Albendazole for lymphatic filariasis (Review)

International Filariasis Review Group (David Addiss, Julia Critchley, Henry Ejere, Paul Garner, Hellen Gelband, Carrol Gamble)

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ABSTRACT

Background

Mass treatment with albendazole, co-administered with another antifilarial drug, is being promoted as part of a global programme to eliminate lymphatic filariasis.

Objectives

To assess the effects of albendazole on patients or populations with filarial infection, and on morbidity in patients with filarial infection; and to assess the frequency of adverse events for albendazole both given singly or in combination with another antifilarial drug (diethylcarbamazine or ivermectin).

Search strategy

We searched the Cochrane Infectious Disease Group's trial register (September 2003), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 3, 2003), MEDLINE (September 2003), EMBASE (September 2003), LILACS (September 2003); and checked the reference lists and contacted experts, international organizations, and a pharmaceutical company.

Selection criteria

Randomized and quasi-randomized controlled trials of albendazole singly or in combination with anti-filarial drugs in people or populations with lymphatic filariasis.

Data collection and analysis

Two reviewers assessed eligibility and trial methodological quality. We calculated relative risks (RR) with 95% confidence intervals (CI) for binary outcomes, and where appropriate, combined them in a meta-analysis using the fixed effect model or random effects model.

Main results

Four small studies met the inclusion criteria (a total of 2473 children and adults, of whom 536 had detectable microfilariae). No effect of albendazole on microfilaraemia was demonstrated in two studies (placebo controlled, RR 0.97, 95% CI 0.87 to 1.09, n = 195). When compared to ivermectin, albendazole performed worse (RR 0.84, 95% CI 0.72 to 0.98, 2 studies of patients initially microfilariae positive, n = 198). When compared to diethylcarbamazine, no statistically significant difference was detected, but numbers were small (n = 56).

Two studies compared albendazole plus ivermectin to ivermectin alone on the presence of microfilaraemia. Results were mixed: one study showed the combination to be more effective (RR 0.27, 95% CI 0.11 to 0.70, n = 52), but the other did not demonstrate a statistically significant difference (RR 1.04, 95% CI 0.87 to 1.25, n = 145). A further study compared albendazole plus diethylcarbamazine to diethylcarbamazine alone and did not demonstrate a difference on microfilaraemia prevalence. No study examined the effects of the drugs on adult worms.

Authors' conclusions

There is insufficient reliable research to confirm or refute whether albendazole alone, or co-administered with diethylcarbamazine or ivermectin, has an effect on lymphatic filariasis.

BACKGROUND

Epidemiology

Lymphatic filariasis is a parasitic infection of threadlike, filarial worms, affecting about 120 million people in more than 80 countries (Michael 1996; WHO 2000). Bancroftian filariasis, caused by infection with *Wuchereria bancrofti* occurs in tropical regions of Asia, Africa, China, the Pacific islands, and in parts of the Caribbean and South America. Brugian filariasis is less common, with *Brugia malayi* occurring in parts of Asia, and *Brugia timori* in Indonesia (FGN 1996).

Filariasis is transmitted by mosquitoes from a number of genera (including *Culex*, *Anophelines*, *Mansonia*, *Ochlerotatus,* and *Aedes*) (Burkot 2002). Female mosquitoes transmit the disease. They are infected when they take blood meals from people with microfilariae, early stage larvae. The larvae develop for about 12 to 15 days in the mosquito to a mature larval stage (Scott 2000), which can establish itself after entering the skin and the lymphatic vessels following a subsequent blood meal. When the mosquito infects the human host, the larvae migrate to the lymph vessels and develop into adult worms, where male and female worms pair. They later produce microfilariae that migrate to the blood and cause microfilaraemia, that is, microfilariae in the blood. The time between being infected and adult worms producing microfilaraemia is estimated to be about 12 months (Mahoney 1971).

Microfilariae move in and out of circulating peripheral blood according to a daily cycle. In most species, microfilarial levels peak during the night between 10 pm to 4 am (Simonsen 1997) – a time when mosquito vectors are actively feeding. In Fiji, Polynesia, and the Philippines, some strains of *W. bancrofti* microfilariae peak during the day (Scott 2000).

