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EFFICACY OF SINGLE-DOSE DIETHYLCARBAMAZINE COMPARED WITH DIETHYLCARBAMAZINE COMBINED WITH ALBENDAZOLE AGAINST *WUCHERERIA BANCROFTI* INFECTION IN PAPUA NEW GUINEA

MOSES J. BOCKARIE,* LIVINGSTONE TAVUL, IRVIN IBAM, WILL KASTENS, FRED HAZLETT, DANIEL J. TISCH, MICHAEL P. ALPERS, AND JAMES W. KAZURA

Papua New Guinea Institute of Medical Research, Madang, Papua New Guinea; Curtin University of Technology, Perth, Western Australia, Australia; Center for Global Health and Diseases, Case Western Reserve University School of Medicine, Cleveland, Ohio

Abstract. The efficacy of diethylcarbamazine alone was compared with diethylcarbamazine plus albendazole in residents of an island in Papua New Guinea endemic for *Wuchereria bancrofti*. There was no statistically significant difference between the two drug regimens in decreasing the microfilaria positive rate at 12 and 24 months after a single-dose treatment with either regimen, e.g., 50.0% clearance of microfilaria at 24 months for diethylcarbamazine alone versus 65.7% clearance of microfilaria for diethylcarbamazine plus albendazole ($P > 0.05$). In contrast, diethylcarbamazine plus albendazole resulted in a significant decrease in Og4C3 antigen prevalence (17%; $P = 0.003$) at 24 months whereas diethylcarbamazine did not (10%; $P = 0.564$). These data showed no statistically significant difference in the efficacy of the two drug regimens in lowering the microfilaria reservoir, but they support the use of diethylcarbamazine combined with albendazole in mass treatment programs on the basis of greater activity against adult worms.

INTRODUCTION

The strategy of the Global Program to Eliminate Lymphatic Filariasis (GPELF) is built on the notion that mass drug administration (MDA) consisting of 4–6 annual cycles of single-dose anti-filarial drugs will reduce the reservoir of microfilaria (MF) to a level that irrevocably stops transmission through the obligatory mosquito vector.[1] Drugs currently recommended for MDA include diethylcarbamazine (DEC) combined with albendazole (ALB), DEC-fortified salt, and ivermectin combined with ALB.[1–4] The latter regimen is used in areas of Africa where onchocerciasis is co-endemic with lymphatic filariasis because DEC may cause severe allergic reactions. A recent report from two sentinel sites in Egypt where pre-intervention MF positive rates were 3.1% and 11.5% has shown that a national control program consisting of five annual cycles of DEC plus ALB can lower the MF prevalence to nearly $\leq 1\%$, a threshold value that is believed to indicate interruption of transmission.[5] In 2005, 42 of the 83 filariasis-endemic countries participated in GPELF and 146 million people were treated with DEC plus ALB, ivermectin plus ALB, or DEC-fortified salt.[6]

Albendazole is the most recent addition to the armamentarium of anti-filarial drugs used for MDA. Similar to related benzimadizole carbamate drugs, the anthelmintic activity of ALB is related to its ability to interfere with tubulin polymerization and microtubule formation. Before its evaluation as an anti-filarial drug, ALB was known to have excellent activity against gastrointestinal nematodes that commonly infect children living in filariasis-endemic areas.[7] This attribute represents added health benefits to MDA programs directed against lymphatic filariasis. Clinical trials examining the efficacy of ALB by itself have shown the drug decreases *Wuchereria bancrofti* MF levels to a lesser extent than DEC or ivermectin[4,8], and that in combination with DEC, it kills adult worms as assessed by reduced filarial antigenemia and motility of adult worms imaged by ultrasonography.[9–11] Direct comparisons of the efficacy of DEC alone with DEC combined with ALB have only been reported from India. The results of such studies are inconsistent with respect to the relative efficacies of the two regimens.[12–17] The objective of the study described here was to compare the efficacy of single-dose DEC alone with DEC combined with ALB on MF and filarial antigenemia in residents of a *W. bancrofti*-endemic area of Papua New Guinea.

