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The co-administration of ivermectin and albendazole — safety, pharmacokinetics and efficacy against *Onchocerca volvulus*

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A randomized, double-blind, placebo-controlled trial was conducted, to determine whether the co-administration of ivermectin with albendazole is safe and more effective against *Onchocerca volvulus* than ivermectin alone, and whether a significant pharmacokinetic interaction occurs. Forty-two male onchocerciasis patients received ivermectin (200 μg/kg) alone, albendazole (400 mg) alone or the combination. Safety was determined from the results of detailed clinical and laboratory examinations before treatment, during hospitalization and on day 30. Microfilaricidal efficacy was estimated from the reductions in skin counts between day 0 (pretreatment) and day 30. To determine efficacy against the adult worms, two independent observers examined histology slides prepared from nodules excised on day 180; changes in the skin counts of skin microfilariae between days 30 and 365 provided additional indicators of the level of adulticidal activity. Pharmacokinetic parameters for ivermectin and albendazole sulphoxide were defined over 72 h post-treatment. The co-administration of ivermectin with albendazole did not produce more severe adverse effects than ivermectin alone. Both nodule examiners found that the combination was not macrofilaricidal and that it was not clearly superior to ivermectin alone in the effects on reproductive activity; this was supported by the similar efficacy of the two regimens in the suppression of skin microfilariae. There was no significant pharmacokinetic interaction. Although the co-administration of ivermectin with albendazole appears safe, it offers no advantage over ivermectin alone in the control of onchocerciasis. The combination does not require an alteration in the dosage of either component.

Human onchocerciasis is an important cause of visual impairment and blindness and of disfiguring skin lesions. These symptoms have important socio–economic effects that justify attempts to control or eliminate the disease. The microfilariae (mff) of *Onchocerca volvulus* are responsible for the pathology of human onchocerciasis and are the parasite form taken up from the skin of the infected individual by the *Simulium* vector. Transmission is sustained by the production and release of mff by adult, female worms that are viable and fertile. Control of the disease can be achieved if the skin can be kept free of mff, by drugs that are suitable for distribution in the endemic areas. However, many of the adverse events that occur during the treatment of onchocerciasis (collectively

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known as the Mazzotti reaction) are the result of systemic and ocular responses to the death of the mff.

Ivermectin is the only drug currently recommended for the control of human onchocerciasis. When given as a single, standard dose, of 150–200 μg/kg bodyweight, it has a potent effect against the mff and also inhibits their release by the adult female worms. However, ivermectin does not kill the adult worms (it is has no significant 'macrofilaricidal' activity) and its block on microfilarial release is reversed a few months post-treatment (WHO, 1995). Thus repeated administration, usually once or twice a year, is needed to keep the skin relatively free of mff. Initial approaches to investigating any inherent macrofilaricidal effect involved an increase in the frequency of ivermectin dosage, or the dose size. Although apparently safe, the administration of several repeated standard doses (Duke *et al.*, 1990, 1991*a*, *b*, 1992; Chavasse *et al.*, 1992; Klager *et al.*, 1996) or large single doses (Awadzi *et al.*, 1995*b*, 1999) showed no clinically useful, additional activity.

An alternate approach is to combine ivermectin with an anthelmintic that has a different mode of action and the potential to reduce the viability and/or reproductive activity of the adult worms. However, owing to the central role ivermectin plays in onchocerciasis control, and the fact that the drug is distributed in the communities mainly by medically unskilled personnel, it is important that any candidate drug does not significantly alter the safety profile or dosage of the ivermectin. Albendazole is a potent, broad-spectrum anthelmintic with a good safety profile in onchocerciasis patients. It has little effect against the mff but has been found to disrupt severely all the intra-uterine stages in the adult, female worms (Awadzi *et al.*, 1991). The results of pharmacokinetic and efficacy studies indicate that a single 800-mg dose of albendazole could be as effective, in the treatment of onchocerciasis, as higher doses (Awadzi *et al.*, 1994). {A smaller dose, of 400 mg, was used in the present study, partly to determine whether this would be as effective as a dose of 800 mg and partly because this is the dose used for the control of lymphatic filariasis (Horton *et al.*, 2000).} Ideally, the combination of albendazole with ivermectin would bring together the microfilaricidal activity and inhibition of microfilarial release unique to ivermectin and the generalized, direct toxicity to the intra-uterine stages unique to albendazole. Should these effects be additive, suppression of microfiladermias beyond that achievable by either drug alone would occur. Should the augmented effects be permanent, the skin could remain free of mff in the absence of re-infection.

