A double-blind comparison of the efficacy and safety of ivermectin and diethylcarbamazine in a placebo controlled study of Senegalese patients with onchocerciasis

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Abstract

Ivermectin (MK-933) has been compared with diethylcarbamazine (DEC) and placebo in a double-blind study in 30 adult male Senegalese patients with *Onchocerca volvulus* infection. 10 patients were randomly assigned to each treatment group. Ivermectin was administered as a single oral dose of 12 mg and DEC as 50 mg daily for two days and 100 mg twice daily for the following six days, total 1·3 g in eight days. Skin *O. volvulus* microfilaria densities remained near pre-study values in the placebo patients, but decreased rapidly with both active drugs to mean values about 2% of pretreatment (Day 8) and then increased slowly, reaching in 12 months about 4% of pre-treatment (ivermectin) and 18% (DEC). This difference is statistically significant. Clinical adverse reactions were recorded in four ivermectin, ten DEC and three placebo patients. One ivermectin and six DEC patients received steroid treatment for relief of these reactions. Serious adverse ocular changes were not seen in any patients, possibly because of the steroid therapy in the DEC patients. Adult *O. volvulus* from onchocercal nodules one and six months after treatment showed no effect of either drug on viability. Intra-uterine developing forms of the microfilariae appeared normal in all three treatment groups at the one month examination but deformed and degenerated forms were evident at six months in the ivermectin group but not in the DEC and placebo patients.

Ivermectin as a single oral dose appears to be a safer and more effective microfilaricidal drug in human onchocerciasis than DEC in the standard multi-dose regimen.

Introduction

Onchocerciasis is a major filarial disease and one of the leading causes of blindness in the Third World countries. This disease, which is caused by the filarial nematode *Onchocerca volvulus*, affects about 40 million people in Africa, Latin America and Yemen. Treatment remains unsatisfactory, even though onchocerciasis has been recognized for many years. Diethylcarbamazine (DEC) and Suramin[R] are the standard drugs of therapy (DUKE *et al.*, 1981; GOODWIN, 1984). DEC must be given daily for 7 to 10 days and is accompanied by severe reactions, including deterioration of onchocercal eye lesions, and may even cause blindness and death (ANDERSON *et al.*, 1976; ANDERSON & FUGLSANG, 1978; BIRD *et al.*, 1980; BRYCESON *et al.*, 1977; FUGLSANG & ANDERSON, 1974; HAWKING, 1978a; MAZZOTTI, 1948; TAYLOR *et al.*, 1980; TAYLOR & GREENE, 1981). Suramin has to be given intravenously once each week for several weeks and is usually accompanied by severe rash, diarrhoea, neurotoxicity, nephrotoxicity and sometimes death (GOODWIN, 1984; HAWKING, 1978b). It is apparent, therefore, that development of a vaccine or a new drug that is safe and effective, preferably one that may be administered orally as a single dose for mass chemotherapy, must continue to be a major research goal.

Ivermectin, first reported by Merck scientists in the late 1970s, is a semi-synthetic macrocyclic lactone with broad antiparasitic activity (CAMPBELL *et al.*, 1983). In 1981 we investigated the clinical efficacy and safety of this new drug (AZIZ *et al.*, 1982; DIALLO *et al.*, 1984) in a placebo controlled study in 32 Senegalese men who had mild *O. volvulus* infection without eye involvement, and found it to be microfilaricidal and to have minimum side effects. A single 5 to 10 μg/kg body-weight oral dose had no effect, but 30 to 50 μg/kg given orally as a single dose caused the skin *O. volvulus* microfilarial (mf) density to decrease to near zero in some patients and to remain near zero for at least 42 days. More than half of the patients were found to have very low mf density in follow-up examinations seven to eight months after treatment.

The findings of that initial study have been confirmed in dose ranging (50 to 200 μg/kg) studies in France (COULAUD *et al.*, 1983, 1984) and in Ghana (AWADZI *et al.*, 1984, 1985) in patients with high skin mf density, some with eye involvement. These studies corroborated the earlier findings that ivermectin caused sustained decreases of skin mf, even in patients with initially high mf density, and was accompanied by minimum side effects.

In the present communication we report our findings from a double blind study comparing the efficacy and safety of ivermectin, DEC and placebo in 30 moderately or heavily infected adult onchocerciasis patients with eye involvement from villages in south-eastern Senegal along the Koulountone River, a tributary of the Gambia River.

