The long term effects of repeated diethylcarbamazine administration with special reference to microfilaraemia and elephantiasis

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[1] Department of Parasitology, University of Indonesia, Jakarta, Indonesia
[2] U.S. Naval Medical Research Unit No. 2, Jakarta Detachment, Jakarta, Indonesia
[3] Nusa Tenggara Timur Provincial Health Office, Indonesia

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F. Partono[1], Purnomo[2], Sri Oemijati[1], A. Soewarta[3]

Summary

The results of mass treatment with 50 mg diethylcarbamazine (DEC) per kg body weight followed by two annual selective retreatments in an area highly endemic for *Brugia timori* infections are described. The criteria for selective retreatment are simple and practical for use in rural areas. An education programme was developed which focused on describing the relationship between adenolymphangitis and filarial infections, the danger of repeated attacks and the efficiency of DEC in eliminating these attacks. Motivated persons in the community were charged with the responsibility of promptly treating all cases with acute clinical manifestations. With this programme the microfilaria rate by finger prick decreased from 24% to 0%, and by Nuclepore filtration from 30% to 5%. The adenolymphangitis rate decreased from 46% to 11% and the 'elephantiasis' rate from 17% to 4%.

Key words: filariasis; *Brugia timori;* treatment; control; Indonesia.

Introduction

Control measures of filariasis using diethylcarbamazine (DEC) have been initiated in many parts of the world but the results have been variable. Many of the control programmes used finger prick blood samples, comparing pre- and post-treatment microfilaria rates to evaluate the progress and the success of the programmes. These prevalence figures, however, represent underestimates, es-

[4] Send reprint request to: Publications Office, U.S. Naval Medical Research Unit No. 2, APO San Francisco, Ca. 96528, USA

Correspondence: Dr. F. Partono, Department of Parasitology, University of Indonesia, Jakarta, Indonesia

pecially when the amount of blood examined is small and the microfilaria densities are low, such as found after treatment. Moreover, there is a segment of the population in an endemic area who have disease manifestations with no microfilaraemia. It follows that some of the success rates obtained represent an overstimate and that the actual post-treatment microfilaria rates are higher than those expressed by finger prick microfilaria prevalences. To evaluate the results of a DEC control programme more accurately, it is necessary to take into account other parameters such as incidence and reversion of microfilaraemias and pre- and post-treatment disease rates. Using these parameters, this paper describes the preliminary results of a DEC control programme from June 1977 to June 1980 in Karakuak, West Flores, Indonesia, an area highly endemic for *Brugia timori* (Partono et al., 1978, 1979).

Materials and methods

The description of the study population and the area were reported earlier (Partono et al., 1978). A house to house census was taken yearly to identify each person by name, age, sex, household, family relationship, length of stay and origin. Clinical histories of recurrent fever, lymphadenitis, lymphangitis, lymphoedema, elephantiasis, hydrocele and chyluria were obtained yearly and each individual examined for acute and chronic signs of filariasis. Persistent lymphoedema and elephantiasis were difficult to differentiate and were considered as elephantiasis. Individuals with elephantiasis were, however, differentiated according to the degree of pitting oedema present; those with no or slight pitting oedema and those with obvious pitting oedema.

Quantitated 20 μl fingertip blood samples were collected between 2000 to 2400 h from nearly every person above 1 year of age during the first 3 years of the study. Venous blood samples (1–2 ml in the first 2 years and 3–4 ml subsequently) were obtained from approximately half of the study population above 4 years of age during the first 2 years and from nearly all of the study population thereafter. Blood samples were processed and examined for microfilariae by methods previously described (Partono and Idris, 1977).

In 1977 all villagers were treated with 5 mg DEC/kg body weight for 10 consecutive doses, excluding infants, pregnant women, the elderly, and those with obvious debilitating disorders. Subsequently, DEC was given selectively in 1978 and 1979 with a total dose of approximately 50 mg/kg body weight. Selection for subsequent re-treatment was based on the following criteria: (1) new comers, (2) persons with microfilaraemia by finger prick before the first mass treatment, and (3) all persons with signs and symptoms of active infections (recurrent attacks of fever and adenolymphangitis) during the post-treatment period. In addition to the yearly administration, DEC was also given to all persons during each attack of fever and adenolymphangitis by the village chief in doses of 3×100 mg/day (1 tablet filarzan[5]) for 10 consecutive days for those 10 years and above and half of the adult dose to children below the age of 10 years. The duration of each attack and side effects of DEC administration were recorded by the village chief.

