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Advantages of an annual single dose of ivermectin 400 μg/kg plus diethylcarbamazine for community treatment of bancroftian filariasis

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Abstract

In 1994 and 1995, 2 supervised single dose treatments for bancroftian filariasis were given to all inhabitants (>3500) aged ≥ 3 years on a Polynesian island. This island is divided into 4 political zones. Each zone was treated with a different dosage of the combination ivermectin (IVR) and diethylcarbamazine (DEC) as follows: (1) IVR 400 μg/kg plus DEC 6mg/kg, (2) IVR 400μg/kg alone, (3) DEC 6mg/kg alone, (4) IVR 400 μg/kg plus DEC 3mg/kg. 1717 inhabitants (aged ≥ 20 years) had venous blood sampled when treated. The reductions in microfilaraemia prevalence rates one year after treatment were, respectively, 32%, 11%, 14% and 32%. The reductions in microfilaraemia levels one year after treatment were, respectively, 96%, 80%, 82% and 95%. Stool specimens from 82 children aged 6 years were examined for intestinal nematodes just before and just after treatment. IVR 400 μg/kg significantly reduced the prevalence and intensity of trichiuriasis. The combination IVR+DEC is a powerful tool for the control of lymphatic filariasis. Further studies are required to determine the appropriate presentation of DEC (salt and/or tablets), the frequency of treatment, and the duration of the control programme necessary to eradicate this disease.

Keywords: filariasis, *Wuchereria bancrofti*, single dose treatment, ivermectin, diethylcarbamazine, *Trichuris*, *Ascaris*, *Ankylostoma*, French Polynesia

Introduction

Single doses of diethylcarbamazine (DEC) at 6 mg/kg given twice yearly to all the population were recommended as the most effective strategy for the control of lymphatic filariasis (WHO, 1992). However, during long-term campaigns, both the motivation of populations and the political commitment of governments may decrease. In French Polynesia, for example, the control programme was stopped in 1982. Ten years later a dramatic recurrence of microfilaria (mf) carrier prevalence was observed (Figure; Moulia-Pelat *et al.*, unpublished report*).

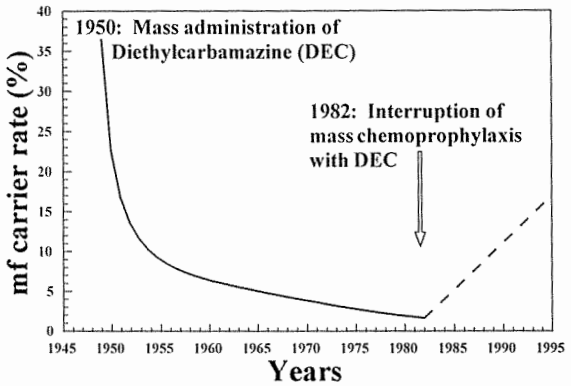

Figure. Prevalence of *Wuchereria bancrofti* microfilaraemia in French Polynesia, 1945–1995.

Ivermectin (IVR) has been tested in areas endemic for *Wuchereria bancrofti* infection since 1987 (DIALLO *et al.*, 1987; KUMARASWAMI *et al.*, 1988; ROUX *et al.*, 1989; OTTESEN *et al.*, 1990; ADDIS *et al.*, 1993). The most effective dosage of IVR was 400 μg/kg (MOULIA-PELAT *et al.*, 1994; NGUYEN *et al.*, 1994). DEC 6 mg/kg or IVR 400 μg/kg alone administered twice yearly to the whole population was a good strategy, but the need for 2 treatments per year was a problem and the programme was ineffective at eliminating microfilaraemia (CARTEL *et al.*, 1992a; Moulia-Pelat *et al.*, unpublished report*).

