with giardiasis in the furazolidone group and 17 in the placebo group). According to the authors the treatment difference is not significant but they did not report standard deviations and cannot provide them now since the data are no longer available (DuPont, personal communication).

METRONIDAZOLE (3 days or longer) versus LONGER OTHER THERAPIES

Parasitological cure

The effects of a long course of metronidazole have been studied in many trials. Ten trials used a negative stool specimen as a measure of cure in symptomatic patients (Al-Waili 1992; Bassily 1970; Chacon 1991; Garg 1972; Guerreiro 1991; Kalayci 1995; Kavousi 1979; Misra 1995a; Quiros Buelna 1989; Vinaychandran 1979). Eight trials used this outcome measure in a mixed patient group (symptomatic and asymptomatic patients together) (Bulut 1996; Dutta 1994; Gascon 1990; Hall 1993a; Leite 1976; Palomino 1970; Romero-Cabello 1995).

In patients with symptoms, there was no difference shown in treatment effect between metronidazole and other longer treatment courses. In all patients (symptomatic and asymptomatic patients together) metronidazole had a higher cure rate but the trial results are heterogeneous. The overall odds ratio (2.41, 95% CI 1.31 to 4.44) probably over estimates the real effect. Because the comparison treatment in various trials did not contain established, regular treatment at optimal dosage, the overall effect (a higher cure rate with metronidazole) is strongly influenced by the study of Hall, who conducted the only methodologically good quality trial, but compared metronidazole with albendazole. (see also the separate analysis for albendazole). The problem with Palomino's study (Palomino 1970) has already been mentioned (the diluting effect of therapy by broxiquiline). Gascon (1990) used an anthelmintic drug (mebendazole) in a relatively low dose that might explain why metronidazole appears more effective. Kalayci (1995) also used mebendazole, but in a longer course than Gascon. In Kalayci's study mebendazole was inferior compared with metronidazole and furazolidone (cure rate 11, 12, 14 out of 15 each respectively). When we exclude the trials of Palomino and Gascon the overall odds ratio for the remaining trials is 1.75 (95% CI 1.02 to 2.99). In this analysis heterogeneity between trials is no longer significant (chi-square 14.1, $df = 14$, $p = 0.4$).

Clinical cure

One trial (Garg 1972) used clinical cure as an outcome measure, defined as relief of symptoms and negative stools. There was no difference between metronidazole and furazolidone in this study (OR 0.97, 95% CI 0.13 to 7.19). In a rather confusing analysis Romero-Cabello (1995) gives data on the disappearance of symptoms but he gives no overall clinical outcome. Abdominal pain, for example, gradually disappears in both groups (albendazole and metronidazole) at the same rate, from approximately 22 res. 20 to 3 and 4 at day 7.

Duration of symptoms

Dutta (1994) reported the duration of complaints: at day 3, 48% of the 48 patients with diarrhoea treated with albendazole were cured versus 36% of the 56 patients with diarrhoea treated with metronidazole. At day seven, one patient in the albendazole group and two patients in the metronidazole group still had diarrhoea. He also mentioned other complaints, such as abdominal pain: this was relieved in 49% of the 58 patients treated with albendazole versus 55% of the 57 patients treated with metronidazole at day three, and 95% and 96% respectively at day seven.

Duration of excretion of cysts

Misra (1995a) mentioned the duration of excretion of cysts which was 3.7 days (standard deviation 1.4) for albendazole versus 4.5 days (SD 1.1) for metronidazole (WMD 0.80, 95% CI 0.15 to 1.45). Although just statistically significant the difference is not very relevant clinically (the investigators describe the results as insignificant).

Side effects

Side effects of metronidazole were reported in seven trials (Al-Waili 1992; Bassily 1970; Chacon 1991; Dutta 1994; Hall 1993a; Kalayci 1995; Kavousi 1979). Heterogeneity between trials is statistically and clinically significant. Metronidazole seems to have more side effects compared with quinacrine, furazolidone, mebendazole or albendazole (OR 1.47, 95% CI 0.51 to 4.20). However, the main side effect of albendazole was excretion of worms and that, in our opinion, is a favourable effect. The side effects of metronidazole are mild: nausea, anorexia and headache. Dutta (1994) found two children in the albendazole group with transient neutropenia, but did not mention duration or severity. Romero-Cabella (1995) did not find any difference in laboratory outcome (haematology and clinical chemistry) between metronidazole and albendazole.

SINGLE DOSE THERAPY VERSUS LONGER THERAPIES WITH IMIDAZOLES

Parasitological cure

Three trials examined the effects of single dose therapy versus longer courses of the same or different drugs on parasitological cure in symptomatic patients: Cimerman 1988 (secnidazole versus metronidazole), Chacon 1991 (secnidazole versus metronidazole), Gupta 1989 (tinidazole single versus tinidazole). Six trials did the same in symptomatic and asymptomatic people: Bulut 1996 (ornidazole single versus metronidazole), Hall 1993a/b (albendazole single versus metronidazole), Oren 1991 (ornidazole versus metronidazole), Speelman 1985b (tinidazole versus metronidazole), Suntornpoch 1981 (ornidazole and secnidazole versus metronidazole).

At first glance, single dose therapy seems to be less effective in the total group (OR 0.33, 95% CI 0.08 to 1.34) but there is statistically and clinically significant heterogeneity between these trials. The total odds ratio is influenced mainly by both large trials by Hall who used an unconventional therapy - albendazole in low doses - as single therapy. The other trials used tinidazole, secnidazole or ornidazole. Insufficient doses cannot explain the difference

between these trials. Excluding Hall, the total odds ratio is 0.60 (95% CI 0.17 to 2.15) and there is no statistically significant heterogeneity detected ($p=0.21$). Thus, there is no evidence of a difference in cure rate between short treatment courses and longer courses in either symptomatic or asymptomatic patients.

Clinical cure

Oren, Suntornpoch and Cimerman used clinical cure as an outcome measure in symptomatic patients. In Oren's study all symptomatic patients were cured in both groups. These studies revealed no difference in clinical cure between single dose and longer therapy (total OR 0.99, 95%CI 0.92 to 1.07).

Duration of symptoms

Oren stated that the mean duration of symptoms after therapy was comparable between the single dose group and the longer metronidazole therapy group (4.6 days versus 5.0 days). However, a standard deviation is not given. No other trial gives information about the duration of symptoms after therapy.