MATERIALS AND METHODS

Study area and study design. The study was reviewed and approved by the Medical Research Advisory Committee of the Papua New Guinea Department of Health and the Institutional Review Board for Human Investigations at University Hospitals and Case Western Reserve University (Cleveland, OH). Persons eligible to participate were residents of all three villages located on Bagabag Island, which is in the Coral Sea 65 km northeast of Madang in Madang Province, Papua New Guinea. Vegetation of the island is mid-mountain tropical forest with areas of re-growth after cultivation. Rainfall is seasonal, with the wet season normally occurring from October to May and the dry season from June to September. Annual average rainfall is 3,400 mm. As in other areas of Papua New Guinea, members of the *Anopheles punctulatus* group of mosquitoes are the vectors of *W. bancrofti*.[18,19] Residents live in traditional houses built from sago palms. Fishing and subsistence farming are the major activities.

After advertising campaigns to explain the objectives of the study to community residents, individuals were asked for informed consent to participate. Assent of children included approval of a parent or guardian. All residents ≥ 2 years of age were eligible to participate; pregnant women were excluded. Individuals who gave informed consent were assigned randomly to receive either a single oral dose of DEC (6 mg/kg of body weight) or DEC in combination with ALB (400 mg given as a single dose regardless of body weight). The drugs were provided by the World Health Organization. Surveys to monitor filarial infection status were performed immediately before witnessed drug administration and 6, 12, and

* Address correspondence to Moses J. Bockarie, Center for Global Health and Diseases, Wolstein Research Building, Case Western Reserve University School of Medicine, 10900 Euclid Avenue, Cleveland, OH 44106-7286. E-mail: moses.bockarie@case.edu

24 months later. We conducted the study between September 1999 and September 2001.

Measurements of filarial infection. Venous blood (2–5 mL, depending on age) was collected in EDTA anti-coagulated tubes between 10:00 PM and 2:00 AM. Nocturnally periodic *W. bancrofti* MF were quantified from a blood volume of 1 mL by light microscopy after Nuclepore® filtration.[20] Results are expressed as MF per milliliter of blood. Filarial antigenemia as an estimate of adult worm load was determined using the Og4C3 antigen enzyme-linked immunosorbent assay.[21,22] The prevalence and intensity of filarial antigenemia were determined and expressed as titer groups as instructed by the manufacturer of the diagnostic kit (TropBio Pty Ltd, Townsville, Queensland, Australia). The results are analyzed according to the level of antigenemia. Titer groups 1 and 2 are classified as negative, titer groups 3 and 4 are designated as low antigenemia, and titer groups 5, 6, and 7 as high antigenemia, as described previously in this population.[23,24]

Data analysis. Drug efficacy was measured for all individuals given either DEC or DEC plus ALB and for the subset of participants found to be Og4C3 antigen positive, i.e., infected with *W. bancrofti*, before drug administration. The MF and Og4C3 levels intensities were compared between treatment groups and across follow-up periods using the non-parametric Kruskal-Wallis test. Because of highly skewed MF distributions, tabulated results are presented as geometric means of all individuals (MF values + 1). Dichotomous outcomes were compared with a chi-square test for population data or McNemar's test for paired samples. Data were analyzed using SAS statistical software version 9.1 (SAS, Carey, NC).

RESULTS

Baseline demography and infection variables. A census conducted six months before the trial began showed that there were 1,477 residents of Bagabag Island. After excluding residents who were ineligible or refused to participate, 1,007 persons (68.2% of the *de facto* population) were treated with a single dose of DEC (n = 497) or DEC combined with ALB (n = 510). Demographic characteristics and pre-treatment infection values of the two groups are summarized in Table 1. The proportion of males and females in the two treatment groups were identical. The mean age of study participants was 23.4 and 24.7 years in the DEC and DEC plus ALB groups. The proportion of individuals who reported sleeping under untreated bed nets was 61.0% for the DEC group and 63.9% for the DEC plus ALB group. Pre-treatment MF prevalence and geometric mean intensity were similar for the two groups (DEC alone, 28.0% and 4.3 MF/mL; DEC plus ALB, 27.1% and 4.0 MF/mL). Approximately twice as many people were Og4C3 antigen positive as MF positive, with no difference in prevalence between the two treatment groups.

