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COMPARISON OF SINGLE-DOSE DIETHYLCARBAMAZINE AND IVERMECTIN FOR TREATMENT OF BANCROFTIAN FILARIASIS IN PAPUA NEW GUINEA

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Abstract. This double-blind study compared the clinical safety and parasitologic efficacy of single-dose regimens of diethylcarbamazine (DEC) and ivermectin for treatment of bancroftian filariasis in Papua New Guinea. Five groups of 10 men each with mean levels of parasitemia ranging from 2,985 to 5,185 microfilariae (mf)/ml were given DEC (6 mg/kg/ of body weight one time or 1 mg/kg, then 6 mg/kg four days later) or ivermectin (220 μg/kg; 20 μg/kg, then 200 μg/kg four days later or 20 μg/kg, then 400 μg/kg four days later). No significant side effects (e.g., acute adenolymphangitis, fever lasting more than eight hours, hypotension) were observed in any of the five treatment groups. The magnitude of reduction in microfilaremia was greater ($P < 0.01$) for the three ivermectin groups versus the two DEC groups in the first 30 days after drug administration (mf levels < 1% of pretreatment values versus 22.6–41.5%, respectively). At 90 and 180 days, mf levels continued to decrease in the DEC groups whereas they increased in the ivermectin groups given a total dose of 220 μg/kg. Eighteen months after drug administration, individuals given DEC or 420 μg/kg of ivermectin had the greatest degree of reduction in microfilaremia (86–90% compared with the pretreatment values). Decreases in parasite antigenemia measured by enzyme-linked immunosorbent assay for a secreted 200-kD adult worm antigen were greatest for the single-dose DEC group (39.7% decrease relative to the pretreatment level versus 7.8–15.7% for the ivermectin groups). These results indicate that single-dose DEC and ivermectin are well-tolerated by *Wuchereria bancrofti*–infected individuals with high levels of microfilaremia. Both drugs lead to sustained reductions in microfilaremia up to 18 months after administration.

Lymphatic filariasis caused by *Wuchereria bancrofti, Brugia malayi,* and *B. timori* is estimated to affect 80 million persons worldwide.[1] Clinical manifestations of infection with these parasites include elephantiasis, genital swelling, and tropical eosinophilia. Although control of mosquito vectors has been successful in decreasing transmission of filariasis in some parts of the world, logistical problems related to repeated insecticide spraying, its cost, and pesticide resistance limit the utility of this approach. Bed nets are useful for decreasing exposure of individuals to mosquito bites, but their utility for sustained control of infection at a community level has not been demonstrated. Mass chemotherapy has therefore been proposed to be the most practical and effective means to limit transmission and reduce morbidity from lymphatic filariasis.[1]

Diethylcarbamazine (DEC) has been the major drug used for treatment of human lymphatic filariasis since 1947. Its immediate activity is directed primarily against blood-borne microfilariae (mf), the parasite stage ingested by the mosquito vector. When DEC is given in conventional doses of 6 mg/kg of body weight over a 10–14-day period (cumulative dose of 72 mg/kg), the level of microfilaremia decreases by approximately 80–90% within several days. Parasitemia is frequently undetectable after completion of therapy. Microfilaremia may remain low for more than six months, but in some endemic areas it has been reported to increase progressively after this time.[2] This drug also kills adult-stage worms, particularly when higher doses are administered.[3]

Repeated doses of DEC are believed to be necessary to cause a significant decrease in transmission and diminish the frequency of morbid complications from chronic infection. Mass delivery of DEC over a 10–14-day period is,

however, not feasible in endemic areas of most less-developed countries. This problem is compounded by the fact that the drug frequently elicits side effects such as fever, transient swelling of the extremities, epididymitis, and scrotal swelling. In addition, persons with high intensities of microfilaremia have a propensity to develop fever and other systemic side effects such as dyspnea.[4, 5] The discovery that ivermectin was highly effective and relatively safe for treatment of infection due to the related filarial parasite *Onchocerca volvulus*[6] prompted evaluation of its efficacy for management of lymphatic filariasis.[7] When single doses of 20–120 μg/kg of ivermectin were given to Indians with *W. bancrofti* infections, an 80% reduction in parasitemia was observed six months after drug administration. Moreover, the severity of acute side effects did not differ from that elicited in persons given a conventional course of DEC.[7, 8] Subsequent reports showed that the decreases in parasitemia persist for one year after treatment (reductions to 0.9% of the pretreatment level were observed at this time).[9–12]

