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IVERMECTIN AS AN ANTIPARASITIC AGENT FOR USE IN HUMANS

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INTRODUCTION

Ivermectin is a derivative of a family of macrocyclic lactones, the avermectins, that are produced by the filamentous bacterium *Streptomyces avermitilis*. Selective hydrogenation of avermectin B_1 yields 22-23-dihydroavermectin B_1, which bears the generic name ivermectin. Much has been written about ivermectin; hundreds of articles have appeared in the scientific literature, and the available information was summarized in a recent monograph (13). The preponderance of reports, however, deal with ivermectin in relation to animal health (and with its analog abamectin in relation to plant health). The present review deals with the efficacy and safety of ivermectin in the treatment and control of human parasitic infections.

INTESTINAL NEMATODES

Ascaris lumbricoides

Anecdotal evidence from onchocerciasis trials suggested that ivermectin may be active against *Ascaris lumbricoides*. This activity was recorded by Whitworth et al (102) who used ivermectin against onchocerciasis in a Sierra Leone community in which a third of the population had *Ascaris* infection. In that community the most common side-effect of treatment was the passage of *A. lumbricoides* in the stool (102).

In a trial in Peru, 20 patients infected with *Ascaris* were given single oral doses of ivermectin at 50–200 μg/kg (or 2 dosages at 100 μg/kg). After 3 days, only about half of them were cured, but by 30 days, fecal examinations revealed that all were totally free of *Ascaris* (59). Similarly, in a trial in Guatamala, 10 patients received single oral doses of ivermectin at 140–200 μg/kg, and all were completely cured after one month (39). In Gabon, 15 patients with *Ascaris* infection were completely cured when examined 23 days after receiving a single oral dose of ivermectin at 200 μg/kg (75). Complete cure was also obtained in 44 cases in Central African Republic (94).

Thus trials in Africa, Central America, and South America have indicated that ivermectin is highly effective against *Ascaris* at well-tolerated dosages.

Hookworms (Anclyostoma, Necator)

Incidental observations in the course of onchocerciasis trials indicated that ivermectin was not active against *Necator americanus* at 5 or 10 μg/kg (7) and "had no effect on hookworms" at dosages up to 200 μg/kg (6).

In a trial in Peru, little if any efficacy was recorded when 52 patients with *N. americanus* or *Ancylostoma duodenale* were given single oral doses of ivermectin at 50–200 μg/kg, or 2 doses at 200μg/kg (59). Similarly, in Guatamala, ivermectin was only slightly effective against hookworm (probably *N. americanus*) when given to 10 patients at 140–200 μg/kg (39). In both

of these trials, the numbers of hookworm eggs in the stool of treated patients was reduced to about half of the pretreatment values. In Gabon, 15 patients with *N. americanus* received a single oral dose of 200 μg/kg, and none had stopped passing eggs after 23 days (75). Ivermectin was also found inactive against *N. americanus* in the Ivory Coast (52) and against *A. duodenale* in Central African Republic (94).

Ivermectin, as presently administered, thus seems to have little or no utility in the treatment of hookworm infection in humans, and is certainly less effective than other medications for this purpose.

The poor activity of ivermectin against human hookworm was surprising because the drug is extremely potent against canine hookworms (for review, see 13). In one study (99), a single oral dose at 10 μg/kg not only resulted in the expulsion of all *Ancylostoma caninum* from treated dogs, but also inhibited the development of eggs recovered from the affected worms. The difference in the human and canine experience may be related to differences in both parasite and host. *N. americanus* seems to be especially insensitive to ivermectin, and when this species is adapted to hamsters, extraordinarily high dosages of ivermectin are needed to remove them from treated animals (72).

The larvae of dog hookworm species cause skin disease, cutaneous larva migrans, in humans, and this condition often requires therapy. Ivermectin has not been studied systematically for efficacy against it, but a few patients have been treated informally. At a remote work camp in French Guayana, ivermectin was applied topically with apparent success (D. Barth & W. Rietschel, personal communication). The product used was probably the injectible cattle product, containing 1.0% ivermectin, and the solution was swabbed directly onto the affected skin. Ivermectin in such solutions does in fact penetrate mammalian skin to a considerable degree, and a topical formulation is used commercially in cattle. Thus, topical ivermectin could very well be an effective and well tolerated treatment for cutaneous larva migrans in humans, but the dosage and tolerability of such treatment are at present unknown. The infections in French Guayana were attributed to *Acylostoma braziliense*. Research has shown that the third-stage larvae of *A. caninum* are killed by ivermectin in vitro at a concentration of 0.025 μg/ml (99). Successful treatment of cutaneous larva migrans with one or two oral doses of ivermectin (12 mg per dose) was recently reported (87a).

Trichuris trichiura

In Peru, ivermectin was tested in 54 patients with *Trichuris trichiura* infection. Most received a single oral dose at 50–200 μg/kg, and efficacy was equivocal. The largest group, 17 patients, received a dosage of 200 μg/kg on two successive days; about 60% of them had negative stool samples after three days, and 100% were apparently cured after 30 days (59). In Guatamala, 12 patients were treated with ivermectin at 140–200 μg/kg, and only 50%

were cured (negative stool sample) within one month. Fecal egg numbers exhibited a mean 93% reduction but this decrease ranged from 75 to 100% in individual patients (39). In the Ivory Coast, dosages up to 200 μg/kg were inactive against *T. trichiura* (52). In Gabon, fecal examinations were done on patients 23 days after treatment with ivermectin at 200 μg/kg; only one of 15 patients had ceased to pass *T. trichiura* eggs (75). Clearly ivermectin is not particularly effective against whipworm *(Trichuris)* infections.

Enterobius vermicularis

In a trial in Peru, 88 patients were shown by the adhesive-tape test to have *Enterobius vermicularis* prior to treatment with ivermectin in single oral doses at 50–200 μg/kg, or doses of 100 or 200 μg/kg on two successive days. Prior to treatment, each patient received a placebo treatment; after treatment each patient received another placebo or a repeat dose of ivermectin. Cure, based on negative tape tests on three successive days, was recorded for 85% of the patients. There was no significant difference in the apparent efficacy of different dosages (59).

Strongyloides stercoralis

INTESTINAL A trial in Peru, while providing data on various gastrointestinal nematodes (see above), was primarily concerned with *Strongyloides stercoralis*. Ivermectin was given to 110 patients with *S. stercoralis*, and efficacy data were obtained for all but 9 of them. All patients received placebo treatment 3 days before receiving ivermectin at dosages of 50–200 μg/kg and all received placebo (or a second dose of ivermectin) on the day following the ivermectin treatment (59). Treatments were coded, but no group of patients was left untreated. Efficacy was based on a comparison of the number of larvae in multiple stools collected before and after treatment. Cure rates at 30 days varied from 67% for the 50-μg/kg dosages to 100% for the subjects receiving two doses at 200 μg/kg; but these values represent to an unknown degree the efficacy of the drug and/or the spontaneous loss of infection. Patients not cured showed a large (>90%) reduction in the number of larvae passed in feces. The investigators considered it unlikely that complete cure had occurred spontaneously in the patients whose stools became negative after treatment. In heavily infected patients, the marked reduction in fecal larval output accompanied marked improvement in clinical condition.