Side effects

Bulut 1996; Hall 1993a/b; Cimerman 1988; Chacon 1991 and Oren 1991 reported on side effects. There was no clinical difference in side effects between single dose therapies and longer courses (except for Hall's study, see above). Bulut mentioned 3 cases out of 10 in the ornidazole group with side effects.

STANDARD SINGLE DOSE (tinidazole) versus OTHER SINGLE DOSE THERAPY

Parasitological cure

Seven trials compared the standard tinidazole regimen (either 1.5g or 2g as a single dose) with other single dose therapies: Bakshi 1978; Jokipii 1982; Gazder 1977; Kyronseppa 1981, in symptomatic patients; Suntornpoch 1981; Speelman 1985a; Nigam 1991, in symptomatic and asymptomatic patients). Tinidazole was no more effective than other single dose therapies, considering parasitological cure (OR 3.39, 95% CI 0.95 to 12.04). However, heterogeneity between the trials is significant ($p=0.01$).

Clinical cure

Five trials (Bakshi 1978; Gazder 1977; Kyronseppa 1981; Nigam 1991; Suntornpoch 1981) used clinical cure (relief of symptoms and negative stools) as the outcome parameter. Tinidazole was more effective (OR 5.33, 95% CI 2.66 to 10.67). There was no significant heterogeneity among the trial results ($p=0.15$). Not surprisingly, standardisation of dose schedules in these trials seems to have resulted in more homogeneous overall results than in the other comparisons.

Duration of symptoms

The trial by Gazder 1977 is the only one giving information about diarrhoea at the end of the follow-up (day 16): 7/38 cases in the tinidazole group still had diarrhoea versus 21/37 patients in the metronidazole group. The odds ratio for absence of diarrhoea was 5.81 (95% CI 2.04 to 16.56).

Side effects

Four trials reported side effects (Kyronseppa 1981; Nigam 1991;

Bakshi 1978; Suntornpoch 1981). There was no difference in occurrence of side effects between tinidazole and other short courses (OR 1.12, 95%CI 0.33 to 3.78).

ALBENDAZOLE VERSUS METRONIDAZOLE

Parasitological cure

Although theoretically promising (Thompson 1993), albendazole is not yet generally used in the treatment of giardiasis. Since the first edition of this review several trials with albendazole have been found. A separate section on this drug is therefore justified.

Five studies described the effects of albendazole. Dutta 1994 and Hall 1993a used single dose treatment. We compared the four studies in which albendazole was used for 3 or more days: Hall 1993a (albendazole 400mg 3 days versus metronidazole), Hall 1993b (albendazole 400mg 5 days versus metronidazole), Misra 1995a and Romero-Cabello 1995 (albendazole 400mg 5 days versus metronidazole).

In Hall 1993a low dose albendazole (400mg per day for 3 days) was shown to be inferior to 5-days metronidazole. In Hall 1993b, 5 days albendazole (400mg per day) showed a comparable cure rate to metronidazole for 5 days (combining all infections, both first and reinfections). Hall obtained a higher cure rate with metronidazole in first infections. In our analysis we included only the first infections and albendazole is less effective than metronidazole overall (OR 0.19, 95% CI 0.08 to 0.48). All effects are in the same direction and heterogeneity between the trials is not significant.

OTHER STUDIES

Three trials did not fit into our pre-specified comparisons.

Murphy (Murphy 1983) investigated two different treatment courses of furazolidone. Eleven of the twelve children treated for 10 days were cured (negative stools and absence of symptoms) versus 2/10 children treated for 5 days (OR 16.9, 95%CI 3.2 to 89.8 in favour of 10 days treatment).

Miyares (Miyares 1988) investigated the effect of propolis in different concentrations compared with a 5-day course of tinidazole in 90 patients. Propolis is a bee glue preparation with possible bactericidal and fungicidal properties. We excluded the 24 asymptomatic patients in our calculations. Thirteen of 39 symptomatic patients treated with tinidazole had a parasitological cure one week after treatment, as did 16/27 symptomatic patients treated with propolis (OR 2.82, 95% CI 1.06 to 7.52 in favour of propolis).

Andrews (Andrews 1995) investigated the efficacy of three different formulas of oral bacitracin (bacitracin, bacitracin zinc and bacitracin with neomycin) compared with neomycin only. No standard therapy was used. At the end of follow-up (day 25), 18/21 patients treated with bacitracin zinc were cured, 14/21 treated with bacitracin, 14/21 treated with bacitracin plus neomycin and 19/22 treated with neomycin only. Except for the neomycin group there was a considerable loss to follow-up (up to 25%).

DISCUSSION

Strength of the evidence

Giardiasis is a common infection and it is rather surprising that there is such a lack of clarity about the indications for treatment and guidelines for optimal treatment. Our review is the first to include such a large number of trials of treatment of Giardia infection. Giardiasis has a worldwide distribution and research on therapy has this distribution too. Our review included a broad spectrum of languages, excluding possible 'tower of babel bias' (Grégoire 1995). The search strategy was extensive with broad search categories and hand-searched journals.

Whilst this review reveals a large number of trials the conduct and reporting quality of most of them is poor. Randomisation procedures and concealment of allocation especially are often not reported or are open to serious bias. The adequacy of concealment of allocation and generation of the randomisation sequence has been shown empirically to influence the results from randomised trials. The poor quality of allocation concealment and randomisation in this field is worrying. Authors and journal editors need to be aware of the relevance of adequate reporting of these methodological issues. Despite the poor quality we decided to pool the trial results but we warn clinicians to consider our pooled odds ratios with caution.

The differences in dose schedules, follow-up duration and laboratory techniques used were a serious problem in analysing the results. The heterogeneity between trials is significant in most comparisons, but we have tried to explain the differences between the trials and their influence on the results. Having so many trials of poor quality, we could not investigate the influence of trial reporting on trial results.

Applicability

Nevertheless, there is little argument against drug therapy for people who are seriously ill with diarrhoea or weight loss in whom giardiasis is found in the stool. This review shows that both metronidazole and tinidazole are effective at eliminating evidence of infection in the stool. Metronidazole is equally effective in parasitological cure as other longer therapies such as furazolidone. Short courses of any drug seem to be less effective than longer courses, but the clinical and statistical heterogeneity between trials is quite large. Tinidazole seems to be the most effective single dose therapy compared to other short therapies in terms of parasitological cure. So far the efficacy of albendazole has not been confirmed. Side effects of all therapies seem to be comparable.

