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The Effects of Ivermectin on Transmission of *Onchocerca volvulus*

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Ivermectin, given to onchocerciasis patients as a single oral dose of 200 micrograms per kilogram of body weight, substantially reduced the uptake of *Onchocerca volvulus* microfilariae by *Simulium yahense*, an efficient black fly vector of the parasite in the tropical rain forests of West Africa. Three months after treatment, patients given ivermectin infected flies at a significantly lower rate than those who had received diethylcarbamazine or placebo, thereby reducing the number of developing larvae in the vector population. This diminished rate of infectiousness was also evident 6 months after treatment. These results strongly suggest that ivermectin could be effective in interrupting transmission of *Onchocerca volvulus* for epidemiologically important periods of time.

HUMAN ONCHOCERCIASIS IS ENdemic in parts of sub-Saharan Africa, the Arabian Peninsula, southern Mexico, Guatemala, Venezuela, Brazil, Colombia, and Ecuador. An estimated 20 to 40 million people suffer from this parasitic disease, which is caused by the filarial nematode *Onchocerca volvulus* (*1*). The adult worms reside in subcutaneous nodules or occasionally lie free in the subcutis (*2*). Females, which may live more than a decade, produce thousands of embryonic forms, the microfilariae. This stage of the parasite is also subcutaneous and actively migrates through the skin where, in concert with the host's immune response, it precipitates intense pruritus with papular rash, depigmentation, atrophy, and a variety of eye lesions. Microfilariae are relatively long-lived and may survive in the skin for up to 30 months (*3*).

The severest form of the disease occurs in the African savannah, where the parasite is transmitted by the bites of blood-sucking female flies belonging to the *Simulium damnosum* species-complex (*4*). The immature stages of the fly live in aquatic habitats; hence parasite transmission occurs in or near these riverine settings. For this reason and because chronic infection with the parasite often results in ocular lesions leading to impaired vision and irreversible blindness, human onchocerciasis has come to be called "river blindness."

The disease has traditionally been controlled by the application of insecticides to infested streams and rivers as a means of killing the larval stage of the black fly vector. A vector control program has been initiated by the World Health Organization in the savannah region of West Africa in an attempt to lower annual transmission rates of the parasite to a level that significantly reduces the risk of blindness (*5*). This program encompasses over 700,000 km², embraces seven countries, and is designed to protect over 10 million people (*1*). The results are encouraging, but the development of insecticide resistance (*6*) and reinfestation of the program area loom as potential problems of considerable magnitude (*7*).

Chemotherapy of human onchocerciasis has been limited to the use of diethylcarbamazine (DEC) for the microfilarial stage of the parasite and suramin as a macrofilaricide (*8, 9*). However, both drugs produce frequent side effects and sometimes major clinical complications (*10*). Ivermectin, a novel semisynthetic drug exhibiting a wide range of pharmacological activity against parasitic nematodes and arthropods of veterinary importance (*11*), has also been shown to be efficacious against the microfilarial stage of *O. volvulus* (*12*). When compared with DEC in a recent double-blind, placebo-controlled trial, ivermectin was shown to be more clinically acceptable as well as more effective in reducing microfilarial skin populations as determined by skin biopsies ("skin snips") (*13*).

We report here the results of several field experiments that complement this clinical evaluation and demonstrate that ivermectin treatment reduced transmission of the parasite for periods of time that could be epidemiologically important [this effect is short-

Table 1. Uptake of microfilariae (mf) (expressed as geometric means) by *Simulium yahense* from patients receiving placebo, DEC, or ivermectin at 3 and 6 months after treatment.

Treatment group	*n*	Mean mf per mg of skin	No. of flies dissected	Mean mf* per fly ($\bar{x}$)	Thoracic mf per fly ($\bar{x}$)	Flies with thoracic mf (%)
			At 3 months			
Placebo	4	40.77	28	34.80	14.10	96.4
DEC	5	12.28	59	4.95†	1.99	57.6
Ivermectin	3	0.54	25	0.32†‡	0.10	12.0
			At 6 months			
Placebo	4	49.63	48	10.52	3.06	75.0
DEC	5	20.05	56	4.26§	2.11	53.6
Ivermectin	3	8.60	34	2.28†‖	0.56	32.4

*Means compared by means of the *t* test with Bonferroni equation. †Significantly different from placebo at $P < 0.001$. ‡Significantly different from DEC at $P < 0.001$. §Significantly different from placebo at $P < 0.008$. ‖Not significantly different from DEC.

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lived with DEC (*14*)]. We were particularly interested in determining the quantitative effects of drug treatment on the level of infection of *Simulium yahense* by *O. volvulus* microfilariae and the developmental fate of the microfilariae in this black fly, a cytospecies that is a highly efficient vector over most of the parasite's range in the tropical rain forests of West Africa. Because *Simulium* spp. concentrate *O. volvulus* microfilariae during ingestion of a blood meal and are generally more sensitive in detecting microfilariae than the skin-snip method, the use of local vectors in xenodiagnosis has been suggested (*15*). We therefore assessed the effectiveness of these drugs in altering the uptake of microfilariae by flies that fed on 12 volunteers from an ongoing comparative clinical efficacy study; three of these individuals had received a single dose of ivermectin; five, an 8-day course of DEC; and four, placebo (*16*). The ability of each patient to infect the local vector was evaluated at 3 and 6 months after treatment in conjunction with clinical examinations.