The current study describes the results of a double-blind trial designed to compare the efficacy and safety of various single-dose regimens of ivermectin and DEC. Single standard doses of each drug (220 μg/kg of ivermectin and 6 mg/kg of body weight of DEC) and split-dose regimens that included a priming dose administered four days earlier were given to Papua New Guineans in whom pretreatment levels of *W. bancrofti* microfilaremia exceeded 3,000 mf/ml. Our results indicate that the severity of acute side effects is minimal following treatment with either drug and that split-dose regimens are no better than single-dose treatment. Single-dose DEC was found to be the most effective drug in terms of its capacity to mediate sustained reductions in microfilaremia and filarial antigenemia 18 months after treatment.

SUBJECTS AND METHODS

Study population

Approval for these studies was obtained from the Institutional Review Board for Human Studies of University Hospitals of Cleveland, Case Western Reserve University, and the government of Papua New Guinea. The experimental protocol was developed by the World Health Organization/Tropical Diseases Research Programme and conducted under the auspices of the Papua New Guinea Institute of Medical Research. All study subjects were informed of the purpose of the study and gave permission for drug administration, venipuncture, and repeated physical examinations.

Fifty adult men who lived in East Sepik Province, Papua New Guinea were selected from a sample of 130 screened for microfilaremia by Nuclepore filtration (Nucleopore Corp., Costar, Cambridge, MA) of 1-ml blood samples obtained between 10:00 PM and midnight.[13] Women were not included in the study since ivermectin has not been approved for use during pregnancy and pregnancy tests were unavailable. Criteria for inclusion in the study included 1) parasitemia exceeding 100 mf/ml blood; 2) lack of symptoms attributable to acute manifestations of lymphatic filariasis, such as fever, lymph node pain, or painful swelling of the scrota and extremities; 3) liver function test results (serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, alkaline phosphatase, bilirubin), renal function test results (blood urea nitrogen, creatinine), and a hematocrit (> 35%) within normal limits.

Treatment protocol

The study was conducted in a double-blind fashion for the first year. Individuals were randomized to one of five treatment groups: 1) DEC, 6 mg/kg of body weight; 2) DEC, 1 mg/kg on day 1 and 6 mg/kg four days later; 3) ivermectin, 220 μg/kg; 4) ivermectin, 20 μg/kg and 200 μg/kg four days later; 5) ivermectin, 20 μg/kg and 400 μg/kg four days later. Persons receiving single doses of DEC or ivermectin were not treated and given placebo on the initial treatment day. Vital signs and medical histories were obtained, and physical examination of the genitalia, major lymph node groups, extremities, and cardiovascular system was performed four times per day for the first seven days after drug administration, and 14, 30, 90, 180 days, and 18 months later. The severity of side effects was evaluated by a clinical scoring system in which the degree of lymph node, extremity, and genital enlargement and induration were assigned a value of 0 (no abnormality), + 1 (mild), + 2 (moderate), or + 3 (severe). Scores for each individual in a treatment group were added and a mean daily score was calcu-

TABLE 1
Acute side effects of diethylcarbamazine (DEC) and ivermectin treatment

Treatment group	Local inflammation side effect score*						Fever T (≥38°C)†
	Lymph nodes		Extremities		Scrotal contents		
	Pre	Post	Pre	Post	Pre	Post	
DEC (6 mg)	2.3	2.4	0.1	0.1	0.6	0.6	2/10
DEC (1 + 6 mg)	3.5	3.4	0.2	<0.1	0.4	0.5	2/10
Ivermectin (220 μg)	2.1	2.2	0	0	0.3	0.3	3/10
Ivermectin (20 + 200 μg)	5.2	4.2	0	0.1	0.7	0.7	2/10
Ivermectin (20 + 400 μg)	4.1	4.7	0.1	0.1	0.2	0.2	1/10

* Mean severity scores were calculated from the composite value for all subjects in a given group as described in the Subjects and Methods. Pretreatment values (Pre) were compared with the calculated daily mean values in the seven days following administration of the drug (Post).
† Values refer to the number of persons who had an oral temperature exceeding 38°C at any time during the seven days following drug administration. No persons had fever before or at the time the drug was given.

lated by dividing the sum by the number of individuals per group. The maximum group score possible for axillary, inguinal, and femoral lymph nodes was 18.0, for extremities 6.0, and for genitalia 6.0.