The effectiveness of treatment in people with milder forms of the illness has not been well studied. Only a few trials have measured

clinical outcomes, and the rest have simply measured stool parasites. This could be a problem as the clinical symptoms of infection are probably less uniform than textbooks suggest. As far as we know, only one case-control study has compared people with giardiasis in their stool with a comparable control group (Hopkins 1991). We have on-going our own investigation in to the epidemiology and clinical course of infections with intestinal parasites in general practice. On the basis of classical complaints (such as loose and foul smelling stools or abdominal cramps) we could not discriminate between parasitological, bacteriological, viral or no infective cause, in patients with diarrhoea for longer than 7 days (n=892; Mank et al, unpublished preliminary results). More sensitive tests will reveal more patients with mild forms of giardiasis, and that will mean doctors facing more questions about effective treatment.

Secondary analyses of the effect of quality of diagnostic tests on outcome measures will be included in the next version of this review.

AUTHORS' CONCLUSIONS

Implications for practice

Doctors can assure patients with *Giardia* parasites in their stools that drugs will reduce infection. Evidence that treatment will also improve symptoms is indirect, and depends on the fact that *Giardia lamblia* frequently produces symptoms. So drug therapy shown to reduce stool infection is assumed to also reduce symptoms.

Trials so far give no indication of how to manage mild or asymptomatic infections. Single dose therapy improves the compliance of the patient, therefore, we favour single dose therapy if the treatments are otherwise equivalent. Tinidazole appears to be the most suitable therapy for symptomatic disease when therapy is necessary, until a new trial demonstrates otherwise. Until now the results of albendazole treatment are disappointing.

Implications for research

There is a need for further work on correlating symptoms with parasite detection tests, and the sensitivity and specificity of newer tests must be compared with existing diagnostic methods. As the

entry criteria and diagnostic methods vary among studies in this review, and because infection can be asymptomatic, good trials are needed to approach this problem in a variety of ways relevant to the country and population.

Studies in low prevalence areas such as Western Europe could examine if giardiasis is more prevalent in cases of chronic diarrhoea than previously thought. Then a protocol for the management of diarrhoea of seven days or longer might be established and tested. Thus a general practitioner with a standard protocol that includes routine testing of the stool for *Giardia* in all patients with a history of at least seven days of diarrhoea, might randomise *Giardia*-positive patients to tinidazole or placebo. Such a study should use at least two parasitological techniques for identifying infection (microscopic examination and immunochemical techniques) to check for real parasitological cure. DNA fingerprinting could be used to classify different *Giardia* strains (Archibald 1991; Upcroft 1990; van Keulen 1995). The follow-up time should be at least 3 weeks. Subgroup analysis on the basis of severity of the complaints will be necessary to answer the question of whether all patients should be treated or only the more serious cases.

In areas of high endemicity, routine presumptive treatment with a single dose (compared with placebo) of any person with diarrhoea could be considered. Albendazole, being also an antihelmintic, is one of the promising drugs. Good quality trials on a large scale are necessary to answer the question of the efficacy of this drug. The results of the four trials so far are not convincing.

Whatever the circumstances, it is clear that these studies need to develop valid measures that assess clinical outcomes, including malaise, abdominal pain and diarrhoea. We are currently conducting such a trial in general practice.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Al-Waili 1992

Methods	Allocated randomly; exact procedure not stated; blinded outcome measurement (stool specimen) parasitological technique not described; blinding patients not described.	
Participants	44 symptomatic children (3-13 years) exact population not described (probable Iraqis).	
Interventions	Mebendazole 200mg/ 3 times daily/ 5 days; metronidazole 200mg /3 times daily/5 days; dose not adjusted to age.	
Outcomes	Parasitological cure on day 7 and 14; side effects.	
Notes	No information on co-morbidity.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Andrews 1995

Methods	Randomisation in family groups, exact procedure not stated; blind examination of stool specimen; formol ether concentration.
Participants	Patients of clinic in Bucharest (Romania), subjects of annual health examinations and cohabitants of Giardia positive members of these two populations. Total 82 subjects with 83 treatments. No information about symptoms.
Interventions	Bacitracin (240.000U) / two times daily/10 days; bacitracin zinc (240.000U)/two times daily/10 days; bacitracin zinc and neomycine (both 120.000U) /two times daily/10 days; neomycine (240.000U)/two times daily/10 days.
Outcomes	Parasitological cure at day 11 and 25 (three negative stool specimens)
Notes	No intention to treat analysis, loss to follow up at day 25 in 2 groups, 25%; no information on co-morbidity.
Risk of bias	

Andrews 1995 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Bakshi 1978

Methods	Randomised; no exact procedure stated; blind stool examination; blinding patients not clear but probable; formol ether concentration technique. Follow up every 4 days until day 16.
Participants	186 children with abdominal symptoms and Giardia cysts in their stools; multicentre trial in Western India.
Interventions	Tinidazole 50mg/kg/single dose; metronidazole 50mg/kg/single dose.
Outcomes	Success (parasitological cure and relief of symptoms); clinical failure (parasitological cure but no relief of symptoms); parasitic failure (persistence of cysts in stool)
Notes	Part of study on E. histolytica; no information on co-morbidity.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Bassily 1970

Methods	Allocated at random; exact procedure not stated; blinding stool examination and blinding patients not described; MIFC-concentration technique.
Participants	52 farmers in villages near Cairo and 28 hospital employees and relatives with recurrent diarrhoea (3-52 years of age)
Interventions	Mepacrine 100mg /3 times day /5 days (children got half dose); metronidazole 250mg/ twice daily /10 days (children got half dose); furazolidone 100mg/4 times daily 7 days (children and adults same) placebo capsules 3 times daily 7 days.
Outcomes	Parasitological cure (all specimens negative during 5 weeks, specimens twice weekly); side effects.