In Guatamala, 10 patients with light *S. stercoralis* infection were given a single oral dose of ivermectin at 140–200 μg/kg. All were negative for *S. stercoralis* when their stools were examined one month later (39). As in the previous study, the protocol did not include any untreated control subjects. In Central African Republic, 53 patients were apparently cured with ivermectin at 200 μg/kg (94).

Thus, the evidence indicates that ivermectin is active against *S. stercoralis*

in humans (as it is against *Strongyloides* spp. in other hosts), but definitive studies are needed. Control of this parasite may be a corollary benefit to mass treatment with ivermectin for the control of onchocerciasis (94).

DISSEMINATED From the earliest days of ivermectin research, the question of its potential utility in disseminated strongyloidiasis has been considered, but this question remains essentially unanswered. It arises because of the continuing need for improved therapy for this dangerous condition; it is unanswered because the condition is relatively rare and because it is difficult to test drugs against it. In the trial conducted in *S. stercoralis* patients in Peru (see preceding section), three of the patients died from causes believed to be unrelated to the parasite or the treatment. They died within three weeks after treatment, and autopsy failed to reveal evidence of tissue-dwelling *S. stercoralis* larvae. However, in the absence of antemortem evidence indicating disseminated infection, the data are inconclusive with respect to the effect of treatment.

Broad-Spectrum Potential

The potential utility of ivermectin in the broad-spectrum control of gastrointestinal nematodes must be assessed in the light of the current armamentarium. Excellent drugs are presently available for such use. They are given orally and are well tolerated, although they differ in details of spectrum and in recommended regimen. None is highly active against all of the important nematodes when given as a single dose. None is dependably or highly curative in human hookworm infection, but ivermectin is unlikely to match these drugs at any dosage that could reasonably be projected. Conceivably ivermectin, if given in multidose regimen or in special formulation, would provide highly effective broad-spectrum activity, but present data and the existence of alternative drugs make exploration of this possibility unlikely.

Ivermectin might be employed with benefit in conjunction with other drugs. In mass treatment campaigns designed to control helminth diseases in children, ivermectin could be administered in conjunction with albendazole and praziquantel (100). Under such circumstances, the effect of ivermectin on intestinal nematodes might complement or even synergize that of albendazole. Because two different modes of action are involved, the effects might even be synergistic, but that remains speculative.

ONCHOCERCIASIS

Ivermectin has been evaluated in clinical trials that may be classified as Phase I (early hospital-based probes with open protocol), Phase II (hospital-based, double-blind trials with diethylcarbamazine as a reference standard), Phase III (hospital-based, double-blind trials comparing selected dosages and building

an additional safety database) and Phase IV (community-based trials). Others have reviewed the subject previously (40, 42, 88, 89).

Early Hospital-Based Probes (Phase I)

Ivermectin was found effective against the skin-dwelling microfilariae of *Onchocerca cervicalis* in horses (36) and *Onchocerca* spp. in cattle in Australia (D. B. Copeman, personal communication), and a trial in human subjects was subsequently arranged. Because of the novelty of the drug and the idiosyncratic toxicity observed in mice, the first human trials were conducted with extreme caution. The initial dose was one twentieth (instead of the usual tenth) of the observed no-effect level of the drug when administered to the most sensitive animal species (11). Hence, the first subjects received a single oral dose of 5 μg/kg. Furthermore, the drug was given, not to noninfected volunteers as would normally be the case (11), but to young men with *Onchocerca volvulus* infections (and light hookworm infections) who stood to benefit directly from any diminution in microfilarial numbers. When neither efficacy nor toxicity was observed, higher dosages were tested (open, placebo-controlled, cross-over protocol). The evidence obtained from skin-snips indicated that single oral dosages of 30 or 50 μg/kg effectively reduced the number of microfilariae recoverable from the skin of treated patients (8, 31, 51). Adverse effects were minor and transient. Patients with high microfilarial densities or with ocular involvement had prudently been excluded from the trial, and thus the results did not indicate whether ivermectin treatment might elicit hypersensitivity reactions caused by the destruction of large numbers of microfilariae, or might mobilize microfilariae and induce ocular invasion, or might exacerbate ocular damage in patients with existing invasion of the eye. Such limitations of the protocol were recognized, as was the need for direct comparison of the new drug with the existing standard, diethylcarbamazine (DEC) (8, 81).

The real significance of the trial, not immediately appreciated by all concerned, was that a new chemical class was shown to reduce microfilarial skin density, without evidence of serious acute toxicity from the drug itself, and as a single oral dose. (The evidence of safety was, of course, very tentative because of the small number of subjects.) The structural novelty of the compound allowed the possibility, however unlikely, of diminished allergic reaction to dead microfilariae in heavily infected patients, and of efficacy against other stages (pre-adult and adult) of *O. volvulus*. In addition, the small single oral dosage of the new drug, even if it should prove inactive against the pre-adult or adult worms, might provide a microfilaricide that would be (even if only for logistical reasons) vastly more suitable than diethylcarbamazine for community use and for large-scale control programs. Additional trials were therefore undertaken.

Taking advantage of the presence in Paris of patients formerly resident in Senegal or Mali, the investigators undertook an open dose–ranging study. Patients without ocular involvement were given single oral doses at 50, 75, or 100 μg/kg (18), and subsequently, dosages of 150 or 200 μg/kg were given to patients, some of whom had ocular involvement (17). The main findings were "the rapid decrease in density of the skin microfilariae after a single oral 150 or 200 μg/kg dose of ivermectin, comparable with the effects of diethylcarbamazine; the persistence of low skin microfilaria density for up to a year in the seven patients followed up; the absence of severe ophthalmological side-effects (such as those seen with diethylcarbamazine); and the mild to moderate and transient nature of the adverse clinical and laboratory effects" (17).

At the same time, a similar open dose–ranging study was conducted in Ghana, using patients with moderate to heavy microfilarial densities (5, 6, 84). Dosages of 50, 100, 150, or 200 μg/kg were given, and "ivermectin slowly eliminated microfilariae from the skin and eye without serious adverse clinical or ocular reactions in all treated groups. . . . Very low levels of skin microfilariae were maintained for nine months. Microfilariae were not eliminated from the eye for at least three months" (6). The drug was not macrofilaricidal, nor was it embryotoxic for the worms. "However, it produced a dose-dependent stimulation of embryogenesis manifest at one month and succeeded by a suppression of embryogenesis at three months after therapy" (6). The three higher dosages were of approximately equal efficacy. Mobilization of microfilariae into blood or eyes was observed in some patients. There was some evidence of postural hypotension in treated patients, but systemic reactions in general were mild.

Hospital-Based Trials with Reference Treatment (Phase II)

Four randomized, double-blind studies, with placebo controls and reference treatment, were conducted in the endemic regions of West Africa. The patients, who were hospitalized during treatment, were adult males. They generally had moderate or heavy skin microfilarial (mf.) densities, and almost all had mild or moderate eye lesions. Treatment consisted of ivermectin (as a single oral dose of 200 μ/kg), or diethylcarbamazine (approximately 0.8 mg/kg × 2 days plus 1.6 mg/kg b.i.d. × 6 days), or matching placebo capsules.