Patients and Methods

Patients

30 male patients aged 18 to 55 years who consented to participate in the study were brought to Dakar, Senegal,

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from their respective villages and were admitted to hospital at the Hospital de Fann, the teaching hospital of the University of Dakar. These patients were selected following a series of clinical and laboratory tests including skin mf determination carried out in the villages. All patients were moderately or heavily infected with *O. volvulus*; skin microfilarial density ranged from 19 to 166 mf/mg skin. Some patients had moderate ocular involvement but none were blind; 23 of the 30 patients had stools positive for the hookworm *Necator americanus*.

Patients were admitted to the research ward of the Infectious Diseases Section of the Hospital de Fann and were assigned by a randomized double-blind allocation schedule to treatment with ivermectin, DEC or placebo. Patients were released from hospital after 28 days and were instructed to return for three- and six-month follow-up examinations. The 12-month examinations were conducted in the patients' villages. The treatment code was broken after the six-month follow-up examination.

Clinical and Laboratory Evaluation

Each patient had a complete physical examination during the two days before initiation of therapy. Patients were kept under close clinical observation for 14 days after treatment; vital signs were taken frequently and all signs and symptoms of clinical adverse reaction were recorded. Physical examinations were again conducted at 21 and 28 days after treatment.

Blood samples were analysed for haemoglobin and haematocrit and for total and differential white blood cells. Samples were also analysed for blood sugar, blood urea nitrogen, serum bilirubin, creatinine, transaminases and alkaline phosphatase. All laboratory determinations were carried out on samples taken the day before therapy (Day 1), the day following the initiation of therapy (Day 2) and again on Days 8, 14 and 28.

Urine samples were analysed for sugar, albumin and pH on Days 1, 2, 4, 8, 14 and 28.

Ophthalmological Examination

All patients had comprehensive ocular examinations before treatment and on Days 2, 4, 8, 14 and 28; most patients also had follow-up examinations at three and six months after treatment. The ocular examination included tests for visual acuity, peripheral visual fields by confrontation, and colour vision. After head-down positioning of the patient, the anterior segments were examined with a slit-lamp and the numbers of microfilariae in the cornea and anterior chamber were recorded. Intra-ocular pressure was measured using a Goldman applanation tonometer and the fundus was examined by direct and indirect ophthalmoscopy after the pupil had been dilated with a mydriatic. Fundus photography and intravenous fluorescein angiography were carried out using a fundus camera.

Parasitological Examination

To detect microfilariae of *O. volvulus*, skin biopsy samples were taken two days before the administration of study drug and on Days 2, 4, 8, 14 and 28 during the period in hospital. Cutaneous biopsies were also carried out 3, 6, 9 and 12 months after study drug treatment in most patients.

Microfilariae were counted in six (bloodless) skin samples taken with a Walser type sclerocorneal punch from both the left and right sides of the iliac crest, the lateral side of the calf and the shoulder, as recommended by the expert committee of WHO (1977). Each biopsy sample was weighed on a torsion balance; samples weighing less than one milligram were discarded. The sample was immediately placed in a well in a flat-bottomed microtitre plate (Dynatech microtitre) containing 0·1 ml of M199 tissue culture medium (Pasteur Institute) adjusted to neutral pH and containing penicillin-streptomycin at a final concentration of 2%.

Samples were stored at room temperature for six hours and then transferred to a microscope slide for counting microfilariae. Skin samples were then transferred to a different well on the same plate containing 0·1 ml of a solution of 0·3 g collagenase (Boehringer, Germany) in 100 ml M199 medium. After 24 hours' incubation at 37°C samples were shredded in the total amount of liquid left in the well, transferred to a slide and microfilariae counted again. The number of microfilariae recorded per biopsy was the sum of the numbers obtained from the pre- and post-collagenase counts. The average concentration of microfilariae for each patient is expressed as the number of microfilariae per mg skin, i.e., the total number of microfilariae counted in all six biopsy samples divided by the total weight in mg of the six samples.

Treatment

Patients were randomly assigned to one of three treatment groups, ivermectin, DEC or placebo. Drugs were provided in sealed coded packages that contained identical numbers of capsules of uniform size and appearance. After an overnight fast, drugs were administered at least one hour before breakfast under close supervision to ensure compliance. 10 patients were given ivermectin as a single dose of 12 mg in two capsules of 6 mg each on Day 1, followed by seven days of identical placebo capsules. 10 patients received DEC as a single dose of 50 mg on Days 1 and 2 followed by 100 mg twice daily on days 3 to 8, a total dose of 1300 mg. The third group of 10 patients received the same number of identical placebo capsules.

