TRANSACTIONS OF THE ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE (2001) 95, 332–335

# Long-term efficacy of single-dose combinations of albendazole, ivermectin and diethylcarbamazine for the treatment of bancroftian filariasis

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## Abstract

In a 'blinded' trial (in Sri Lanka, 1996–98) of 47 male asymptomatic microfilaraemic subjects with *Wuchereria bancrofti* infection, the safety, tolerability and filaricidal efficacy of 3 single-dose combination regimens were compared: albendazole 400 mg with ivermectin 200 μg/kg, albendazole 400 mg with diethylcarbamazine citrate (DEC) 6 mg/kg or albendazole 600 mg with ivermectin 400 μg/kg. Treated subjects were followed-up for 24 months. This represents the first long-term study using combinations of albendazole with DEC or ivermectin in the above doses against bancroftian filariasis. All subjects had pre-treatment microfilaria (mf) counts over 100/mL. All 3 treatments significantly reduced mf counts, with the albendazole–DEC-treated group showing the lowest mf levels at 18 and 24 months post-treatment. Filarial antigen tests suggested that all 3 treatments had significant activity against adult *W. bancrofti*; albendazole–DEC combination had the greatest activity according to this test, with antigen levels decreasing to 30·5% of pre-treatment antigen levels, 24 months after therapy. All 3 treatments were clinically safe and well tolerated. These results suggest that a single dose of albendazole 400 mg together with DEC 6 mg/kg is a safe and effective combination for suppression of microfilaraemia of bancroftian filariasis that could be considered for use in filariasis control programmes based on mass treatment of endemic populations.

**Keywords:** filariasis, *Wuchereria bancrofti*, chemotherapy, drug combinations, albendazole, ivermectin, diethylcarbamazine, Sri Lanka

## Introduction

Filariasis control programmes are increasingly moving toward a strategy of repeated annual single-dose mass treatment of endemic populations. Safe and effective single-dose regimens should not only improve compliance and coverage, but also decrease costs by simplifying drug distribution. There is no agreement on the ideal drug and its dose. Diethylcarbamazine citrate (DEC) has been used, initially as prolonged courses and subsequently as a single dose, for management of filarial infection (OTTESEN & RAMACHANDRAN, 1995). Recent studies have shown that combinations of DEC and ivermectin (iver) given as a single dose were more effective in reducing microfilaraemia than either drug given singly (CHODAKEWITZ, 1995; DREYER *et al.*, 1995). During this period it was also shown that the anthelmintic drug albendazole (alb) has macrofilaricidal effects on prolonged treatment (JAYAKODY *et al.*, 1993). Hence, in 1996 we carried out a study to determine the safety, tolerability and efficacy of single-dose combinations of albendazole with ivermectin, as well as albendazole with DEC for treatment of bancroftian filariasis (ISMAIL *et al.*, 1998). In that study albendazole, ivermectin and DEC were used in doses of 600 mg, 400 μg/kg and 6 mg/kg, respectively. Combination of albendazole with ivermectin or albendazole with DEC produced dramatic decreases in microfilaraemia over a period of 15 months. Filarial antigen levels also decreased throughout the period with all 3 combinations of drugs. The greatest decrease in antigenaemia was seen with the albendazole–DEC combination. The present study was designed to determine whether albendazole and ivermectin in doses of 400 mg and 200 μg/kg respectively and albendazole and DEC in doses of 400 mg and 6 mg/kg respectively would produce similar results over a period of 24 months. The albendazole 600 mg plus ivermectin 400 μg/kg arm was included for comparison.

