Effect of two successive annual treatments with single doses of ivermectin on microfilaraemia due to *Wuchereria bancrofti* var. *pacifica*

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Abstract

Between 1986 and 1988 a single-blind, dose-ranging study was carried out in French Polynesia to determine the efficacy and tolerability of single 50, 100, 150 and 200 μg/kg doses of ivermectin in *Wuchereria bancrofti* carriers. Forty male microfilariae (mf) carriers between 18 and 50 years of age, in whom mf density was ≥20 mf/ml, were treated twice at a one-year interval. Twelve months after the second treatment, in carriers who were given a dose ≥100 μg/kg, mean mf density was 4–7% of the initial pretreatment mf density. Therefore, several successive annual treatments with single doses ≥100 μg/kg of ivermectin should result in reducing mf densities to a very low level. Nevertheless, at 9 months after the second treatment, residual parasitaemia ranged from 1 to 2182 mf/ml (median 85) in 30 patients. Finally, in patients with pretreatment mf counts ≤150 mf/ml, mean mf density was 2·8 and 8·9 mf/ml, respectively, during the 2 six-month periods following treatment, while in patients with pretreatment mf densities >150 mf/ml (median 1500) it was 92·3 and 334·1 mf/ml during the same periods. These results suggest that, when implementing filariasis control programmes, the best strategy might be administration of several treatments with a single dose of ivermectin every 6 months to the entire population, at least in French Polynesia. Afterwards, when mf densities had been reduced to a relatively low level (100–150 mf/ml), annual treatments could be considered.

Introduction

Since the beginning of the 1980s, ivermectin, a new macrolid antibiotic, has been shown to have microfilaricidal activity, first in onchocerciasis (AZIZ *et al.*, 1982) and then in Bancroftian filariasis (DIALLO *et al.*, 1987; OTTESEN *et al.*, 1987; KUMARASWAMI *et al.*, 1988). In 1986, a single-blind, dose-ranging study was carried out in French Polynesia to determine the tolerability and the efficacy of single 50, 100, 150 and 200 μg/kg doses of ivermectin in 40 carriers of *Wuchereria bancrofti* var. *pacifica*. The results of this study indicated that treatment with single doses of ivermectin was effective in reducing both microfilaraemia in carriers without inducing severe side effects (ROUX *et al.*, 1989) and transmission by the vector mosquito, *Aedes polynesiensis* (CARTEL *et al.*, 1990). In 1987, one year after the initial treatment, the 40 carriers were re-treated with similar single doses of ivermectin and followed-up during one year. This paper was to analyse the effect of the 2 successive treatments on the evolution of microfilaraemia.

Patients and Methods

The study population consisted of 40 apparently healthy male Polynesian microfilariae (mf) carriers, between 18 and 50 years of age, in whom mf density was ≥20 mf/ml. The main criteria for exclusion were: allergies or drug intolerance, renal or hepatic diseases, and intake of antifilarial drugs during the preceeding 2-year period. After both the nature and the objective of the trial were explained, informed consent was obtained from all the carriers.

The 40 patients were given the 2 treatments described above and were followed-up as outpatients at the Public Health Clinic of Huahine, a small island near Tahiti. They were divided into 4 groups; carriers of groups 1, 2, 3 and 4, respectively, were given a single dose of 50, 100, 150 or 200 μg/kg of ivermectin divided amongst 5 similar capsules containing 0·75, 1, or 4 mg of ivermectin or placebo to achieve the appropriate dose. Pretreatment evaluation included complete physical examination, complete blood cell count, determination of total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and creatinin levels in sera, urinalysis, a chest radiogram and electrocardiogram. All biological tests were performed at the laboratory of the Institut Malardé in Tahiti. Blood mf densities were determined using the Nuclepore® filtration method, on the day of each treatment and on days 1, 7, 30, 90, 180, 270 and 360 thereafter. 2 ml of heparinized blood were collected and filtered through a Nuclepore membrane, which was then Giemsa-stained for counting microfilariae.

The effect of ivermectin treatments on microfilaraemia was assessed by (i) the proportion of treated mf-positive carriers who became negative after treatment, (ii) the recurrence of microfilaraemia after treatment, and (iii) the weighted mean mf density during the 2 six-month periods following treatment, calculated from mf densities on days 1, 30, 90, 180, 270 and 360. Because the frequency of mf density determinations was different, the method of calculation for weighted mean mf densities was slightly different during the first and the second 6-month post-treatment periods. During the first 6-month period after treatment, the weighted mean mf density was calculated as $[((mfD1+mfD30/2) + (((mfD30+mfD90)/2)\times 2) + ((mfD90+mfD180)/2)\times 3]/6$ (where mfD1 is the mf density on day 1, etc.), and during the second 6-month period it was calculated as $(mfD180+mfD270+mfD360)/3$.