Nodule Examination

Palpable onchocercal nodules were surgically excised from nine patients on Day 28 and from seven patients six months after treatment. Each nodule was weighed and subjected to collagenese digestion to expose the adult *O. volvulus* worms, which were then examined for viability and reproductive status (SCHULZ-KEY *et al.*, 1977). Digestion was carried out at 30°C using 0·3% collagenase, and the number of living and dead male and female adult worms isolated from each nodule recorded, noting the proportions that were immature young, old, degenerating and calcifying. Selected adult female worms were sectioned and the contents examined for detailed evaluation of the developing forms of the microfilariae.

Data Analysis

All data through 12 months after treatment were entered into the computer; the double-blind code was not broken until after the six-month follow-up data had been entered. Statistical analysis was based on one way analysis of variance with t test for multiple comparisons when comparing means of treatment groups. Other analyses were performed using Student's t test and Fisher's exact test.

Results

Pre-treatment Findings

10 patients were randomly assigned to each of three treatment groups and received double-blind packaged ivermectin, DEC or placebo. As shown in Table 1, the patients in these groups were of similar mean age. Nine patients in the ivermectin group had palpable onchocercal nodules compared to seven and nine patients in the DEC and placebo groups respectively.

Dermatological manifestations of onchocerciasis were present in two ivermectin patients (two pruritus), three DEC patients (one pachyderma, two vitiligo) and three placebo patients (one pruritus, two pachyderma, one vitiligo). Two additional placebo patients had inguinal lymphadenopathy. These differences in clinical features were not statistically significant.

Pre-treatment skin microfilarial densities were below 90 mf/mg skin in all 10 ivermectin patients; one DEC and two placebo patients had densities above 90 mf/mg. The geometric mean densities by treatment

group, 34·0 (ivermectin), 44·5 (DEC) and 51·0 (placebo), were not statistically significantly different.

Pre-treatment ophthalmological findings have been summarized in Table 2. Two patients in the ivermectin group, six in the DEC group and nine in the placebo group had ocular lesions attributed to onchocerciasis. Both ivermectin patients had lesions of the posterior segment, one with chorio-retinitis and optic nerve atrophy and one with intra-retinal deposits and epithelial pigment abnormality of the retina. Among the six DEC patients were two with chorio-retinitis, one of whom had optic nerve atrophy. Choroido-retinal lesions were also seen in one patient in the placebo group. Visual fields were abnormal in one patient in the ivermectin group; colour vision was abnormal in three patients in the DEC group and two in the placebo group. Keratitis was present in one patient in each of the DEC and placebo groups. Microfilariae were present in the cornea in one ivermectin and three placebo patients

Table 1—Pre-treatment patient data

Treatment group[a]	mean age (yrs)	Patients with palpable nodules	Patients with cutaneous lesions and/or inguinal adenopathy	mean[b] mf/mg skin
MK-933	32·4	9	2	34·0
DEC	33·5	7	3	44·5
Placebo	31·4	9	5	51·0

[a]Ten patients per group.
[b]Geometric means; no significant differences between groups.

Table 2—Patients with pretreatment ocular lesions

Lesion	Treatment Group MK-933	DEC	Placebo
Visual field abnormality	1	—	—
Colour vision abnormality	—	3	2
Keratitis	—	1	1
Mf in cornea	1	—	3
Mf in anterior chamber	1	4	6
Tyndall effect	1	2	—
Optic nerve atrophy	1	1	—
Intra-retinal deposits	1	—	—
Retinal pigment epithelium atrophy	1	2	—
Retinal pigment epithelium abnormality	1	—	—
Chorio-retinitis	1	2	1
Total patients*	2	6	9

*Most patients had more than one ocular lesion before treatment.