Clinical features

Many people with filariasis may be asymptomatic most of the time. However, even people without clinical symptoms often have lymphatic changes, including lymphangiectasia (widening of the lymphatic vessels), and thickening of the spermatic cord (Addiss 2000; Dreyer 2000), which can be detected through imaging studies. Clinical symptoms and signs include hydrocoele (excess fluid inside the scrotal sac), lymphoedema (swelling and enlargement of affected areas of the body), and elephantiasis (long standing enlargement and swelling of the limbs, scrota, or breasts associated with skin thickening).

Historically, filarial infection has been diagnosed by examining a blood smear for microfilariae. But even if blood is taken at night, not all infections are detected because microfilarial levels are very low in many people. Antigen assays, which became available for field use during the 1990s, are more sensitive and can be used for blood collected during the day or night (Weil 1997) because they indicate the presence of the adult worm and do not depend on the temporal presence of microfilariae. Ultrasound imaging can demonstrate the presence of live adult worms (Dreyer 1995).

How the filarial worm causes disease is not well understood. The following have been proposed: adult worms living in and damaging lymph vessels; immunologic reactions to the presence and death of filarial worms; secondary infections of affected areas, which contribute significantly to both acute and chronic disease manifestations (Dreyer 2000). Researchers have also suggested that toxins released by *Wolbachia* (endosymbiotic bacteria found within the cells of filarial worms) cause disease (Taylor 2001). Some or all of these processes may be important.

Control

Control strategies aim to reduce microfilariae in the community to levels that prevent transmission (Ottesen 1997; Ottesen 1999). Treatment of individuals with clinical disease is generally only partially effective (at least in part because there is no drug that reliably kills the 'macrofilariae', the adult worms). Mass drug administration programmes therefore aim for a sustainable reduction in community microfilarial loads below a critical threshold, or a complete clearance of microfilariae, to have an appreciable impact on transmission. The 'Global Alliance to Eliminate Lymphatic Filariasis' recommend yearly, single-dose, two-drug regimens (either albendazole plus diethylcarbamazine (DEC); or albendazole plus ivermectin), for at least five years (corresponding to the reproductive lifespan of the adult worm) to prevent transmission. However, the critical threshold below which no further transmission will take place is unclear, and may depend on the vector species in the locality. Some mosquitoes (for example, *Aedes polynesiensis*, some culicine mosquitoes in India and the Americas) may be more efficient at lower microfilarial densities (a process known as limitation). Higher treatment coverage for longer periods, or other strategies such as vector control, may be required in areas where these vectors are responsible for a high proportion of transmission (Burkot 2002; Pichon 2002).

Ivermectin and DEC both kill microfilariae, and DEC may have

some temporary sterilizing effect or actually kill adult worms, so one treatment with either drug can affect microfilarial levels for many months. Reductions of 90% from pre-treatment microfilarial levels have been seen after single dose DEC or ivermectin, even one year after treatment (Ottesen 1999). The impact on transmission can be enhanced, if currently available antifilarial drugs demonstrate a killing or sterilizing effect on adult worms, in addition to their effect on microfilariae. There are concerns that over reliance on a limited range of drugs may eventually cause resistance, although there is little direct evidence that this is currently a problem in filariasis (Barat 1997; Geerts 2001).

It has been observed that some infected people lose their microfilariae in the absence of treatment (Vanamail 1990). However, overall microfilarial prevalence rates are believed to be relatively stable over time in endemic communities in the absence of community treatment (Meyrowitsch 1995), with new, microfilaraemic infections replacing those whose microfilaraemia subsides (Vanamail 1990; Weil 1999). Nevertheless, lymphatic filariasis has been eliminated from some areas such as the Choiseul Island (Solomon Islands) and Australia using vector control methods (Pichon 2002; Burkot 2002), and parts of China using DEC-medicated salt and other DEC regimens (Gelband 1994).

Diethylcarbamazine and ivermectin

DEC has been in use for filariasis for more than 50 years. In the early years of control the recommended regimen for DEC was 6 mg/kg daily for 12 days (WHO 1984). Later, clinical and community trials determined that single doses given at various intervals —weekly, monthly, annually, and biannually — were equally effective (Eberhard 1989; Andrade 1995; Simonsen 1995). There is reasonable evidence from ultrasound and clinical observations that DEC kills some adult worms (macrofilariae) after single doses (Figueredo-Silva 1996; Noroes 1997; Addiss 2000).