Microfilarial uptake by *S. yahense* 3 months after treatment was significantly reduced after both ivermectin and DEC treatment (Table 1). Ivermectin was significantly more effective than DEC in limiting the numbers of microfilariae per fly (geometric means of 0.32 and 4.95, respectively). This striking reduction in the infectiousness of ivermectin-treated patients also lowered the numbers of microfilariae that were able to reach the thorax, a key epidemiological feature, and the percentage of flies with thoracic microfilariae was also greatly suppressed. The reduced skin loads of microfilariae and the decreased microfilarial uptake were also evident at 6 months after treatment; values for patients who had received ivermectin and DEC remained significantly lower than for patients who had received placebo. Although the mean microfilarial uptake by flies that fed on patients given ivermectin was no longer significantly lower statistically than that from patients given DEC, the geometric mean thoracic microfilarial load (0.56 versus 2.11) and the percentage of flies with microfilariae in the thorax (32.4 versus 53.6 percent) remained substantially lower.

Developing larvae were greatly reduced at both 3 and 6 months in *S. yahense* fed on patients given ivermectin (Table 2). The mean loads of these larvae (0.24 and 1.69 per fly, respectively) are noteworthy for both epidemiological and clinical reasons because they suggest that ivermectin-treated individuals would contribute much less to the general worm burden of a human population, thus limiting levels of overall infection and possibly ocular disease (*17*). Statistical data for *O. volvulus* infective-stage larvae (L_3s) at 3 months were not calculated because of high fly mortality on days 5 to 8; however, the high correlation between mean number of developing larvae per fly and mean number of L_3s per fly at 6 months suggests that the numbers of L_3s per fly at 3 months would be essentially the same as the number of developing larvae. Even if we allow for substantial error, this means on a population basis that flies feeding on ivermectin-treated individuals would be virtually unable to transmit the causative agent of human onchocerciasis for as long as 3 months and, probably, 5 to 6 months.

In order to evaluate the ability of each patient to infect *S. yahense* at 3 and 6 months after treatment, we also examined the relation between mean skin microfilarial density and (i) mean microfilarial uptake and (ii) subsequent larval development in the vector (*18*). There was a high degree of correlation (r_s values of 0.727 to 0.944; $P < 0.01$) between microfilarial skin density and parasite uptake and development, an indication that skin density is strongly predictive of the infectiousness of an individual. At 3 months, all ivermectin-treated patients were less able than patients given DEC and placebo to infect flies with microfilariae that penetrated the thorax and subsequently developed (Fig. 1, a through c). These individuals also infected fewer flies with microfilariae that were able to enter the thorax (Fig. 1d).

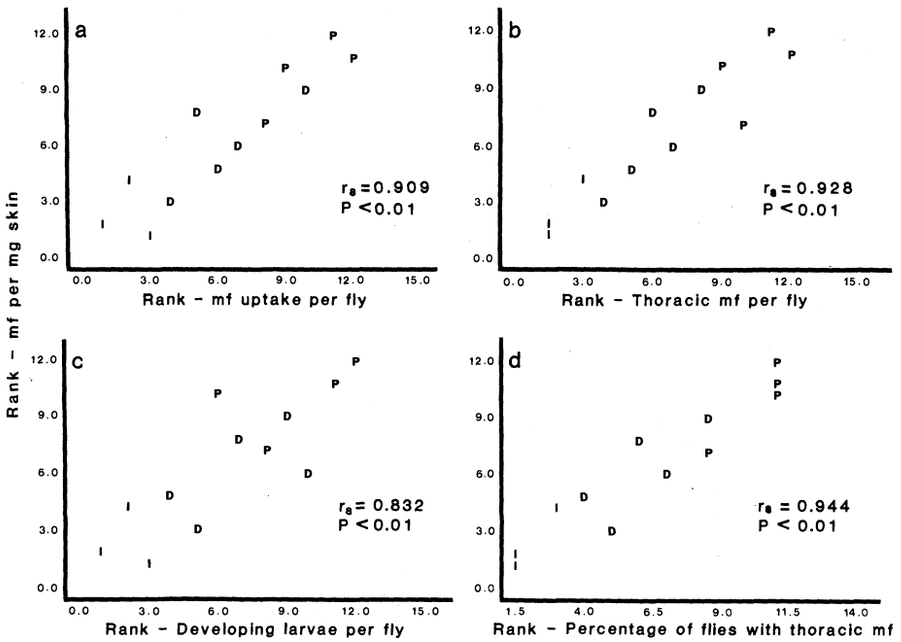

Fig. 1. The parasite-vector relation between *Onchocerca volvulus* and *Simulium yahense* at 3 months after treatment of onchocerciasis patients with ivermectin (I), diethylcarbamazine (D), or placebo (P): (a) uptake of microfilariae (mf); (b) infection of the thoracic musculature of *S. yahense* after penetration of the gut; (c) development of *O. volvulus* larvae ("sausage" stage, L_2, L_3) ≥4 days after ingestion by *S. yahense*; (d) percentage of flies with microfilariae in the thoracic muscles.