Table 3—Haematology and blood chemistry data*

Laboratory Variable	Normal Range	MK-933 Day −2	MK-933 Day 14	DEC Day −2	DEC Day 14	Placebo Day −2	Placebo Day 14
Haemoglobin	13·5-18 g/dl	11·7	13·6	12·7	15·2	12·1	13·1
Haematocrit	40-44%	39	39·5	43·2	42·3	41·2	39·5
Leucocytes	5000-8000/mm^3	5962	10077	6752	11747	5286	7708
Glucose	0·7-1·0 g/l	0·8	0·9	0·7	0·7	0·8	0·8
Nitrogen	0·1-0·5 g/l	0·29	0·35	0·32	0·34	0·25	0·40
Creatinine	6-11 mg/l	10·2	10·4	7·8	8·9	8·0	9·9
Total bilirubin	0-11 mg/l	5·5	5·1	6·6	6·4	8·2	5·0
SGOT	1-26 μ/l	11·6	8·6	9·8	12·4	13·8	9·6
SGPT	1-32 μ/l	8·9	9·3	7·5	14·8	7·8	11·3
Alkaline phosphatase	85-213 μ/l	83·4	68·6	119·9	80·1	96·9	70·8

*Mean values per treatment group.

and in the anterior chamber in one ivermectin, four DEC and six placebo patients; Tyndall effects were observed in one ivermectin and two DEC patients and intra-retinal deposits in one ivermectin patient. Pre-treatment laboratory findings in all three groups were within normal limits (Table 3).

Post-treatment Findings

1. *Clinical Adverse Reactions*

Clinical adverse reactions are recorded by treatment group in Table V. The four patients in the ivermectin group included two with pruritus, one with rash and oedema of the thighs and one who developed swelling of the scrotum and inguinal lymphadenopathy on Day 3 and high fever (40·4°C) on Day 7. All symptoms were controlled with a one to two-day course of antihistamine treatment except in the patient with scrotal swelling, who received steroid treatment for two days in addition to antihistamine.

All 10 patients in the DEC group had clinical adverse reactions, including pruritus (10 patients), papular rash (four), rash and oedema (one), fever (six), inguinal lymphadenopathy (five), arthralgia (two) and conjunctivitis (three). High fever, rash and oedem of the thigh appeared in one patient on Day 3 and drug treatment was interrupted for one day (Day 5). All 10 patients received symptomatic treatment with antipyretics and antihistamines; six of the ten also received steroid therapy.

Only three patients in the placebo group had clinical adverse reactions—pruritus (three patients) and papular rash (one). One patient in this group received antihistamine therapy to relieve pruritus.

Clinical adverse reaction considered severe and requiring steroid therapy occurred in one patient in the invermectin group, six in the DEC group and none in the placebo group.

Significant laboratory abnormality was noted only in the total WBC counts in ivermectin and DEC patients on Day 14; these values were significantly higher than the pre-treatment levels (Table 3). There were no changes in the placebo group.

2. *Ophthalmological Findings*

The ophthalmological data recorded in the course of this study and reported below were complete, or nearly so, for all ophthalmological measurements except fluorescein angiography, which was carried out before and three months after treatment in only four ivermectin and four DEC patients. No significant changes after treatment were observed in the records for these patients.

Significant changes were not observed in the ophthalmological findings in the ivermectin group, except that mf in the cornea and the anterior chamber in one patient before treatment were no longer present at three and six months, and mf that had appeared in the anterior chamber after treatment in four patients

Table 4—Skin density of *O. volvulus* microfilariae

Study day	MK-933	DEC	Placebo
−1	34·0[a] (100)[b]	44·5 (100)	51·0 (100)
2	5·3 (16)	9·5 (21)	60·0 (117)
4	1·3 (4)	2·8 (6)	68·6 (134)
8	0·7 (2)	0·6 (1)	77·5 (152)
14	0·6 (2)	1·8 (4)	69·0 (135)
28	1·2 (4)	4·1 (9)	79·8 (156)
90[c]	1·1 (3)	6·5 (15)	48·3 (95)
180[c]	0·9 (3)	9·6 (22)	73·7 (145)
270[c]	1·0 (3)	6·8 (15)	45·0 (88)
360[c]	1·3 (4)	7·9 (18)	38·1 (75)

[a] Geometric mean, microfilariae per milligram skin.
[b] Percentage of pretreatment (day −1) values.
[c] Ten patients in each treatment group, except that only 9, 8, 9 and 9 DEC patients and 8, 9, 9 and 9 placebo patients returned to the hospital for the 3, 6, 9 and 12-month follow-up examinations.

