COMPARISON OF IVERMECTIN AND DIETHYLCARBAMAZINE IN THE TREATMENT OF ONCHOCERCIASIS


Abstract  We compared ivermectin with diethylcarbamazine for the treatment of onchocerciasis in a double-blind, placebo-controlled trial. Thirty men with moderate to heavy infection and ocular involvement were randomly assigned to receive ivermectin in a single oral dose (200 μg per kilogram of body weight), diethylcarbamazine daily for eight days, or placebo. Diethylcarbamazine caused a significantly more severe systemic reaction than ivermectin (P<0.001), whereas the reaction to ivermectin did not differ from the reaction to placebo. Diethylcarbamazine markedly increased the number of punctate opacities in the eye (P<0.001), as well as the number of dead and living microfilariae in the cornea over the first week of therapy. Ivermectin had no such effect. Both ivermectin and diethylcarbamazine promptly reduced skin microfilaria counts, but only in the ivermectin group did counts remain significantly lower (P<0.005) than in the placebo group at the end of six months of observation. Analysis of adult worms isolated from nodules obtained two months after the start of therapy showed no effect of either drug on viability. Ivermectin appears to be a better tolerated, safer, and more effective microfilaricidal agent than diethylcarbamazine for the treatment of onchocerciasis. (N Engl J Med 1985; 313:133-8.)

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microfilariae. Persons who had received a course of antifilarial therapy within the previous year were excluded. The subjects were told about the design of the study and its possible risks and benefits, and consent was documented by thumbprint or signature. At the beginning of the study, none of the subjects had sight-threatening ocular disease or other indications for urgent intervention with diethylcarbamazine. The protocol was reviewed and approved by the Institutional Review Board for Human Investigation, University Hospitals of Cleveland and Case Western Reserve University School of Medicine; by the Advisory Council, Liberian Institute for Biomedical Research; and by the Secretariat Committee on Research Involving Human Subjects of the World Health Organization.

Clinical Evaluation

Subjects underwent a complete physical and ocular examination before the start of treatment. Complete ocular examination included testing for visual acuity with an illiterate E chart; for visual fields, by confrontation with an 8-mm red target; and for color vision, with AO pseudoisochromatic plates. After the patient had been positioned with his head down for two minutes, the cornea and anterior chamber of each eye were examined with a Topcon SL5D photographic slit lamp and any microfilariae were counted. Intraocular pressure was measured by applanation tonometry, and the fundus was examined by direct and indirect ophthalmoscopy after pupillary dilatation. Further detailed examination of the retina was performed with a slit lamp using a triple-mirror contact lens, which provides a magnified image of the posterior segment of the eye. Fundus photography and intravenous fluorescein angiography were performed with a Topcon FE fundus camera. Photographs and angiograms were subsequently evaluated in a masked fashion, in which the patient’s identity and date of examination were obscured. Screening laboratory tests included determination of total white blood cell count and differential count, with examination of peripheral-blood film, hematocrit, and multichannel chemistry screen. Urine samples were examined for protein, pH, and specific gravity, and the sediments for cellular elements and crystals.

Subjects were screened by history, physical examination, and laboratory evaluation to rule out other disease processes. In addition, it was ascertained that all subjects were lifelong residents of Liberia and therefore had been exposed only to the endemic forest strain of O. volvulus.

Post-treatment evaluation consisted of complete ocular examination, including fundus photography and angiography but not measurement of intraocular pressure; evaluation was repeated on Days 2, 4, 6, and 14 and at three and six months. Physical examinations were performed at these same intervals as well as on each day during the first eight days and on the 10th day of hospitalization.

In order to quantify the systemic reaction to therapy, a clinical-reaction score was developed as a modification of the method of Awadzi. Pruritus, severity of rash, extent of rash, lymph-node enlargement, joint symptoms and signs, and fever were graded on a scale of 0 to 3, and a reaction score — the total of the seven values — was calculated for each subject for each day of examination (Table 1). All subjects were present during the first two weeks of the study. At the examination at three months, three men in the ivermectin group and two men in the placebo group were absent; at six months, three men in the ivermectin group and one man in the placebo group were absent. Three of the four persons who were absent at six months had also missed the examination at three months.