Ivermectin is used for the treatment and community control of onchocerciasis (which is caused by another filarial worm, *Onchocerca volvulus*) and more recently has been effective in community control programs for lymphatic filariasis (Cartel 1990; Coutinho 1994; Cao 1997). It can be used in many places, but is particularly important in areas where both onchocerciasis and lymphatic filariasis coexist, because DEC can cause eye damage if given to individuals with onchocerciasis. However, recent ultrasound studies suggest that adult worms are not killed by ivermectin, even at high doses over a period of six months (Dreyer 1996; Addiss 2000).

Adverse effects of antifilarial drugs can be serious (though almost never fatal) and prevent people from completing treatment. The most serious appear to be due to a host immunologic reaction to the dying worms (WHO 1984; Dreyer 1994). These effects include fever, headache, malaise, muscle pain, and blood in urine. Local effects include localized pain, tender nodules, lymphadenitis (inflammation of the lymph nodes), and lymphangitis (inflammation of lymph vessels) (Addiss 2000).

Albendazole

Albendazole has been used widely to treat intestinal parasites since the late 1980s and may have a potential role in lymphatic filariasis control (Ottesen 1999). A report from an informal consultation organized by the World Health Organization suggests that albendazole in repeated high doses has a killing or sterilizing effect on adults of *W. bancrofti* (CDS/FIL 1998; Sri Lanka (Jaya1993)). However, the data in the report are scanty and it remains unclear whether adding albendazole to either DEC or ivermectin improves cure, prevents further transmission, or influences the occurrence of adverse events. A narrative review by Horton 2000 from the company that manufactures albendazole did not demonstrate that adding albendazole to either drug increased the frequency or severity of adverse events. The company manufacturing albendazole state that this drug does not have a role in morbidity management — it will not treat the symptoms in people already affected by filariasis (GSK 2003) — but at least one trial has considered the effectiveness of albendazole in reducing both disease progression and incidence of new symptoms (such as hydrocoele) (Ghana (Dunyo 2000)). We therefore include this as a secondary outcome.

In this review, we aim to summarize the evidence for the effects of albendazole alone or in combination with DEC or ivermectin in both the individual treatment and transmission control of lymphatic filariasis.

OBJECTIVES

(1) To assess the effects of albendazole on patients or populations with filarial infection.

(2) To assess the effects of albendazole on morbidity among patients with filarial infection (incidence of new disease or progression of existing symptoms)

(3) To assess the frequency of adverse events for albendazole both given singly or in combination with another antifilarial drug (DEC or ivermectin).

RESULTS

Albendazole versus placebo

In all participants (both microfilariae positive or negative at baseline)

Microfilaraemia

Haiti (Beach 1999) did not detect a statistical difference in prevalence of microfilaraemia for albendazole (22/145) versus placebo (20/139) (RR 1.05, 95% CI 0.60 to 1.84; Graph 01-01).

Antigenaemia prevalence

Ghana (Dunyo 2000) reported no statistical difference in the numbers circulating filarial antigen positive at baseline or 12 months (albendazole 105 at baseline, 110 at 12 months; placebo 103 at baseline, 102 at 12 months).

Clinical disease

At 12 months post-treatment Ghana (Dunyo 2000) detected no statistical difference in the development of hydrocoele between albendazole (1/129) and placebo (1/126) (RR 0.98, 95% CI 0.06 to 15.45; Graph 01-02). No new cases of acute filariasis and leg lymphoedema were observed. Similarly, there were no differences in improvement of symptoms in lymphoedema between the albendazole group (3/13) and placebo group (2/9) (RR 1.04, 95% CI 0.22 to 5.01; Graph 01-03), or in hydrocoele between the albendazole group (3/8) and placebo group (5/10) (RR 0.75, 95% CI 0.25 to 2.23; Graph 01-03). No statistically significant differences were detected, but the studies lacked power for clinical outcomes, so clinically important differences cannot be ruled out.

Adverse events

Ghana (Dunyo 2000) did not detect a difference in systemic adverse events between the albendazole group (31/336) compared to placebo group (33/314) (RR 0.88, 95% CI 0.55 to 1.40; Graph 01-04). No local or severe adverse events were reported. Table 06 displays frequency of specific adverse events.

