IVERMECTIN IN THE TREATMENT OF BANCROFTIAN FILARIAL INFECTION IN ORISSA, INDIA

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Abstract. Ivermectin treatment has evaluated for its efficacy and side reactions in sixty patients of Orissa with Bancroftian filarial infection and microfilaremia. Ivermectin was administered as a single oral dose at four dosage levels (20, 50. 100 and 200 µg/kg), and both microfilarial clearance and associated side reactions were monitored in a double blind fashion. Blood microfilariae were cleared in all patients at all dosages within 1 to 14 days. In most patients microfilariae reappeared by third month. The microfilaria appearance by third and sixth month averaged 12.2 to 44 percent of pretreatment values in the fourstudy groups. Side reactions were encountered in almost all patients, the commonest being fever. headache, weakness, myalgia and cough which occured most prominently 12 to 72 hours after treatment. Side reactions were more frequent and severe in patients with high microfilaria counts. Clinical reaction scores for each group were independent of the dose administered. The 200 µg dose group showed significantly more rapid microfilariae clearance and its delayed reappearance as compared with the other dosage groups and without inducing significantly greater clinical reaction scores.

INTRODUCTION

Lymphatic filariasis is a major health problem in India, with 22 million people being microfilaremic and another 16 million showing symptoms and signs of filariasis (Sharma *et al*, 1983; WHO, 1984). Orissa, situated on the eastern coast of the country is highly endemic for Bancroftian filariasis, where the prevalence rate of the disease and microfilaremia is as high as 37.2% and 15.8% in certain endemic villages (Kar, 1986). With diethylcarbamazine (DEC) as the only drug available for treatment of human filariasis, the goal of the National Filariasis Control Program (NFCP) could not be achieved as multiple doses of the drug over 2 weeks had to be given and because of the associated side effects (Sasa et al. 1963: Sundaram *et al.* 1971; Hawking, 1979). Hence, it appeared essential to have an alternative drug that was safe, elective, easy to administer and more acceptable to population requiring treatment.

Ivermectin is now the drug of choice in onchocerciasis and more than 1,000,000 people have already been successfully treated in Africa and Latin America (Lariviere *et al.* 1985). It has been shown to be as effective as DEC. Studies on the susceptibility of *Wuchereria bancrofti* infection to ivermectin and the optimal dosage required for maximal microfilaricidal effect have recently been carried out in a number of places (Diallo *et al.* 1987; Kumaraswami *et al.* 1988; Roux *et al*, 1989). While a single oral dose has been found to be just as effective in decreasing microfilaremia as the usual full course of DEC for 3 months post treatment (Ottensen *et al*, 1990), there has been some variation in the estimation of the optimal drug dose in different regions. This difference might possibly result from the variations which exist in the population characteristics studied or from differences in the parasites in various endemic areas. In Orissa. where the density of infection is generally high and certain atypical manifestations of infection have been described (Kar, 1986) a trial on ivermectin was initiated to determine the optimal dosage of the drug needed for clearance of *W. bancrofti* microfilaremia with fewest associated side reactions.

MATERIALS AND METHODS

Patient population

Asymptomatic microfilaria carriers from endemic villages were detected through blood surveys. Sixty men aged 18-40 years (median age 22.5 years) with *W. bancrofti* infection (more than 100

mf/ml) were included in the trial. All of them were above 31 kg body weight. Each patient consented to participate in the trial after the nature and scope of the study had been explained. The treatment protocol was approved by the ethical committee of the Indian Council of Medical Research.

Pre-drug assessment

Clinical: All individuals were hospitalized for IO days (3 days before receiving the drug and for at least a week thereafter). Each patient was subjected to a pretreatment evaluation which included detailed clinical history, physical examination, hematologic evaluation (hematocrit, hemoglobin percentage, total and differential white cell counts), serum chemistry studies (bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and creatinine), urinalysis (routine and microscopic), chest X-ray and electrocardiogram.