The combination of IVR+DEC given once a year would be a powerful new tool for the effective control of lymphatic filariasis; it would permit a shorter distribution programme without the chance of recurrence. A safety trial (phase II) in December 1992 (MOULIA-PELAT *et al.*, 1993) showed that the combination was safe. This was followed by a double-'blind' study (phase III) on Moorea Island in French Polynesia in 1993–1995, in which the combination of IVR+DEC was the most effective for an annual treatment strategy (GLAZIOU *et al.*, 1994a; MOULIA-PELAT *et al.*, 1995). This paper described a mass treatment campaign (phase IV) comparing different dosages of the combination during a pilot trial in one community. The results of this trial will determine the treatment recommended for the lymphatic filariasis control programme in French Polynesia.

Patients and Methods

The study was carried out in Tahaa, an island of the Society Archipelago 200 km north-west of Tahiti in French Polynesia, which has a high prevalence rate of mf carriers; 16% of the population aged ≥40 years were found to be mf carriers by examination of 20 mm^3 blood obtained by finger prick.

Tahaa Island is divided into 4 political zones with comparable populations (800–1200) and mf prevalence rates. Each zone was assigned a different treatment, IVR 400 μg/kg+DEC 6 mg/kg in zone 1, IVR 400 μg/kg alone in zone 2, DEC 6 mg/kg alone in zone 3 and IVR 400 μg/kg+DEC 3 mg/kg in zone 4. Annual single treatments were given beginning in February 1994. All inhabitants above 3 years of age were treated, except pregnant women, and observed for one or more days to monitor any adverse reactions. Every household in each zone was visited daily for 4 weeks by one of 3 teams composed of a physician and a health worker. Before each treatment, venous blood samples were collected from all inhabitants ≥20 years of age for determination of microfilaraemia using the membrane filtration technique. The efficacies of treatments were assessed on the basis of the subsequent mf carrier prevalence rates and geometric mean mf densities in carriers. The protocol was approved by the local ethical committee and the World Health Organization. The population of Tahaa was informed about the aim and design of the study.

During the first treatment round (February 1994), an open study was performed on children 6 years old to assess the efficacy of the treatments on intestinal worm infections. A stool examination (direct microscopical examination and concentration if necessary) was performed on each child before, and one week after, treatment.

Statistical analysis of the results was carried out with the aid of the χ^2 test or Student's t test, as necessary.

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Results

Filariasis

In February 1994, 3711 of the eligible inhabitants (98%), including 1784 females and 1927 males, were treated with IVR and/or DEC; 125 (3·4%) experienced adverse reactions, 96 of grade 1 (moderate) and 29 of grade 2 (severe: unable to perform daily activities). The intensity of adverse reactions was not correlated with the treatment, but it was correlated with the pretreatment microfilaraemia. None of the reactions was considered serious and all disappeared spontaneously or after treatment with paracetamol. During the house-to-house survey for blood sampling and supervised treatment, we observed 42 cases among 1942 adult inhabitants examined (2%) with specific clinical signs of lymphatic filariasis: 4 with hydrocele (probably an underestimate), 16 with elephantiasis, 16 with lymphoedema, and 6 with filarial itch ('craw-craw') in the 4 zones; all were observed in inhabitants aged more than 40 years. An overall mf prevalence rate of 22% (418/1942) was observed in the adult population of all 4 zones.

In February 1995, the population of Tahaa Island was treated again. There is appreciable migration in Tahaa: about 10% of the population moves in or out during one year. Therefore, only 3685 individuals treated during the first year were re-treated during the second year (97% of the eligible inhabitants), of these 121 (3·3%) experienced adverse reactions, 106 of grade 1 and 15 of grade 2; none of them was serious.

Finally, 1717 inhabitants had venous blood samples taken at each round of treatment in February 1994 and February 1995. Evaluation of our study was done with this cohort. Table 1 summarizes the reduction in the proportion of mf carriers and in microfilaraemia one year after the first treatment. Combinations of the 2 drugs provided the most effective treatments: both the combined treatments reduced the carrier rate and the geometric mean microfilaraemia significantly ($P<0·001$ and $P<0·0001$ respectively) compared to either IVR or DEC alone. After IVR 400 μg/kg+DEC 6 mg/kg, no new mf carrier was detected amongst the previously amicrofilaraemic inhabitants one year after the first treatment ($P<0·01$ compared to the other 3 treatments).