Microfilaremia and parasite antigenemia

Two-milliliter blood samples were obtained between 10:00 PM and midnight and processed by Nuclepore filtration to quantify microfilaremia. Both a 1-ml volume of blood and a 0.1-ml volume diluted 1:10 in normal saline were processed so that accurate measures of the intensity of microfilaremia in persons with high parasitemias could be obtained. To compare the efficacy of the various treatment regimens, individual values were normalized so that the reduction in microfilaremia is expressed as a percent of the pretreatment level. Levels of soluble parasite antigenemia prior to drug administration and 18 months later were evaluated by a monoclonal antibody–based enzyme-linked immunosorbent assay that detects a 200-kD adult worm product in human serum.[14]

Statistical analysis

The Wilcoxon rank-sum test was used to evaluate the significance of differences in severity of acute side effects among the groups. For fever, the chi-square test for differences in frequency of occurrence was used. Group differences in the percent reductions of microfilaremia were tested for significance by Student's *t*-test using log-transformed mf counts + 1. The Kruskal-Wallis test was used to evaluate differences in the magnitude of reduction in filarial antigen levels between pretreatment and 18-month post-treatment serum samples. *P* values less than 0.05 were considered significant.

RESULTS

Patient groups

The mean ages of men in each of the study groups were similar (range 25–31 years old). There were no significant differences among the groups in the mean pretreatment levels of microfilaremia (calculated as the geometric mean of mf/ml + 1). The values for each of the groups were the following: DEC (6 mg/kg) 4,689 mf/ml; DEC (1 + 6 mg/kg) 2,985 mf/ml; ivermectin (220 μg/kg) 4,235 mf/ml; ivermectin (20 + 200 μg/kg) 5,185 mf/ml; ivermectin (20 + 400 μg/kg) 5,147 mf/ml. Pretreatment levels of microfilaremia obtained immediately before drug administration were within 20% of the value measured two weeks earlier.

Side effects of treatment

Pretreatment lymph node inflammation (axillary, inguinal, and femoral) was minor and did not vary among the groups (range of scores 2.1–5.2, with a possible maximum of 18.0) (Table 1). The most common site of lymph node swelling and induration was inguinal (7–9 persons per group). Epitrochlear, cervical, supraclavicular, or infraclavicular lymph node enlargement were observed in 1–3 persons per group. There was a minor degree of induration and swelling of the extremities and scrota (i.e., hydroceles) prior to drug administration (the respective ranges of severity scores were 0–0.2 and 0.2–0.7).

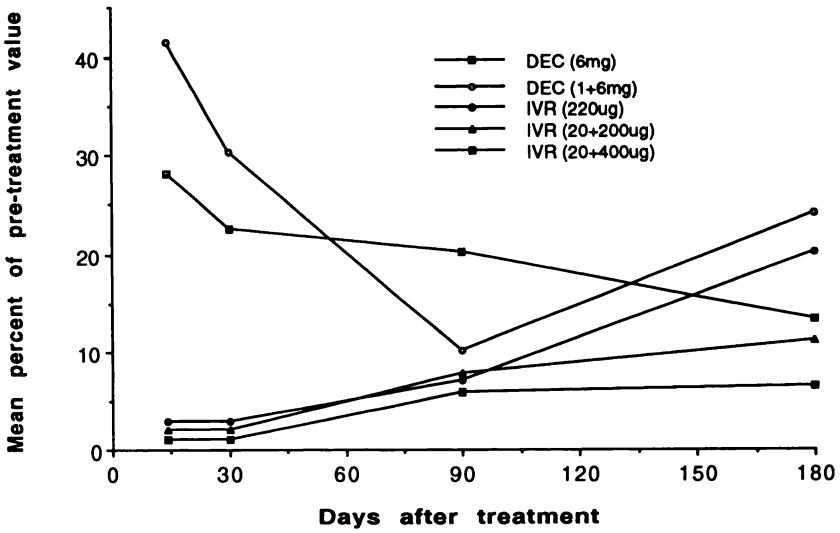

FIGURE 1. Percentage of pretreatment values of microfilaremia 14–180 days following administration of diethylcarbamazine (DEC) or ivermectin (IVR).

