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Control of bancroftian filariasis in an endemic area of Polynesia by ivermectin 400 μg/kg

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Abstract

Community treatment with ivermectin was implemented in Opoa, French Polynesia from April 1991 to October 1993. All consenting inhabitants aged 3 years or more were treated with twice-yearly single doses of ivermectin, pregnant women excepted. A dosage of 100 μg/kg was used for the 3 first treatments and then abandoned because it did not reduce the prevalence of microfilariae (mf) carriers. With a dosage of 400 μg/kg dosage, this prevalence decreased dramatically from 21% to 7%, and the mf level in carriers dropped to only 0·5% of its initial value after 3 treatments. The 400 μg/kg dosage was well tolerated and compliance was excellent. The twice-yearly single dose strategy with ivermectin at 400 μg/kg is safe and highly effective for filariasis control in an endemic area.

Keywords: filariasis, *Wuchereria bancrofti*, ivermectin, community treatment, Polynesia

Introduction

From April 1991 to October 1993, a pilot control project against bancroftian filariasis was implemented in the district of Opoa in French Polynesia, where this disease is endemic. The project was based on the use of semi-annual single doses of ivermectin (CARTEL *et al.*, 1992a). During an earlier trial (NGUYEN *et al.*, 1994), dosage with 100 μg/kg of ivermectin (IVR100) was abandoned after 3 successive treatments because it proved ineffective in reducing microfilaraemia and microfilariae (mf) prevalence. Based upon the promising results reported in the Caribbean islands with ivermectin at 400 μg/kg (IVR400) (RICHARDS *et al.*, 1991; EBERHARD *et al.*, 1992), and after a preliminary study to assess the efficacy and the safety of this dosage (CARTEL *et al.*, 1992b), semi-annual treatment with IVR400 was applied in Opoa.

Here we report the final results of this strategy after 3 mass treatments with IVR400.

Patients and Methods

The trial was conducted in Opoa, Raiatea, Leeward Islands, French Polynesia. The patients and methods have been described in detail previously (NGUYEN *et al.*, 1994). Briefly, all inhabitants aged 3 years or more (excepting pregnant women, detected by urine test for pregnancy one week before treatment) were treated every 6 months with single doses of 400 μg/kg of ivermectin. Three mass treatments were performed with this dosage between October 1992 and October 1993. Before each treatment, venous blood was taken from all consenting inhabitants aged 15 years or more for the determination of microfilaraemia in 1 mL of blood (by the Nuclepore® membrane filtration technique). Blood samples were collected mainly between 15:00 and 19:30, even though no significant diurnal variation of microfilaraemia determined by this method has been observed with *Wuchereria bancrofti* var. *pacifica* (see MOULIA-PELAT *et al.*, 1993).

Side effects of the treatment were graded according to intensity as 0, no side effect; 1, mild to moderate (but not interfering with daily activities); and 2, severe (subject unable to perform daily activities). These side effects were managed by a physician and, if necessary, paracetamol was used as symptomatic treatment.

During the trial, the population of Opoa and the local health authorities were notified not to use diethylcarbamazine, the other antifilarial compound available in French Polynesia.

The principal criteria of efficacy were the prevalence of mf carriers and the change in geometric mean microfilaraemia (GMM) in carriers. The percentage of 'bad responders' (mf carriers in whom the mf level was higher 6 months after treatment than before) was considered as a secondary criterion.

For statistical analysis, mf counts were transformed to $\log(x+1)$ to normalize the distribution. Analysis of variance with repeated measures was used to compare the GMM after each treatment. The Kruskal–Wallis nonparametric test was used when the variances were not homogenous (as determined by the Bartlett test). Neuman–Keuls *post hoc* tests (WINER, 1971) were used for multiple inter-group comparisons between different times of treatments. Proportions were compared using the χ^2 test. All values of $P \leq 0.05$ were considered to be statistically significant.

Results

Effectiveness of ivermectin 400 μg/kg for control

Prevalence of microfilariae carriers. The prevalence of mf carriers decreased significantly from 21% to 7% ($P<0.001$) after 3 treatments with IVR400 (Table 1). Although the difference between the second and third treatments was not statistically significant ($P=0.057$), the overall trend was downward.

Information about migration of the inhabitants in the district of Opoa was collected every 6 months during each treatment, because migration can bias carrier

Table 1. Results of sequential examination of subjects with bancroftian filariasis after ivermectin treatment

	Before initial treatment	Six months after treatments with ivermectin					
		100 μg/kg	100 μg/kg	100 μg/kg	400 μg/kg	400 μg/kg	400 μg/kg
Date	April 1991	October 1991	April 1992	October 1992	April 1993	October 1993	April 1994
No. sampled[a]	577 (97·5%)	584 (96·8%)	610 (96·4%)	569 (94·2%)	598 (94·6%)	584 (94·7%)	548 (95·3%)
Microfilaraemia prevalence	21·4%	21·1%	21·2%	20·7%	14·9%	10·1%	6·9%
GMM (92 subjects)[b]	489·8 (100%)	145·3 (29·7%)	90·6(18·5%)	84·2(17·2%)	12·8(2·6%)	4·4(1%)	2·6(0·5%)
GMM (122 subjects)[c]	330 (100%)	115·5 (35%)	71·3(21·6%)	63·1(19·1%)	14·1(4·3%)	5·5(1·7%)	3·6(1·1%)