Parasitological: Blood microfilaria (mf) levels per ml of blood were assessed at 9.30 pm thrice before treatment by Nuclepore membrane filtration (using 3 μm filter from Nuclepore Corporation. Pleasanton, CA, USA). The average value of the mf count of the three pre-drug days was taken as pre-drug mf count.

Study design

After the pre-treatment evaluation, the subjects were randomly allocated to four different dosages of ivermectin (20, 50, 100 and 200 μg/kg). The drug was administered as single oral dose to each patient on an empty stomach at 9.00 am in the morning. The drug allocation and the assessment were carried out in a double blind fashion.

Post-drug assessment

The vital signs and clinical findings were monitored by a check list every four hours for two days, every 6 hours for next two days and daily thereafter for the remaining three days. Serum chemistry studies were carried out in the 2nd and 7th days of drug administration. Post treatment periodic follow up examinations were carried out in the hospital on day 14, 30, 90 and 180. These included clinical history, physical examination and complete blood cell count.

The microfilaria levels of the blood were assessed at 12 and 36 hours and on days 7, 14, 30, 90 and 180 after treatment. The results were expressed as the number of microfilariae per milliliter of blood or a percentage of mean number of the pretreatment count for each patient.

Assessment of side effects

Each adverse reaction (like fever, anorexia. cough, chill, weakness, headache, etc) was given a scale of 0-3 (none, mild, moderate or severe). The side reaction scores of all 7 days in the hospital were summed to generate the 'total reaction scores' for each individual. These scores were used to assess the relationship between side effects of treatment and either the drug dose or parasite loads of patients.

Statistical analysis

Analysis of variance was carried out to observe the effect of different drug dosage with the microfilaria level at different points of time. Statistical evaluations were also done by student's r-test, wherever necessary. For comparison involving microfilaremia levels, microfilaria counts were logarithmically transformed before the analysis were carried out.

RESULTS

Efficacy of ivermectin in clearing microfilaremia

The pretreatment microfilaria count of sixty study cases ranged from 123 to 10,000 mf/ml of blood (Median-1, 698, GM = 1.338). The geometric means (GM) of microfilaria of the four groups of patients receiving 20, 50, 100 and 300 μg/kg of the drug were 1,283.7, 1,537.2, 812.81 and 2,000.1/ml of blood respectively. These counts were significantly different ($p < 0.001$) from each other. There was an abrupt fall ($p<0.01$) in the mean (GM) blood microfilaria levels after the single dose of ivermectin, with nearly 98% of the circulating microfilariae being cleared within 12 hours in all dose groups. In most patients, the mf count dropped to 0-2/ml of blood within 14 days of drug administration except in one case whose lowest count achieved 67/ml (drug dose 20 μg/kg, pretreatment mf count; 721/ml). The microfilaria clearance was most effective in the group receiving

200 µg/kg dosage. However these mf clearances were not permanent. The count started to rise gradually. The average (GM) mf levels rose to 12.2 and 44% of the pre-treatment value at the third and sixth months, respectively. In addition to the initial clearance being significantly less rapid in the group that received the 20 µg dose, the return of microfilaremia came more rapidly. The highest dose group (200 µg/kg) which had experienced the most abrupt initial fall of parasite count, had a reappearance rate that was also relatively slow. The mf reappearance rate at sixth month was 21 and 66 % of pre-drug counts in the 200 and 20 µg dose groups, respectively (Fig 1). In the 50 and 100 µg groups the mf clearance and reappearance followed intermediate patterns. Analysis of variance revealed significant effect ($F= 64.36$, $p<0.005$) of different dosage on the clearance of microfilaria level.