Bassily 1970 (Continued)

Notes	All patients hospitalised during five weeks; high incidence of other protozal infections.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Bulut 1996

Methods	Open randomised design; randomisation and allocation procedure not clearly stated; only fresh stool examination by blinded technician.	
Participants	60 children after screening program in Turkey (mean age 8.7y), 40 patients with symptoms	
Interventions	mebendazole 100mg trice daily (one day) mebendazole 100mg trice daily (7 days) metronidazole 15mg/kg once daily (7 days) ornidazole 40mg/kg single dose (one day)	
Outcomes	parasitological cure (3 negative stool specimens 2 weeks after completion of treatment) side effects	
Notes	No intention to treat; loss to follow up 20% no separate description of results of asymptomatic and symptomatic children	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Chacon 1991

Methods	Randomised; exact procedure not stated; blinding stool examination and blinding patients not described; concentration technique (Faust).	
Participants	57 symptomatic children (1-16 years) outpatient clinic Mexico City (Mexico)	
Interventions	Furazolidone 7mg/kg/day/ 7 days; metronidazole 20/mg/kg day/ 5 days; secnidazole 30 mg/kg/ single dose.	

Chacon 1991 (Continued)

Outcomes	Parasitological cure week after end treatment; side effects.	
Notes	No information on symptoms and co-morbidity.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Cimerman 1988

Chen et al. 1988

Methods	Randomised; exact procedure not stated; blinding stool examination and blinding patients not described; concentration technique (Faust).	
Participants	112 symptomatic patients (16-79y); Brasilia; low mean symptom score on 4 point Likert scale at baseline (0.03-0.66)	
Interventions	Secnidazole 2g/ single dose; metronidazole 250mg/ twice daily /5 days.	
Outcomes	Parasitological cure (negative stools on day 14 and 21 after end of treatment); symptom score (nausea, diarrhoea etc.) on a Likert scale; side effects.	
Notes	Treatment of other parasites after end of study.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Dutta 1994

Methods	Randomisation with open number lists; blind evaluation of outcome (stools); method of stool examination not clearly stated, only fresh stools	
Participants	150 children (2-10 years) hospitalised in 3 hospitals in India; probably all symptomatic	
Interventions	Albendazole 400mg /single dose / 5 days; metronidazole 7.5mg/kg/day/3 times daily/ 5 days.	

Dutta 1994 (Continued)

Outcomes	Parasitological cure day 14 and 21; symptoms (day 7,14,21); side effects.	
Notes	Children with other parasitoses and malnutrition were excluded	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Garg 1972

Methods	Randomly allocated, exact procedure not stated; blinding of stool examination and blinding patients not described; only fresh stools.	
Participants	81 patients (age 8 months - 9 years); outpatient clinic in Meerut (India); symptoms not described; mixed infection excluded	
Interventions	Metronidazole 20mg/kg/day/ 3 doses daily/ 7 days; furazolidone 6mg /kg/day/ 3 doses daily /7 days.	
Outcomes	Parasitological cure; symptoms.	
Notes	Success, parasitic failure and total failure exactly stated; exact numbers in study groups not mentioned (probably 41 in metronidazole and 40 in furazolidone group)	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Gascon 1990

Methods	Random number list; exact procedure not stated; blinding of stool examination and blinding patients not described; parasitological technique not described.	
Participants	Population not defined, probably out-patient clinic for tropical diseases in Spain; 19 patients (age 28 +- 12); symptoms not described.	

Gascon 1990 (Continued)

Interventions	Mebendazole 200mg/ 3 times daily/ 5 days; metronidazole 250mg/ 3 times daily/ 7 days.	
Outcomes	Parasitological cure (days 3, 7, 30).	
Notes	Parasitological examination not described; no information on co-morbidity.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Gazder 1977

Methods	Random order; exact procedure not stated; blinding of stool examination not described; blinding patient not described exactly but probably acceptable; parasitological technique not described. Follow up day 4, 8, 12, 16.	
Participants	100 children (mean age 5.5y) with symptoms and positive stools (outpatient clinic Calcutta, India)	
Interventions	Metronidazole 50mg/kg (single dose); tinidazole 50mg/kg (single dose).	
Outcomes	Cure: negative stools and relief of symptoms probable failure: negative stools but persistent complaints failure: positive stools and persistent symptoms duration of diarrhoea; side effects.	
Notes	One of the few studies with information on time until end of excretion of Giardia and end of symptoms; relatively few other parasitoses.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Guerreiro 1991

Methods	Randomised, but allocation procedure not clear; blinding examinations and patient not stated; direct smears, Kato and duodenal aspirate. Follow up time not stated.	
Participants	70 symptomatic children, outpatient clinic in Venezuela.	
Interventions	Metronidazole 15mg/kg, divided in 3 doses/ 10 days; metronidazole 30mg/kg, divided in 3 doses/ 10 days; metronidazole 50mg/kg, divided in 3 doses/ 10 days.	
Outcomes	Parasitological cure	
Notes	21.5% of children were malnourished.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Gupta 1989

Methods	Randomised, exact procedure not stated; stool examination blinded; blinding patients not described; formol-ether concentration.	
Participants	20 symptomatic adults (18-32y) with Giardia cysts in stools (Bombay, India)	
Interventions	Tinidazole 2g /single dose/tablets; tinidazole 150mg/ twice daily/7 days/tablets.	
Outcomes	One month after treatment: d-xylose absorption; faecal fat excretion; gut transit time; parasitological cure.	
Notes	No information on co-morbidity.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hall 1993a

Methods	Random allocation (computer program, sealed envelopes opened in the field); blind stool examination, but patients not blinded; fresh stools and formol ether concentration method.	
Participants	Children (5-10 y); urban slum Bangladesh; screening of 768 children; 678 Giardia cases (some more than once)	
Interventions	Phase 1 albendazole 600mg/ single dose; albendazole 400mg/single dose/ 3 days; metronidazole 125mg/ 3 times daily/ 5 days.	
Outcomes	Parasitological cure (3 samples over 10 days); side effects; reinfection rate; distinction was made between first infections and 'all' infections (probably not according to a predetermined plan)	
Notes	No information on symptoms (asymptomatic carriers also treated); high incidence of worms and Giardia	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Hall 1993b

Methods	Random allocation (computer program, sealed envelopes opened in the field); blind stool examination, but patients not blinded; fresh stools and formol ether concentration method.	
Participants	Children (5-10 y); urban slum Bangladesh; screening of 768 children; 678 Giardia cases (some more than once)	
Interventions	Phase 2 albendazole 800mg/ single dose; albendazole 400mg/ single dose/ 5 days; metronidazole 125mg/ 3 times daily/ 5 days.	
Outcomes	Parasitological cure (3 samples over 10 days); side effects; reinfection rate; distinction was made between first infections and 'all' infections (probably not according to a predetermined plan)	
Notes	No information on symptoms (asymptomatic carriers also treated); high incidence of worms and Giardia	