## Patients and Methods

After obtaining informed consent 47 'healthy' male asymptomatic microfilaraemic volunteers aged 18–58 years were admitted to the National Hospital of Sri Lanka in Colombo during August–November 1996. Blood samples (1 mL) were filtered through a 3-μm pore size Nuclepore membrane for microfilariae (mf) counting. All subjects had pre-treatment mf counts above 100/mL. Albendazole (Zentel) and DEC (Banocide) were obtained from SmithKline Beecham, UK, and Burroughs Wellcome, India, respectively. Ivermectin was supplied from Merck Sharp & Dohme, France. Patients were stratified according to their pre-treatment mf counts and randomly allocated to 1 of 3 single-dose treatment groups (Table 1). The study was blinded to the extent that patients and clinicians evaluating adverse effects, and laboratory staff carrying out safety tests and measuring mf and antigen levels, were unaware of individual treatments. All patients were hospitalized for 4 days. They were admitted in the evening of Day 0 and a night blood sample was taken that day. Treatment was given after breakfast on Day 1 under the direct supervision of the investigators. The patients were closely monitored for adverse symptoms and signs during hospitalization and discharged after a night blood sample had been taken on Day 3. The patients were followed-up in the community for 24 months. Blood samples for mf (1 mL) and serology were taken at 2 weeks and at 1, 2, 3, 6, 9, 12, 15, 18 and 24 months. A clinical examination of the patients was also done at these times. Serum samples were stored at −20°C pending antigen analysis.

The geometric mean microfilaraemia levels, pre- and post-treatment for each group, were calculated using the formula

$$GM_{\bar{y}} = \sqrt[n]{y_1, y_2, y_3 \ldots y_n}$$

Microfilaraemia is expressed as geometric mean data for each group, using the '$n + 1$' convention to accommodate values of zero (i. e., adding 1 to all values prior to log transformation of the data and subtracting 1 from the anti-log of the mean of the log-transformed data). The reduction in microfilaraemia post-treatment was expressed as a percentage of the pre-treatment means.

Soluble *Wuchereria bancrofti* antigen was detected in the sera by a monoclonal antibody-based antigen-capture enzyme-linked immunosorbant assay as previously described (ISMAIL *et al.*, 1996). Relative antigen levels were calculated by dividing the antigen content of post-treatment sera by the antigen content of the pre-treatment serum of the same patient and converting the result to a percentage.

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Ethical clearance for this study was obtained from the institutional ethics review committee.

*Statistical analysis*

The results of the mf data and the antigen concentrations were compared by repeated measures ANOVA. Adverse effects were analysed using log linear models.

## Results

*Microfilaraemia*

Pre-treatment mf counts in the 47 patients ranged from 116 to 6524/mL, and the geometric mean pre-treatment mf levels in the 3 groups are given in Table 1.

Following treatment all 3 groups showed substantial reductions in microfilaraemia to less than 3% of the respective pre-treatment levels (Fig. 1). The combination of alb 400 mg–iver 200 μg/kg was found to be as effective as alb 600 mg–iver 400 μg/kg in reducing microfilaraemia. Both regimens with ivermectin showed a greater clearance of microfilaraemia compared to the alb 400 mg–DEC 6 mg/kg regimen up to 9 months post-treatment ($P < 0.001$ for all time points under 9 months by repeated measures ANOVA). Thereafter the differences were less marked. The percentage pre-treatment microfilaraemia levels in the alb 600–iver 400 and alb 400–iver 200 treatment groups increased slightly after the 12 months and were equivalent (2·31% and 2·87% respectively) at 24 months. The percentage pre-treatment microfilaraemia levels in the alb–DEC-treated group showed a gradual decline during the same period to 0·44% at 24 months. The relative mf levels were statistically equivalent among the 3 groups at each of these later time points.

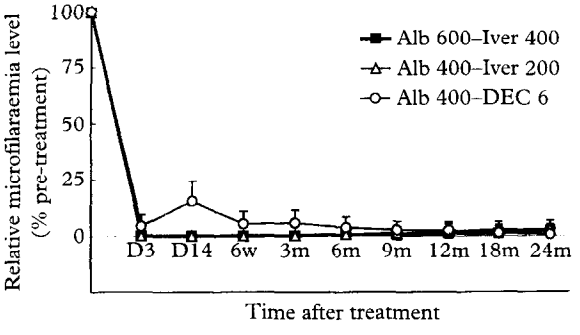


Fig. 1. Relative microfilaraemia levels (as a percentage of the pre-treatment count) after single-dose treatment with albendazole 400 mg plus DEC 6 mg/kg (○), albendazole 400 mg plus ivermectin 200 μg/kg (△) and albendazole 600 mg plus ivermectin 400 μg/kg (■). The points shown are the geometric mean values for each treatment group; vertical lines indicate the standard error. Both regimens that included ivermectin showed a greater clearance of microfilaraemia compared to the alb 400 mg–DEC 6 mg/kg regimen up to 9 months post-treatment ($P < 0.001$ for all time points <9 months by repeated measures ANOVA). D, days; w, weeks; m, months.