In participants microfilariae positive at baseline (microfilariae negative excluded)

Microfilaraemia

Haiti (Beach 1999) found no difference in prevalence between albendazole (22/29) and placebo (20/29) at four months (RR 1.10, 95% CI 0.80 to 1.51). Similarly, Ghana (Dunyo 2000) found no difference in prevalence at 12 months (62/71 albendazole, 62/66 placebo) (RR 0.93, 95% CI 0.83 to 1.04). A combined estimate from these two trials shows no difference in microfilaraemia between albendazole and placebo (RR 0.97, 95% CI 0.87 to 1.09, n = 195; Graph 01-05).

Microfilarial density (percentage reduction)

Haiti (Beach 1999) estimated the reduction in geometric mean microfilarial density. The reductions were 63.8% (14.1 to 5.1) in the albendazole group, and 43.0% (9.3 to 5.3) in the placebo group at four months (not statistically significant). Ghana (Dunyo 2000) reported geometric mean microfilarial density at baseline and 12 months (with percentage reduction). The density decreased from 798 to 251 (68.5%) in the albendazole group compared to 971 to 845 (13.0%) in the placebo group, but this was not statistically significant (P = 0.10). An 'area under the curve' analysis from this study found an increase in microfilariae geometric mean intensity in the placebo group from 2536 to 2740 (8.4% increase), and a decrease in the albendazole group from 1535 to 1233 (19.7%); again this was not statistically significant (P = 0.12). The latter analysis was limited to those with complete data collection and microfilarial density of over 100 microfilariae/µl at baseline (*see* Table 04).

Antigen density (percentage change)

Ghana (Dunyo 2000) reported that reported that unit geometric mean microfilarial density (measured by circulating filarial antigen) had increased by 47.5% of the pretreatment level in the placebo group, but decreased to 83.1% of the pretreatment level in the albendazole group, but this difference was not statistically significant (P = 0.11) (Table 05).

Albendazole versus ivermectin

In all participants (both microfilariae positive or negative at baseline)

Microfilaraemia

Haiti (Beach 1999) did not demonstrate a difference in microfilarial prevalence at follow up between groups allocated to albendazole (22/145) or ivermectin (20/150) (RR 1.14, 95% CI 0.65 to 1.99; Graph 02-01).

Antigenaemia prevalence

Ghana (Dunyo 2000) reported no difference in the numbers circulating filarial antigen positive at baseline or 12 months (albendazole: 105 at baseline, 110 at 12 months; ivermectin: 99 at baseline, 101 at 12 months).

Clinical disease

Ghana (Dunyo 2000) found no differences in (1) the risk of developing hydrocoele in the albendazole (1/129) and ivermectin (1/133) groups (RR 1.03, 95% CI 0.07 to 16.31; Graph 02-02); (2) improvements in lymphoedema in the albendazole (3/13) and ivermectin (2/13) groups (RR 1.50, 95% CI 0.30 to 7.55; Graph 02-03); and (3) improvements in hydrocoele in the albendazole (3/8) and ivermectin (2/9) groups (RR 1.69, 95% CI 0.37 to 7.67; Graph 02-03). However, sample sizes were small and confidence intervals wide.

Adverse events

Ghana (Dunyo 2000) detected no difference in systemic adverse events between the albendazole (31/336) and ivermectin (36/295) groups (RR 0.76, 95% CI 0.48 to 1.19; Graph 02-04).

In participants microfilariae positive at baseline (microfilariae negative excluded)

Microfilaraemia

Haiti (Beach 1999) reports microfilarial prevalence at 4 months follow up: 22/29 in the albendazole group and 17/28 in the ivermectin group (RR 0.80, 95% CI 0.56 to 1.15; Graph 02-05).

Ghana (Dunyo 2000) also reported this outcome: 62/71 in the albendazole group and 52/70 in the ivermectin group (RR 0.85, 95% CI .72 to 1.00; Graph 02-05). Pooling the two studies, albendazole was slightly worse at clearing microfilariae, but this only just reached statistical significance (RR 0.84, 95% CI 0.72 to 0.98; Graph 02-05).

Microfilarial density (percentage reduction)

Haiti (Beach 1999) reported on the percentage reduction in geometric mean microfilarial density. The values at baseline and four months follow up (with percentage reductions) were 14.1 and 5.1 (63.8% reduction) for albendazole, and 15.5 to 1.5 (90.2% reduction) for ivermectin. No test of statistical significance was applied. Ghana (Dunyo 2000) measured mean values at baseline and 12 months follow up (with percentage reductions). For albendazole, this was from 798 to 251 (68.5% reduction); and for ivermectin, from 640 to 124 (80.6% reduction); no statistical significance test was reported. An 'area under the curve' analysis from this study found a decrease in the albendazole group (from 1535 to 1233, 19.7%) and in the ivermectin group (from 1731 to 759, 56.2%). The latter analysis was limited to those with complete data collection and microfilarial density of over 100 microfilariae/µl at baseline (*see* Table 04).