Hall 1993b (Continued)

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Jokipii 1982

Methods	Alternation; groups were compared afterwards; blind examination of stools; blinding patients not stated, but probable; fresh stools, formol ether concentration and duodenal aspirate	
Participants	105 symptomatic students in Helsinki (Finland); mostly travellers from Leningrad/St Petersburg; mean age 25	
Interventions	Ornidazole 1.5g/ single dose; tinidazole 1.5g/ single dose.	
Outcomes	Duration of symptoms; parasitological cure (negative stools during follow up); duration of excretion of cysts; side effects; follow up after 1, 2, 4 and 8 weeks (3 specimens in each period)	
Notes	One of the few studies with information on the duration of symptoms	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Kalayci 1995

Methods	randomised; exact procedure not stated; blinding of stool examination parasitological examination not clear, three samples at follow-up. Follow-up 7-10 days after treatment	
Participants	45 symptomatic children (34 months-16y), out-patient clinic university hospital Turkey; long lasting symptoms (45-120 days)	
Interventions	Mebendazole 200mg/trice metronidazole 5mg/trice furazolidone 2mg/kg 4 times daily all 10 days.	

Kalayci 1995 (Continued)

Outcomes	parasitological cure; side effects.	
Notes	no information on co-morbidity	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kavousi 1979

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Methods	Consecutive numbers (odd, metronidazole; even, quinacrine); blinding stool examination not described (always same technician); blinding of patients not described; zinc flotation concentration technique. Follow up 5 days, 1 month, 6 months.	
Participants	160 symptomatic children (pediatric outpatient clinic, Iran)	
Interventions	Quinacrine/ 8mg/kg /3 doses/ 5 days; metronidazole/125-250mg/ 1-3 times daily (depending on age)/5 days	
Outcomes	Parasitological cure (follow up 5 days, 1 month, 6 months); most patients 3 stool specimens each period; side effects.	
Notes	Large loss to follow up at 1 month and 6 months (>50%).	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kyronseppa 1981

Methods	Random order; exact procedure not stated; blinding of stool examination and blinding patients not described; formol ether concentration.	
Participants	50 symptomatic patients with positive stools for Giardia (outpatient clinic (?) Helsinki, Finland)	
Interventions	Metronidazole/ 2g /single dose/2 days; tinidazole/ 2g/ single dose.	

Kyronseppa 1981 (Continued)

Outcomes	Follow up at week 2 and 4 (2 stools specimens each). Cure: disappearance of symptoms.	
Notes	Co-morbidity excluded.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Leary 1974

Methods	Randomisation not described (allotted at random); blinded stool examination; fresh stool specimen (single specimen including at follow up); exact techniques not described	
Participants	76 symptomatic children (diarrhoea) outpatient clinic in South Africa; mean age 3.4 year	
Interventions	Metronidazole/ 1g/single dose, 25 ml/suspension; metronidazole /1g/ single dose, 25ml/ 2 consecutive days/suspension; placebo / 25ml/days?/same suspension as other groups).	
Outcomes	Parasitological cure follow up was different: single dose and placebo day 5 and 17; two day course day, 14 and 29	
Notes	25 percent of children were malnourished, comparable in the groups	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Leite 1976

Methods	Randomisation procedure not stated; blinding not described; formol ether concentration.	
Participants	30 patients; clinic in Rio de Janeiro attending because of other illnesses (e.g. bronchopneumonia, pyelonephritis) age 1-63y	
Interventions	Metronidazole 250mg /single dose /10 days; ornidazole 250mg/ single dose /10 days; (children adapted doses).	

Leite 1976 (Continued)

Outcomes	Parasitological cure during 3 examinations (7, 14, 21 days); symptoms.	
Notes	High prevalence of helminths (40-60%); high percentage of co-medication (43%).	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Misra 1995a

Methods	Open randomised design; no description of allocation and randomization procedure; no blinding of outcome; fresh stool examinations and formol-ether concentration.	
Participants	64 hospitalized children (2-12y) India. Symptoms unclear (chronic diarrhea, febrile conditions, severe malnutrition excluded), but most had abdominal symptoms or anorexia	
Interventions	metronidazole 7.5mg thrice daily (5 days) albendazole 400mg once daily (5 days).	
Outcomes	parasitological cure (daily till day 7, afterwards day 14 and 21) symptoms (daily till day 7, afterwards day 14 and 21) adverse effects 'as experienced by parents'	
Notes	loss follow up : 4 albendazole, 3 metronidazole before day 7, complete follow up in 18 (albendazole) and 16 metronidazole (day 21). All children had negative stools on day 7, but one out of 16 in metronidazole and 2 out of 18 in albendazole had positive stools at day 21	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Miyares 1988

Methods	Random number list, exact procedure not stated; blinding patients and stool examination not described; exact parasitological technique not described (duodenal aspirate)	
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Miyares 1988 (Continued)

Participants	48 children (10 months-15y) and 90 adults (20-60y), Cuba; in only 90 patients parasitological outcome was measured, of which 66 had symptoms	
Interventions	Propolisina (bee glue) / two different concentrations/ 5 days; tinidazole /1.5g/ single dose/ 5 days.	
Outcomes	Parasitological cure and symptoms, one week after end treatment	
Notes	No information on co-morbidity.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Murphy 1983

Methods	Table of random numbers; exact procedure not stated; blinding stool examination and patient not stated; fresh stools, formaldehyde solution acetate concentration, (iodine stained), selected patients duodenal aspirate (unknown selection)	
Participants	22 symptomatic patients (mean age 14 months), outpatient clinic, Dallas, USA	
Interventions	Furazolidone 8mg/kg /3 doses daily/ 5 days; furazolidone 8mg/kg/ 3 doses daily/ 10 days.	
Outcomes	Cure: negative stools (1, 2, 4 weeks).	
Notes	Dose effect study; follow up time in both groups not comparable	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Nigam 1991

Methods	Randomisation chart; exact procedure not stated; blinding stool examination and patients not described; formol ether concentration.	
Participants	75 patients (mean age 20.2y) of hospital in Gorakhpur, India; 38% were asymptomatic, 39% had intermittent diarrhoea, 91% had chronic and 8% acute diarrhoea	

Nigam 1991 (Continued)