The absolute mf density pre- and post-treatment and the number of patients who were completely cleared of microfilaraemia post-treatment are shown in Tables 1 and 2, respectively.

*Adverse effects*

The adverse effects during the week following treatment were similar to those seen in Sri Lankan patients in previous studies using ivermectin, DEC and albendazole combinations in the treatment of asymptomatic microfilaraemics. Fever (in 63·0%), headache (in 43·5%), myalgia (in 32·6%) and weakness (in 30·4%) were the main adverse effects encountered. The adverse effects were transient, not lasting more than 1–2 days, and required no intervention other than administration of paracetamol in a few cases. The adverse effects were not related to the treatment schedule. When the mean reaction scores for each adverse effect were calculated as indicated previously (ISMAIL *et al.*, 1996), the scores increased with increasing pre-treatment mf levels particularly in respect of fever, headache and myalgia; however, this reached statistical significance only with regard to headache. Three patients (all treated with alb–DEC) developed scrotal swellings: 1 at 3 days post-treatment which disappeared by 2 weeks, another at 2 weeks post-

**Table 1. Absolute microfilaria densities in the Sri Lankan trial of single-dose chemotherapy for bancroftian filariasis: pre- and post-treatment values (1996–98)**

| | Absolute microfilaria density, range (GM) | | | | |
|---|---|---|---|---|---|
| Treatment | Pre-treatment | 6 months | 12 months | 18 months | 24 months |
| DEC 6 mg/kg + Alb 400 mg | 164–5426 | 0–442 | 0–722 | 0–984 | 0–413 |
| ($n = 16$) | (1012·9) | (38·3) | (23·4) | (12·8) | (4·5) |
| Alb 400 mg + Iver 200 μg/kg | 270–2806 | 0–499 | 0–856 | 0–1046 | 0–962 |
| ($n = 16$) | (1222·5) | (8·9) | (22·4) | (31·5) | (35·2) |
| Alb 600 mg + Iver 400 μg/kg | 116–6524 | 0–466 | 0–1704 | 0–2094 | 0–811 |
| ($n = 15$) | (922·6) | (5·7) | (9·3) | (10·2) | (21·4) |

Alb, albendazole; DEC, diethylcarbamazine; Iver, ivermectin; GM, geometric mean. The pre-treatment GM values in the 3 treatment groups did not differ significantly.

**Table 2. Number of patients cleared of microfilaraemia after single-dose chemotherapy (Sri Lanka, 1996–98)**

| | | Number cleared of microfilaraemia (%) | | | |
|---|---|---|---|---|---|
| Treatment | No. of patients | 6 months | 12 months | 18 months | 24 months |
| DEC 6 mg/kg + Alb 400 mg | 16 | 3/16 (19%) | 1/14 (7%) | 3/14 (21%) | 6/13 (46%) |
| Alb 400 mg + Iver 200 μg/kg | 16 | 4/14 (29%) | 2/14 (14%) | 2/16 (12%) | 4/15 (27%) |
| Alb 600 mg + Iver 400 μg/kg | 15 | 6/15 (40%) | 5/14 (36%) | 4/13 (31%) | 3/14 (21%) |

Alb, albendazole; DEC, diethylcarbamazine; Iver, ivermectin.

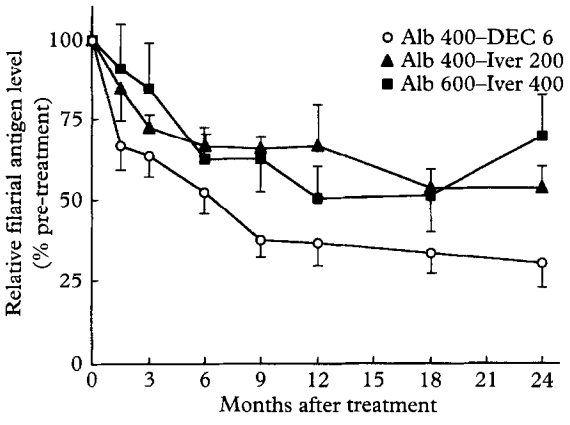


Fig. 2. Relative filarial antigen levels (as a percentage of the pre-treatment antigen levels) in the different treatment groups: albendazole 400 mg plus DEC 6 mg/kg (○), albendazole 400 mg plus ivermectin 200 μg/kg (▲) and albendazole 600 mg plus ivermectin 400 μg/kg (■). The points shown are the means; vertical lines indicate the standard error. The enhanced reduction in antigen concentration after alb 400–DEC 6 mg/kg vs other treatment groups was statistically significant at 24 months ($P < 0.05$).