There were no acute changes in the degree of inflammation following drug administration (Table 1). For example, hydroceles of minor (+1) to moderate (+2) severity were present in 2–3 men per group before treatment and did not increase after administration of DEC or ivermectin. Temperatures exceeding 38°C occurred in two or three persons per group during the initial seven days following drug administration. Elevated temperatures lasted less than eight hours, did not recur, and were not associated with hypotension. Respiratory symptoms and other changes in physical examination results and vital signs were not observed.

Results of repeat examinations performed 14, 30, 90, 180 days, and 18 months after drug administration did not show any differences compared with the pre-treatment period. No patient withdrew from the study because of side effects.

Acute effects of DEC and ivermectin on intensities of microfilaremia

Changes in mf levels during the initial 180 days following drug administration are shown in Figure 1. Ivermectin given at any of the three doses tested was significantly more effective than both DEC at 14 and 30 days ($P < 0.01$). Groups treated with ivermectin had less than 1% of pretreatment levels of microfilaremia compared with means of 22.6–41.5% for groups treated with DEC. No dose-related differences were observed for either drug at these timepoints.

By day 90, parasitemia increased to 5.8–7.8% of the pretreatment values in the groups treated with ivermectin, with no significant differences in the three doses. Microfilaremia increased further by 180 days, although a significant change ($P < 0.05$) was observed only in persons treated with a single 220-μg/kg dose. In contrast, the group treated with 6 mg/kg of DEC had a progressive decrease in mf levels at 90 and 180 days. Reductions in mf levels were similar in the single-dose DEC group and the 220 μg/kg and 20 + 200 μg/kg ivermectin groups 180 days after treatment.

Effects on microfilaremia and parasite antigenemia 18 months post-treatment

Microfilarial and filarial antigen levels observed 18 months after treatment relative to pretreatment values are shown in Figure 2. The group treated with a single 6-mg/kg dose of DEC showed the greatest reduction in mf levels at this timepoint (278 mf/ml or a 90.5% reduction relative to the pretreatment value). This value was significantly greater ($P < 0.01$) than those of groups given a single or split dose of 220 μg/kg of ivermectin (< 74% reduction). Microfilaremia was decreased by 86.3% in recipients of 420 μg/kg of ivermectin, which was not significantly different