[a]Percentages of eligible inhabitants ≥15 years old whose blood was examined are given in parentheses.
[b]Geometric mean microfilaraemia per mL in cohort of 92 subjects with complete data (see text); numbers in parentheses show the percentage occurrence of microfilaraemia, calculated as (GMM after treatment/initial GMM)×100.
[c]GMM in all 122 subjects, including those with incomplete data (see text); percentages in parentheses calculated as shown in footnote b.

prevalence. Some mf carriers emigrated, while some new inhabitants of the district were themselves mf carriers. In fact, very few mf carriers were involved in migration and their number was too low to bias the mf carrier prevalence. However, migration of amicrofilaraemic people was somewhat irregular, and could have affected the prevalence by changing the size of the denominator. During the third treatment, when the rate of emigration was considerable, the smaller denominator prevented the reduction in prevalence achieving statistical significance.

Among the mf carriers detected at the beginning of IVR400 treatment who were sampled at each time interval, 65% were amicrofilaraemic 6 months after the third IVR400 treatment.

Change in geometric mean microfilaraemia

To analyse the evolution of the GMM, only the cohort of mf carriers detected at the outset of the trial was considered. Of the 122 mf carriers (37 females and 85 males) detected in April 1991, 92 fully completed the treatments and were blood-sampled each time, and 30 had incomplete data. The GMM of these 92 carriers decreased significantly after the first IVR400 treatment ($P<0{\cdot}001$). This reduction of the GMM persisted through the second and third treatments. Six months after the third treatment, the GMM was only 0·5% of the pre-treatment level (Table 1).

Analysis of the available information about the 30 mf carriers who had incomplete data (13 females and 17 males) did not suggest any specific characteristic (age, sex, adverse reactions, microfilaraemia) which distinguished them from the other 92 mf carriers. Their GMM followed the same trend as that of the whole group. Nevertheless, the size of this group could have impaired the validity of the previous analysis. Consequently, we considered the maximal bias hypothesis. All missing values of these 30 persons were replaced by their last value, determined just before their last treatment. Analysis on this basis of the whole group of 122 revealed essentially the same results as those obtained for the group of 92 mf carriers: the same pattern of reduction in GMM was observed after each treatment (Table 1).

If the beginning of the IVR400 strategy was taken as time 0, analysis of the cohort who were microfilaraemic at that time produced similar results: after 3 mass treatments, the GMM was 2·6% of the pre-treatment level.

The percentage of 'bad responders' among treated inhabitants was about 2·5% after each of the 3 treatments with IVR 400 (Table 2). Analysis of this phenomenon is somewhat difficult, because sometimes a 'good responder' (a patient with decreased microfilaraemia after treatment) became a 'bad responder' at the next treatment, and conversely. Furthermore, the data were incomplete for some of them (due to emigration or absence). However, several points should be emphasized. (i) More males than females were 'bad responders'. (ii) The number of 'bad responders' was significantly lower ($P<0{\cdot}000001$) with IVR400 than with IVR100; only 15 of the 112 'bad responders' (13%) to IVR100 at one time or another remained 'bad responders' with IVR400. (iii) The range of microfilaraemia was less extensive after several treatments, especially with IVR400, but the GMM of 'bad responders' did not decrease significantly despite successive treatments, either with IVR100 or IVR400. (iv) Finally, among 'bad responders', the proportion of patients with low-level microfilaraemia (≤50 mg/mL) was significantly higher ($P=0{\cdot}015$) with IVR400 than with IVR100; in other words, with IVR400 'bad responders' were mainly low-level mf carriers.

Adverse reactions and acceptability of ivermectin at 400 μg/kg

Adverse reactions were rare after 3 treatments with IVR400. During the third treatment, only 1 of 865 treated inhabitants experienced an adverse reaction of grade 1. This person had low microfilaraemia (10 mf/mL). Symptoms associated with the 29 adverse reactions to the 3 mass treatments were, in order of frequency, weakness (69%), headache (65%), myalgia (62%), arthralgia (48%), fever (41%), anorexia (28%), cough (7%), shivering (7%), dizziness (3%), diarrhoea (3%), arrhythmia (3%), and slight haemoptysis (3%). All these symptoms regressed and disappeared within 6–72 h, either spontaneously or after treatment with paracetamol. None of these reactions was dangerous for the patients. Adverse reactions were less frequent after 3 treatments.

On average, 96·8% (872 persons) of the eligible inhabitants were treated during the 3 mass treatments. This percentage was roughly similar at each of the 3 successive semi-annual treatments with IVR400. Most of the inhabitants who were not treated were temporarily absent from the area (fishing, other professional activities, visits to relatives, etc.). During the 3 years of the programme, only one inhabitant refused treatment—an old woman who never accepted treatment, for personal reasons.