The villagers were taught to recognize acute and chronic signs of filariasis. The nature of the disease, the mode of transmission, treatment, prevention, and the side effects of DEC administration were also explained. Community participation to control the disease was encouraged. Motivated persons in the community were assigned the responsibility of promptly treating all cases with acute clinical manifestations. Patients with signs and symptoms of active filariasis were instructed to contact the village chief or local school teacher to receive DEC.

[5] Mecosin Indonesia

Results

Population turn over. The village had a population of 202 persons in 1977. in June 1978, 195 persons remained; 15 had left the village, 2 had died, 5 babies had been born, and 5 new individuals had moved into the village. In June 1979, 193 persons were present; 8 had left, 3 had died, 1 baby had been born, and 8 people had moved into the village. In June 1980, the census was 194; 7 persons had left the village, 1 had died, 7 babies had been born, and 2 people had moved into the village.

Microfilaraemias. Fifty persons had microfilaraemia in 1977, 48 determined by finger prick and 2 by Nuclepore filtration. On the basis of finger prick blood samples 21 had microfilaria counts of 1–20, 17 counts of 21–50, 7 counts of 51–100 and 3 counts of 101–300. The prevalence of microfilaraemias by finger prick decreased from 24% in 1977 to 0.5% in 1978 and 0 in 1979 (Table 1); finger blood samples were not collected in 1980. The prevalence of microfilaraemias by Nuclepore filtration were 30% in 1977, 14% in 1978, 5% both in 1979 and 1980 (Table 1). Fifteen (34%) of the 50 original positive carriers were still positive 1 year after the first course of DEC, 9 (20%) positive 1 year after the second course, and 4 (9%) positive 1 year after the third course (Table 2). During

Table 1. The long term effects of repeated DEC treatment on *Brugia timori* microfilaria and diseases rates

	1977	1978	1979	1980
No. of population	202	195	193	194
Mf. rate (20 μl)	48/200 (24*)	1/195 (0.5)	0/193	NE**
Mf. rate (filtration)	29/96 (30)	16/118 (14)	10/187 (5)	10/184 (5)
Adenolymphangitis rate	93/202 (46)	35/195 (18)	36/193 (19)	22/194 (11)
Elephantiasis rate	35/202 (17)	25/195 (13)	18/193 (9)	8/194 (4)

* number positive/number examined (percentage)
** NE = not examined

Table 2. The long term effects of repeated DEC administrations on microfilaraemia

	1977		1978		1979		1980
	Pre-R	Post-R	Pre-R	Post-R	Pre-R	Post-R	Pre-R
Original positives	50	16/50 (32)*	15/44 (34)	3/44 (7)	9/46 (20)	3/46 (7)	4/44 (9)
Original negatives	150	0/150	0/139	0/139	0/132	0/132	5/132

* number positive/number examined (percentage)

Table 3. The course of microfilaraemia of *Brugia timori* infected persons after reported treatment with diethylcarbamazine

Patients	No.	1977		1978		1979		1980
		Pre-R	Post-R	Pre-R	Post-R	Pre-R	Post-R	Pre-R
	5	+	+	−	−	−	−	−
	1	+	+	−	−	−	−	+
	1	+	+	−	−	+	+	+
	4	+	+	+	−	−	−	−
	1	+	+	+	−	+	+	−
	1	+	+	+	+	+	−	−
	2	+	+	NE*	NE	NE	NE	NE
Original	1	+	+	NE	NE	+	+	+
	17	+	−	−	−	−	−	−
Positive	4	+	−	+	−	−	−	−
	1	+	−	−	−	+	−	−
	1	+	−	−	−	+	−	+
	2	+	−	+	−	+	−	−
	2	+	−	+	+	−	−	−
	2	+	−	NE	NE	NE	NE	NE
	2	+	−	−	−	−	NE	−
	1	+	−	−	−	−	NE	NE
	1	+	−	+	−	−	NE	NE
	1	+	−	NE	NE	+	−	−
Total	50	50	16	15	3	9	3	4
New comers ...	1	NE	NE	NE	NE	NE	−	+
	1	NE	NE	+	−	+	−	−
Total	2			1	0	1	0	1
Original negatives	5	−	−	−	−	−	−	+
Total	5	0	0	0	0	0	0	5
Grand total	57	50	16	16	3	10	3	10

* NE = not examined

each post-treatment period several original positive carriers converted from negative to positive and others reverted from positive to negative (Table 3). During 1977–1978, 7 persons reverted to negative, 9 converted to positive and 6 continued to be positive (persistent microfilaraemia). Five of the 6 patients (83%) with persistent microfilaraemia had microfilaria counts of more than 51 per 20 μl of blood before receiving DEC. During 1978–1979, 2 persons reverted

Table 4. The long term effects of repeated DEC administrations on adenolymphangitis