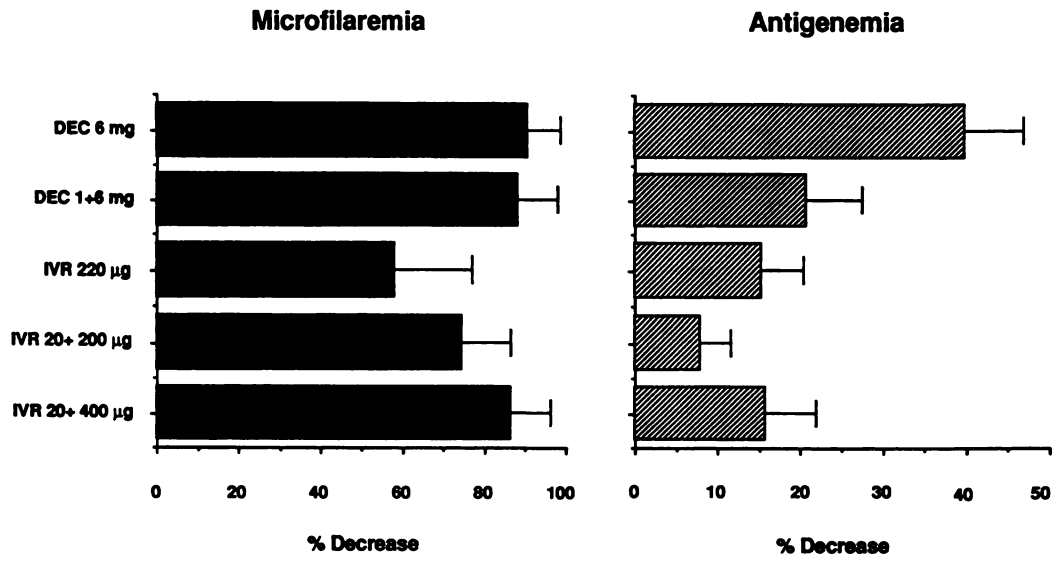

FIGURE 2. Reduction in microfilaremia and parasite antigenemia 18 months after treatment with diethylcarbamazine (DEC) or ivermectin (IVR). Bars show the maen ± SEM.

($P > 0.05$) than the means of the two groups receiving DEC.

Changes in parasite antigenemia for the pretreatment versus 18-month follow-up periods are summarized in the right panel of Figure 2. The greatest decrease in circulating parasite antigen level (39.7%) was observed in persons treated with a single dose of DEC and this effect was significantly greater ($P < 0.01$) than that observed in either of the groups treated with 220 µg/kg of ivermectin. The mean reduction in antigenemia value for the single-dose DEC group was also greater than those observed in the split-dose DEC and ivermectin 20 + 400 µg/kg groups, but these differences were not statistically significant ($P > 0.05$)

DISCUSSION

The current study describes the relative parasitologic efficacy and clinical safety of various single-dose regimens of ivermectin and DEC in Papua New Guinean men with *W. bancrofti* microfilaremia. Conventional (220 µg/kg of body weight) and higher than standard doses of ivermectin (420 µg/kg) were compared with 6 or 7 mg/kg doses of DEC. Because the rapid onset of microfilaricidal activity of either drug may cause immediate systemic side effects, the possible benefit of administering a lower or priming dose of ivermectin or DEC four days before the full dose was evaluated in three of five groups.

With respect to clinical safety, few adverse reactions occurred during the first seven days following administration of either drug. Hypotension, changes in blood pressure, or dyspnea were not observed in any subject, all of whom were examined four times per day. Although low-grade fevers developed in 20–30% of subjects in each of the DEC and ivermectin treatment groups, these lasted less than eight hours and did not recur. In addition, lymphatic inflammation was not exacerbated by any of the treatments, despite the fact that pre-existing lymph node enlargement and hydroceles were common. These results suggest that, from the perspective of patient tolerability, single doses of DEC and ivermectin are equally suitable for community-based mass chemotherapy programs, especially for persons with high levels of microfilaremia who may be at greater risk for side effects.[4,5] This problem is germane to Papua New Guinea, where the intensities of parasitemia frequently exceed 1,000 mf/ml[13] (mean levels exceeded 3,000 parasites/ml in the current report). Our previous attempt to use a standard 12-day course of 72 mg/kg of DEC caused fevers that lasted several days and swelling and pain of the extremities and scrotal contents in 30% of subjects (unpublished data).

The relative abilities of DEC and ivermectin

to induce an acute decrease in microfilaremia differed markedly in that the latter drug caused a more rapid and greater reduction. The level of parasitemia was less than 1% of the pretreatment values within 14–30 days in persons given ivermectin, whereas it was 22–30% for recipients of DEC. Similar observations have been recently reported for Haitian subjects given the same doses of DEC and ivermectin.[15] Taken together with the lack of immediate or severe clinical reactions, these data suggest that the potent acute microfilaricidal activity of single-dose ivermectin may be useful for treatment in endemic areas where mf loads are high.

In contrast to the differences in the parasitologic effects of each drug in the first 30 days following treatment, the levels of microfilaremia in recipients of DEC continued to decrease at 90 and 180 days post-treatment, whereas they increased in persons given 220 μg/kg of ivermectin. By 18 months post-treatment, recipients of single doses of 6 mg/kg of DEC had intensities of microfilaremia that were less than 10% of pretreatment level versus 42% for persons treated with a single 220-μg/kg dose of ivermectin. Interestingly, the highest dose of ivermectin (20 then 400 μg/kg) effected a sustained reduction in microfilaremia similar to that mediated by DEC.