Awadzi *et al.* (1995*a*) combined ivermectin with albendazole, the drugs being separated by 1 week. Thus administered, a pharmacokinetic interaction was avoided and the safety of the treatment regimen was defined. However, the combination proved no more effective than ivermectin alone. In the present study, the two drugs were given concurrently, as a single dose. The primary objective was to determine if the combination was more efficacious than ivermectin alone against the adult worms. Other variables investigated included safety and tolerability, efficacy against the mff, and the pharmacokinetics of the ivermectin and albendazole when given separately and in combination. The strength of the relationship between the degree of drug exposure, microfilaricidal efficacy and the severity of adverse events in the individual patient was also evaluated.

PATIENTS AND METHODS

Patients

The patients investigated came from communities in the River Tordzi basin, in the forested region of south–eastern Ghana. The area is without vector control and not covered by the national ivermectin-distribution programme. Fifty-eight men in good general health, aged 19–54 years, with moderate to heavy *O. volvulus* microfiladermias and palpable onchocercal nodules were initially

recruited. Each gave his verbal informed consent, and this was witnessed by two members of the community who signed and dated a form for each volunteer. This form certified that the contents of the information sheet (that described the trial protocol) had been communicated to, and been understood, by the subject, and that the subject had freely agreed to submit to any necessary, additional examinations. The results of further clinical and laboratory screening led to 16 of the recruits being excluded, because they had abnormal liver enzymes (10), fewer than 15 mff/mg skin (four) or cellulitis of the right leg (one), or refused to have their eyes examined (one). The 42 remaining subjects were enrolled in the trial, which took place between December 1997 and January 1999 at the Onchocerciasis Chemotherapy Research Centre (OCRC) at Hohoe in Ghana. The Ethics Committee of the Ghanaian Ministry of Health, and the World Health Organization's Secretariat Committee for Research Involving Human Subjects (SCRIHS) approved the protocol prior to the initiation of the study.

Treatments

The trial was randomized, double-blind and placebo-controlled. Merck (Merck & Co., Inc., Whitehouse Station, NJ) provided 6-mg tablets of ivermectin and matching placebo tablets, whereas SmithKline Beecham (Brentford, U.K.) provided 200-mg tablets of albendazole and matching placebo tablets. Patients were randomized into three treatment groups (14 per group), using three columns of random integers generated using the MINITAB computer programme (MINITAB Inc., State College, PA). This group size has given acceptable conclusions in a previous exploratory study of similar design (Awadzi *et al.*, 1994). The members of the ivermectin group each received two 6-mg tablets of ivermectin and two placebo tablets to match the albendazole. Those in the albendazole group each received two 200-mg tablets of albendazole and two placebo tablets to match the ivermectin. The other patients, who formed the combination group, each received two 6-mg tablets of ivermectin plus two 200-mg tablets of albendazole. All of the tablets were given, after an overnight fast, from 07.00 hours on day 1 of treatment, under the direct observation of a medical officer and two nurses. The time of administration and the number and types of tablets given were recorded for each patient. A standard breakfast (Awadzi *et al.*, 1994) was taken 2 h later.

Blinding

Individuals uninvolved with monitoring the trial carried out the randomization procedure, assignment to treatment regimens, and the packaging of the tablets. The envelopes containing details of the treatment regimen for each patient were not accessible to any investigator. Individuals unaware of the treatment regimens administered the drugs and performed the laboratory tests and drug analyses. In order to prevent un-blinding by the laboratory changes associated with the Mazzotti reaction (WHO, 1987), results were only made available to the clinical assessors before completion of the day-30 visit if clinically significant adverse events occurred. The study code was broken only after all clinical, pharmacokinetic and laboratory data collected up to the end of the study had been validated.

Monitoring Efficacy Variables

The primary efficacy variable was the death of the adult worms or their permanent sterilization. The viability and reproductive activity of such worms were determined by examination of histopathology slides prepared from onchocercal nodules removed on day 180. At this time, all located nodules were aseptically excised, under local anaesthesia using 1% xylocaine, and processed as described previously (Awadzi *et al.*, 1997); also available were sections from 148 nodules excised previously from 36 untreated patients. One patient in the ivermectin-treated group

declined nodulectomy but provided all other laboratory specimens. A person uninvolved with their interpretation coded all the slides in such a way as to mask their origin. Slides were read initially at Hohoe (by 'Reader 1') and then independently by a second observer ('Reader 2'). The features recorded are listed in Tables 2 and 3.