On the day of re-treatment, mf density was nil in 6 patients; because the aim of the study was to evaluate the long-term effect of 2 successive treatments in a population of carriers, these patients were retained in the study and their mf density was considered as being 1 mf/ml for calculation of geometric mean mf counts per group.

Table 1. Microfilarial counts in *Wuchereria bancrofti* carriers treated with two successive annual single doses of ivermectin

Groups and treatments	Microfilarial counts[a] Pretreatment	Days after treatment 1	7	30	90	180	270	360
1. (50 μg/kg)								
1st treatment	647·1	8·17	2·21	1·8	167·4	323·1	137·8	352·3
2nd treatment	352·3	4·9	1·27	4·17	40·8	16	49·2	160·5
2. (100 μg/kg)								
1st treatment	469·7	4·5	0	0	23·6	59·4	34·7	82·6
2nd treatment	82·6	1·75	0	1·31	34	3·5	5·1	20·2
3. (150 μg/kg)								
1st treatment	842·8	6·2	1·25	0	33·7	118·6	335·9	430·7
2nd treatment	430·7	5·6	1·17	0·1	76·5	38·5	93·7	170
4. (200 μg/kg)								
1st treatment	720·4	1·44	1	1·5	33·6	38·7	160·3	189·3
2nd treatment	189·3	2·1	0	2·7	13·5	31·9	12·9	48

[a]Geometric means per group of 10 carriers.

Table 2. Microfilarial density per group during six-month periods following two successive treatments with single doses of ivermectin

Groups and treatments	Weighted geometrical mean microfilarial densities: After first treatment year, First 6 months	After first treatment year, Second 6 months	After second treatment year, First 6 months	After second treatment year, Second 6 months
1. (50 μg/kg)	182	417·8	45·1	100
2. (100 μg/kg)	23·6	90	14·2	10·6
3. (150 μg/kg)	63	355·5	46·5	115·1
4. (200 μg/kg)	23·5	172·5	15·7	43·9

Statistical analysis was by Pearson's χ^2 test, Student's t test, the Wilcoxon t test and Mann and Witney's U test (SCHWARTZ, 1981). For comparison, mean mf counts and mean mf densities per group of carriers were expressed as geometric means.

Results

Before the first treatment, mf densities ranged from 30 to 3000 mf/ml, and geometric mean mf counts for the 4 groups (647·1, 469·7, 842·8 and 720·4) were not significantly different ($P>0·05$). Before the second treatment (360 d after the first treatment), mf densities were nil in 6 patients (2 in group 1, 3 in group 2 and 1 in group 4), while they ranged from 3 to 3825 in the 34 others; geometric mean mf counts for the 4 groups (352·3, 82·6, 430·7 and 189·3) were not significantly different ($P>0·05$). Both the first and second treatments were followed by a rapid decrease in mf counts in all of the carriers. After the first treatment, complete mf clearance was observed in 4 of the 10 carriers treated with 50 μg/kg ivermectin and in 29 of the 30 carriers treated with the 3 higher doses; after the second treatment, complete clearance was observed in 29 of the 34 carriers with pretreatment microfilaraemia: 4 of the 8 carriers treated with 50 μg/kg and 25 of the 26 treated with the 3 higher doses.

Geometric mean mf counts and recurrence percentages per group on days 1, 7, 30, 90, 180, 270 and 360 after each treatment are shown in Table 1. Three months after the first treatment, mf recurrence percentages were 25·9, 5, 4 and 4·7% in groups 1, 2, 3 and 4, respectively. The geometric mean mf count was significantly higher ($P<0·05$) in group 1 than in the 3 groups treated with higher doses. Six, 9 and 12 months thereafter, no significant difference ($P>0·05$) in geometric mean mf counts was observed between the 4 groups. Twelve months after the first treatment, recurrence percentages were 54·4, 17·6, 51·1 and 26·3 of pretreatment mf levels in groups 1, 2, 3 and 4, respectively. After the second treatment, no significant difference ($P>0·05$) in geometric mean mf counts was observed between the 4 groups at any time in the one-year follow-up; at 12 months, mf levels had risen to 24·8, 4·3, 20·2 and 6·7% of the initial pretreatment mf levels (before the first treatment). In summary, the mf reduction was roughly 50–60% 12 months after each of the 2 treatments in groups 1 and 3 (respectively treated with 50 and 150 μg/kg ivermectin), and 75–80% in groups 2 and 4 (respectively treated with 100 and 200 μg/kg ivermectin).