Interventions	Metronidazole/ 50mg/kg/ single dose; tinidazole/ 50 mg/kg/ single dose.	
Outcomes	Parasitological cure at day 4, 8, 12 ; cure rate (negative stools and symptoms at day 12).	
Notes	41% of patients had chronic protein malnutrition.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Ockhuysen 1989

Methods	Double blind randomisation, exact procedure not stated; fixed stools, trichrome staining.	
Participants	191 children with acute diarrhoea in rural Mexico; only 23 had Giardiasis	
Interventions	Furazolidone 7.5mg/kg day plus ORS versus placebo and ORS.	
Outcomes	Duration of diarrhoea (hours).	
Notes	Giardiasis not equally divided in both groups (6 in furazolidine group, 17 in placebo); co-morbidity exactly described.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Oren 1991

Methods	Open randomised schedule; exact procedure not stated; blinding stool examination and patients not described; Faust concentration technique.	
Participants	75 kibbutzim children in Israel (mean age 2.5y); 65 symptomatic and 10 asymptomatic	
Interventions	Ornidazole 40mg/kg/ single dose; metronidazole 20mg/kg in 3 doses/ 7 days.	

Oren 1991 (Continued)

Outcomes	Mean duration clinical recovery; parasitological cure at day 21; symptoms at day 21.	
Notes	No information on co-morbidity; longer duration of symptoms and more weight loss in ornidazole group at baseline	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Palomino 1970

Methods	Double blind; exact procedure not stated; stool examination blinded; patient blinded (but different therapy schedules); Zinc flotation in PVA fixed stools. Follow up 11, 13, 15 days.	
Participants	187 patients (mostly children); Santiago, Chile; more treatments than patients (226 treatments) 26% asymptomatic patients.	
Interventions	Acranil <10 years:10mg/kg suspension; >10 years: 300mg tablets /5 days. Metronidazole <10 years: 20mg/kg tablets; >10 years 750mg tablets/ 5 days. Furazolidine <10 years: 10mg/kg suspension; >10 years: 400mg tablets/5 days. Paromomycine <10 years: <50mg/kg suspension; >10 years: 1500mg/capsules/ 5 days. Broxoquilone and brobenzoxaldine (Intestopan) in standard doses /tablets/5days. Placebo <10 year: suspension ; >10 years:1 placebo tablet/5 days. Daily dose was in all groups divided in small doses and given 3-4 times daily	
Outcomes	Parasitological cure (all specimens negative); side effects.	
Notes	Unclear whether second treatment different from treatment first occasion	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Quiros Buelna 1989

Methods	Randomly assigned (exact procedure not stated); single blind; parasitological technique not described.	
Participants	100 symptomatic children (age 2-15 y) in Mexico; other infections excluded.	
Interventions	Furazolidone 20- 80mg/kg/day /4 times daily /10 days; Metronidazole 7.5-30mg/kg/day/ 3 times daily /10 days.	
Outcomes	Parasitological cure (negative stools at 3 consecutive days after treatment)	
Notes	18% loss to follow-up; no intention to treat analysis.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Romero-Cabello 1995

Methods	Open randomised design; no clear description of randomization and allocation procedure; fresh stool examination and zinc (?) flotation; no description of blinding.	
Participants	100 children (4-11y) positive on screening in Mexico (42% had abdominal pain, 39% loss of appetite, only 8% diarrhea)	
Interventions	metronidazole 7.5mg trice daily/ 5 days albendazole 400mg once daily/5 days.	
Outcomes	parasitological cure daily from day 1 till 7 , afterwards day 14 and 21; symptoms daily from day 1 till 7 , afterwards day 14 and 21; side effects	
Notes	no separate results of symptomatic and asymptomatic patients	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Speelman 1985a

Methods	Randomisation by drawing therapy-chart from envelope; blinded examination of stool examination; blinding patients not described; formol ether concentration. Follow up twice weekly for 4 weeks.	
Participants	Part 1: expatriate residents in Bangladesh in a regular survey; inclusion positive for Giardia in stool specimens (symptomatic and asymptomatic)	
Interventions	Part 1 Metronidazole 60mg/kg /single dose; tinidazole 50mg/kg /single dose.	
Outcomes	Parasitological cure (negative stools in whole follow up (twice weekly 4 weeks)	
Notes	No information on co-morbidity.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Speelman 1985b

Methods	Randomisation by drawing therapy-chart from envelope; blinded examination of stool examination; blinding patients not described; formol ether concentration.	
Participants	Part 2 Travellers and residents bringing stools for examination; positive for Giardia (symptomatic and asymptomatic)	
Interventions	Part 2 Tinidazole 50mg/kg single dose; metronidazole 50mg/kg /single dose/ 3 days.	
Outcomes	Parasitological cure (negative stools in whole follow up (twice weekly 4 weeks); side effects (part 2).	
Notes	No information on co-morbidity	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Speelman 1985b (Continued)

Allocation concealment?	High risk	C - Inadequate
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Suntornpoch 1981

Methods	Allocation in treatment groups by week of inclusion; blinding of stool examination; and blinding patients not described; formol ether concentration.
Participants	121 children regardless of symptoms, mean age 5.7 (range 0-12 y); outpatient clinic Bangkok (Thailand); less diarrhoea in metronidazole group (15% vs 22% in tinidazole and 30% in secnidazole)
Interventions	Tinidazole 50 mg/kg single dose (max 2 gram); ornidazole 50 mg/kg single dose (max 2 gram); metronidazole 20 mg/kg / 5 days .
Outcomes	Follow up at 7, 14 and 21 days; cure (negative stools at day 21 and relief of symptoms).
Notes	No information on co-morbidity.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Vinaychandran 1979

Methods	Randomised; no exact procedure stated; blinding of stool examination and blinding patients not described; formol ether concentration and duodenal aspirate.
Participants	39 patients of gastroenterology clinic New Delhi (India).
Interventions	Metronidazole 200mg/3 times day/ 7 days; furazolidone 100mg/ 4 times day /7 days.
Outcomes	Parasitological cure at day 15 (3 negative stools or negative duodenal aspirate)
Notes	No information on co-morbidity; 25% of all patients continued to be symptomatic at day 14.