Antigenaemia density (percentage reduction)

Ghana (Dunyo 2000) reported that unit geometric mean microfilarial density (measured by circulating filarial antigen) had decreased to 83.1% of the pretreatment level in the albendazole group, and 70.3% in the ivermectin group (no statistical test applied) (Table 05).

Albendazole plus ivermectin versus ivermectin

In all participants (both microfilariae positive or negative at baseline)

Microfilaraemia

Haiti (Beach 1999) estimated a statistically significant 65% reduction in microfilarial prevalence for the combination (7/151) compared to ivermectin alone (20/150) (RR 0.35, 95% CI 0.15 to 0.80; Graph 03-01).

Antigen prevalence

Ghana (Dunyo 2000) reported no difference in the numbers of participants positive for circulating filarial antigen at baseline or 12 months (albendazole plus ivermectin: n = 121 at baseline, n = 122 at 12 months; ivermectin n = 99 at baseline, n = 101 at 12 months).

Clinical disease

Ghana (Dunyo 2000) found no difference in new cases of hydrocoele between the combination treatment (2/147) compared to ivermectin (1/133) (RR 1.81, 95% CI 0.17 to 19.73; Graph 03-02). This study also observed no differences in improvement in lymphoedema between the combination (2/13) and ivermectin (2/13) (RR 1.00, 95% CI 0.16 to 6.07; Graph 03-03), and no differences between combination treatment (4/10) and ivermectin (2/9) in hydrocoele (RR 1.80, 95% CI 0.43 to 7.59; Graph 03-03). Again, the studies were not designed to detect changes in clinical outcomes, therefore confidence intervals are very wide.

Adverse events

Ghana (Dunyo 2000) recorded more adverse events with the combination treatment (47/332) compared to ivermectin (36/295), but this was not statistically significant (RR 1.16, CI 0.77 to 1.74; Graph 03-04). Table 06 displays the occurrence of specific adverse events.

In participants microfilariae positive at baseline (microfilariae negative excluded)

Microfilaraemia

Haiti (Beach 1999) reported a 73% reduction in microfilariae for the combination of albendazole and ivermectin (4/24) compared to ivermectin alone (17/28) at four months (RR 0.27, 95% CI 0.11 to 0.70, random effects model; Graph 03-05). However, Ghana (Dunyo 2000) found no difference between the combination (58/75) and ivermectin (52/70) (RR 1.04, 95% CI 0.87 to 1.25, random effects model; Graph 03-05). The pooled RR indicated no significant difference for the combination compared to ivermectin alone, but the confidence intervals are wide. The RR is 0.57 (95% CI 0.13 to 2.48) using the random effects model and 0.87 (95% CI 0.71 to 1.06) using the fixed effect model (Graph 03-05).

Microfilarial density (percentage reduction)

Haiti (Beach 1999) reported a reduction in geometric mean microfilarial density in the combination group from 13.7 to 0.3 (97.8%) compared to 15.5 to 1.5 (90.2%) in the ivermectin group at four months ($P < 0.05$). Ghana (Dunyo 2000) reported a reduction in geometric mean microfilarial density in both groups after 12 months: from 614 to 78 (87.3% reduction) in the combination group compared to a change from 640 to 124 (80.6% reduction) in the ivermectin group. This was not statistically significant ($P = 0.80$). An 'area under the curve' analysis from this study found a decrease in the combination group (from 1280 to 393, 69.3%) and the ivermectin group (from 1731 to 759, 56.2%); this difference was not statistically significant ($P = 0.26$). The latter analysis was limited to those with complete data collection and microfilarial density of over 100 microfilariae/µl at baseline (*see* Table 04).

Albendazole versus DEC

Two very small studies compared albendazole to DEC. Sri Lanka (Jaya1993) compared albendazole (n = 16) to DEC (n = 13) and attempted to follow up participants for up to 19 months. They reported that all participants in this extended follow up lived nearby and had received treatment in addition to the study intervention,

but the nature of this is unclear. India (Pani 2002) compared albendazole alone (n = 19) and DEC (n = 17), with albendazole and DEC co-administered (n = 18). All participants were microfilariae positive at baseline.