The long-term effects of DEC and ivermectin on microfilaremia have also been evaluated in other endemic areas. In Tahiti, Cartel and others treated *W. bancrofti var. pacifica*–infected individuals with a single 6 mg/kg dose of DEC and noted that the mean intensity of microfilaremia was 20.8% of the pretreatment level at one year.[16] In contrast, persons given a single 100 μg/kg dose of ivermectin had mf levels that were 11.3% of the pretreatment values. Comparison of these data with those reported in the current study is difficult since there were significant differences in pretreatment mf levels in the Tahitian treatment groups, and because we did not evaluate parasitemia at one year post-treatment. Nevertheless, it is noteworthy that we also observed that recipients of 6 mg/kg of DEC had greater reductions in mf levels at 180 days and 18 months relative to persons given 220 μg/kg of ivermectin. In Haiti, Addiss and others reported that persons given single doses of DEC had parasitemias that were 8.2% of the pretreatment levels one year after treatment, whereas persons given 220 μg/kg or 420 μg/kg of ivermectin had mean values of 4.9% and < 1%, respectively.[15] Differences in the relative efficacy of DEC and ivermectin described in the Haitian study and the current report may be related to several factors. First, intensities of microfilaremia in the Haitian population are much lower than those in Papua New Guinea (mean pretreatment levels of 500–800 versus 3,000–6,000 mf/ml). Second, *W. bancrofti* mf from these two endemic areas may differ in their relative sensitivities to DEC and ivermectin. Third, Papua New Guinean and Haitian subjects were examined at different times after drug administration (18 months and one year, respectively). We conclude from our data that single doses of DEC are superior to currently recommended doses of ivermectin for induction of sustained reductions in microfilaremia.

In another study from Haiti, these investigators reported the results of a two-year follow-up of three groups of subjects treated with 1 mg of ivermectin followed by DEC (6 mg/kg for 12 days), 200 μg/kg of ivermectin, or 200 μg/kg of ivermectin for two days.[17] The mean percentages of the pretreatment mf values for each of the groups were 0.17, 6.39, and 4.37, respectively. The value for the DEC group was significantly less than those of the ivermectin groups. These results indicate that a standard 10–12-day course of DEC, like that of single-dose therapy that we describe, leads to sustained reduction of parasitemia. Our findings also imply that single 6-mg/kg doses of DEC or high doses of ivermectin (> 420 μg/kg) reduce adult worm viability and/or fecundity, an effect previously believed to occur when conventional (72 mg/kg) or even higher doses of DEC have been used.[3]

To examine in more detail whether there were differences in the capacities of DEC and ivermectin to reduce total filarial worm burdens, the levels of parasite antigenemia before and 18 months after drug administration were compared. The greatest decrease in parasite antigen levels occurred in recipients of 6 mg/kg of DEC. This observation suggests that single-dose DEC has partial macrofilaricidal activity against *W. bancrofti* in addition to its effects on mf and adult worm fecundity.

In conclusion, this study has shown that single-dose therapy with either ivermectin or DEC results in significant reduction and long-term suppression of microfilaremia in bancroftian filariasis. Differences in kinetics of the anti-microfilarial activities of the two drugs suggest the possibility that combined therapy might be superior

to either drug given alone, as has been observed by other investigators.[15, 17] Ivermectin would induce an immediate and nearly complete elimination of mf, whereas single-dose DEC would lead to a sustained decrease in parasitemia and elimination of adult worms, as suggested by the observations of Kimura and others.[18] This strategy theoretically maximizes the reduction in transmission resulting from deceased mf loads and prevents exacerbation or induction of lymphatic pathology due to accumulation of adult worms. Evaluation of these drugs alone or in combination should take into account the likelihood of there being differences in transmission intensity and wide variability of mf intensities in different geographic areas (e.g., mean mf levels in the Papua New Guinea study population exceed 3,000 mf/ml versus values of ~700 in Haiti[17]). In addition, if a primary goal of therapy is to diminish the supply of mf available to develop into infective larvae in the mosquito vector, it will be important to analyze results of such trials in terms of the cumulative reduction in mf levels with time (e.g., between two weeks and 1–2 years of drug administration).

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