Risk of bias

Bias	Authors' judgement	Support for judgement
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Allocation concealment?	Unclear risk	B - Unclear
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ORS - oral rehydration solution U - units PVA -

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ayad el Masry 1978	Allocation procedure not described; 55 patients (symptoms not described) got tinidazole and 20 other infected male patients got a placebo
Bassily 1987	No attempt at randomisation.
Cacopardo 1995	Only patients with treatment failures on metronidazole (3-5 treatment courses) were included in this study. Twenty patients randomised between albendazole (400 mg twice daily 7 days) and albendazole (same dose) in combination with metronidazole (250 mg trice daily 7 days)
Cho 1976	Despite title, no attempt at randomisation; 3 groups of 10 patients (tinidazole, metronidazole and placebo)
Craft 1981	Randomisation not on patients; data extraction not possible because of lack of clear description of data (more events than patients); trial is often cited when efficacy of furazolidine is described
Gazder 1978	Exact copy of Gazder 1977.
Gorbea Robles 1989	Contact sought with Rhone Poulenc (pharmaceutical company of secnidazole) but no clear statement was given whether a randomisation procedure was used
Gupta 1978	No description of any attempt at randomisation.
Jokipii 1978	No randomisation; both treatment arms were compared afterwards; trial is, however, often cited
Levi 1977	Does not meet inclusion criteria.
Levi, Avila 1977	Double publication with Levi 1977 (American J Trop Med Hyg).
Misra 1995 b	Double publication with Misra 1995 b (in the same journal in the same year)
Ozeretskovskaia 1989	Not a randomised trial (follow-up of two patient groups both with tinidazole but from different manufacturers)
Pampuch 1985	No description of randomisation.

(Continued)

Sabachareon 1980	5 groups but no description of any attempt at randomisation (“each batch of patients received one of the five regimes”)
Seshadri 1984	Trial on anemia, giardia is only a confounder; trial found in trial register CRG Parasitic Diseases
Welch 1978	4 groups (placebo, metronidazole twice daily, tinidazole single dose, tinidazole 3 days), but no attempt at randomisation

DATA AND ANALYSES

Comparison 1. ANY DRUG THERAPY VERSUS PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 parasitological cure	3	382	Odds Ratio (M-H, Random, 95% CI)	11.51 [2.29, 57.98]
1.1 infection with symptoms	2	156	Odds Ratio (M-H, Random, 95% CI)	37.42 [0.36, 3843.68]
1.2 infection with or without symptoms	1	226	Odds Ratio (M-H, Random, 95% CI)	5.28 [2.51, 11.12]
2 duration of diarrhoea in symptomatic patients (hours)	1	23	Mean Difference (IV, Fixed, 95% CI)	-27.50 [-54.99, -0.01]

Comparison 2. METRONIDAZOLE (3 day course or longer) versus other therapy (3 days or longer)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 parasitological cure	18	1378	Odds Ratio (M-H, Random, 95% CI)	2.41 [1.31, 4.44]
1.1 infection with symptoms	10	578	Odds Ratio (M-H, Random, 95% CI)	1.14 [0.58, 2.22]
1.2 infection with or without symptoms	8	800	Odds Ratio (M-H, Random, 95% CI)	5.65 [2.46, 13.00]
2 clinical cure (relief of symptoms and negative stools)	1	81	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.13, 7.27]
3 duration of excretion of cysts	1	57	Mean Difference (IV, Fixed, 95% CI)	0.80 [0.15, 1.45]
4 side effects	8	1305	Odds Ratio (M-H, Random, 95% CI)	1.47 [0.51, 4.20]

Comparison 3. SINGLE DOSE VERSUS LONGER THERAPY

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 parasitological cure	9	713	Odds Ratio (M-H, Random, 95% CI)	0.33 [0.08, 1.34]
1.1 infection with symptoms	3	179	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.12, 4.84]
1.2 infection with or without symptoms	6	534	Odds Ratio (M-H, Random, 95% CI)	0.23 [0.04, 1.23]
2 clinical cure (relief of symptoms and negative stools)	3	308	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.47, 2.61]
3 side effects	5	956	Odds Ratio (M-H, Fixed, 95% CI)	2.52 [1.43, 4.43]

Comparison 4. SINGLE DOSE STANDARD TINIDAZOLE (1.5-2g) VERSUS OTHER SINGLE/SHORT COURSES

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 parasitological cure	7	627	Odds Ratio (M-H, Random, 95% CI)	3.39 [0.95, 12.04]
1.1 infection with symptoms	4	431	Odds Ratio (M-H, Random, 95% CI)	2.14 [0.45, 10.26]
1.2 infection with or without symptoms	3	196	Odds Ratio (M-H, Random, 95% CI)	6.50 [0.63, 67.22]
2 clinical cure (relief of symptoms and negative stools)	5	499	Odds Ratio (M-H, Fixed, 95% CI)	6.13 [3.89, 9.66]
3 absence of diarrhoea at end of follow-up in symptomatic patients	1	75	Odds Ratio (M-H, Fixed, 95% CI)	5.81 [2.04, 16.56]
4 duration of symptoms in symptomatic patients	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 side effects	4	399	Odds Ratio (M-H, Random, 95% CI)	1.12 [0.33, 3.78]

Comparison 5. ALBENDAZOLE VERSUS OTHER

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 parasitological cure	4	417	Odds Ratio (M-H, Fixed, 95% CI)	0.16 [0.05, 0.54]

Comparison 6. FURAZOLIDINE 10 DAYS VERSUS 5 DAYS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 clinical cure	1	22	Odds Ratio (M-H, Fixed, 95% CI)	44.0 [3.38, 573.41]

Comparison 7. PROPOSOLINA VERSUS TINIDAZOLE

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 clinical cure	1	66	Odds Ratio (M-H, Fixed, 95% CI)	2.91 [1.05, 8.04]

Analysis 1.1. Comparison 1 ANY DRUG THERAPY VERSUS PLACEBO, Outcome 1 parasitological cure.

Review: Drugs for treating giardiasis

Comparison: 1 ANY DRUG THERAPY VERSUS PLACEBO

Outcome: 1 parasitological cure

Analysis 1.2. Comparison 1 ANY DRUG THERAPY VERSUS PLACEBO, Outcome 2 duration of diarrhoea in symptomatic patients (hours).

Review: Drugs for treating giardiasis

Comparison: 1 ANY DRUG THERAPY VERSUS PLACEBO

Outcome: 2 duration of diarrhoea in symptomatic patients (hours)

Analysis 2.1. Comparison 2 METRONIDAZOLE (3 day course or longer) versus other therapy (3 days or longer), Outcome 1 parasitological cure.