Effect of DEC versus DEC combined with ALB on MF. Of the 1,007 participants from whom blood was obtained before treatment, 729 donated blood samples at the 24th month post-treatment survey: 381 in the DEC group and 348 in the DEC plus ALB group. Considering all participants regardless of their pre-treatment infection status (i.e., including both filarial antigen–positive [infected] and filarial antigen–negative [uninfected] persons given anti-filarial drugs, as is done in control programs where infection status prior to MDA is not known), MF prevalence decreased by 40.7% for the group given DEC alone and by 43.9% for the group given DEC combined with ALB. There was no difference between the two groups in MF positive rates at 24 months (16.6% for DEC alone versus 15.2% for DEC plus ALB; $P = 0.68$). The corresponding 24-month post-treatment MF intensities were 0.7 and 0.5 MF/mL ($P = 0.53$). The proportionate decreases in MF intensities for DEC and DEC plus ALB were 87.5% and 83.7%.

A total of 245 participants who were Og4C3 antigen positive at baseline provided blood for MF quantification at baseline and at the 6, 12, and 24 months post-treatment surveys. A total of 119 participants were given DEC alone; 126 were given DEC combined with ALB. Table 2 shows the pre-treatment and post-treatment MF rates and intensities. The baseline MF-positive rate and geometric mean MF intensity for the DEC and DEC plus ALB groups were similar (52.1% and 24.4 MF/mL versus 55.5% and 25.4 MF/mL; $P = 0.58$). The proportion of study participants who cleared their MF at six months was greater for those given DEC plus ALB than DEC alone ($P = 0.011$). At 12 months, the MF clearance rate for DEC plus ALB (34.3%) was still greater than for DEC alone (25.8%), but this difference was not statistically significant ($P = 0.29$). At 24 months, the proportion of individuals who converted from MF positive to MF negative continued to increase in both groups. Although MF clearance was greater for DEC combined with ALB than for DEC alone, the difference was not statistically significant ($P = 0.07$). With respect to the geometric mean MF level, there was a trend for lower values in the DEC plus ALB versus the DEC group. The differences between the groups was not statistically significant ($P = 0.17$–0.60).

Effect of DEC versus DEC combined with ALB on Og4C3 antigenemia. Og4C3 antigen data for the 245 antigen-positive participants described in Table 2 were available from the 6- and 12-month post-treatment surveys. At six months, four persons in the DEC group and four persons in the DEC plus

TABLE 1
Baseline characteristics of individuals allocated to receive either DEV alone or DEC in combination with ALB*

	DEC alone	DEC plus ALB	Total
No. in treatment group	497	510	1,007
No. of males (%)	260 (52.3)	268 (52.4)	528 (52.4)
Mean age in years	23.4	24.7	24.1
No. sleeping under untreated bed nets (%)	303 (61.0)	326 (63.9)	629 (62.5)
No. MF positive (%)	139 (28.0)	138 (27.1)	277 (27.5)
Geometric mean MF intensity, Mf/mL (range)	4.3 (0–18,891)	4.0 (0–16,403)	4.1 (0–18,891)
No. Og4C3 antigen positive (%)	271 (54.5)	256 (50.2)	527 (52.3)

* DEC = diethylcarbamazine; ALB = albendazole; MF = microfilaria.