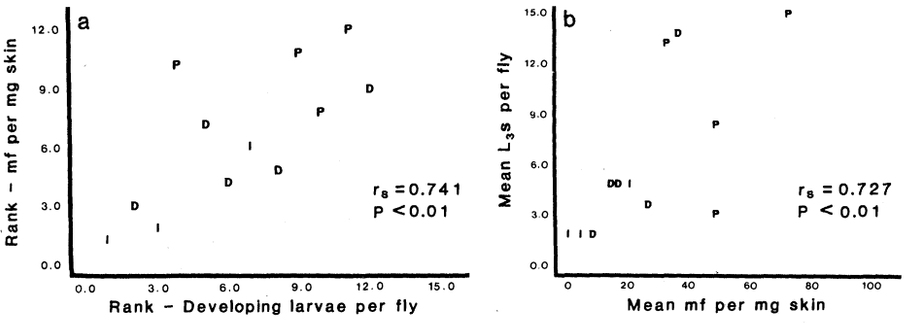

Fig. 2. The parasite-vector relation between *O. volvulus* and *S. yahense* at 6 months after treatment of onchocerciasis patients with ivermectin (I), diethylcarbamazine (D), or placebo (P): (a) development of *O. volvulus* larvae ("sausage" stage, L_2, L_3) ≥4 days after ingestion by *S. yahense*; (b) production of *O. volvulus* infective-stage larvae (L_3s).

Table 2. Development of *Onchocerca volvulus* larvae (expressed as geometric means) in *Simulium yahense*. Developing larvae were considered to be late L_1 ("sausage" stage), L_2, and L_3s; numbers include all worms dissected from flies ≥3 days after infection. Because of low fly survival for days 5 to 8, means for L_3s were not calculated at 3 months; however, every patient but one (an ivermectin recipient) contributed microfilariae that developed to one or more L_3s. All flies were dissected ≥7 days after infection.

Treatment group	*n*	No. of flies dissected	No. of developing larvae per fly ($\bar{x}$)	No. of flies dissected	No. of infective-stage* larvae per fly ($\bar{x}$)
			At 3 months		
Placebo	4	50	5.11		
DEC	5	59	1.94		
Ivermectin	3	50	0.24		
			At 6 months		
Placebo	4	80	9.28	72	8.20
DEC	5	95	3.68	80	3.29
Ivermectin	3	63	1.69	56	1.67

*Natural infection rates of 7.4 percent at 3 months and 10.9 percent at 6 months; infective rates (L_3s only) were 3.2 and 2.5 percent, respectively.

These same correlations were observed at 6 months for two of the three ivermectin-treated patients (Fig. 2a); the third subject essentially mimicked the status of several patients given DEC and one person given placebo. In terms of the efficiency of conversion of skin microfilariae to L_3s within the vector black flies, two of the three ivermectin-treated patients were less efficient at 6 months than four of the five DEC-treated patients and all members of the placebo group (Fig. 2b).

In view of the differences in dosage and treatment schedule between ivermectin and DEC, and the differentials in efficacy and in preventing L_3 production for substantial periods of time, we believe that ivermectin would be superior to DEC under field circumstances in a chemotherapy campaign to interrupt transmission of *O. volvulus* over a wide area. The strategy of reducing microfilarial skin loads by chemotherapy to levels below those necessary for effective transmission of L_3s has been suggested by Duke (*19*). If proven clinically safe, ivermectin would be particularly useful where parasite transmission is limited by seasonality (*20, 21*) or by vector inefficiency (*22*) or is confined by discrete ecological boundaries (*23*).

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14. This investigation was conducted at the Liberian Agricultural Company near Buchanan, Liberia. Volunteers were sought from a group of 30 patients, and eventually a subset of 12 was selected by an impartial clinician. Prior to volunteering, the subjects were made fully aware of the design and requirements of the study. This explanation was given orally in English and in Bassa. The written protocol had been reviewed and approved by the Cornell University Institutional Review Board for Human Subjects; by the Advisory Council, Liberian Institute for Biomedical Research; and by the Secretariat Committee on Research Involving Human Subjects of the World Health Organization.
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16. The subjects were drawn from a pool of patients who had been randomly assigned into three groups for clinical evaluation. This resulted in an even distribution with regard to age, weight, number of palpable onchocercomata, skin microfilarial counts, and skin lesions (*13*). The treatment backgrounds of the patients were unknown to us at the time of volunteering and for ~4 months thereafter. Treatment regimens were as follows: DEC ($n = 5$), a single oral dose of 50 mg on each of the first 2 days, followed by 100 mg twice daily for the remaining 6 days; placebo ($n = 4$), daily for 8 days; ivermectin ($n = 3$), a single oral dose of 200 μg/kg followed by a placebo for the next 7 days.
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