Table 5—Clinical adverse experience

	Number of patients		
	MK-933	DEC	Placebo
Pruritus	2	10	3
Papular rash	0	4	1
Oedematous rash	1	1	0
Hyperthermia (>38°C)	1	6	0
Painful inguinal adenopathy	1	5	0
Arthralgia, asthenia, myalgia	1	4	0
Swelling of scrotum	1	0	0
Conjunctivitis	0	3	0
Total patients	4	10	3

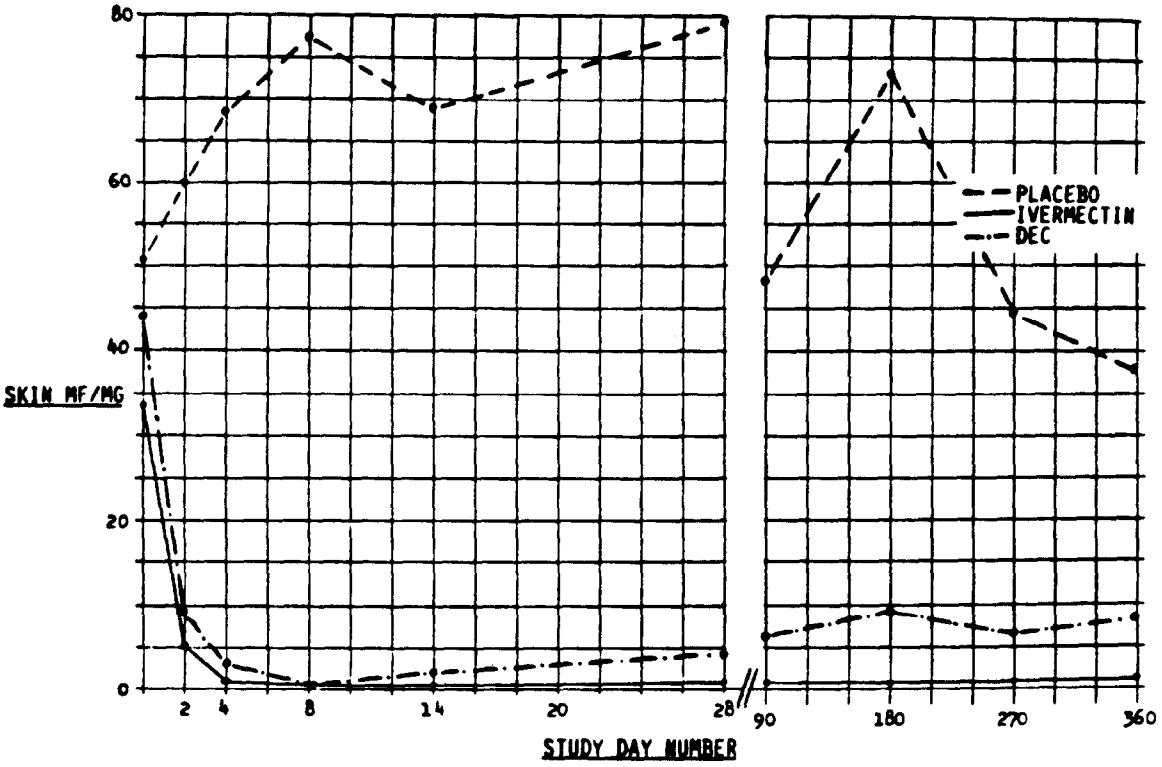

Fig. 1. *O. volvulus* microfilariae: skin density

were no longer present in three patients at six months. Tyndall effect seen in one patient before the study was not seen after treatment; this patient also had intra-retinal deposits before treatment and on Day 8.

In the DEC group mf were not seen in the cornea either before or after treatment. Mf in the anterior chamber in four patients before treatment were not found after Day 4 and mf that had appeared after treatment in the anterior chamber in one patient were no longer present after three months. Tyndall effect seen in two patients before treatment disappeared after treatment; this effect was also seen in a third patient on Day 28. Intra-retinal deposits were observed in three patients—two only on Day 8 and one on Days 8 and 28 and at three months. Two patients had chorio-retinitis before treatment; the condition had cleared in one at three months. New choroido-retinal lesions appeared in a third patient on Day 4 and were present through Day 28. Three patients had conjuctivitis after treatment.

In the placebo group, corneal mf present in three patients before treatment were not seen at the six-month examination and mf in the anterior chamber before treatment in six patients were still present at six months. Tyndall effects were seen in one patient on Day 28; intra-retinal deposits were found in two other patients on Day 8.

3. *Skin Microfilaria Count*

Six ivermectin patients were free of skin mf at one or more of the follow-up examinations; complete absence of skin mf was not observed in any DEC patients at any examination.