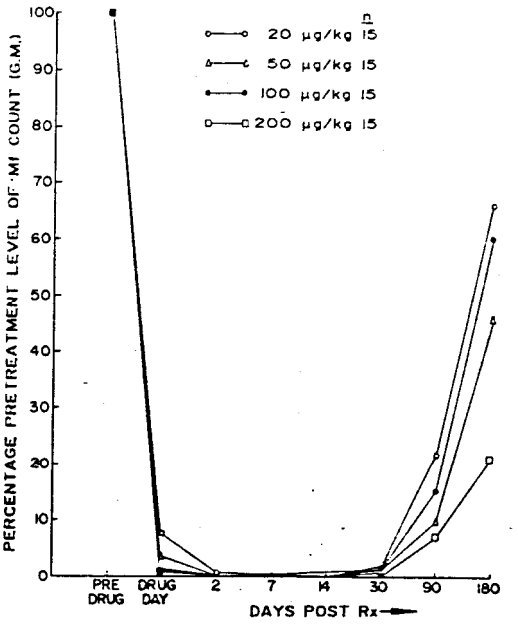

Fig 1–Kinetics of microfilaria clearance and recurrence in all dose groups of ivermectin treatment (n = 60).

Side effects

The severity of each clinical finding was graded on a scale of 0 to 3 (none, mild, moderate or severe). Within 12-24 hours of drug administration 97% of the patients experienced mild to moderate side reactions. The commonest side effects were fever, headache, weakness and lethargy. The time course of these events was similar for all patients. These reaction peaked in intensity between 24-48 hours of therapy and subsided by 48-72 hours. Even at their peak intensities the side effects were generally mild to moderate. These were easily managed with simple medication such as paracetamol and throat lozenges for relief. Postural hypotension was observed only in four subjects, each treated with a different drug dosage: it manifested as tachycardia beginning at 24 hours and persisted only for 8 hours except in one patient with high microfilaremia (20 µg/kg dosage) who remained intermittently posturally hypotensive until the 4th day.

The serum chemistries and electrocardiograms were within the range of normal values. A transient rise in serum alkaline phosphatase level was observed in four cases on the 2nd day but this returned to normal values on the 7th day. Passage of round worms was reported by three patients following treatment.

The total average symptom scores. peak scores and percentage of. patients showing symptoms were analysed (Tables 1, 2).

To determine whether the side effects of the treatment were drug dose related or merely a function of the microfilaria parasite burden, the mean reaction scores were compared among patient groups. It was observed that the group treated with 100 µg/kg of ivermectin had the lowest mean reaction score, which was significantly different from that of the 50 µg ($p<0.025$) and 200 µg ($p < 0.05$) group (Fig 2). Total mean reaction scores were further compared between two groups with low and high microfilaremia. The reaction scores obtained in the two low dose groups were independent of their microfilaria status. However, in the rest (100 and 200 µg/kg) the mean reaction scores were significantly higher ($p<0.05$) in high microfilaremics (Fig 3).

DISCUSSION

Various clinical trials with ivermectin in the treatment of onchocerciasis have proven its efficacy as a potent microfilaricide with relatively few side reactions and subsequently its usefulness in control programs (Greene *et al*, 1985; WHO, 1989).

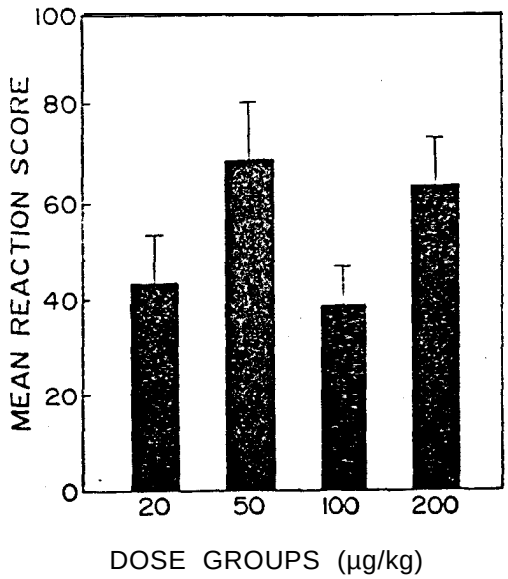

Fig 2–Post treatment mean reaction scores for ivermectin study groups (n = 60).