Microfilaraemia

India (Pani 2002) reported no statistically significant difference in microfilarial prevalence at 360 days (14/19 on albendazole compared to 14/17 on DEC). Sri Lanka (Jaya1993) stated that 85% of the participants treated with albendazole (numerator and denominator unclear) and 67% of the participants treated with DEC (8/12) still had detectable microfilariae at six months. At the extended follow up of 15 to 19 months, 50% of participants in both groups were microfilariae positive (5/10 on both albendazole and DEC), but a substantial proportion of participants had been lost to follow up. The data are displayed graphically but should be viewed with caution (Graph 04-01).

Antigenaemia prevalence

India (Pani 2002) reported no statistically significant difference in prevalence of filarial antigenaemia at any point during the study (P > 0.05). The percentage reduction was 83% on albendazole and 87% on DEC (by immuno-chromatographic card test), and 83% albendazole and 80% DEC (by Og4C3 (ELISA test kit)) (Table 03).

Microfilarial density(percentage reduction)

India (Pani 2002) reported no statistically significant difference in percentage reductions in geometric mean microfilarial density at any of the time points when this was measured (days 3, 7, and 360). The percentage reductions at 360 days compared to pre-therapy values were 97.4% for albendazole and 89.6% for DEC. However, microfilarial density appeared to fall faster during the first 7 days on DEC compared to albendazole (Table 03).

Sri Lanka (Jaya1993) also found large reductions in microfilarial density at six months for both treatment groups; the geometric mean microfilarial density had fallen to 1.91% of its initial value for those treated with albendazole and 0.81% for those treated with DEC. At the extended follow up (15 to 19 months), there was no statistically significant difference in the geometric mean microfilarial densities (3 for albendazole and 2 for DEC) (Table 03). Similarly to India (Pani 2002), microfilarial density appeared to fall faster during the first 28 days on DEC compared to albendazole.

Antigenaemia density

India (Pani 2002) reported statistically significant reductions in mean optical antigen density by Og4C3 assay in both groups at 360 days (reduction of 0.41 on albendazole, P < 0.0001 for the pre-intervention value compared to the post-intervention value, 0.32 on DEC; P < 0.0001 for pre-intervention versus post-intervention value) (Table 05).

Adverse events

India (Pani 2002) reported no severe adverse events in any group. Those observed were transient (not lasting beyond 6 days) and included fever, myalgia, and headache. There was no difference in the proportion reporting any systemic adverse events between albendazole (8/19, 42.1%) and DEC (9/17, 52.9%) (RR 0.80, 95% CI 0.40 to 1.59; Graph 04-02). The authors used a score for assessing adverse reactions. The mean score of adverse reaction intensity was lower for albendazole (1.8, standard deviation 3.0) compared to DEC (5.6, standard deviation 7.1) (P < 0.05). However, the validity and clinical significance of this scoring system is uncertain. In Sri Lanka (Jaya1993), 11 of 15 participants receiving the full treatment regiment for albendazole developed "scrotal syndrome"; this was classified as 'severe' for two men, moderate for two, and mild for the other 7. None of the participants on DEC developed similar symptoms (RR 12.19, 95% CI 0.77 to 194.03; Graph 04-03). One participant on DEC had fever, right hypochondrial pain, and repeated vomiting, and was withdrawn from the study. However, the drug doses were much higher in this trial than in the other three. Participants were given albendazole twice a day, or DEC once a day for three weeks. All other trials tested a single dose of albendazole plus DEC or ivermectin.

Albendazole plus DEC versus DEC

Microfilaraemia

India (Pani 2002) found no statistically significant difference in microfilarial prevalence at 360 days (13/18 on albendazole plus DEC compared to 14/17 on DEC; Graph 05-01).

Antigenaemia prevalence

India (Pani 2002) reported no statistically significant difference in prevalence of filarial antigenaemia at any point during the study (P > 0.05). The percentage reduction was 75% on albendazole plus DEC compared to 87% on DEC (by immuno-chromatographic card test), and 81% on albendazole plus DEC compared to 80% on DEC (by Og4C3) (Table 03).