Review: Drugs for treating giardiasis

Comparison: 2 METRONIDAZOLE (3 day course or longer) versus other therapy (3 days or longer)

Outcome: 1 parasitological cure

(Continued ...)

Analysis 2.2. Comparison 2 METRONIDAZOLE (3 day course or longer) versus other therapy (3 days or longer), Outcome 2 clinical cure (relief of symptoms and negative stools).

Review: Drugs for treating giardiasis

Comparison: 2 METRONIDAZOLE (3 day course or longer) versus other therapy (3 days or longer)

Outcome: 2 clinical cure (relief of symptoms and negative stools)

Analysis 2.3. Comparison 2 METRONIDAZOLE (3 day course or longer) versus other therapy (3 days or longer), Outcome 3 duration of excretion of cysts.

Review: Drugs for treating giardiasis

Comparison: 2 METRONIDAZOLE (3 day course or longer) versus other therapy (3 days or longer)

Outcome: 3 duration of excretion of cysts

Analysis 2.4. Comparison 2 METRONIDAZOLE (3 day course or longer) versus other therapy (3 days or longer), Outcome 4 side effects.

Review: Drugs for treating giardiasis

Comparison: 2 METRONIDAZOLE (3 day course or longer) versus other therapy (3 days or longer)

Outcome: 4 side effects

Analysis 3.1. Comparison 3 SINGLE DOSE VERSUS LONGER THERAPY, Outcome 1 parasitological cure.

Review: Drugs for treating giardiasis

Comparison: 3 SINGLE DOSE VERSUS LONGER THERAPY

Outcome: 1 parasitological cure

Analysis 3.2. Comparison 3 SINGLE DOSE VERSUS LONGER THERAPY, Outcome 2 clinical cure (relief of symptoms and negative stools).

Review: Drugs for treating giardiasis

Comparison: 3 SINGLE DOSE VERSUS LONGER THERAPY

Outcome: 2 clinical cure (relief of symptoms and negative stools)

Analysis 3.3. Comparison 3 SINGLE DOSE VERSUS LONGER THERAPY, Outcome 3 side effects.

Review: Drugs for treating giardiasis

Comparison: 3 SINGLE DOSE VERSUS LONGER THERAPY

Outcome: 3 side effects

Analysis 4.1. Comparison 4 SINGLE DOSE STANDARD TINIDAZOLE (1.5-2g) VERSUS OTHER SINGLE/SHORT COURSES, Outcome 1 parasitological cure.

Review: Drugs for treating giardiasis

Comparison: 4 SINGLE DOSE STANDARD TINIDAZOLE (1.5-2g) VERSUS OTHER SINGLE/SHORT COURSES

Outcome: 1 parasitological cure

Analysis 4.2. Comparison 4 SINGLE DOSE STANDARD TINIDAZOLE (1.5-2g) VERSUS OTHER SINGLE/SHORT COURSES, Outcome 2 clinical cure (relief of symptoms and negative stools).

Review: Drugs for treating giardiasis

Comparison: 4 SINGLE DOSE STANDARD TINIDAZOLE (1.5-2g) VERSUS OTHER SINGLE/SHORT COURSES

Outcome: 2 clinical cure (relief of symptoms and negative stools)

Analysis 4.3. Comparison 4 SINGLE DOSE STANDARD TINIDAZOLE (1.5-2g) VERSUS OTHER SINGLE/SHORT COURSES, Outcome 3 absence of diarrhoea at end of follow-up in symptomatic patients.

Review: Drugs for treating giardiasis

Comparison: 4 SINGLE DOSE STANDARD TINIDAZOLE (1.5-2g) VERSUS OTHER SINGLE/SHORT COURSES

Outcome: 3 absence of diarrhoea at end of follow-up in symptomatic patients

Analysis 4.4. Comparison 4 SINGLE DOSE STANDARD TINIDAZOLE (1.5-2g) VERSUS OTHER SINGLE/SHORT COURSES, Outcome 4 duration of symptoms in symptomatic patients.

Review: Drugs for treating giardiasis

Comparison: 4 SINGLE DOSE STANDARD TINIDAZOLE (1.5-2g) VERSUS OTHER SINGLE/SHORT COURSES

Outcome: 4 duration of symptoms in symptomatic patients

Analysis 4.5. Comparison 4 SINGLE DOSE STANDARD TINIDAZOLE (1.5-2g) VERSUS OTHER SINGLE/SHORT COURSES, Outcome 5 side effects.

Review: Drugs for treating giardiasis

Comparison: 4 SINGLE DOSE STANDARD TINIDAZOLE (1.5-2g) VERSUS OTHER SINGLE/SHORT COURSES

Outcome: 5 side effects

Analysis 5.1. Comparison 5 ALBENDAZOLE VERSUS OTHER, Outcome 1 parasitological cure.

Review: Drugs for treating giardiasis

Comparison: 5 ALBENDAZOLE VERSUS OTHER

Outcome: 1 parasitological cure

Analysis 6.1. Comparison 6 FURAZOLIDINE 10 DAYS VERSUS 5 DAYS, Outcome 1 clinical cure.

Review: Drugs for treating giardiasis

Comparison: 6 FURAZOLIDINE 10 DAYS VERSUS 5 DAYS

Outcome: 1 clinical cure

Analysis 7.1. Comparison 7 PROPOSOLINA VERSUS TINIDAZOLE, Outcome 1 clinical cure.

Review: Drugs for treating giardiasis

Comparison: 7 PROPOSOLINA VERSUS TINIDAZOLE

Outcome: 1 clinical cure

WHAT'S NEW

Date	Event	Description
14 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 1995

Review first published: Issue 1, 1996

Date	Event	Description
10 April 1998	New citation required and conclusions have changed	Substantive amendment

DECLARATIONS OF INTEREST

We certify that we have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of the review (e.g. employment, consultancy, stock ownership, honoraria, expert testimony).

SOURCES OF SUPPORT

Internal sources

- Institute for Research in Extramural Medicine (EMGO), Netherlands.

External sources

- Department for International Development, UK.
- European Commission (Directorate General XII), Belgium.

NOTES

The Editor withdrew this review as of Issue 2, 2007. This review will be reinstated following a substantive update.

INDEX TERMS

Medical Subject Headings (MeSH)

Antiprotozoal Agents [*therapeutic use]; Furazolidone [therapeutic use]; Giardiasis [*drug therapy]; Metronidazole [therapeutic use]; Tinidazole [therapeutic use]

MeSH check words

Humans