No significant difference ($P>0·05$) in the geometric means of weighted mean mf densities between the 4 groups was observed at any of the 4 six-month periods following each treatment. Conversely, the weighted mean mf density during the second 6-month period following both the first and the second treatments was significantly higher ($P<0·0001$) than during the first period in each of the 4 groups (except groups 1 and 2 after re-treatment), as well as in the 40 patients considered as a whole.

Without regard to the dose received, we considered the 40 carriers treated twice at a one-year interval as one group of 80 treated carriers. Of them, 15 harboured a pretreatment mf density ≤150 mf/ml, and 53 had an mf density >150 mf/ml (12 carriers were excluded either because their mf density was nil on the day of retreatment, or because blood samples could not be collected from them 12 months after treatment). In the former 15, the mean mf density was 2·8 during the first 6-month period following treatment and 8·9 during the second period: in the latter 53 it was 92·3 during the first six-month period and 334·1 during the second.

Discussion

The results of the 12-month follow-up after the re-treatment confirm the main findings of the previous study. Treatment with a single dose of ivermectin was effective in reducing mf levels in all of the carriers, and, by day 7 after both the first and the second treatment, the proportion of treated carriers who became mf-negative was significantly lower in patients treated with a 50 μg/kg dose than in those given the 3 higher doses. Nevertheless, no significant difference could be found between the geometric mean mf counts in the 4 groups at any time during the 12-month period following the second treatment.

The reason why, with respect to mf recurrence, ivermectin at a dosage of 150 μg/kg appeared less effective than at a dosage of 100 μg/kg is not clear, but it was possibly due to the small number of patients included in each group. However, our results indicate that, 12 months after each treatment, the recurrence rate was about 20% of the pretreatment mf density in the carriers treated with ivermectin at a dose ≥100 μg/kg and that, after 2 successive annual treatments, it was 4–7% of the initial mf density (before the first treatment). Thus several successive annual treatments should result in reducing mf densities to a very low level. Despite these good results, mean mf densities were substantial during the second 6-month period following each treatment and (except for groups 1 and 2 after the second treatment) significantly higher than during the first treatment. Without regard to the dose received, considering the 40 carriers as a whole, the residual parasitaemia (assessed on mf counts at 9 months) ranged from 2 to 2386 mf/ml (median 737) and from 1 to 2182 mf/ml (median 85) during the second 6-month period following, respectively, the first and second treatments. Though the range of microfilariaemia was similar in the 2 series, residual parasitaemia was significantly lower after the second treatment than after the first. Even so, a median residual parasitaemia of about 80 mf/ml may be considered high and able to ensure retransmission by vectors (SAMARAWICKREMA *et al.*, 1985). Finally in carriers with pretreatment mf counts ≤150 mf/ml (median 77), mean mf densities were very low during both the first and the second 6-month periods following treatment (2·8 and 8·9 respectively). Conversely, in carriers with pretreatment mf counts >150 mf/ml (median 1500), mean mf densities were still substantially high during the first 6-month period (92·3) and significantly higher during the second period (334·1).

Our results suggest that successive, spaced 100 μg/kg doses of ivermectin might constitute an effective strategy for filariasis control. The question of the frequency of administration to be chosen for mass campaigns is an important issue. Since, in the current study, weighted mean mf densities were consistently higher during the second 6-month period following annual treatments than during the first, ideally administration of a single dose of ivermectin every 6 months appears to be necessary. On the other hand, once pretreatment mf densities have been reduced to relatively low levels (100–150 mf/ml), the necessity of retreatment every 6 months appears to be less evident. This observation is consistent with the conclusions of a study on efficacy of single spaced doses of diethylcarbamazine for treatment of lymphatic filariasis carried out in Samoa (KIMURA *et al.*, 1985). According to our findings, one may speculate that administration of medication, repeated every 6 months, to the entire population could be the best strategy when implementing control programmes with ivermectin, at least in the population of French Polynesia. Annual administration could then be considered when mf densities had been substantially reduced. This hypothesis should be tested in a double-blind study in which mf carriers would be treated either with placebo or with effective medication after successive single doses of ivermectin given every 6 months had reduced mf densities to a level of 100–150 mf/ml.

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