Microfilarial density (percentage reduction)

Again, there was no difference in percentage reductions in geometric mean microfilarial density. The percentage reductions at 360 days compared with pre-therapy values were 95.4% for albendazole and 89.6% for DEC (Table 04).

Antigenaemia density

There were statistically significant reductions in mean optical antigen density by Og4C3 assay in both groups at 360 days in India (Pani 2002) (reduction of 0.40 on albendazole plus DEC, P < 0.0001 for pre-intervention compared to post-intervention value, 0.32on DEC; P < 0.0001 for pre-intervention versus post-intervention value) (Table 05).

Adverse events

India (Pani 2002) reported no difference in the proportion reporting any systemic adverse events between albendazole plus DEC (11/18, 61.1%) and DEC alone (9/17, 52.9%) (RR 1.15, 95% CI 0.65 to 2.06; Graph 05-02), or in the mean score of adverse reaction intensity for albendazole plus DEC (6.7, standard deviation 6.6) compared to DEC alone (5.6, standard deviation 7.1).

DISCUSSION

The review was designed to assess the effects of albendazole alone or in combination with currently recommended antifilarial drugs, ivermectin, or DEC. Although the review has considered the effects of albendazole alone, the main interest and strategy of the 'Global Alliance to Eliminate Lymphatic Filariasis' is in the effectiveness of combinations of different antifilarial drugs (Ismail 1998; Shenoy 1999). Of particular interest is the effectiveness of adding albendazole (thought to be macrofilaricidal) to single dose regimens of ivermectin (thought to be mainly microfilaricidal) or DEC (possibly both microfilaricidal and macrofilaricidal) (CDS/FIL 1998; Ottesen 1999).

All the included studies were designed primarily to assess the effectiveness of albendazole to treat individuals; none have explicitly considered its effects on transmission in whole communities. We identified only four studies, and most are small. All were described as randomized but had other important limitations. In particular, losses to follow up were very high (above 20%) in all studies except for India (Pani 2002), and this may lead to imbalances in the comparison groups. Differences in design (microfilariae-positive participants only versus microfilariae-positive and microfilariae-negative participants at baseline, variable outcome measurement and reporting, and length of follow up) made it difficult to compare the studies. In particular, some trials report outcomes mainly for those who are microfilariae positive at baseline (Ghana (Dunyo 2000)). Outcomes for all participants in the trial, regardless of baseline microfilarial status, would be preferable in assessing the community impact of mass treatment strategies. Only two of the studies report changes in antigenaemia prevalence or density in addition to microfilarial prevalence and density (Ghana (Dunyo 2000); India (Pani 2002)). However, there was broad agreement between changes in both these outcome measures in these two studies. None of the studies objectively examined the effects of antifilarial medication on the viability of adult worms. As adult worms are responsible for the production of microfilariae, the extent to which antifilarial drugs affect worm viability is an important outcome.

Albendazole alone was not effective in reducing microfilarial prevalence (Haiti (Beach 1999); Ghana (Dunyo 2000)), or circulating filarial antigens (Ghana (Dunyo 2000)), compared to placebo. Ivermectin appears more effective than albendazole in both these trials, and a meta-analysis indicates a marginal but statistically significant 16% reduction in the RR of microfilarial prevalence after treatment for those who were microfilariae positive at baseline in favour of ivermectin.

In one trial, the combination of albendazole and ivermectin was better than ivermectin alone after four months follow up (Haiti (Beach 1999)), but in the other trial in which this combination was examined they were about the same after 12 months follow up (Ghana (Dunyo 2000)). The lack of measurements at similar intervals made it impossible to know if the results were substantially alike. It is possible that by 12 months microfilariae levels had risen sufficiently to dampen the actual effect of the drugs in the Ghana (Dunyo 2000). The dose of ivermectin was also lower in Ghana (Dunyo 2000) than in Haiti (Beach 1999). Investigators in the two trials used different techniques to assess microfilariae: thick film method in 20 µl of blood with measurement at night in Haiti (Beach 1999); and the counting chamber method in 100 µl of blood with measurement during the day in Ghana (Dunyo 2000).