TABLE 2

Impact of single-dose treatment with DEC alone or DEC combined with ALB on MF-positive rate and MF mean intensity forOg4C3 antigen-positive persons at 6, 12, and 24 months post-treatment*

Treatment group	DEC alone n = 119	DEC plus ALB n = 126	P†	Total n = 245
Pre-treatment				
No. MF+ (%)	62 (52.1)	70 (55.5)	0.59	132 (53.9)
Geometric mean MF/mL (maximum)	24.4 (13,752)	25.4 (14,181)	0.86	24.94
6 months post-treatment				
No. MF+ (%)	56 (47.1)	51 (40.5)	0.30	107 (43.7)
% MF clearance	9.7	27.1	0.01	18.9
Geometric mean MF/mL (maximum)	7.49 (4,477)	4.46 (3,333)	0.21	5.77
12 months post-treatment				
No. MF+ (%)	46 (38.7)	46 (36.5)	0.73	92 (37.6)
% MF clearance	25.8	34.3	0.29	30.3
Geometric mean MF intensity (maximum)	4.27 (1,939)	3.47 (8,400)	0.60	3.38
24 months post-treatment				
No. MF+ (%)	31 (26.1)	24 (19.0)	0.19	55 (22.4)
% MF clearance	50.0	65.7	0.07	58.3
Geometric mean MF intensity (maximum)	1.52 (3,691)	0.82 (1,063)	0.17	1.13

* For definitions of abbreviations, see Table 1.
† *P* value for DEC alone versus DEC plus ALB.

ALB group became antigen negative (3.3% and 3.2%). At 12 months, the proportion of individuals who converted from antigen positive to antigen negative continued to increase but there was no difference between the two treatment regimens (13.4% for DEC and 11.9% for DEC plus ALB; $P = 0.68$). Because of logistical reasons at the 24-month post-treatment survey, plasma was not available for the same individuals. However, plasma could be processed from 271 individuals who were observed pre-treatment and at 24 months post-treatment (n = 123 for DEC and n = 148 for DEC plus ALB). Between baseline and 24 months post-treatment, three individuals who had been given DEC plus ALB converted to an antigen-positive status and five individuals given DEC alone became antigen positive. Overall, antigen prevalence decreased from 65% to 56% in the individuals who received DEC plus ALB ($S = 8.895$, $P = 0.003$) but only from 54% to 53% in the individuals who received DEC alone ($S = 0.333$, $P = 0.564$). The decrease in Og4C3 antigen concentration and Og4C3 antigen clearance among antigen positive individuals was consistently greater with the DEC plus ALB treatment relative to DEC alone (Table 3). Among antigen-positive individuals, 16.7% who received DEC plus ALB cleared their antigenemia versus 10.4% of those who received DEC alone ($\chi^2 = 1.25$, $P = 0.259$).

DISCUSSION

Results of our study show that a single dose of DEC alone and DEC combined with ALB are equally effective in lowering the MF reservoir. Although DEC combined with ALB led to a greater reduction in MF prevalence at six months relative to DEC by itself (27.1% versus 9.7% clearance), there was no difference between the two treatments at 12 and 24 months (Table 2). We also observed no difference in the MF positive rate when persons without microfilaremia before drug administration were included in the analysis. This latter observation is relevant to the GPELF strategy because all residents of communities that meet the criterion for MDA, i.e., community MF-positive rate ≥ 1%, will be given antifilarial drugs regardless of infection status (which will not be known before MDA begins because pre-treatment screening for infection is performed on a limited number of individuals). The drug combination, however, appears to be superior in terms of its activity against adult worms, as estimated by changes in Og4C3 filarial antigenemia. Two years after administration of a single dose of DEC plus ALB, a greater proportion of persons converted from antigen-positive to antigen-negative status (16.7%) compared with persons given a single dose of DEC alone (10.4%) (Table 3). This apparent cure of infection occurred despite ongoing transmission of *W. bancrofti* during the follow-up period after MDA, as documented by the observation that 8 of 108 individuals identified as antigen negative before MDA were antigen positive 24 months later (three had been given DEC plus ALB as part of the MDA and five had been given DEC as part of the MDA).