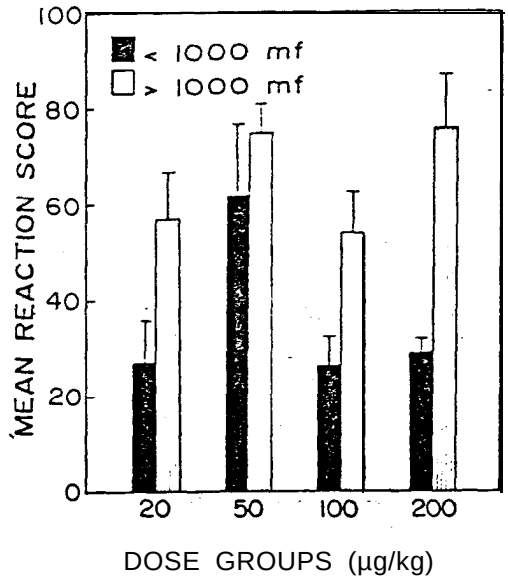

Fig 3–Post treatment mean reaction scores for predrug high and low mf counts in four ivermectin dose groups.

Table 1

Adverse reactions seen in *Wuchereria* patients treated with various single oral doses of ivermectin.

Sign/Symptom	% of population with symptoms				
	20 µg/kg n=15	50 µg/kg n=15	100 µg/kg n=15	200 µg/kg n=15	Total n=60
Fever	93	100	100	100	98
Anorexia	80	100	53	67	75
Nausea	20	60	20	27	32
Cough	33	80	53	73	60
Giddiness	67	87	60	67	70
Diaphoresis	60	53	47	47	52
Chill	73	100	73	87	83
Headache	93	100	86.7	93	93
Lethargy	87	100	73	87	87
Weakness	93	100	80	93	92
Myalgia	47	93	73	67	70
Arthralgia	33	67	47	60	52
Vomitting	7	33	0	20	15
Sore throat	33	47	40	60	45
Abd pain	20	33	20	47	30

Table 2

Comparison of reaction scores seen in *Wuchereria bancrofti* patients with high or low mf counts (n = 60).

Symptoms	Average total score		Peak score		% of patients with symptoms	
	LM	HM	LM	HM	LM	HM
Fever	6.8	11.7	1.5	2.1	95.8	100.8
Diaphoresis	1.0	1.4	0.4	0.6	45.8	55.5
Chill	1.7	4.8	0.7	1.3	66.7	94.4
Headache	4.7	7.5	1.0	1.6	87.5	97.2
Lethargy	2.8	0.8	1.0	1.2	75.0	94.4
Weakness	3.6	8.0	0.9	1.2	83.3	97.2
Myalgia	3.5	4.5	0.7	1.0	58.3	77.3
Arthralgia	1.2	1.7	0.4	0.6	37.5	61.1
Anorexia	2.4	6.7	0.8	1.1	58.3	86.1
Nausea	0.4	1.7	0.2	0.4	16.7	41.7
Vomitting	0.1	0.4	0.1	0.2	8.3	19.4
Giddiness	2.2	5.3	0.7	1.2	50.0	83.3
Sore throat	1.6	2.3	0.4	0.6	37.5	50.0
Cough	2.5	4.1	0.5	0.9	41.7	72.2
Abd pain	0.9	1.1	0.3	0.4	20.8	36.1

LM = mf count < 1000/ml of blood (n =24)
HM = mf count > 1000/ml of blood (n=36)

The developments gave hope for similar application of ivermectin in lymphatic filarial infections as well. However, there is currently only limited experience on the effectiveness of this drug in various dose ranges from a few endemic areas (Diallo *et al.* 1987; Kumaraswami *et al,* 1988; Roux *et al,* 1989) and it remains a possibility that regional differences may show variations either in the response of infected patients to ivermectin therapy or in the susceptibility of the parasites, that will have important implications for the control program if the drug can eventually be used. Understandably, there is a need to have wider experience of its effects in various population groups before an optimal dose of the drug can be recommended for control programs. The present study therefore evaluated four doses of ivermectin to assess their relative efficacy and side reaction in patients with moderate to very high levels of *W. bancrofti* microfilaria in Orissa, India