Fig. 1 and Table 4 show the mean skin mf density in the three treatment groups during the entire 12-month observation period. Microfilarial densities in the placebo group remained high throughout the period of observation and had decreased sharply by Day 2 in both the ivermectin and DEC groups, continuing to decrease until Day 8 in the DEC patients (to 4% of pre-treatment level) and Day 14 in the ivermectin group (to 2% of pre-treatment level). Microfilarial density then increased slowly in both groups reaching mean values of 4% of the pre-treatment level (ivermectin) and 18% (DEC) at the 12-month follow-up examination. This difference is statistically significant. The difference between the two active drug groups was significant also at the six-month examination (0·9 mf/mg v. 9·6 mf/mg).

It is noted that one patient in the ivermectin group who had 51·8 mf/mg skin before treatment responded atypically to the study drug for unknown reasons; skin mf density was above 16% of the pre-treatment level in this man throughout the period of observation. Four other patients in this group with high pre-treatment mf density (40·4 to 67·5 mf/mg) and five with low mf density (19·1 to 29·7 mf/mg) responded well to ivermectin.

Effects on adult O. volvulus. Easily palpable onchocercal nodules were surgically removed from nine patients (four ivermectin, one DEC, four

Table 6—Onchocercal nodule examination

Treatment Group	No. of Patients	Nodules Excised	No. of Male worms Alive	Male worms Degen*	Female worms Alive	Female worms Degen
Month 1						
MK-933	4	8	12	1	15	3
DEC	1	2	4		5	1
Placebo	4	14	37		61	5
Month 6						
MK-933	3	5	5		7	1
DEC	1	3	6		10	1
Placebo	3	4	8		13	

*Degenerated

placebo) on Day 28 and seven patients (three ivermectin, one DEC and three placebo) at the six-month follow-up examination. Table 6 shows the number of adult *O. volvulus* obtained from the two treatment groups and the intrauterine content of developing forms of the microfilariae. It is apparent that neither DEC nor ivermectin is lethal to the adult parasites. At one month after treatment, both active drug groups showed evidence of increased embryogenesis; however, at six months there was essentially no change in the DEC and placebo while most of the female worms in the ivermectin group contained dead, degenerated and deformed microfilariae.

Discussion

The objective of this study was to evaluate the efficacy and tolerance of ivermectin compared to DEC in the treatment of onchocerciasis. DEC, the standard therapy, is known to have severe side effects and to cause deterioration of eye lesions in some patients (ANDERSON *et al.*, 1976; ANDERSON & FUGLSANG, 1978; BIRD *et al.*, 1980; MAZZOTTI, 1948; TAYLOR *et al.*, 1980; TAYLOR & GREENE, 1981).

The patients entered in the three treatment groups were generally comparable. With respect to tolerance, adverse effects following DEC treatment were observed in all patients and were similar to but less severe than those reported previously (BRYCESON *et al.*, 1977; HAWKING, 1978a; MAZZOTTI, 1948). In the present study, six patients needed three to five days of antihistamine and steroid therapy. It is possible that the reduced severity observed in this group of DEC patients was due to the relatively low initial mf loads and the gradual increase of daily DEC dosage during the first three days, with a total of only 1300 mg administered over an eight-day period. Antihistamine and steroid therapy in six of the DEC patients may also have ameliorated the severity of the reactions.

Ivermectin was well tolerated, confirming the earlier reports (AWADZI *et al.*, 1984; AZIZ *et al.*, 1982; COULAUD *et al.*, 1983; DIALLO *et al.*, 1984). All patients received a single 12 mg dose; individual patients received from 180 to 260 μg/kg of ivermectin. It was anticipated that patients who received the higher doses might have relatively more severe side effects; the only ivermectin patient treated with steroid was one who received 245 μg/kg and had a severe reaction including fever and scrotal swelling. It is interesting to note that this patient's 19-year-old son, who was in the DEC group, had fever, rash and oedema of the thigh and was also treated with steroid. There were no ocular reactions in the ivermectin group; however, three patients in the DEC group had conjunctivitis and intra-retinal deposits were observed in one patient.

Clinical adverse reactions in the ivermectin group were generally less severe than those seen with DEC therapy. This difference may be accounted for by the mechanism of action of ivermectin which is believed to be a gamma-aminobutyric acid (GABA) agonist (CAMPBELL *et al.*, 1983; TERADA *et al.*, 1984) and thus causes paralysis of the parasite. We may speculate that the paralysed mf are then removed by the patient's reticulo-endothelial system before massive amounts of toxic material are released into the circulation from degenerating mf.