SENEGAL The study involved 30 patients; all had moderate or heavy skin microfilarial densities and some had mild or moderate eye lesions (28, 30, 32). Both medications resulted in about 98% reduction in skin mf. density by day 8. After 1 year, the density was still 82% less than pretreatment values in

the DEC patients and 96% in the ivermectin patients (the difference between the drugs was significant).

GHANA The trial was done in 59 patients with moderate to heavy infection and ocular involvement (4, 22). Treatment with DEC eliminated mf. from the anterior chamber in 8 days, whereas ivermectin eliminated them in 6 months. The authors found that DEC and ivermectin reduced the skin mf. counts to a similar extent over 6 months, but the subsequent rise in mf. count was significantly greater in the DEC group than in the ivermectin group. Both groups experienced some mobilization of mf. into the blood. It was suggested that the slower elimination in the ivermectin patients may have resulted partly from the inability of the larger ivermectin molecule to pass from blood to aqueous-humor.

MALI The study was done on 30 patients with ocular involvement (10, 55, 98). In the DEC patients, the number of mf. in the anterior chamber was rapidly reduced to zero in some patients but rose again within 6 months. In the ivermectin patients, mf. were gradually eliminated over the 6-month period. Skin mf. density began to fall in both groups by day 2, and reached a low of 4% of pretreatment value on day 8 (DEC group) and a low of 1% of pretreatment value on day 28 (ivermectin group). At 1 year after treatment, the counts had risen to 45% of pretreatment (DEC group) or 9% of pretreatment (ivermectin group).

LIBERIA The trial was done on 30 patients with moderate to severe infection and ocular involvement (41, 90). Both medications resulted in prompt reduction in skin mf. counts to almost zero; the lowest count was on day 8 for DEC and on day 14 for ivermectin. Numbers of mf. rose gradually in both groups. After 6 months, the counts in the ivermectin group (but not in the DEC group) were still significantly lower than in the placebo group. Treatment with DEC, but not ivermectin, resulted in more living and dead mf. in the cornea. Both medications reduced the numbers of mf. in the anterior chamber; the effect was slower in the ivermectin group. A separate trial, which departed from the standard protocol of the four primary Phase II trials, was conducted on 50 Liberian patients (1). The results of the Phase I ivermectin trials had raised the question of whether the clinical performance of DEC could be improved to match that of ivermectin simply by increasing the DEC dosage. Ivermectin, as a single oral dose at 150 μg/kg was therefore compared to high oral and/or cutaneous dosages of DEC, accompanied by corticosteroid treatment to suppress possible hypersensitivity reactions. Skin mf. counts were reduced by more than 90% following all treatments. After two months, the numbers of mf. had started to rise in the DEC patients, but not in the ivermectin patients.

The DEC treatment was associated with some apparent mobilization of mf. into the cornea and the urine, but the ivermectin treatment was not. Both medications resulted in reduced numbers of mf. in the anterior chamber of the eye after two months. The most striking difference between the two medications was that adverse systemic and ocular reactions were fewer and less severe with the use of ivermectin (see section on safety in humans).

Large-Scale Hospital-Based Trials (Phase III)

These studies involved larger numbers of patients (about 50 per group). The studies were double-blind, the patients were hospitalized for treatment, and the trials were done not only in Africa but also in Central America.

LIBERIA A study was done on 200 patients with moderate to severe onchocerciasis (42, 60, 101), and detailed ophthalmological examinations were done on 39 persons who had severe ocular damage (92). The dosages used were 100, 150, and 200 μ/kg. All three dosages gave comparable reduction in mf. at 3, 6, or 12 months after treatment. The lowest counts were recorded at three months, at which time they were almost zero. At the 12-month interval, treatments (and placebo) were reassigned so as to give subgroups of patients receiving (*a*) treatment once a year for two years at 100, 150, or 200 μ/kg; (*b*) treatments at each of these dosages, given at a two-year interval; or (*c*) three treatments at 150 μ/kg given at six-month intervals (89). As expected, retreatment given when mf. counts began to rise resulted in renewed reduction. The investigators concluded that a dosage of 150 μ/kg, given yearly, represented the best regimen in terms of efficacy and safety. Treatment reduced the numbers of mf. in the cornea and in the anterior chamber of the eye. Even in patients with severe ocular involvement, lesions did not worsen (except perhaps in one patient), and the clinical condition of the eye generally improved.

GHANA A study of 198 patients was conducted in the savannah region of Northern Ghana, where vector control had been successfully applied (3, 21). The patients, men and women, had moderate to heavy infections, but had dead and dying adult *O. volvulus* and diminishing numbers of skin and ocular mf. because of the prior interruption of transmission. Ivermectin dosages of 100, 150, or 200 μ/kg gave at least 97% reduction in skin mf., and the effect persisted for more than a year. The two higher dosages were superior to the lowest dosage. All three dosages eliminated mf. slowly (3–6 months) from the cornea and anterior of the eye.

MALI A study was done on 234 patients with skin densities of at least 20

mf./mg and with moderate or severe ocular involvement (98). Ivermectin dosages of 100, 150, or 200 μg/kg were compared with placebo treatment. Skin mf. counts were reduced by 79% after 3 days and by 92% after six months (all dosages). After one year, the counts were reduced by 87% from pretreatment levels. The numbers of mf. in the placebo group also fell during the trial, but were always higher than in the ivermectin groups. Ocular mf. counts increased slightly in the first three days after ivermectin treatment, but then diminished gradually to give a reduction of more than 90% after three months.

IVORY COAST A trial involving 220 male patients was conducted (52, 53, 54). The pretreatment skin mf. values were 59–64 mf./mg, and many patients had ocular involvement. By 4 days after treatment with ivermectin at 100, 150, or 200 μg/kg, the mf. count in the skin was significantly reduced, and after 3 months it had reached undetectable levels in almost all patients. The count then rose gradually and after 1 year had reached 10–18% of the original value. The number of mf. in the cornea and anterior chamber of the eye was significantly reduced at 3, 6, or 12 months after treatment.

Many of the patients in this trial were re-treated with ivermectin at half-yearly or yearly intervals, while others received repeated placebo treatment. Repeated ivermectin treatments were highly successful, and mf. were essentially eliminated in patients receiving three doses at 200 μg/kg at half-yearly intervals. For the reduction of mf. in the cornea or anterior chamber, two doses at a yearly interval were better than one (regardless of dosage).

TOGO Trials have involved about 200 patients (44, 46, 47). Ivermectin dosages of 100, 150, or 200 μg/mg markedly reduced the numbers of mf. in skin and in the cornea and anterior chamber of the eye.

Large-Scale Community-Based Trials (Phase IV)

Ivermectin has been used in several community-based programs and mass treatment campaigns (25, 64, 68, 73, 77, 79, 97, 102). More than 600,000 patients have been treated, and the findings have been analyzed (74). Apart from exceptions noted below, the target dosage was 150 mg/kg, and recipients were weighed individually in order to adhere closely to this dosage. The emphasis in these trials, apart from the fundamental objective of disease control, was to monitor adverse reactions and to insure that the dosage could eventually be used without individual medical supervision (see section on safety in humans). Information was also gathered on the effect of treatment on infection status (on a community basis, not an individual basis) and on the status of vector infection (see section on effect on transmission).

