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Use of mebendazole in combination with DEC in bancroftian filariasis

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A pilot study was conducted in an endemic village for bancroftian filariasis to find out the compliance and antifilarial action of large doses of mebendazole (30 mg/kg/day). Thirty eight patients with early clinical filariasis and 16 with asymptomatic microfilaraemia were treated, under supervision. 'The compliance for drug consumption was high and there were no serious adverse reactions. Majority of the side effects were gastrointestinal and mild. The drug, in combination with diethylcarbamazine (DEC), showed microfilaricidal effect, but the effect was similar to that seen with DEC alone. In as many as 5 of the 13, who were followed at 1 yr, microfilaria persisted at the end of 1 yr, though with a reduced density. Prolonged (1 yr) treatment with mebendazole in combination with DEC did not have a beneficial effect in most patients with clinical disease.

Diethylcarbamazine (DEC) has been the drug of choice in the treatment of filariasis for nearly four decades[1,2]. In the past decade, several new compounds have been tried and found to possess antifilarial activity[3-6]. One of them, mebendazole, an antihelmenthic, has been shown to have some microfilaricidal action[7-9], but, in view of its poor enteric absorption[10], it needs to be given in large doses. In such larger doses, patient compliance was found to be lower due to gastrointestinal side effects[7-9].

A pilot study was conducted to find out the compliance and possible adverse reactions associated with large doses of mebendazole and to develop the methodology and tools for conducting a field trial. This paper reports the findings on compliance, adverse reactions and antifilarial activity of mebendazole.

Material & Methods

Study population : The pilot study was community based and conducted in 1983-85 in the village Thomur, Chingleput district, Tamil Nadu, endemic for *Wuchereria bancrofti*. In all, 54 patients, in the age group 15-64 yr, were admitted into the study. Care was taken to exclude pregnant women in view of the possible teratogenic effect of

mebendazole[11]. Sixteen patients had asymptomatic microfilaraemia and 38 patients had clinical filariasis, which included 3 patients of acute lymphadenopathy, 15 of chronic genital disease (9 having hydrocele), 12 of lymphoedema of limbs and 8 patients with both genital and limb disease. However, patients with elephantiasis of genitals or limbs were not included. The age and sex distribution of the study population is shown in Table I, separately for the microfilaraemic and clinical filariasis groups.

Regimen used : Earlier observations had suggested that repeated courses of DEC for a prolonged duration would be beneficial in clinical filariasis[12,13], and that mebendazole was a new promising microfilaricidal compound[7-9]. Therefore, as a pilot experiment, patients with clinical filariasis were given DEC (6 mg/kg) and mebendazole (30 mg/kg) daily for 12 days (intensive phase) and weekly for 1 yr (continuation phase). Mf carriers were given 12 days of intensive treatment only. Seven of them were treated with mebendazole and DEC and the other 9 with DEC alone. Individuals with acute episodes, during the followup phase, were treated with mebendazole and DEC for 12 days.

Table I. Age and sex distribution of the study population

Age-group (yr)	Mf group		Disease group	
	Males	Females	Males	Females
15-24	6	4	12	2
25-34	–	1	5	2
35-44	–	–	9	5
45-54	1	3	–	2
55-64	–	1	1	–
Total	7	9	27	11

Procedures : In a clinic set up in the village, the prescribed chemotherapy was administered under direct supervision of trained field staff. A comprehensive, precoded clinical form was developed to record the details of clinical examination, by a physician. All patients were examined at intake, at the end of intensive phase and at 6, 12 and 24 months. All clinical assessments were made without the knowledge of the earlier results. Also, 1 m of blood was obtained, by venepuncture after 2200 h, at all the above time points, except at 24 months, and examined for mf by membrane filtration technique (MFC)[14]. In addition, weekly surveillance was maintained during the first year for symptoms of adverse reactions, non-compliance or acute filarial attacks.

Results & Discussion

Compliance : Among the 38 patients in the clinical disease group, in 2 patients treatment was stopped for medical reasons (one each with peptic ulcer and severe vomiting) and one patient defaulted. Of the remaining 35, 31 (89%) consumed more than 80 per cent of the prescribed chemotherapy in spite of the very heavy dose (12-20 tablets at a time) of mebendazole, while the remaining 4 consumed less than 80 per cent of the prescribed chemotherapy. In both the clinical disease and mf groups, compliance for night blood specimens by venepuncture was also high (193 specimens collected of the required 208).