treatment which persisted for 18 months before it regressed and the last presented at 3 months and was not seen at the next follow-up visit at 6 months. All swellings were small, non-tender and did not cause discomfort to the patient.

Seven patients (1 in the alb 600–iver 400 group, 2 in the alb 400–iver 200 group and 4 in the alb 400–DEC group) showed mild elevation of liver enzymes. In all patients the elevation was mild and transient returning to normal levels by Day 14. Serum creatinine level showed minimal increases in 4 patients (1 in the alb 600–iver 400 group, 2 in the alb 400–iver 200 group and 1 in the alb 400–DEC group). In 2 of these patients the creatinine level returned to normal by Day 14 and in the other 2 by Day 42.

*Antigen data*

Figure 2 shows the changes in the serum concentrations of filarial antigens with time for the 3 treatment groups. Antigen concentrations decreased significantly from pre-treatment concentrations in all 3 groups during the 24-month follow-up. Antigen concentrations fell more slowly in the alb 400–iver 200 group than in the other 2 groups, but this difference was significant only at the 6-month time point. None of the treated subjects completely cleared the antigenaemia. This finding is consistent with other trials of single-dose treatment regimens. The greatest reduction in relative antigen concentrations was seen in the alb 400–DEC group (relative antigen concentration 30·5% at 24 months) but the difference between groups was significant only at the 24-month time point ($P < 0.05$).

## Discussion

This study has shown for the first time that the combination of albendazole 400 mg with ivermectin 200 μg/kg is as effective as the combination of albendazole 600 mg with ivermectin 400 μg/kg in reducing the microfilaraemia of *W. bancrofti* infections over a 24-month period to less than 3% of pre-treatment values. mf levels were reduced to under 1% of pre-treatment levels in subjects treated with alb–DEC. This study did not compare the efficacy of combinations of antifilarial drugs with monotherapy using DEC, ivermectin or albendazole as this has been done in previous studies (CHODAKEWITZ, 1995; DREYER *et al.*, 1995; ISMAIL *et al.*, 1998). It would have been ideal to include 3 single-drug treatment arms, namely albendazole, ivermectin and DEC alone in this study for comparison. However, this was not done as recruitment of more volunteers was becoming difficult and it would have prolonged the study unduly. Long-term studies are needed to determine whether microfilaraemia is permanently suppressed to very low levels after this treatment. This is important because it would affect the number of cycles of treatment needed to interrupt transmission in endemic areas.

All 3 regimens used were well tolerated and safe with minimal adverse effects. Antigen levels significantly decreased from pre-treatment levels in all 3 groups throughout the study with the greatest reduction seen in the alb 400 mg–DEC 6 mg/kg group (relative antigen level 30·5% at 24 months, i.e., a 69·5% reduction). These results are consistent with the findings in our previous albendazole combination study where alb–DEC produced a significantly higher reduction (77% at 15 months post-treatment) of adult antigen levels than either alb–iver or DEC–iver combinations (ISMAIL *et al.*, 1998). A recent study from South India has shown the efficacy of combination alb–DEC therapy against brugian filariasis (SHENOY *et al.*, 1999).

ADDISS *et al.* (1997), in a study conducted on Haitian children with bancroftian microfilaraemia, assessed the effect of a single-dose combination of albendazole 400 mg and ivermectin 200–400 μg/kg. The period of follow-up in that study was 4 months. Their findings on the microfilaricidal effect are similar to the results of our study. Unfortunately antigen studies were not performed in their study. The advantages of using a combination of albendazole with ivermectin is that it causes a rapid initial decrease in microfilaraemia which would have a positive impact in reducing transmission. This same combination also has a significantly greater effect against *Trichuris* infections than a combination of albendazole plus DEC (ISMAIL & JAYAKODY, 1999). BEACH *et al.* (1999) reported that a combination of albendazole plus ivermectin was a more efficacious treatment for intestinal helminthiasis and bancroftian filariasis in Haitian children, resulting in nutritional benefits not found with either drug alone; however, a combination of albendazole plus DEC was not used in that study. The disadvantage of using ivermectin outside countries endemic for loiasis and onchocerciasis (where DEC cannot be used) would be its non-availability and high cost.