Effect on the Parasite

MICROFILARIAE The earliest clinical trials made clear that ivermectin treatment of onchocerciasis patients resulted in lower numbers of mf. recoverable from the skin. The investigators made this determination by counting the mf. that emerged from saline-soaked skin-snips taken from the patients before and after treatment. It was not clear whether the observed reduction reflected (*a*) paralysis of mf. and inability to migrate from the piece of tissue; (*b*) death of mf.; (*c*) inward retreat of mf. before snips were taken; or (*d*) failure to emerge from snips for reasons other than paralysis or death. Because the effect is apparent within 2 or 3 days after treatment, it can hardly be attributed to a suppression of larval output by affected adult worms and consequent failure to replace skin-dwelling mf. lost by natural attrition. A rapid posttreatment reduction in eosinophilia (57) further suggests a direct action on mf.

The reduction in mf. count in the eye, following ivermectin treatment, was associated with fewer local reactions (punctuate opacities) than in the case of DEC treatment, and the investigators (98) suggested that this result may occur because the mf. are paralyzed rather than immediately killed or because the mf. are affected only after they migrate out of the eye and become exposed to effective levels of the drug in other tissues. Migration out of the eye is unlikely to result from drug effect because ivermectin does not appreciably enter the eye. Chronic lesions in the cornea may in part be the result of autoantibodies induced by mf., but studies with *Onchocerca lienalis* in guinea pigs revealed no change in the production of such antibodies following treatment with ivermectin (33).

Early clinical observations suggested that ivermectin might kill mf. directly in the skin with consequent blood eosinophilia (4), but also that the slower elimination of mf. from the eye (requiring a few months instead of a few days) might be due to some indirect mechanism such as the wandering of mf. from the drug-free eye to the surrounding drug-laden tissue (23). Reductions of mf. numbers in both skin and eye were associated with fewer and milder hypersensitivity reactions, and this observation suggested that the mechanism, while not necessarily the same in both sites, was at least different from the mechanism of DEC in both sites.

Soboslay and his colleagues addressed the question of how ivermectin affects mf. by recovering mf. from treated patients and measuring their motility in an in vitro motility assay (85). The study was done in conjunction with the clinical trials in Liberia. When skin-snips were taken 24 hours after treatment, the mf. that emerged showed a clear and probably dose-related reduction in motility. At the same time, direct observation of mf. in the anterior chamber of the eye revealed abnormal motility in mf. from 24 of 94 ivermectin-treated patients but only 1 of 28 placebo-treated patients (85).

A difference in the effects of ivermectin and DEC on mf. was also suggested by observations made in the course of a Phase II study (9). Mobilization of mf. into blood was slower with ivermectin treatment (peak in 4 days) than with DEC treatment (peak in 2 days). Mobilization into the urine also occurred, but in the ivermectin patients, the mf. number remained very small.

When exposed to low concentrations of ivermectin in vitro, the mf. of *O. volvulus* exhibit an altered movement but not paralysis (58). In an attempt to demonstrate paralysis after in vitro treatment, skin-snips from patients were soaked in saline to allow emergence of mf., subsequently fixed and later digested with collagenase to reveal mf. that had failed to emerge. Before treatment, about 80% of mf. emerged during routine soaking (as in other studies). After treatment, the expected dramatic fall in mf. density in the skin occurred (as reflected by emergence into saline), but the percentage of mf. that emerged from the snips rather than remaining in situ was only slightly reduced. The reduction was statistically significant and dose-related, but even at the highest dosage of 200 μg/kg it was only 16%. The investigation concluded that this small reduction did not support the hypothesis that ivermectin acted primarily by paralyzing the mf.

The above investigation was conducted in Togo, and a similar study was done in Guatamala (77). Again skin-snips were soaked in saline in the usual way and were subsequently fixed and then digested in collagenase to reveal mf. that might not have emerged into saline. The patients had received ivermectin at 150 μg/kg. At 6 hours after treatment, the number of mf. emerging from skin-snips actually increased by about one third. At 48 hours, the number had fallen to only 13% of its original level. The numbers of mf. recovered from digested snips decreased very little in this period, so that the proportion that failed to emerge in saline increased from about 20% to about 50%. Nevertheless, the numbers in the digest were small at all times, and the lack of any absolute increase in their number indicated (as in the above study) that the decline in the number of mf. recovered by the usual saline method is not the result of immobilization of mf. in the skin. Indeed, the authors suggest that the mf. in the skin are mobilized by the treatment of the host, and retreat from the subepidermal layer of the skin into the deeper layers. If that is the case, their subsequent fate remains a mystery. (The authors noted a slight mobilization of mf. into blood and urine, but, like other investigators, they conclude that such mobilization is much less marked than in the case of DEC therapy.)

Attempts were made to titrate the concentration of ivermectin required to kill mf. when incubated in vitro at 37°C for 24–48 h. Concentrations comparable to those obtained in treated patients (10–50 ng/ml) had little effect. A concentration of 10,000 ng/ml killed about 50% of the mf., but 30,000 ng/ml

was required to kill all of them. On the other hand, mf. that had been incubated for 30 min in cold solutions of ivermectin, at concentrations as low as 100 ng/ml, failed almost completely to develop when inoculated into susceptible black-flies (16).

It is apparent from the above studies that the effect of ivermectin on mf. in the skin is far from clear. Undoubtedly a direct effect reduces mf. numbers, as opposed to a lack of repopulation following natural attrition, and the reduction in the number of mf. that emerge from skin-snips does not seem to be attributable to the paralysis of affected mf. Possibly the mf. die and are quickly resorbed, and possibly they simply flee the scene for destinations unknown, but no direct evidence supports either conjecture.

THE ADULT WORMS Following a single ivermectin dose, the numbers of mf. in the skin fall rapidly (suggesting, as stated, an effect on the mf. rather than the adult worm) and rise slowly after a lapse of several months, suggesting that the adult worms have not been killed. It does not follow, however, that the adult worms have been unaffected, and throughout the clinical efficacy trials the investigators attempted to document changes in the adults. The very slow reappearance of mf. in the skin could reflect a relatively rapid resumption of larviposition with a long period for the numbers of progeny to build up to reach the skin-snip detection threshold. Alternatively the observation could be attributed to an effect on the adult worms, resulting in a prolonged delay before the females resumed shedding mf. Almost all of the drug is excreted in the feces within 13 days after treatment (B. White-Guay, personal communication), so persistence of drug residues is unlikely to account for the prolonged suppression of microfilarodermia.