Parasitologic Examination

Skin was obtained from either side of the scapular, upper buttock, and calf regions by means of a 1.5-mm Holth-type corneoscleral biopsy instrument. The specimens were placed in a humidified plastic Petri dish, weighed, and transferred individually to microtiter plate wells containing 0.1 ml of tissue-culture medium (minimal essential medium [KC Biologicals, Lenexa, Kans.]), penicillin (100 U per milliliter), and streptomycin (100 μg per milliliter). The flat-bottom microtiter plates (96 wells [Costar, Cambridge, Mass.]) were incubated at room temperature for three to six hours, and the number of microfilariae in each well was counted with an inverted microscope. Stool was examined by bright-field microscopy of a saline suspension.

Experimental Design

Subjects were assigned to one of three agents (diethylcarbamazine, ivermectin, or placebo) and hospitalized for the first two weeks of the study and again at three and six months. The three treatments were well balanced in terms of possible risks and benefits. Diethylcarbamazine had the advantage of known efficacy, but the disadvantage of substantial toxicity. Ivermectin had the advantage of apparently lower toxicity but it did not have the disadvantage of chronic infection with O. volvulus. Placebo was included in the study because the reactions associated with diethylcarbamazine chemotherapy have been recognized as similar to the disease process itself. As noted above, the protocol included a provision for treatment of the placebo group with the better regimen at the conclusion of the study.

Treatment Protocol

Eighteen subjects were admitted to one hospital, and 12 to another with similar conditions. Otherwise, there was no blocking or stratification of subjects. They were assigned to treatment according to computer-generated random numbers. Drugs were provided in sealed, coded packages containing identical numbers of capsules of uniform size and color. This ensured that neither the investigators nor the study subjects were able to discern the type of treatment given. The code was not broken until after the completion of the six-month examination. All capsules were administered under close observation, to ensure compliance. Ivermectin was given in a single dose of 12 mg (approximately 200 μg per kilogram) on the first day of treatment, and diethylcarbamazine in a single dose of 50 mg on each of the first two days, followed by 100 mg given twice daily, to complete an eight-day course. Additional medications included aspirin for headache, fever, myalgia, or arthralgia, and antihistamine (diphenhydramine hydrochloride) for pruritus or inability to sleep. These medications were administered at the subject’s request. All subjects were hospitalized for the first two weeks of the study.

Nodule Analysis

Two months after the start of therapy, any palpable nodules were aseptically excised, transferred to tissue-culture medium, and subjected to collagenase digestion according to the technique of Schulz-Key et al. Digestion was carried out at 30°C with 0.3 per cent of the previous year were excluded. The subjects were told about the design of the study and its possible risks and benefits, and consent was documented by thumbprint or signature. At the begin-
collagenase, and the numbers of alive and dead male and female adult worms per nodule were determined. The viability of worms was judged on the basis of the preservation of the integrity of internal and external structures as determined by light microscopy.

**Data Analysis**

Data were gathered in a double-blind fashion and entered for computer analysis before the treatment code was broken. Statistical analyses were based on analysis of covariance (to adjust for differences at base line), with use of the two-tailed t-test for multiple comparisons when means for treatment groups were compared. All microfilaria counts and counts of punctate opacities were logarithmically transformed before statistical analysis; the means reported are geometric. Other analyses were performed with Student’s t-test or Fisher’s exact test.

**Results**

**Pretreatment Findings**

Random assignment of the subjects into three groups containing 10 subjects each resulted in an even distribution with regard to age, weight, number of palpable onchocercomatous nodules, skin microfilaria counts and skin lesions, and presence of intestinal helminths (Table 2).

Detailed ocular examination showed that there were no significant differences among the three groups in the prevalence and distribution of intraocular microfilariae and corneal changes (Table 2). Examination of the vitreous and retina showed minimal to mild grades of onchocercal chorioretinopathy in all subjects, with varying amounts of intraretinal pigment and mottling of the retinal-pigment epithelium. Angiography revealed mild degrees of focal window defects and irregular granular hyperpigmentation and hypopigmentation in all subjects. The presence and severity of these mild abnormalities were evenly distributed among the three groups. Visual fields and color vision were normal except in one subject in the placebo group, who had red-green color blindness. The optic nerve was normal in all subjects.