All four drug dosage groups showed similar microfilarial clearance patterns (Fig 1). but the group receiving the highest dose (200 µg/kg) showed the most rapid clearance, maintained the lowest level of microfilaremia for the longest period of time and with the lowest microfilarial recurrence levels (20.9%) 6th months post-treatment. Clearance of microfilariae from the blood was complete in 37% (n=46) of subjects within two weeks. Nearly 98% of circulating microfilariae was cleared within twelve hours of drug administration. But the fall in the mf levels was not permanent and the counts started to rise gradually from the 30th day onwards. Possibly. these 'recurring' microfilariae were derived from those adult worm(s) that were not affected/killed by a single dose of ivermectin (Roux *et al.* 1989). Trials in Tahiti (Roux *et al.* 1989) and Senegal (Diallo *et al.* 1987) indicated that a dose of 100 µg or more of ivermectin per kg was more effective than that of 50 µg as microfilaricide and was not accompanied by frequent side effects. However, studies in South India have shown that doses of ivermectin at 20-25 µg/kg were just as effective as those at 200 µg/kg in reducing the degree of microfilaremia and importantly, were associated with either significantly fewer side effects or a tendency

towards fewer side reactions than that with higher doses.

In the present study, it was clear that the highest dose (200 µg/kg) was most effective in clearing microfilaremia but it was difficult to assess the relationship of the dose with the side reactions as the mf level in the four dose groups were not comparable. The total average score of symptoms like anorexia, cough, giddiness, vomiting and abdominal pain was high in the 50 and 200 µg/kg dose groups (Table 1). It may be noted that more of high microfilaremics were included in the above two groups. The average total reaction score of patients receiving 20 and 100 µg were less than those receiving 50 and 200 µg/kg doses (Fig 2). This shows that the average reaction score is independent of drug dose. The total average reaction scores were found to be significantly higher ($p < 0.001$) in the groups with high blood mf levels (> 1000 mf/ml) (Table 2). Symptoms like vomiting, sustained cough, severe anorexia and giddiness were found mostly in the high microfilaria groups. This indicates that the side reactions following drug administration were rather the manifestation of host inflammatory response to dying microfilariae (Piessens and Beldekas, 1979; Ottesen 1987; Campbell, 1989). This was consistent with the present observation that within 12 to 24 hours of drug administration 97% of patients started complaining discomfort when the maximum mf death occurred. These reactions reached maximum intensity between 24 to 48 hours of therapy and subsided by 48 to 72 hours. All these side reactions disappeared with the clearance of microfilaria.

In the present observation four patients with high pretreatment mf count developed postural hypotension. Postural hypotension has been seen with DEC treatment both in onchocerciasis (Bryceson *et al.* 1977; Awadzi *et al,* 1982) and lymphatic filariasis (Kumaraswami *et al.* 1988). Thus the observed phenomenon was not related to direct effect of drug although there is evidence in cats that gamma-aminobutyric acid antagonists (as ivermectin has been shown to be) (Campbell *et al.* 1983) can be hypotensive (Metheson *et al,* 1986).

Though mf clearance was observed equally in all the groups, in the 200 µg/kg dose group there was better mf clearance, delayed reappearance and side reactions were within tolerable limits. To determine the exact relationship of dose with associated side reactions, patients with comparable mf counts may be studied with different doses. Besides, further studies are needed to evaluate the effect of multiple doses or single doses of ivermectin in preventing reappearance of microfilaria or eradicating adult parasite from host.

Study results (efficacy) contrast markedly from those reported from Madras and Haiti but similar to Polynesia. Perhaps differences relate to intensity of infections in these patients–something we can not measure except very indirectly from mf levels and inferentially from the prevalence levels in various regions. It may be, as has been found in onchocerciasis that initial treatment at more frequent intervals (1-3 months) would be necessary to achieve maximal benefit in mf reduction in individuals with high infection living in regions of high transmission whereas less frequent drug administration would be sufficient in areas of relatively low infection prevalence.

In our case, results here are the "poorest" in terms of effectiveness of the single dose of ivermectin in reducing microfilaremia. These observations are extremely important and must be explained or at least taken into consideration, before optimal ivermectin based control strategies are formulated.

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