The levels of microfiladermia (mff/mg skin) were evaluated and any ocular parasites were counted pretreatment and on days 4, 8, 30, 180, 270 and 365 (Awadzi *et al.*, 1995*b*). Briefly, one skin snip was taken from each subject at each time-point from both iliac crests and both calves, using a Walser-type corneoscleral punch. Each snip was weighed on an analytical balance and then incubated overnight in isotonic saline in a well of a flat-bottomed microtitre plate. The mff that emerged were counted under an inverted microscope, and the counts used, with the snip weights, to give estimates of the level of microfiladermia (mff/mg skin). There were thus four estimates of the level of microfiladermia for each subject at each time-point. Mff in the anterior chamber of each eye were counted, after head-down positioning for 5 min, using a 900 slit-lamp (Haag-Streit, Könitz, Switzerland).

All patients were present at each visit. The microfilaricidal effect of the treatment regimens was based on the reduction in the level of microfiladermia between day 0 (pretreatment) and day 30. In addition, the extent to which this reduction was maintained between days 30 and 365 gave indirect evidence of the effect of treatment on the adult worms.

Monitoring Safety Variables

The safety of the treatment regimens was followed, over the first 30 days, in terms of Mazzotti-reaction scores (Awadzi, 1980; Hero *et al.*, 1992), the severity of other adverse effects causally related to treatment, post-treatment (day-1, -2, -3 or -8) changes in the electrocardiogram (ECG), and clinically significant changes in laboratory parameters (as compared with the ranges considered 'normal' by the OCRC). The protocols for the ocular examinations and for the tests that define the various laboratory profiles (all conducted pretreatment and on days 4 and 8) have been described previously (Awadzi *et al.*, 1995*b*). For each subject, symptoms and vital signs were recorded on 12 occasions pretreatment, to establish baseline criteria, and then at least three times daily post-treatment. A detailed physical examination was performed daily. Adverse events other than the Mazzotti reaction were categorized as mild, moderate or severe. Patients were monitored in hospital until day 9 of treatment and reported for re-examination on day 30.

Drug-concentration Measurements and Definition of Pharmacokinetic Parameters

Samples (10 ml) of heparinized blood were taken pretreatment and at 1, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 h. Blood was drawn over the first 12 h through an indwelling butterfly needle kept patent with isotonic saline. Samples were centrifuged (2000 $\times$ *g*, 15 min) so that the plasma could be separated and kept frozen, at -70°C, until assayed. Plasma concentrations of albendazole sulphoxide (Hoaksey *et al.*, 1991; Rawden *et al.*, 2000) and ivermectin (Edwards *et al.*, 1988) were determined by reversed-phase HPLC. To assess systemic exposure to each agent, alone and in combination, the area under the curve (AUC) of plasma concentration *v.* time, up to the last experimentally determined concentration (C_{last}), was determined by the linear trapezoidal rule. Extrapolation to infinity (C_{last}/k), where k is the apparent terminal-elimination rate constant determined by log–linear regression of the post-absorptive phase, then gave $AUC_{0-\infty}$.

Data Analysis

The clinical and laboratory data were double-entered and verified using the VALIDATE programme, part of version 6.0 of the Epi Info software package (Centers for Disease

Control and Prevention, Atlanta, GA). In general, initial analyses involved a simultaneous comparison of all groups. Paired group comparisons were then made, for features in which the regimens differed significantly. The null hypothesis was rejected when $P < 0.05$.

Mazzotti-reaction scores were analysed using the MOOD test for comparison of medians, within MINITAB. The frequencies of other adverse events were compared using χ^2 Fisher's exact tests. The Mann–Whitney *U*-test was used for the pharmacokinetic data. Analysis of efficacy against the adult worms was done separately for Readers 1 and 2. Comparisons of the percentages of adult worms and nodules with the various features listed in Tables 2 and 3 initially involved all three treatment groups. The ivermectin and the combination groups were then directly compared, and similarly, the albendazole and untreated groups, using χ^2 tests and the EPITABLE software in the Epi Info package. For the microfiladermias, the four estimates (mff/mg) for each subject at each time-point were summed and then logarithmically transformed prior to calculation of geometric means (mff/4 mg). Analysis of variance (ANOVA) was then used to compare microfiladermias in the three groups, the unpaired Student's *t*-test to compare the geometric means for two groups at various time-points, and the paired *t*-test to compare the values, at adjacent time-points, within the groups. Counts of ocular mff were generally low and highly variable within and between groups. Analysis of the effect of treatment on such parasites was thus limited to a description of the pattern of response within each group.