	1977	1977–1978	1978–1979	1979–1980
Original positives	93	27/87 (31)*	29/83 (35)	20/80 (25)
Original negatives	109	7/98 (7)	4/91 (4)	1/85 (1)

* number positive/number examined (percentage)

Table 5. The long term effects of repeated DEC administrations on elephantiasis

Elephantiasis	1977	1978	1979	1980
With slight/ no pitting oedema	23	21/22 (96)*	14/21 (67)	8/21 (38)
With obvious pitting oedema	12	3/11 (27)	3/11 (27)	0/11

* number positive/number examined (percentage)

to negative, 6 original positive and 1 new-resident converted to positive and 1 remained positive. During 1979–1980, 1 person reverted to negative, 2 converted to positive and 2 remained positive. In 1978 one new arrival was found to be positive and in 1980 another converted to positive. Original negatives in 1977 did not convert to positive during the first 2 years of the control programme, however, during 1979–1980, 5 persons converted to positive (Tables 2 and 3). All 5 had received only 1 course of DEC during the 3-year period. Newborns did not convert to positive during the control programme.

Adenolymphangitis. At the time of the first survey in 1977, 93 persons had clinical histories of recurrent adenolymphangitis, 3 showed acute signs of adenolymphangitis and 5 had abscesses. The prevalence of adenolymphangitis decreased from 46% in 1977 to 18% in 1978, 19% in 1979 and 11% in 1980 (Table 1). Of those with clinical histories of adenolymphangitis in 1977, 27 (31%) were still positive with histories of AL within the first post-treatment period, 29 (35%) were still positive within the second post-treatment period, 20 (25%) remained positive within the third post-treatment period (Table 4). Of the original negatives, 7 (7%) became positive between 1977 and 1978, 4 (4%) between 1978 and 1979, and 1 (1%) between 1979 and 1980. One new-resident had history of adenolymphangitis in 1978, 3 in 1979 and 1 in 1980. None of the newborns developed symptoms during the control programme. The loss of working days due to episodic attack of adenolymphangitis, as recorded by the village chief, decreased gradually from 474 between 1977–1978 to 147 between 1978–1979 and to 89 between 1979–1980.

Elephantiasis. In 1977 there were 35 persons with elephantiasis; 23 with slight or no pitting oedema and 12 with obvious pitting oedema. The duration of elephantiasis before receiving DEC ranged from 3 months to 13 years. Three persons had elephantiasis for less than 1 year, 18 from 1–3 years, and 14 more than 3 years. The prevalence of elephantiasis decreased from 17% in 1977 to 13% in 1978, 9% in 1979 and 4% in 1980 (Table 1). Each person received between 1 and 9 courses of DEC (mean = 3.5 courses), depending upon the number of recurrent adenolymphangitis attacks they experienced in the control programme. During the study period 2 persons had left the village and 1 had died. After receiving several courses of DEC, the number of persons with slight or no pitting oedema decreased from 23 in 1977 to 21 (96%) in 1978, 14 (67%) in 1979 and 8 (38%) in 1980 (Table 5). Of these 8 persons, 3 had elephantiasis of the lower arm in 1977, however, none had arm involvement in 1980. The number of persons with obvious pitting oedema decreased from 12 in 1977 to 3 (27%) in 1978, 3 (27%) in 1979 and 0 in 1980. There was 1 person with no previous history of lymphoedema who developed persistent pitting oedema in 1978 after receiving DEC. However, the pitting oedema disappeared after receiving 3 additional courses of DEC. One person had elephantiasis with obvious pitting oedema when he moved into the village in 1979. After receiving 2 courses of DEC he had no signs of elephantiasis or pitting oedema.

Side reactions. Of 197 persons treated in 1977, 173 (88%) had side reactions (Partono et al., 1979). Reactions on re-treatment, however, were remarkably mild, even with a higher daily dose of DEC. Side reactions were seldom associated with subsequent courses of DEC.

Discussion

One of the major objectives of the WHO-TDR Programme on the control of lymphatic filariasis is to improve the effectiveness of DEC and to determine the most practical dosage schedule that can be implemented with minimal skills and resources. The recommended total dose to control Brugia filariasis is 36 mg DEC per kg body weight (WHO, 1974). Varying schedule have been used in different countries in Southeast Asia with total dosages ranging from 18–72 mg (WHO Bi-Regional Research Study Group on Brugian Filariasis, 1979). In Bancroftian filariasis a standard course of 72 mg DEC appeared to be insufficient for adequate control (Ciferri et al., 1969; Kessel et al., 1970). In some instances, even 2 or 3 repeated full therapeutic DEC courses failed to clear Bancroftian microfilaraemias (Desowitz and Southgate, 1973). Our experience in treating individual carriers of Malayan and Timorian filariasis indicated that 50 mg DEC/kg often did not clear microfilaraemia (Partono, unpublished data).