Two very small trials compared albendazole to DEC (India (Pani 2002); Sri Lanka (Jaya1993)). Neither found any statistically significant differences in microfilarial prevalence or density at any of the time points measured. Sri Lanka (Jaya1993) included an extended follow up at 15 to 19 months. There was no statistical difference in microfilarial prevalence or density between the two groups at this point, but the numbers were very small and a high proportion had been lost to follow up. India (Pani 2002) also found no statistically significant differences between albendazole alone, DEC alone, and albendazole plus DEC at one year follow up. Follow up was complete, but this trial lacked statistical power.

Although all trials provided data on geometric mean microfilarial density, lack of reporting of standard deviations or confidence intervals made it impossible to include these results in a meta-analysis. A reduction in geometric mean microfilarial density was observed for all treatments including placebo, and the reduction appeared greater for active treatments (albendazole, DEC, and ivermectin), but tests of statistical significance were not always carried out or reported.

The effect of treatment on clinical disease was not remarkable in any of the comparison groups. This is not surprising as effect sizes for clinical outcomes were small and the studies were not powered to detect small clinical benefits.

No severe adverse events or localized reactions were reported in three of the trials (Haiti (Beach 1999); Ghana (Dunyo 2000); India (Pani 2002)). Sri Lanka (Jaya1993) found a very high incidence of "scrotal syndrome" among those treated with albendazole, but the doses of both albendazole and DEC were very much higher than in the other trials. One trial reported that people in the ivermectin group were more likely to report any systemic adverse event compared to albendazole, but this was not significant

(Ghana (Dunyo 2000)). One trial reported a significantly lower intensity of adverse events in the albendazole group, compared to DEC, or albendazole combined with DEC, but no statistical difference in the proportions reporting any adverse events (Ghana (Dunyo 2000)). The death of worms is associated with the development of adverse events, so differences in the reporting of adverse events between albendazole, ivermectin, or DEC groups may reflect differences in the macrofilaricidal properties of the drugs (Addiss 2000). However, the studies lack statistical power to identify differences in reporting of adverse events.

AUTHORS' CONCLUSIONS

Implications for practice

Based on limited data, the evidence suggests that albendazole alone is not better than placebo, ivermectin, or DEC at clearing blood microfilariae. Results from two studies that compared albendazole plus ivermectin to ivermectin alone were inconsistent. There was little difference in the effects detected with albendazole alone, DEC alone, or albendazole co-administered with DEC from two very small studies. All the studies were underpowered to assess the effects of albendazole — alone or in combination — on morbidity or adverse events. Five ongoing trials are examining the benefits of adding albendazole to ivermectin or DEC.

The conclusions of this review are based on trials that have only randomized and treated individuals. Therefore they should be cautiously extrapolated to large scale, population-based mass drug administration programmes.

Implications for research

We found only limited data. Further large well-designed studies are required. For example, studies to:

- compare the effects of albendazole alone, albendazole plus DEC, and albendazole plus ivermectin on treating and controlling lymphatic filariasis;
- measure the impact of albendazole in mass drug administration campaigns;
- evaluate other interventions (against the parasite or the vector) to augment mass drug administration.

Complete clearance of blood microfilariae theoretically represents the most reliable strategy for interrupting transmission. But this may be difficult to achieve in practice, as apart from DEC, currently available antifilarial drugs mainly act on microfilariae with no demonstrable macrofilaricidal activity. A drug that kills both microfilariae and adults is clearly ideal, and there is an argument for more research on the effects of antifilarial drugs on the adult worm. This could be assessed objectively, as with ultrasound detection, on a relatively small number of infected individuals.

It is also not known how low microfilarial densities need to fall in order to successfully interrupt transmission from the various vector species. As microfilaraemia is an intermediate outcome reflecting infectivity of the human host, it is important to assess comparative effectiveness of drugs that aim to interrupt transmission. Techniques for assessing microfilariae in blood and outcome measures for microfilarial densities need to be standardized with complete reporting of means and standard deviations.

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No details.. Ongoing study No details..
Beach MJ.

Dahoma (ongoing)

Assessment of safety and efficacy of ivermectin and albendazole co-administration.. Ongoing study No details..

Das (ongoing)

Cluster randomized trial of ivermectin, DEC, and albendazole.. Ongoing study No details..

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INDEX TERMS

Medical Subject Headings (MeSH)

Albendazole [therapeutic use]; Diethylcarbamazine [therapeutic use]; Elephantiasis, Filarial [*drug therapy]; Filaricides [*therapeutic use]; Ivermectin [therapeutic use]; Randomized Controlled Trials

MeSH check words

Humans