RESULTS

The baseline characteristics of the 42 subjects enrolled in the study are summarized in Table 1. There was a fairly uniform distribution of features between the treatment groups. Onchocercal skin and ocular lesions were uncommon and $< 60\%$ of subjects had mff in the anterior chamber.

Effects on the Adult Worms

The total number of nodules available from 41 treated patients was 162 (Reader 1) or 159 (Reader 2); Reader 2 considered that three of the specimens presented to him were not onchocercomata. When the nodule features in the three treatment groups were

TABLE 1. *Baseline characteristics of the 42 patients treated with ivermectin, albendazole or the combination*

Feature	Treatment		
	Ivermectin	Albendazole	Ivermectin + albendazole
No. of patients	14	14	14
Mean age and (range) (years)	36 (19–54)	36 (25–50)	39 (22–54)
Mean weight and (range) (kg)	56.5 (44.0–65.5)	56 (45.0–65.0)	61.5 (52.0–82.5)
Mean height and (range) (cm)	167.9 (150.5–180.0)	166 (154.0–174.0)	168.1 (157.0–176.0)
NO. AND (%) OF PATIENTS WITH:			
Onchodermatitis	1	0	2
One or two nodule sites	9 (64)	12 (86)	12 (86)
More than two nodule sites	5 (36)	2 (14)	2 (14)
Visual acuity between 6/4 and 6/6	12 (86)	13 (93)	12 (86)
Visual-field loss	0	2	0
Microfilariae in the anterior chamber	6 (43)	11 (79)	8 (57)
Corneal microfilariae/opacities	0	2	2
Lesions of the posterior segment	0	3	2

compared, both readers found that there were no differences in the effects of treatment on the viability of the adult worms. However, there were differences in the effects on the reproductive activity of the adult, female worms. The data for the two-group comparisons are shown for each observer in Tables 2 and 3 (although the results of the three-group comparisons are not presented, all relevant data are available in these tables). In the direct comparison between ivermectin and ivermectin plus albendazole (Table 2), Reader 1 found no significant difference between the two groups in any of the features examined. The only difference found by Reader 2 was that embryogenesis was suppressed more by the combination than by ivermectin alone {$\chi^2 = 7.32$; degrees of freedom (df) = 1; $P = 0.007$}. In the direct comparison of albendazole with no treatment (Table 3), Reader 1 found a significantly greater proportion of dead or moribund adult female worms in the albendazole group ($P = 0.005$). The proportions of dead or moribund worms found in the three treated groups were very similar for each observer (Tables 2 and 3). For Reader 2, these were also similar to that found in untreated subjects, indicating the lack of an effect of treatment on the vitality of the adult worms. This is in line with the known effects of ivermectin and albendazole. Both readers found no difference, between albendazole and no treatment, in the effect on adult-worm reproductive activity. However, Reader 2 thought that nodules from untreated subjects were more likely to

TABLE 2. *The effects of treatment with ivermectin (13 patients) or ivermectin plus albendazole (14 patients) on the viability and reproductive activity of the adult worms of* Onchocerca volvulus

	Treatment					
	Ivermectin		Ivermectin + albendazole		*P**	
Feature	Reader 1	Reader 2	Reader 1	Reader 2	Reader 1	Reader 2
No. of nodules	48	47	66	65		
NO. AND (%) OF FEMALE WORMS:						
Total	64	73	97	109		
Dead or moribund	26 (40.6)	12 (16.4)	41 (42.3)	22 (20.2)	0.836	0.525
Dead and calcified†	7 (10.9)	1 (1.4)	16 (16.5)	5 (4.6)	0.324	0.442
Live	38 (59.4)	61 (83.6)	56 (57.7)	87 (79.8)		
NO. AND (%) OF LIVE FEMALE WORMS:						
Producing embryos	21 (55.3)	26 (42.6)	22 (39.3)	19 (21.8)	0.127	0.007
With degenerate embryos‡	16 (76.2)	6 (23.1)	20 (90.9)	4 (21.1)	0.372	0.842
Not producing embryos	17 (44.7)	35 (57.4)	34 (60.7)	68 (78.2)		
With relict/degenerate embryos§	6 (35.3)	10 (28.6)	5 (14.7)	22 (32.4)	0.185	0.694
NO. AND (%) OF MALE WORMS:						
Total	30	27	38	35		
Dead or moribund	14 (46.7)	2 (7.4)	11 (28.9)	3 (8.6)	0.132	0.762
Live	16 (53.3)	25 (92.6)	27 (71.1)	32 (91.4)		
No. and (%) of live male worms with normal spermatogenesis	13 (81.2)	17 (68)	19 (70.4)	21 (65.6)	0.668	0.85
NO. AND (%) OF NODULES:						
With microfilariae in the capsule	18 (37.5)	11 (23.4)	19 (28.8)	9 (13.8)	0.327	0.192
In which no male worm was seen	19 (39.6)	22 (46.8)	31 (47.0)	35 (53.8)	0.433	0.462