The present study was based on the following considerations: (1) Initial mass treatment would decrease the microfilaria rate and density of the entire

population. (2) All persons found positive by finger prick before the initial mass treatment would be re-treated. Selection of carriers for re-treatment should be made by the simple and inexpensive standard thick blood smear. The use of expensive Nuclepore filtration, as in this study, should only be used as a tool to monitor post-treatment microfilaraemias. In the control of Bancroftian filariasis it was shown that most microfilaria carriers after DEC therapy occurred among the original positive carriers (Ciferri et al., 1969; Mahoney and Kessel, 1971). Thus, it is necessary to re-treat original carriers more intensively than other members in the community, thereby, avoiding expensive and unnecessary yearly mass treatment. (3) All new-residents should be treated to prevent introduction of new carriers. (4) All persons with adenolymphangitis should be re-treated as recurrent attacks of adenolymphangitis are regarded as indicative of active infection. Re-treatment of active cases was designed to reduce the possibility of recurrence, shorten duration of illness and prevent future development of elephantiasis.

Health education is necessary so that affected persons may themselves realize the true nature and ultimate danger of those attacks. Community participation is essential and motivated persons in the community, such as school teachers or even persons with elephantiasis, should be utilized. They should be trained to recognize and record active cases and to provide DEC immediately. A simple dosage schedule of DEC is necessary to avoid confusing lay persons responsible for delivery of the drug. At the end of the consolidation phase of the control programme, a sufficient supply of DEC should be left in the village to continue treatment of active cases by the people themselves.

Results of this study indicate that 1 course of DEC given by mass treatment was not sufficient to adequately control Timorian filariasis. Persons who had microfilaraemia before DEC treatment often remained positive after the initial treatment and were re-treated with several courses of DEC. It is interesting to note that several original positive carriers who were negative immediately after DEC therapy converted to positive within 1 year. The possibility that their living habits subject them to reinfection could not be substantiated, since the overall living conditions of the villagers are similar. On further examination of the data presented in Table 3, it is tempting to speculate that these cases should be regarded as recurrences, probably due to inadequate treatment.

Although the microfilaria prevalence rate remained stable during the last 2 years, careful analysis of individual carriers after receiving DEC suggested different epidemiological implications. In 1979 all microfilaria positive carriers manifested patent infections before the first treatment and these cases were classified as recurrences due to inadequate treatment. In 1980, 5 original negative persons converted to positive for the first time, and are considered as having new infections.

The ideal time to reinstitute mass treatment is open to discussion. Variable time periods of 1–5 years have been suggested for practical reasons. Results of

this study on Timorian filariasis indicated that a second mass treatment should be given 3 years after the initial mass treatment.

The problem of elephantiasis remains complex. According to Oomen (1969) elephantiasis is a state of diffuse thickening of the skin and subcutaneous tissue of peripheral parts of the body due to oedema and hypertrophy. Theoretically it is distinguished from pure lymphoedema by the presence of hypertrophy and fibroplasia. The tendency of fibroplasia to follow lymphoedema is variable and is not an inevitable sequel. Between lymphoedema and pure elephantiasis at both ends of the spectrum, a mixture of varying degree of lymphoedema and elephantiasis exist. In our experience, the differentiation between pure lymphoedema and elephantiasis with pitting oedema was clinically not easy, especially among a barefooted farming population where thickening of the skin on the extremities is a common finding (Partono and Purnomo, 1978; Partono et al., 1979). Of 35 elephantiasis patients with varying degrees of pitting oedema in 1977, 2 persons had left the village and 1 had died. After several courses of DEC only 8 remained affected in 1980. The best results were obtained in the group of persons with obvious pitting oedema. It may well be that many of these cases had long standing persistent lymphoedema with relatively recent developing fibroplasia. This assumption is in accordance with our experience in neighbouring villages of West Flores. In relatively newly established endemic villages, many persons with elephantiasis were favourably affected by DEC (Partono, unpublished data). But in long established endemic villages, very few were so affected. Of 3 persons with hydrocele in Karakuak, none were favourably affected by the treatment.

Preliminary results obtained in this study were encouraging. The microfilaria rate decreased considerably and the post-treatment densities were extremely low. Persons with new infections may have acquired the disease by visiting neighbouring untreated villages. Some active infections remained in spite of repeated treatment with DEC. However, the number of persons acquiring active infections yearly decreased considerably and the total number of lost working days due to filariasis decreased remarkably.

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