Data from the very first clinical trial of ivermectin suggested a "suppressive effect on worm reproduction," although the results were tentative and nothing indicated whether the effect was "macrofilaricidal activity or chemosterilization" (7). Almost immediately, further data, based on nodulectomy and collagenase digestion, indicated that "ivermectin was neither macrofilaricidal nor embryotoxic but there were changes in the numbers of developing embryos in the adult females . . ." (5). Many of the adult worms were apparently derived from old infections, and the level of reproductive activity was low even in worms taken from untreated control patients. Only 42% of the females contained embryos or mf. In worms recovered one month after treatment with ivermectin at 200 μg/kg, 67% of the females contained mf. and the numbers of mf. were much higher than in the controls. Thus, at first an apparent "stimulation of embryogenesis" occurred as had been seen with other medications. This process was followed by a marked decrease in reproductive activity at three months after treatment. The decrease did not result from chemosterilization because ova were still present in the uteri of the

female worms, and spermatozoa were present in the testes of the males. There was, however, a drastic decline in the number and condition of embryos and mf. in the uteri, with many of them showing clear signs of degeneration. The investigators concluded that mf. develop normally after treatment, but that they "are not released" and that they "degenerate and are resorbed after several weeks or months in the uteri" (6, 84). Similar observations were made in conjunction with Phase II and Phase III trials (2, 28). At one month after treatment, worms from ivermectin and DEC patients had uteri with developing mf. that appeared normal. At six months, the developing mf. in the DEC group again appeared normal, but in the ivermectin group, inspection of the worms "appeared to show that developing forms of mf. had not been released and were deformed, dead or degenerating in the uterus" (28). In another Phase II study, ivermectin treatment was again followed by increased numbers of embryos in the female worms at one month, and by degeneration of mf. in the female worms at six months (4). Degeneration of intra-uterine mf. became a well confirmed feature of ivermectin treatment (55, 83, 84), as did the failure of the drug to kill the adult male or female worms (12, 28, 32, 41, 55, 84).

In one study, histological techniques were used to examine the effects of ivermectin on reproductive processes of the worms. The dosages used had been 150 or 220 μg/kg, and the effects were assessed on the basis of nodules taken at 10 months after treatment. No effect was observed on embryogenesis or early mf. development (up to the coiled stage), nor was an effect seen on spermatogenesis in the males. In examining worms with stretched (essentially fully developed) mf., the investigators found that the majority of mf. were dead in 7% of the control worms, and in 66% of the ivermectin worms. Nuclear remnants of mf. were seen in 4% of the control worms, but 52% of the ivermectin worms. Despite the degeneration of large numbers of mf., some had apparently survived and been shed by the maternal worm, because almost 30% of the nodules contained free mf. that appeared to be alive (12).

In the course of several clinical trials, nodules were excised from more than 100 patients, providing abundant data on the condition of adult worms following treatment with ivermectin or DEC (84). Neither drug killed the adult worms. In worms collected one month after ivermectin therapy, the intra-uterine mf. were viable and the proportion of early and late stages was normal. At 2 months, the number of mf. was elevated, but about half were dead or degenerate. At 3 and at 6 months, 85% of the mf. were dead or degenerate, and early stages were rare, although some worms showed signs of recent insemination. At 9 and at 12 months, some worms still contained mostly degenerate mf., but many had a normal mixture of embryos and mf. It was concluded that ivermectin treatment had not blocked embryogenesis but had caused mf. to be retained in the uteri until they degenerated and were resorbed. New cycles of the reproductive process had then begun.

The question remains of whether a more intense ivermectin therapy would kill adult *O. volvulus,* and this question is being addressed. In Liberia, 30 patients were given ivermectin at 150 μg/kg every 2 weeks for a total of 6 treatments. Preliminary data indicate little or no reduction in the number of live worms in nodules removed from these patients 4 months later (34).

Ivermectin inhibits the motility of adult *Onchocerca gutturosa* in vitro, but only at high levels (95). Combining ivermectin with various known macrofilaricides did not reveal any synergistic action against male adult *O. gutturosa* or female adult *O. volvulus* in vitro (96). Ivermectin by itself affects the behavior and metabolism of adult *O. volvulus* in vitro, but only at concentrations higher than those obtained in clinical use (87).

Effect on Transmission

The treatment of human populations with ivermectin could affect transmission in two ways. First, lowering the mf. density in the skin of treated individuals would diminish the pool of mf. available for pick-up by vector flies. Some flies would feed on persons with few mf. or even no mf. in their skin. Second, the mf. taken up from treated people might be defective and prove incapable of reaching the infection stage and infecting other human beings.

In the course of a Phase II trial in Liberia, patients were given ivermectin at 200 μg/kg and their ability to serve as a source infection for the local species of vector fly was assessed at three and six months after treatment (19). At both time periods, the mf. uptake by flies was significantly reduced, as was the number of mf. that reached their developmental site in the thorax of the flies. The effect was more pronounced than in the case of patients whose mf. load had been reduced by DEC therapy. These observations led to the conclusion that the ivermectin "could be effective in interrupting transmission of *Onchocerca volvulus* for epidemiologically important periods of time" (19).

A study in Ivory Coast also demonstrated a striking reduction in the percentage of flies that took up mf. from ivermectin-treated patients and in the numbers taken up (71). The number of mf. ingested by the flies was in fact even less than could be expected on the basis of the observed reduction in mf. density in skin.

This effect was also examined in Guatamala where patients were given 2 doses of ivermectin at 200 μg/kg, spaced 7 months apart (20). Treatment resulted in "almost complete suppression of developing or infective larvae in the vector population for a six month period" (20). The suppression of the infectiousness of patients for flies was evident not only in the group mean, but in the data for the individuals with the highest skin densities. It was concluded that regularly spaced ivermectin treatments at the community level would likely result in the elimination of infective flies.

The Phase IV trial conducted in Liberia provided another indication of the

effect of treatment on transmission. Large numbers of children and adults were treated annually in a highly endemic area. Continued examination of mf.-negative children was of particular importance because it monitored the incidence of new patent infections in a community following general treatment of that community. By this means, the investigators showed that the incidence declined over two years by 35–45% (65, 91). They concluded that "ivermectin can be important in reducing the transmission of onchocerciasis" (91).

In this Liberian Phase IV trial, a detailed study of vector flies was also undertaken (97). The data were collected after the second of a series of annual ivermectin treatments (150 μg/kg). The number of flies landing and biting the members of this community remained the same as before treatment, but the number of flies harboring *O. volvulus* larvae fell by 94–95%. The number of flies in which the larvae had reached the infective (L_3) stage fell by 82–89%. The calculated monthly transmission potential fell by 75%. Also, the number of worm larvae in flies caught in neighboring districts where the mass treatment program was not in effect declined substantially. This reduction may have resulted from migration of flies or of people, but the explanation is uncertain.

The largest of the Phase IV trials was carried out in Ghana, where approximately 15,000 people were treated in a period of a few days, and here, too, entomological studies were conducted to assess the effect on transmission (73). The skin mf. density fell by 96% within two months, but rose earlier than expected, to give a decrease of 88% at four months after treatment. The total reservoir of mf. available for transmission (based on skin densities in treated and untreated members of the community) fell by about 70–80% at two months but was reduced very little at four months. Disection of more than 30,000 flies revealed a "dramatic and consistent reduction in vector infection" (73). Data on the number and developmental status of larvae in the flies led to the calculation that, within three months after treatment, the transmission of onchocerciasis had been reduced by 65% (based on infective larvae). It was concluded that transmission, under these circumstances, would continue at an unacceptably high level.