In conclusion, our study has confirmed the prior finding that single-dose combination therapies provide long-term suppression of *W. bancrofti* microfilaraemia to very low levels. We recommend the combination of albendazole 400 mg plus DEC 6 mg/kg as the preferred choice for community treatment of bancroftian filariasis because of its greater macrofilaricidal activity shown by the decline in filarial antigenaemia, its low cost and availability. Combination therapy with the broad-spectrum anthelmintic albendazole provides an additional bonus in community treatment over DEC monotherapy because it provides a benefit for many people who do not have filariasis by treating common intestinal helminths. Additional studies are needed to measure the impact of mass therapy on transmission of filariasis in communities and to determine whether mass therapy with single-dose combination regimens can eliminate filariasis in communities and regions.

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## Book Reviews

**Selection of Basic Laboratory Equipment for Laboratories with Limited Resources.** W. L. Johns & M. M. El-Nageh. Alexandria: World Health Organization, Regional Office for the Eastern Mediterranean, 2000. 260pp. Price US$ 9.50 (+ 25% p+p). ISBN 92-9021-245-4.

The authors are to be congratulated for tackling such a difficult subject and producing a book that is both informative and readable. The book is divided into 3 sections: choosing and buying laboratory equipment, energy requirements for laboratory equipment, and information annexes. The first of these (choosing and buying) provides detail of points to consider when selecting equipment, the buying business, procurement, obtaining quotations and how to avoid high-pressure selling. It also includes common consumer problems, the care and maintenance of equipment and standard operating procedures. The dangers of buying second-hand items and use of home-made equipment are also covered. The second section provides valuable advice on energy requirements including hand power, generators, power surges and cuts, use of batteries and solar energy. The final section consists of 10 annexes including specification sheets, sample forms, ordering and storage, a glossary of terms and useful references.

It would not be possible to list suppliers of equipment for such a large geographical area; however, the authors have provided an address for several countries which offers advice on low-profit, second-hand and reconditioned equipment.

This book is a valuable addition in laboratories in low-income countries and is recommended for those involved in the purchase of equipment. I commend the authors for providing a highly readable, informative book on this difficult subject.

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**District Laboratory Practice in Tropical Countries, Part 2.** M. Cheesbrough. Cambridge: Cambridge University Press, 2000. vi+434pp. Price £40.00. ISBN 0-521-66545-0 (paperback). Low-price edition available to developing countries, ISBN 0-521-66546-9.

This second part continues a series of publications produced to assist laboratories in tropical countries and, as with previous volumes, it typifies the highly commendable series of texts. The author, with the valuable help of a large number of experts, has set out to cover in detail tests used in microbiology, haematology and blood transfusion with emphasis being placed on quality assurance, good laboratory practice and the use of standard operating procedures.

The section on microbiological tests gives details of the examination of all the common clinical specimens and includes those for sputum, various swabs, effusions, urine, blood and faeces. Each specimen type includes a section which provides a summary of the examinations including macroscopic, microscopic and culture, the type of culture media used and possible results on a daily basis. The centre section contains 116 colour pictures of bacteria, fungi, HIV tests, normal blood cells and those with malaria parasites. As with other illustrations the photography is of a high standard. The second of 3 chapters describes haematological procedures ranging from collection of blood, various tests including haemoglobin, red cell indices, ESR, the investigation of sickle-cell disease and bleeding disorders. The final chapter describes methods used in blood transfusion and includes quality assurance, donation and storage, grouping and compatibility testing. The final sections contain lists of recommended books, an appendix listing 90 media, stains, solutions, etc., with details of reagents and method of preparation, and finally an appendix giving useful addresses.

In conclusion, this book, along with Part one, is worth having in any tropical laboratory for general use, and in particular for those involved in training of laboratory staff.

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