The data reported here are the first from Papua New Guinea comparing the efficacy of single-dose DEC with DEC plus ALB given a manner consistent with how the drugs will be deployed in MDA programs in this country and other disease-endemic regions where administration of DEC is in-

TABLE 3

Decrease and clearance of Og4C3 antigenemia 24 months following treatment with DEC alone or DEC in combination with ALB*

	DEC alone			DEC plus ALB		
Baseline antigenemia	No. antigen positive at baseline	No. (%) decreasing to low antigenemia	No. (%) converting from positive to negative	No. antigen positive at baseline	No. (%) decreasing to low antigenemia	No. (%) converting from positive to negative
High	61	9 (14.7)	5 (8.2)	85	16 (18.8)	11 (12.9)
Low	6	–	2 (33.3)	11	–	5 (45.5)
Total antigen positive	67	–	7 (10.4)	96	–	16 (16.7)

* For definitions of abbreviations, see Table 1.

dicated, such as Pacific islands, Asia, Latin America, and areas of Africa where onchocerciasis and loiasis are not endemic. The addition of 1,007 study subjects from Papua New Guinea, 527 confirmed to be Og4C3 antigen positive before treatment, substantially increases the number of observations that can be used to analyze the potential additive effects of ALB to DEC monotherapy.

Few studies have evaluated the relative efficacy of DEC alone versus DEC combined with ALB. A systematic review of all published randomized studies of drugs used in MDA programs and a separate systematic review of ALB administration for lymphatic filariasis control conducted five years after the adoption of this regimen by the GPELF identified only three studies that directly compared DEC alone to DEC plus ALB.[12,24–27] Consistent with results reported here, no statistically significant difference in MF status was observed in these studies between DEC alone and DEC combined with ALB, although the most recent trial involving 80 MF-positive school children in Haiti showed a difference in MF density at six-months post-treatment.[26]

The most comprehensive studies of ALB and DEC to date have been from Tamil Nadu, India, where changes in MF-positive rates and filarial antigenemia have been monitored after one, two, and three annual cycles of MDA with DEC alone or DEC plus ALB.[13–15] Although the ecology and epidemiology of lymphatic filariasis in this area of India and Papua New Guinea are different (e.g., culicine mosquito vector and low pre-treatment MF-positive rates in India versus anopheline mosquito vector and higher MF positive rates in Papua New Guinea), both found a greater effect of the ALB combination on MF prevalence only at six months after one MDA. Larger sample sizes or additional MDAs may be necessary to detect a moderate and cumulatively greater effect of the ALB against MF, as was observed in the Indian study. After three annual MDAs, the ALB combination was found to be clearly and significantly superior to DEC alone. Comparative differences in antigenemia clearance between treatments failed to achieve statistical significance in our study or in India. Yet paradoxically, both studies demonstrated a significant decrease in antigen prevalence for the ALB treatment but not for DEC alone. It may be concluded that the ALB treatment is superior to DEC, but that recent sample sizes have not been adequately large to detect the difference in hypothesis testing. These results highlight a moderate but potentially important effect of ALB on MF and antigenemia in the context of MDA.

Considering the superior efficacy of single dose DEC plus ALB over DEC alone demonstrated here in reducing *W. bancrofti* antigenemia and the added benefit of ALB on treating childhood geohelminth infections and improving nutrition,[7] our results support the recommendation that ALB be included in filariasis MDA programs. In addition, since these and other data provide more field-based information to quantify the relative efficacy of the three MDA regimens recommended by GPELF, it is hoped they can be used to refine mathematical models of filariasis transmission that will inform decisions concerned with continuation and termination of national and regional elimination programs.

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Authors' addresses: Moses J. Bockarie, Fred Hazlett, Daniel J. Tisch, and James W. Kazura, Center for Global Health and Diseases, Case Western Reserve University, Cleveland, OH. Livingstone Tavul, Irvin Ibam, and Will Kastens, Papua New Guinea Institute of Medical Research, Madang, Papua New Guinea. Michael P. Alpers, Curtin University of Technology, Perth, Australia.

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