Reduction or elimination of microfilarodermia is clearly of potential clinical benefit to a treated individual. Further, the more people whose mf. load is lightened, the less likely it is that flies will acquire their infection and transmit it. The practical impact of community treatment, however, will depend on many factors. Treatment in one region (e.g. areas of Central America where *Simulium ochraceum* is the black-fly vector) may be more amenable to the interruption of transmission than others (e.g. areas of Africa where *Simulium yahense* is the vector). The impact of ivermectin programs on disease transmission will depend on the efficacy of vector control programs, the isolation of communities, and the ecological and climatic determinants of fly

propagation. While the chief aim of the current distribution of ivermectin is the alleviation and prevention of disease in treated people, investigators are continuing to look for ways to make strategic treatment programs pay dividends in terms of epidemiological control.

Causal Prophylaxis

Ivermectin is used at very low dosage to prevent the maturation of *Dirofilaria immitis* in dogs, and it was thought that a similar prophylactic utility might be attainable in human onchocerciasis. Even if not used with prophylactic intent, regular treatment at, say, half-yearly intervals, might provide prophylaxis as well as therapeusis; that is, it might block the maturation of immature worms as well as exercising its effects on the adults and the mf. In both *D. immitis* and *O. volvulus,* the immature filarial worms (L_3 and L_4) migrate through subcutaneous tissues after entering the body via insect bite. In both instances, ivermectin is active against the mf. stage and affects the adult stage without killing it.

To test the prophylactic potential of ivermectin against *O. volvulus,* an experiment was carried out in chimpanzees (93). On day 0 of the experiment, chimpanzees were inoculated with infective larvae. Six of them received ivermectin at 200 μg/kg on day 0. Six received the same dosage on day 28. Six were left untreated. During the succeeding three months, skin-snips showed that one chimpanzee treated on day 0 had developed a patent infection, suggesting perhaps a variable efficacy against the L_3 developmental stage. Four animals treated on day 28, and four untreated controls also became patent, indicating a lack of activity against the L_4 state.

Thus, although ivermectin is being used for clinical prophylaxis, preventing the onset of dermal and ocular lesions, it is unlikely to offer causal prophylaxis. Daily medication might be effective if activity against L_3 larvae were to be confirmed or enhanced, but would hardly be practicable. Treatment at monthly intervals (and presumably at longer intervals) would evidently not provide prophylaxis at dosages currently considered acceptable.

OTHER FILARIAL INFECTIONS

Wuchereria bancrofti

About 400 patients with bancroftian filariasis have been treated with ivermectin at dosages ranging from 10 to 400 μg/kg. The results, summarized below, indicate that the drug is at least as potent against the blood-dwelling mf. of *Wuchereria bancrofti* as against the skin-dwelling mf. of *O. volvulus.*

SENEGAL In an open trial involving 16 male patients, ivermectin was given as a single oral dose at 50 or 100 μg/kg. The mf. disappeared from the blood

within three days (not examined in the higher-dose group until day 14) and reappeared within three months (29).

FRENCH POLYNESIA In an open trial with 40 male patients, ivermectin was given at 50, 100, 150, or 200 μg/kg (once). At all dosages, mf. counts fell by more than 99% within six days (82). Counts started to rise again after one month, and by 6 months had reached 53% of pretreatment level (50 μg/kg) or 5–17% of pretreatment level (100–200 μg/kg).

In another trial in French Polynesia, healthy carriers of *W. bancrofti* (mf.-positive) were treated with ivermectin at 100 μg/kg or DEC at 3 mg/kg or DEC at 6 mg/kg. The efficacy of ivermectin in clearing mf. was superior to that of DEC at one week and one month after treatment, but not at three or six months (15). At the six-month mark, ivermectin offered no advantage over DEC in terms of mf. reduction, number or nature of adverse effects, or convenience (single oral dose in all cases). In French Polynesia, DEC is routinely given to carriers as single doses, at half-yearly intervals. The twelve-month data are pending.

Another French Polynesian study was designed to examine the effect of ivermectin on transmission as well as on mf. levels (14). Healthy carriers were given ivermectin at 50, 100, or 150 μg/kg. Dosages of 100 μg/kg, or higher, gave >99% reductions in mf., but the effect was temporary, as expected. Mosquitoes fed on treated carriers at six months after treatment were subsequently shown to have fewer infective larvae than mosquitoes fed on untreated carriers. The above experiment was extended by re-treating the same carriers with their respective dosages at one year after the initial treatment. The results suggested that the best strategy might be to treat entire populations every six months until mf. counts are substantially reduced, and then change to annual treatments.

INDIA An open trial was conducted on 40 male patients, and the dosages used were 25, 50, 100, and 200 μg/kg (single oral dose). At all dosages, mf. disappeared within 5–12 days (49). Microfilaremia reappeared by three months and reached 14–32% of pretreatment level by six months, with all dosages giving similar results. The equivalent efficacy observed at 50 and especially at 25 μg/kg is remarkable, because the other trials (above) suggested that 100 μg/kg, or higher, was superior to lower dosages in curtailing the rise in mf. following the initial posttreatment decline.

To assess the potential value of ivermectin more thoroughly, a randomized, double-blind trial was conducted in India, and DEC was used as a reference (63). Forty male patients were included in the trial. Capsules of identical appearance were used to deliver (*a*) ivermectin at approximately 21 μg/kg followed by placebo daily for 12 days; (*b*) ivermectin at approximately 126

μg/kg followed by placebo for 12 days; (*c*) DEC at approximately 3 mg/kg followed by DEC at approximately 6 mg/kg daily for 12 days; (*d*) placebo for 5 days. All treatments (other than the placebo) were highly effective, clearing mf. from the blood by 12 days in all ivermectin patients and in most DEC patients. At 3 months after treatment, mf. counts were comparably low in ivermectin and DEC patients. By 6 months, the mf. counts in the ivermectin groups had risen to 18–20% of their pretreatment values, while in the DEC group the count had risen to 6% of the pretreatment value.

A third trial in India was carried out on 40 male patients to compare (*a*) ivermectin at 10 μg/kg, followed by placebo for 12 days; (*b*) ivermectin at 20 μg/kg, followed by placebo for 12 days; (*c*) DEC at 6 mg/kg for 12.5 days; or (*d*) placebo alone (63). All treatments except the placebo resulted in almost complete disappearance of mf. within 12 days. Inexplicably, the 10 μg/kg dosage of ivermectin appeared to be the most effective, based on the rate at which mf. reappeared after 1 month.

HAITI Efficacy of a drug against the adult stage of *W. bancrofti* is usually assessed, for want of a more direct means, by following the mf. counts for a prolonged period after treatment. For such a purpose ivermectin was given to patients in Haiti and mf. levels were followed for a year (76). Ivermectin was given at 20 μg/kg and then, five days later, was given at 200 μg/kg once, or 200 μg/kg on two successive days. For comparison, DEC was given (in a conventional regimen of 72 mg/kg over 13 days) five days after the ivermectin 20-μg/kg dose. After the lapse of a year, the mf. counts in all groups were still reduced by more than 90% from pretreatment levels. The reappearance of mf. in the earlier clinical trials indicated the survival of adult worms. The remarkably long suppression of mf. seen with high ivermectin dosages in this trial raises the possibility that ivermectin, like DEC, may somehow affect adult *W. bancrofti*.