Discussion

Under field conditions, the semi-annual IVR400 strategy reduced the prevalence of mf carriers from 21% to 7% after 3 treatments (i.e., a 70% reduction). The apparent absence of a significant decrease in prevalence between the second and third treatments was probably due to the lack of power of the χ^2 test, because the number of treated inhabitants was lower during the third treatment than during the second (due to more emigration than immigration). However, the 70% reduction of prevalence, or the clearance of microfilaraemia in 65% of carriers, after 3 semi-annual treatments can be considered as an excellent result, especially as the membrane filtration technique was used, a method which detects more low-level mf carriers than the blood film method. In lymphatic filariasis, the use of ivermectin for mass treatment is still uncommon and data are limited. In comparison to other control strategies for lymphatic filariasis based on the use of diethylcarbamazine (DEC), the current results indicated that IVR400 is a noteworthy alternative strategy. In Samoa, where the strategy of a 6 mg/kg annual single dose of DEC was applied during 3

Table 2. Characteristics of patients with bancroftian filaraisis who were 'bad responders' to ivermectin treatment

	Six months after treatment with ivermectin					
	100 μg/kg	100 μg/kg	100 μg/kg	400 μg/kg	400 μg/kg	400 μg/kg
Date	October 1991	April 1992	October 1992	April 1993	October 1993	April 1994
Bad responders[a]						
No.	39 (7·5%)	60 (11·2%)	60 (11·4%)	13 (2·5%)	17 (3·1%)	11 (2%)
Percentage with low microfilaraemia[b]	50%	47·5%	35%	58%	61%	80%
Male:female ratio	3·9	3·3	2·4	12	1·8	4
GMM[c]	33·2(32)[1–8177]	56·9(71)[1–8288]	105·4(178)[1–4811]	44·3(32)[1–3927]	35·2(32)[1–1547]	26·2(32)[3–459]

[a]Microfilaraemic subjects in whom microfilaraemia 6 months after treatment was greater than the value before treatment. The percentage was calculated as (number of bad responders/number of inhabitants who were subsequently examined twice)×100.
[b]Bad responders with microfilaraemia ≤50 microfilariae/mL.
[c]Geometric mean microfilaraemia per mL; median in parentheses, range in square brackets.

years, the reduction in prevalence was 50% and the intensity of microfilaraemia remained constant despite an initial decrease (KIMURA *et al.*, 1992). In northern Trinidad, excellent results were obtained by NATHAN *et al.* (1982): 70% of mf carriers became amicrofilaraemic, but only after 12 monthly doses of 6 mg/kg of DEC. The efficacy of the IVR400 semi-annual strategy was similar to that of annual treatments using a combination of ivermectin and DEC. After 2 years, the residual microfilaraemia was about 0·5% (MOULIA-PELAT *et al.*, 1996).

In this study, the percentage of 'bad responders' was low among all treated inhabitants. This bad response cannot be entirely explained by bad compliance, because the ivermectin intake was mainly supervised. This means that, even if the control programme is correctly applied, there will always be some carriers who remain microfilaraemic, usually with low-level microfilaraemia. Nevertheless, in some of them this level can be enough to infect mosquitoes and maintain the endemicity of the infection, especially as the vector (*Aedes polynesiensis*) supports the development of more infective (L3) larvae as the intensity of microfilaraemia decreases (PICHON *et al.*, 1974; FAILLOUX *et al.*, 1995). The problem of the 'bad responders', whatever its mechanism, is important in a control programme, because the existence of such individuals means that there will probably be no end to such a programme. Can this bad response be overcome by several repeated treatments? Can the level of microfilaraemia be reduced enough to interrupt transmission to mosquitoes? Longer field trials than those we have conducted so far are necessary to address these questions.

The compliance of the population was excellent, probably because adverse reactions were rare and benign. A dosage of 400 µg/kg has no major drawback (ADDISS *et al.*, 1991; RICHARDS *et al.*, 1991; CARTEL *et al.*, 1992; GLAZIOU *et al.*, 1994; NGUYEN *et al.*, 1994). This compound was safe even at a higher dosage (i.e., 800 µg/kg), as used recently for onchocerciasis (AWADZI *et al.*, 1995). The wide use of ivermectin for mass treatment can be considered without taking special precautions.

In view of the very good results obtained by different teams in India (GELBAND, 1994) and in China (FAN, 1990) with DEC-medicated salt, the concomitant use of IVR400 and DEC-medicated salt would be interesting to consider, because ivermectin induces rapid clearance of microfilaraemia and DEC-medicated salt can maintain microfilaraemia at a very low level. Such a combined control strategy might be highly effective, with good population compliance and low costs. Moreover, such a strategy could be used safely even in areas where onchocerciasis or loasis were endemic.

In short, semi-annual single doses of ivermectin at 400 µg/kg form a highly effective and safe strategy for the control of lymphatic filariasis in French Polynesia.

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