**Systemic Reactions during Therapy**

Analysis of clinical-reaction scores showed marked differences among the three groups (Fig. 1 and Table 3). Although scores in all groups were similar before treatment, those in the diethylcarbamazine group rose to more than twice those in the ivermectin group after treatment (P < 0.001); reactions to diethylcarbamazine started earlier and persisted longer than the mild reactions to ivermectin. The scores for the ivermectin and placebo groups did not change significantly during the study. Mild asymptomatic hypotension (systolic pressure less than 90 mm Hg), not requiring specific therapy, occurred in two subjects in the ivermectin group, on Days 2 and 8, respectively.

In addition to the above symptoms and signs, a number of minor, nonspecific events were observed in all three groups, with no significant differences between the groups. The requirement for aspirin and antihistamines was higher in the diethylcarbamazine group than in the other two groups (Fig. 2).

Subjects with marked fever (temperature above 39°C) were examined for the presence of malaria parasites (thick smears of peripheral venous blood). One subject in the diethylcarbamazine group was found to have circulating trophozoites and was treated with chloroquine phosphate; two other subjects, both in the ivermectin group, were treated empirically for the possibility of malaria.
malaria, in the absence of positive smears. Comparing blood samples obtained before treatment with samples drawn on Day 14 showed no significant changes in serum levels of bilirubin, alkaline phosphatase, aspartate aminotransferase, or creatinine in any subject.

By error, one person in the ivermectin group received a single dose of 50 mg of diethylcarbamazine on Day 2, after his ocular and physical examinations. There were no apparent changes in the findings on physical examination or total reaction score as a result of this occurrence. However, a mild fever on that day could have been due to diethylcarbamazine.

**Ocular Changes with Therapy**

In the anterior segment of the eye, the most striking change was the marked increase in the mean number of punctate opacities in the cornea in the diethylcarbamazine group during the first two weeks of therapy (from 0.6 to a maximum of 12.3 [on Day 8], \(P<0.001\)). In contrast, the number of punctate opacities in the ivermectin group did not increase significantly. The diethylcarbamazine group had a greater number of punctate opacities than either the ivermectin or the placebo group on Days 4, 8, and 14 (\(P<0.05\) and \(P<0.005\), respectively). Limbal inflammation developed in 9 of the 10 men in the diethylcarbamazine group, but in only 4 of the 10 in the ivermectin group. Mild bilateral anterior uveitis developed in two subjects in the diethylcarbamazine group on Days 2 and 4 but resolved without therapy.

There was a significant increase in the mean number of dead microfilariae in the cornea by Day 8 in subjects treated with diethylcarbamazine (from 0.4 to 10.9, \(P<0.001\)), and in the number of live microfilariae (\(P<0.025\)). There were no significant changes in the number of dead or living microfilariae in the cornea in the ivermectin or placebo group during the study.

The number of microfilariae in the anterior chamber in the diethylcarbamazine group fell progressively after Day 2, to a level significantly lower than that in the placebo group on Day 14 (\(P<0.005\)). In contrast, the count in the ivermectin group did not change significantly during the first two weeks but was significantly reduced at three and six months (\(P<0.01\)). The count in the placebo group showed no change.

Detailed examination of the posterior segment of the eye revealed no changes in the pattern or severity of intraretinal pigment deposition, the granularity of retinal pigment epithelium, or intraretinal deposits in any of the subjects. Fluorescein angiography showed a single transient window defect in a diethylcarbamazine recipient at three months, which had resolved by six months. In addition, a small window defect in one eye of a man in the placebo group showed improvement over the six-month study period. No subject had optic neuritis, optic atrophy, or optic-nerve leakage according to fluorescein angiography. Small areas of focal retinitis developed in one subject in each group within the first three months, with resolution by six months. The one subject in the ivermectin group who received a single dose of diethylcarbamazine had no worsening of preexisting mild limbal inflammation and no other changes that could be ascribed to diethylcarbamazine.

Moderate peripheral constriction of the visual field
Discussion

In a direct comparison of ivermectin with diethylcarbamazine for the treatment of *O. volvulus* infection, ivermectin appeared to be a clearly superior agent. Its efficacy was comparable to that of diethylcarbamazine, although it was administered in a single oral dose and diethylcarbamazine was given for eight days. Furthermore, treatment with ivermectin was associated with less severe and fewer serious systemic and ocular reactions than treatment with diethylcarbamazine.