Intestinal nematodes

In the 82 children examined before the first treatment, *Trichuris* (=*Trichocephalus*) was the commonest nematode seen. *Ascaris*, *Oxyuris* and *Ankylostoma* (hookworms) were much less common. Multiple infections were very frequent (Table 2). Thirty-nine children (48%) were infected with *Trichuris* before treatment and only 16 (20%) one week after treatment. The intensities of *Trichuris* infection differed significantly among the zones, being 29% in zone 1, 41% in zone 2, 53% in zone 3, and 68% in zone 4 ($P<0·05$). Nevertheless, comparing the 2 zones receiving single dose treatments, IVR 400 μg/kg alone (zone 2) reduced the infection rate significantly more than DEC 6 mg/kg alone (zone 4) ($P<0·001$).

Discussion

Adverse reactions occurred at similar rates after the first and second treatments, but severe reactions were fewer (12%) after the second round than after the first (23%; $P<0·05$). This is in agreement with other studies (CARTEL *et al.*, 1992b; SABRY *et al.*, 1991; NGUYEN *et al.*, 1994; MOULIA-PELAT *et al.*, 1995). This decrease in the proportion of severe side effects after several treatments is important for compliance during a control programme.

Specific clinical signs of lymphatic filariasis were observed in aged inhabitants only. There are 3 possible reasons for this: (i) filariasis is a cumulative disease (WHO, 1992) and clinical signs become visible only 10 or 20 years after infection; (ii) people aged less than 40 years have been treated for filariasis for most of their lives during the 30 years control programme started in Polynesia in 1950; and (iii) old people are more reluctant to participate in filariasis treatment.

Table 1. Results of treatment of filariasis with single doses of ivermectin and/or diethylcarbamazine

	Treatment[a]			
	1	2	3	4
Total no. studied	510	412	352	443
No. of mf carriers				
1994 (before treatment)	89	122	86	87
1995 (after treatment)[b]	60 (0)	109 (10)	74 (4)	59 (8)
Reduction[c]	32%	11%	14%	32%
Geometric mean microfilaraemia (per mL)				
1994	270	251	355	214
1995	10	49	63	11
Reduction[d]	96%	80%	82%	95%

[a]Single doses of (1) ivermectin 400 μg/kg plus diethylcarbamazine (DEC) 6 mg/kg, (2) ivermectin 400 μg/kg, (3) DEC 6 mg/kg, and (4) ivermectin 400 μg/kg plus DEC 3 mg/kg.
[b]Numbers of new carriers of microfilariae (mf)—i.e., those negative in 1994 but positive in 1995—are shown in parentheses.
[c]Percentage of microfilaraemic subjects who became amicrofilaraemic after one treatment.
[d]Reduction in mean microfilaraemia level after one treatment.

Table 2. Results of stool examinations of children before and one week after treatment with ivermectin and/or diethylcarbamazine

Treatment[a]	No. of children[b]	*Trichuris*[c]		Other intestinal nematodes[c,d]	
		Before	After	Before	After
1	24	7 (4+3)	1 (0+1)	–	2 *Ox* (1+1), 1 *An* (0+1)
2	22	9 (6+3)	1 (0+1)	1 *Ox* (1+0), 4 *As* (3+1)	1 *Ox* (0+1), 1 *An* (0+1)
3	14	8 (5+3)	7 (3+4)	–	–
4	22	15 (13+2)	7 (3+4)	3 *Ox* (1+2), 2 *An* (1+1)	2 *Ox* (1+1), 1 *An* (0+1)

[a]Single doses of (1) ivermectin 400 μg/kg plus diethylcarbamazine (DEC) 6 mg/kg, (2) ivermectin 400 μg/kg, (3) DEC 6 mg/kg, and (4) ivermectin 400 μg/kg plus DEC 3 mg/kg.
[b]Number of 6 years old children studied during one week.
[c]Numbers in parentheses are those infections detected by direct examination+those detected only after concentration.
[d]*An*=*Ankylostoma*, *As*=*Ascaris*, *Ox*=*Oxyuris*.