Ophthalmological observations revealed no significant changes from pre-treatment findings in the ivermectin and placebo patients; however, there were new lesions in the retina in one DEC patient. Ocular changes in the posterior segment have been reported recently following DEC therapy (ANDERSON & FUGLSANG, 1978; BIRD *et al.*, 1980; TAYLOR & GREENE, 1981); no such changes were observed in any patient in this study.

Mean skin mf densities had decreased sharply by Day 2 in both the ivermectin and DEC treatment groups, and reached similar low values (about 2% of pre-treatment) by Day 8. Density then increased slowly in the ivermectin group reaching about 4% of the pre-treatment level at the 12-month examination. In the DEC group, the density had increased to 18% of the pre-treatment level at 12 months. This difference is statistically significant.

The reason for this prolonged effect of ivermectin on the skin microfilarial density, compared to DEC, is not clear; however, one possible explanation may be the effect of ivermectin on the adult female *O. volvulus*. Analysis of females from nodules in the ivermectin patients at six months after therapy appeared to show that developing forms of the mf had not been released and were deformed, dead or degenerating in the uterus. In contrast to this finding, intra-uterine development of mf in the DEC group appeared normal, i.e., similar to that observed in the placebo group. Examination of female worms at 9 and 12 months after therapy may further elucidate the mechanism of this effect of ivermectin. As observed in

this study, DEC has been previously shown to have no effect on embryogenesis (RIVAS-ALCALA *et al.*, 1981; SCHULZ-KEY, 1984).

A suppressive effect of ivermectin on embryogenesis in *Dirofilaria immitis* has been reported in dogs (ANANTAPHRUTI *et al.*, 1982), resulting in a reduction in circulating microfilariae and inhibition of embryonic development in the female worms. This effect has been shown to be more pronounced and more prolonged when dogs received a second dose six months after the initial treatment. In a study with the red imported fire ant (RIFA) *Solenopsis invicta*, ivermectin has been shown to inhibit reproduction at extremely low dosages (LOFGREN & WILLIAMS, 1982). It has also been reported that ivermectin causes irreversible cell and tissue damage to the ovaries of RIFA queens (GLANCEY *et al.*, 1982).

Effects on embryogenesis have not been observed in the higher animals in pre-clinical safety assessment studies. Ivermectin at repeated doses of 0·4 mg/kg was found to have no effect on reproduction in cattle, sheep, horses, pigs, dogs and rats, and foetotoxicity was seen only at maternotoxic levels.

A single 0·4 mg/kg dose of ivermectin given to bulls, rams and ewes, and 0·6 mg/kg given to stallions and boars, had no ill effects on breeding performance or on semen quality (CAMPBELL & BENZ, 1984). Single oral doses of 200 μg/kg (0·2 mg/kg) every few months are therefore expected to be relatively safe for both men and women. Ivermectin should not be given to pregnant women; although the drug has been found neither teratogenic nor foetotoxic in rats and rabbits at doses as high as 1·5 mg/kg for several days, it was without such effects only up to 0·2 mg/kg in mice. In addition, reproduction and acute toxicity studies in rats have shown that neonates are significantly more susceptible to the toxic effects of this drug (Robertson, unpublished data).

The results of this study show that the immediate microfilaricidal activity of ivermectin is comparable to that of DEC; however, the ivermectin effect is comparatively long lasting. Ivermectin has also been shown to be free of adverse ocular effects and generally well-tolerated. These findings may be very significant from the point of view of controlling the disease, since these patients were from an area outside the Onchocerciasis Control Program (OCP).

The prolonged suppression of skin mf by ivermectin may interfere with the intake of *O. volvulus* microfilariae by the blackfly vector for extended periods, leading to interference with transmission of this disease. Ivermectin could, therefore, play a crucial role in both the treatment and prevention of onchocerciasis. Chemotherapeutic control of this devastating disease using a single dose of ivermectin every 6 to 12 months in areas with minimal medical supervision may thus become a reality if further studies confirm our observations.

Acknowledgements

The authors wish to recognize the skilled assistance of Ms. R. Caamano, Dr. R. Harman, Ms. M. Klausner and Dr. J. Shih in the preparation of this manuscript.

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Accepted for publication 11th July, 1985.