Diethylcarbamazine has been the standard therapy for *O. volvulus* infection for over three decades. Although it is a highly efficient drug in terms of its microfilaricidal action, its severe side effects and complications limit its use.1-6 Of particular concern in recent years have been the ocular changes associated with diethylcarbamazine, especially those involving the posterior segment of the eye.3-6,20 In one study in heavily infected Sudanese patients with advanced ocular damage, visual-field loss was observed in 5 of 18 patients in the first few days after diethylcarbamazine therapy.6 In addition, fluorescein angiography demonstrated extensive new changes in retinal-pigment epithelium and optic neuritis. In another study in Liberia, visual-field loss after diethylcarbamazine administration was observed in 3 of 20 subjects.20 Thus, it is of particular interest that in the present study, ivermectin did not cause significant changes in the posterior segment of the eye. However, only one subject in the diethylcarbamazine group had changes in visual fields, and only one other diethylcarbamazine recipient had a window defect in the retinal-pigment epithelium. Therefore, with respect to the posterior segment of the eye, the safety of ivermectin relative to that of diethylcarbamazine is not totally ensured by this study and must be confirmed by further trials in subjects with more advanced disease.

The efficacy of ivermectin, as judged by its ability to eliminate microfilariae from the skin and ocular tissues, was at least as good as that of diethylcarbamazine, and as a result of its more sustained effect, perhaps better. Thus, ivermectin might have the advantage, in addition to the decided advantage of being given in a single dose, of being given less frequently than diethylcarbamazine. However, further testing in subjects with a wide range of infection and from various bioclimatic regions will be necessary in order to determine its full potential.

### Table 4. Significance of Differences between the Study Groups in Number of Microfilariae.

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>14</th>
<th>3 mo</th>
<th>6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEC vs. placebo</td>
<td>&lt;0.001</td>
<td>&lt;0.005</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
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<tr>
<td>Ivermectin vs. placebo</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.005</td>
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<tr>
<td>Ivermectin vs. DEC</td>
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<td></td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
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*A dash denotes P>0.05.*
establish the optimal dose and frequency of drug administration.

It has been assumed that the intense reaction associated with diethylcarbamazine therapy results from massive death of microfilariae. However, the disparity between the microfilaricidal activity of ivermectin and the relative lack of reaction associated with its use suggests that, in addition to microfilarial killing, other factors may play a part in the reaction to diethylcarbamazine. Examples of such factors include the ability of diethylcarbamazine to activate granulocytes,21,22 its effects on prostaglandin and leukotriene metabolism,23,24 and its ability to enhance complement activation by microfilariae.25 Diethylcarbamazine also causes redistribution of microfilariae, which results in their appearance in the blood, urine, cerebrospinal fluid, cornea, and anterior chamber in relatively large numbers.26,27 The absence of this effect during ivermectin treatment could certainly account for some of the differences between the two agents noted in this study. Indeed, the data showing little increase in the numbers of microfilariae in the cornea and anterior chamber after ivermectin treatment support this hypothesis.

The precise mechanism of action of ivermectin against helminths remains undetermined. Its behavior as an agonist of gamma aminobutyric acid is thought to explain its activity against nematodes.11,18 Other reported biologic properties of the avermectins include an effect on embryogenesis in O. volvulus16 and Dirofilaria immitis;29 inhibition of chitin metabolism30,31 and damage to the ovaries of ants.31 The present trials support a predominantly microfilaricidal effect, but additional studies are obviously necessary to establish the optimal dose, the precise mechanism of action against O. volvulus, and the degree of safety, particularly in persons with advanced ocular damage.

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### Table 5. Totals of Adult Worms Isolated from Onchocercomatous Nodules Two Months After Treatment.

<table>
<thead>
<tr>
<th>Characteristics of Worms</th>
<th>Ivermectin</th>
<th>Diethylcarbamazine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>37</td>
<td>43</td>
<td>59</td>
</tr>
<tr>
<td>Dead</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Female</td>
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<td></td>
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<tr>
<td>Alive</td>
<td>82</td>
<td>91</td>
<td>101</td>
</tr>
<tr>
<td>Dead</td>
<td>3</td>
<td>4</td>
<td>10</td>
</tr>
</tbody>
</table>

*Isolated from 19 nodules in the ivermectin group, 19 nodules in the diethylcarbamazine group, and 32 nodules in the placebo group.

### References