A mf prevalence rate of 16% was estimated during our pretrial study. In 1994, the first round confirmed a mf prevalence rate of 22% (418/1942) for all of Tahaa Island. Our rapid diagnostic method underestimated the mf prevalence rate for several reasons: (i) in our comparative study of detection methods for evaluation of microfilaraemia (MOULIA-PELAT *et al.*, 1992) we included the 15–19 years age group which is relatively low in mf cariers; (ii) the sensitivity of a 20 mm^3 blood film is inadequate to detect persons with low microfilaraemia. However, determination of the mf carrier prevalence rate in individuals aged 40 years or more by the conventional blood film method is an easy and useful way to evaluate correctly the extent of lymphatic filariasis in a population; the membrane filtration technique remains a reference technique in therapeutic trials, until rapid monitoring techniques such as detection of antigenaemia (WEIL *et al.*, 1991) become available.

The most important result was the confirmation of the effectiveness of the combination of IVR plus DEC, already indicated by the phase III trial in Moorea (MOULIA-PELAT *et al.*, 1995). A reduction in mean microfilaraemia level of 96% one year after one single mass treatment strongly supported the recommendation of the drug combination for a lymphatic filariasis control programme in French Polynesia and in other countries with no filariasis due to *Loa loa*. Either drug alone reduced the microfilaraemia level one year after treatment by about 80%. Control programmes using only one drug are not adequate and should no longer be recommended. There was no significant difference between the results obtained with the 2 dosages of DEC when administered in combination with IVR. If the results in 1996 (one year after the second treatment) are consistent with those after one treatment, the combination of IVR with 3 mg/kg of DEC should be sufficient, resulting in a reduction in the number of tablets which should greatly improve compliance. However, the absence of new mf carriers after the first treatment with IVR plus DEC at 6 mg/kg should be borne in mind when considering the best dosage of DEC to combine with IVR.

The combination could be a very powerful tool for the control of lymphatic filariasis. An annual 'filariasis day' could become a reality. Nevertheless, there is a major practical problem in setting up a control programme based upon the combination: IVR is not presently available for sale to the general public. Until IVR is approved for use against lymphatic filariasis, an annual 'filariasis day' using only DEC will result in lower motivation among the population and thus a rebound of mf prevalence in the long term. The use of DEC medicated salt is a possible solution; this medicated salt has been exported from India since 1994. Several studies (JINGYUA *et al.*, 1992; GELBAND, 1994; Meyrowitsch *et al.*, unpublished report*) have demonstrated the effectiveness and ease of drug distribution using DEC salt. If IVR becomes available, the regimen for a short-term control programme without the chance of a rebound could be IVR 400 μg/kg every year and DEC salt every day. This therapeutic schedule would maintain the advantages of the combination of IVR and DEC. With a short programme of 2–5 years, the motivation of the population and the political commitment should remain high; it may therefore be possible to eradicate lymphatic filariasis. Indeed, lymphatic filariasis has recently been identified by the International Task Force for Disease Eradication as one of only 6 eradicable infectious diseases (OTTESEN & RAMACHANDRAN, 1995).

IVR at 400 μg/kg was also very effective against intestinal nematodes, in particular *Trichuris*, as reported in other studies (CAMPBELL, 1993; GLAZIOU *et al.*, 1993, 1994). IVR is also effective against scabies and head lice and as an anthelmintic. IVR is thus indeed the drug of choice for mass treatment, and its wide spectrum of effect is an important advantage in a global strategy of public health.

In conclusion, the combination of IVR and DEC should be a powerful tool for the control of lymphatic filariasis. Further studies are needed to specify the appropriate presentation of DEC (salt and/or tablets), the frequency of treatment, and the duration of the control programme necessary to eradicate this disease.

*Meyrowitsch, D. W., Simondsen, P. E. & Makunde, W. H. DEC medicated salt. Results of a pilot study in Tanzania. Working paper, Filariasis Meeting, Penang, Malaysia, 22–24 August 1994. [This paper can be obtained from TDR Communications, World Health Organization, 1211 Geneva 27, Switzerland.]

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