OTHER LOCALES A dose-finding study is being carried out in Brazil, and preliminary results suggest high efficacy against mf. even at a dosage as low as 20 μg/kg. Other studies are in progress in Egypt, China, Sri Lanka, and Kenya (D. C. Neu, personal communication).

PRACTICAL UTILITY In lymphatic filariasis, a drug with microfilaricidal activity presents perplexing problems in relation to practical utility. Removal of mf. may not prevent the progressive morbidity typical of filariasis because that is generally thought to be associated with the adult worms. Removal of mf. will, however, render a patient noninfectious to mosquitoes, and thus such a drug can be of immense value in public health programs in geographically circumscribed regions. The potential value of ivermectin in such situ-

ations is being assessed. Matters of potency and duration of effect still need to be clarified, and it is uncertain whether the drug would elicit fewer or milder adverse reactions than DEC, but ivermectin's one-dose treatment would doubtless represent a major advantage over the usual multidose regimen of DEC. In some circumstances, however, DEC, too, can be effective in a single oral dose (15). The critical issue is whether single-dose ivermectin treatment is superior to single-dose DEC treatment. Studies to address this question are in progress.

Brugia, Mansonella, Loa

Tests of ivermectin against *Brugia malayi* in leaf monkeys indicated that the mf. are sensitive to ivermectin but the adults are not (56). Trials against *B. malayi* in humans are in progress in India, Indonesia, and Malaysia. Results have not been published formally, but a preliminary communication indicates that ivermectin at 20 to 200 μg/kg, single oral dose, results in an 85–90% reduction in mf. over a three-month period (62).

In five patients with *Mansonella perstans,* ivermectin at 200 μg/kg did not reduce the mf. counts (75). This result was in keeping with observations made previously (6). On the other hand, a single dose, at 140 μg/kg, appeared to clear mf. in a patient with *Mansonella ozzardi,* and the absence of mf. even after nine months suggested an effect on the adult worm (61).

In a trial in Gabon, ivermectin was tested in 35 subjects with *Loa loa,* and in 17 subjects with *L. loa* plus one or two other filarial species (75). At dosages of 100, 150, or 200 μg/kg (but not at 50 μg/kg), numbers of mf. were greatly reduced, but the parasites were not eliminated.

EFFICACY AGAINST OTHER PARASITES

The avermectins have shown some activity against the intestinal phase of *Trichinella spiralis* infection at very high dosage in laboratory animals, but no activity against the muscle phase in mice or swine and enigmatic activity against the muscle phase in rats (13). Although these tests have not been definitive, ivermectin would probably not be useful in human trichinellosis.

The potent activity of ivermectin against several species of itch mite in various host species (13) has raised the possibility that the drug might be useful in human scabies.

Ivermectin at dosages up to 200 μg/kg was found inactive against *Plasmodium falciparum* in onchocerciasis patients (52). When administered in various dosage regimens, ivermectin was not active against *Schistosoma mansoni, Fasciola hepatica,* or *Hymenolepis diminuta* in laboratory rodents (D. A. Ostlind, personal communication).

Ivermectin paralyzed *Angiostrongylus cantonensis* in vitro at extremely low concentration, but in vivo tests have apparently not been reported (13).

SAFETY IN HUMANS

Evidence of the safety of ivermectin in humans has been obtained, not from studies in healthy subjects, but rather (*a*) indirectly from laboratory toxicological data (50) and (*b*) directly from the clinical efficacy trials. The overwhelming impression gained from the early clinical trials was that ivermectin was safe enough to justify more extensive trials, and the accumulated experience thus gained has led to its widespread use in community-based trials.

Safety and Tolerability in Onchocerciasis

Adverse reactions reported during the early probes included itching, dizziness, edema, mild Mazotti reaction, and minimal ocular inflammation in patients with ocular involvement. These effects were generally mild and transient.

In the Phase II trials, adverse reactions were milder and less frequent than in patients given DEC. This difference applied not only to the common systemic effects, but also to painful swelling of lymph nodes associated with mobilization of mf. into the nodes (1). One patient who received ivermectin at 245 μg/kg had a severe reaction including fever and scrotal swelling (28). Postural hypotension occurred in 4 of 19 patients in one of the open hospital-based trials (6), and hypotension was recorded in both ivermectin and DEC patients in a double-blind trial (4). These trials made apparent that, while certain reactions are common to both ivermectin and DEC, itching, painful swelling of lymph nodes, and rash tend to be more common with DEC therapy, whereas fever is more common with ivermectin (4).

In the Phase III trials, the investigators observed that ivermectin may slow the progression of ocular lesions and can be used even in patients with severe ocular lesions (42, 60, 92). In 39 patients with severe ocular onchocerciasis, "marked improvement was seen in the ocular status of the group as a whole" (92). It was also reported that severe postural hypotension (manifested by various signs, including dizziness, weakness, sweating, and tachycardia) occurred in some patients given ivermectin at 150 or 200 μg/kg, but not at 100 μg/kg (3). In 6% of 116 patients, mild ocular inflammation was seen, but it was resolved without treatment, and with no sequelae. In one trial, the number of patients with punctate keratitis was significantly reduced after ivermectin treatment (52). Treatment was well tolerated even when repeated at 6-month intervals (53).

Homeida et al (45) reported that ivermectin prolonged prothrombin time in the blood of certain treated patients in the Sudan and that this prolongation was associated with hematomatous swellings. However, review of data on the administration of more than 15,000 doses of ivermectin in Liberia failed to disclose any bleeding disorders (69), and a study in Haiti failed to demonstrate any prolongation of prothrombin time (78).

In Sierra Leone, a comparison was made of the side-effects in 629 ivermectin-treated subjects (100–200 μg/kg) and 623 placebo-treated controls (102). Data from this community-based trial yielded the startling figure of 34% "side-effects" in the ivermectin group and 11% in the placebo group. The most common side-effect, however, was the beneficial one of expulsion of *Ascaris lumbricoides* from ivermectin-treated persons. The most frequent adverse side-effects in the ivermectin group were itching/rash, muscle or joint pain, fever, and headache. Each of these effects occurred in 7–9% of the ivermectin subjects and in 1–4% of the placebo subjects (all figures to nearest whole number). The investigators concluded that "community-based treatment of onchocerciasis with ivermectin can cause substantial morbidity" (102). More than 95% of the reactions were reported in the first 3 days posttreatment.

Ivermectin was well tolerated by onchocerciasis patients even when given at 150 μg/kg every two weeks, for a total of six treatments (34). This regimen represents the most intensive ivermectin treatment so far reported in humans.