Adverse reactions : In spite of the large daily dose of mebendazole (1200-2000 mg), in only one patient with clinical filariasis, vomiting was severe and necessitated termination of

mebendazole. Ten (26%) of the 38 patients with clinical filariasis and 6 (38 %) of the 16 patients with mf had mild side effects which were mainly gastrointestinal and subsided in a few days with symptomatic treatment. Similar findings have been reported by other investigators using mebendazole[7,8]. In these studies, the drug was used in a lower dosage (6 mg/kg), in contrast to the present study (30 mg/kg). However, it should be noted that reports, based on animal experiments, indicate that mebendazole may have some teratogenic effect[11].

Acute attacks : During the one year of intensive surveillance, 10 attacks of acute filariasis were treated; 8 (21%) of the 38 in the disease group and 2 (13 %) of the 15 in the mf group. This difference was not statistically significant. Of the patients with acute attacks in the mf group, one each belonged to the two regimens.

Post treatment status : *Mf group* : At the end of the intensive phase, 6 of the 9 patients treated with DEC were positive for mf, although with a reduced density, while only one of the 6 patients treated with mebendazole + DEC was found to be positive (Table II). But this difference was not maintained at 6 months and 1 yr. Two of 4 patients in the mebendazole + DEC group and 3 of 9 in the DEC group were still mf positive at the end of 1 yr. Thus, although based on small numbers, the data in Table II

Table II. Status of microfilaraemics before and after treatment

Patient no.	Age	Sex	mf density (using MFC technique) at			
			intake	end of Rx	6 months	1 yr
			Mebendazole+DEC :*			
1	19	M	> 1000	0	Absent	40
2	16	F	978†	0	0	Ref
3	16	F	825	3	11	Left
4	33	F	231	0	13	2
5	46	F	78	0	0	0
6	18	M	5	0	0	0
			DEC alone :			
1	57	F	> 1000	4	8	4
2	15	M	900	4	9	5
3	23	F	532	8	0	0
4	23	M	286†	0	0	0
5	15	F	153	6	0	0
6	48	F	90	4	0	0
7	54	M	5	7	0	8
8	15	M	2	0	0	0
9	52	F	2	0	0	0

*one patient who died due to snake bite, excluded
†patient developed acute attack and was retreated

suggest that the treatment, whether mebendazole + DEC or DEC alone, had microfilaricidal effect, both in terms of rate of clearance and density, and that this effect was similar for the two regimens. It was also seen that 4 of the 5 patients in whom mf persisted at 1 yr had high pretreatment mf counts. The persistence of mf, though with markedly reduced density, in as many as 5 (38 %) of the 13 patients, who were followed at 1 yr, could be due to the partial effect of the drug, at least in a proportion of patients, on the adult filarial worms[3,4,15]. Similar findings on the microfilaricidal action of mebendazole have been reported earlier[7,8].

Disease group: Out of the 38 patients treated, in 2 patients treatment was stopped for medical reasons, 1 defaulted and 2 were absent for the examination at 2 yr. The pretreatment clinical status in the remaining 33 patients is shown in Table III as also that at the end of 2 yr. Of these 33, 30 patients had completed 80 per cent or more of the chemotherapy prescribed. In 30 patients evidence of clinical filarias was still seen at the end of 2 yr, in spite of prolonged treatment using mebendazole in combination with DEC. In 3 female patients, all with filarial oedema, the disease disappeared at the end of 2 yr.

All the 38 patients in the disease group were mf negative at the start of the study. Blood samples were collected in 37 and 29 of them at 6 months and 1 yr respectively. All the specimens were negative for mf except for 1 patient (with 1 mf) at 1 yr.

In conclusion, the pilot experience suggested that *(i)* mebendazole in large doses along with DEC had no serious side effects, *(ii)* the microfilaricidal effect of mebendazole + DEC was similar to that seen with DEC alone, although based on small numbers, and *(iii)* prolonged treatment with mebendazole in combination with DEC did not have a

Table III. Status of clinical disease before and after chemotherapy

Initial disease status	Total patients	Disease status at the end of 2 yr					
		No. Disease	(a)	(b)	(c)	(d)	(e)
(a) Acute lymphadenopathy	3	–	3	–	–	–	–
(b) Chronic inflammation of cord and/or testes	4	–	2*	–	–	1	1
(c) Hydrocele	8	–	2*	1	3*	–	2
(d) Lymphoedema of limbs	11	3	1	–	–	7	–
(e) Both genital and limb disease	7	–	–	1	2	–	4
Total	33	3	8	2	5	8	7

*Three patients received < 80 per cent of the prescribed chemotherapy

beneficial effect in most patients with clinical filariasis.

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