De Sole et al (25–27, 66) have thoroughly reviewed West African trials in which more than 60,000 people were treated (25–27). In one of these reviews, covering 50,929 persons, the authors (27) concluded: "Of those treated, 9% reported with adverse reactions, 2.4% with moderate reactions, and 0.24% with severe reactions. Most reactions were reported during the first day of follow-up, the most frequent severe reaction being severe symptomatic postural hypotension (in 49 cases). Three cases of transient but severe dyspnoea were considered life-threatening but their relationship with ivermectin treatment is uncertain. The incidence of adverse reactions was directly related to skin microfilarial load and was highest in the foci with the highest endemicity levels."

The observation that side-effects are more pronounced in patients with high mf. loads is consistent with the belief that side-effects are associated with mf. destruction rather than intrinsic toxicity. In this context, it is of interest that reactions seem to be more pronounced in Europeans who acquire onchocerciasis as adults living in Africa, and it has been suggested that this is because such individuals, having had less exposure to the parasite, have less tolerance to the antigens released by disintegrating microfilariae (24).

Almost nothing is known, however, about the disintegration of mf. following ivermectin therapy. The rate of adverse reactions may be related to the mechanism of parasite destruction. In an analysis of the overall clinical experience with ivermectin, the adverse reactions associated with both ivermectin and DEC have been tabulated in detail (37). The authors of this study noted that the Mazzotti reaction was mild or absent in ivermectin therapy; that mild or moderate hypotension occurred in 9 of 199 treated patients in 4 trials and was symptomatic in only 5 of them; and that such episodes have also been

associated with DEC therapy. The investigators suggested that the lower rate of severe adverse reactions following the use of ivermectin rather than DEC may result from the spastic paralysis (even if only partial) of ivermectin-affected mf., followed by removal by the reticulo-endothelial system—as compared to the outright killing of mf. by immune effector cells that have been made more adherent as a result of DEC treatment of the host (37, 85). Clearly much remains to be discovered about the mechanism of mf. destruction and its relationship to adverse reactions.

A recent report warns that the rate of moderate or severe reactions may be higher when ivermectin is used in hyperendemic areas in which vector control has not been implemented. A reaction rate of 32% was recorded for a group of 87 patients in Sierra Leone, many of whom had severe ocular disease prior to treatment (80, 86).

Safety in Other Infections

In lymphatic filariasis, as in onchocerciasis, ivermectin treatment has been well tolerated (29, 49, 63). In general, fever, headache, and myalgia were more common than rash and tenderness of lymph nodes, whereas the opposite situation generally occurs in the use of DEC.

Treatment of other helminth infections has been too infrequent to yield meaningful safety data, but serious unexpected reactions have not been recorded in the trials reported thus far.

Safety in General

A few cases of accidental exposure to ivermectin have occurred. A man injected himself in the hand with about 4 ml cattle Ivomec, and developed pallor, nausea, and transient pain and numbness in the hand (43). The dosage would have been about 570 μg/kg. In other cases of accidental exposure, the reactions included irritation at injection site, nausea, vomiting, abdominal pain, tachycardia, hypotension, hypothermia, urticaria, and stinging sensation in the eye (43).

Pregnancy has been a basis for exclusion of women from ivermectin treatment programs, and this policy reflected a basic precaution rather than any anticipated fetal toxicity. In practice, however, women may be treated inadvertently before their pregnancy becomes known. In a study in Liberia involving some 14,000 persons who were treated annually for three years, a total of 203 children were born to women who had received ivermectin during pregnancy. The occurrence of birth defects in children from treated or untreated mothers, or from a reference population, did not differ significantly. Rates of miscarriage or stillbirth did not differ, nor was there any difference in the subsequent development or disease patterns of the babies (67). Because of the limited sample size, continued surveillance is considered necessary.

Ivermectin appears to be very safe, but safety is always relative. The therapeutic index of the drug appears to be high in those human applications for which it has been tested. Idiosyncratic or strain-related susceptibility to ivermectin occurs in mice and dogs in which fatal reactions have followed exposure to dosages that normally are well tolerated (50). Such reactions are therefore a possibility in other species, but there is no evidence of them in humans.

In communities with a high prevalence of onchocerciasis, ivermectin is being given to residents without screening for infection status. As mentioned, one report has suggested a risk of substantial morbidity in the use of ivermectin in onchocerciasis (102), but another commentator, emphasizing the safety of the drug and pointing out that the few serious reactions have developed slowly over several hours and have been amenable to clinical management, has called for a relaxation of the current controls on its use (70). In both instances, and in the other trials reviewed above, the real issue is not whether the drug is safe enough to be used on a community basis. Rather, the issue is the risk-benefit ratio and the degree of supervision that should be applied. Perhaps the current status is best summarized by the findings of a comprehensive review of onchocerciasis trials that covered approximately 51,000 people in West Africa: "Treatment resulted in 98% reductions in mean microfilarial loads at all endemicity levels. The benefit of treatment largely compensated for the discomfort due to adverse reactions, which were all transient and managed successfully. Ivermectin thus appears to be sufficiently safe for large-scale treatment but monitoring by resident nurses for at least 36 hours is recommended" (27). Further endorsing the safety of ivermectin in community use, a subcommittee of the World Health Organization estimated that more than 120,000 doses of ivermectin had been given to some 70,000 persons, and concluded that the "drug is extremely safe and is without known pharmacological side-effects in humans" (103). As distribution of ivermectin continues to expand, especially in areas with high microfilarial burdens, the need for medical or paramedical supervision will become more clearly defined.

CURRENT DRUG DISTRIBUTION

Late in 1987, Merck and Company announced that it would provide ivermectin (Mectizan®) free of charge for the treatment of onchocerciasis in humans. The Mectizan formulation of the drug is registered for human use only. Early in 1988, a Mectizan Expert Committee was formed "to devise and oversee a process for donating Mectizan to medically responsible and operationally sound community-wide, mass treatment programmes" (38). The members, who are recognized experts in tropical medicine, were appointed on the joint recommendation of Merck and Company and the World Health Organization.

The committee was set up as an independent body with a secretariat at the Carter Center in Atlanta, Georgia. The objectives and activities of the committee have been described (35).

Since September 1988, when applications were first received, the committee has granted approval for distribution of Mectizan in 30 of the 32 known endemic countries (20 in Africa, 5 in Latin America). Additional applications are under review. Mectizan is in the form of small tablets, each containing 6.0 mg ivermectin. For a 60 kg person, the prescribed dosage is one and a half tablets. More than three million such tablets have so far been shipped to the treatment programs, and this number will increase greatly as more applications are approved and more distribution programs are implemented. At least 600,000 persons have already been treated. Physicians and clinics with a need to treat small numbers of patients on an individual rather than community basis do not need to seek approval from the Mectizan Expert Committee. They may instead obtain the drug by applying directly to Merck and Company.

Clearly, the mass-treatment programs and the small-scale clinical administrations of Mectizan have not yet resulted in the treatment of all persons at risk of clinical onchocerciasis. To some [see, for example, Pond (70)] the distribution program seems too restrictive and cumbersome because of the degree of supervision demanded. As field experience accumulates, the restrictions may be eased to the extent that they remain compatible with responsible medical practice (37).

Mectizan is not currently approved for the treatment of any human disease other than onchocerciasis.

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