*Based on comparison of proportions in each defined feature.
†The percentages shown are of the total population of adult female worms.
‡The percentages shown are of the live females producing embryos.
§The percentages shown are of the live females not producing embryos.

TABLE 3. *Comparison of the effects of treatment with albendazole (14 patients) and no treatment (36 subjects) on the viability and reproductive activity of the adult worms of* Onchocerca volvulus

	Treatment					
	Albendazole		None		*P**	
Feature	Reader 1	Reader 2	Reader 1	Reader 2	Reader 1	Reader 2
No. of nodules	48	47	148	147		
NO. AND (%) OF FEMALE WORMS:						
Total	58	70	208	233		
Dead or moribund	23 (39.7)	10 (14.3)	45 (21.6)	33 (14.2)	0.005	0.747
Dead and calcified†	8 (13.8)	0 (0.0)	26 (12.5)	11 (4.7)	0.794	0.137
Live	35 (60.3)	60 (85.7)	163 (78.4)	200 (85.8)		
NO. AND (%) OF LIVE FEMALE WORMS:						
Producing embryos	23 (65.7)	28 (46.7)	109 (66.9)	103 (51.5)	0.895	0.511
With degenerate embryos‡	4 (17.4)	1 (3.6)	23 (21.5)	4 (3.9)	0.875	0.631
Not producing embryos	12 (34.3)	32 (53.3)	54 (33.1)	97 (48.5)		
With relict/degenerate embryos§	2 (16.7)	1 (3.1)	6 (11.1)	9 (9.3)	0.964	0.454
NO. AND (%) OF MALE WORMS:						
Total	30	24	84	71		
Dead or moribund	7 (23.3)	1 (4.2)	8 (9.5)	5 (7.0)	0.108	0.988
Live	23 (76.7)	23 (95.8)	76 (90.5)	66 (93.0)		
No. and (%) of live male worms with normal spermatogenesis	16 (69.6)	20 (87.0)	62 (81.6)	55 (83.3)	0.345	0.937
NO. AND (%) OF NODULES:						
With microfilariae in the capsule	22 (45.8)	15 (31.9)	88 (59.5)	77 (52.4)	0.098	0.014
In which no male worm was seen	21 (43.8)	26 (55.3)	68 (45.9)	78 (53.1)	0.791	0.787

*Based on comparison of proportions in each defined feature.
†The percentages shown are of the total population of adult female worms.
‡The percentages shown are of the live females producing embryos.
§The percentages shown are of the live females not producing embryos.

have mff in the capsule than nodules from patients treated with albendazole ($\chi^2 = 5.98$; df = 1; $P = 0.014$).

Effects on the Microfilariae

The changes in skin mff over time are summarized in Table 4. There was no significant difference between the groups in the initial microfilarial counts (ANOVA; $F = 1.17$; $P = 0.32$). Subsequently, however, the groups were dissimilar at all time-points ($P < 0.001$), owing to the marked differences in microfilarial counts between the ivermectin- and albendazole-treatment groups. In those treated with ivermectin (alone or with albendazole), counts fell rapidly and successively until day 30, at which time the initial counts had been reduced by 99%. There was no difference between the two ivermectin-treated groups in the rate at which mff were killed or in the microfilaricidal efficacy. On the other hand, the counts in those given albendazole alone were very variable and the overall reduction by day 30 was only 22%. Although counts of skin mff in both ivermectin-treated groups were found to have increased slightly at each visit after day 30, up to day 365, the two groups were similar in the percentage reductions on initial counts achieved and these remained >90% at 1 year. In the albendazole group, the day-180 counts were found to be higher than those recorded on day 30 but later counts were lower; the reduction on the initial count achieved at day 365 was <33%.

TABLE 4. *The effects of treatment with ivermectin alone (14 patients), albendazole alone (14 patients) or ivermectin plus albendazole (14 patients) on microfiladermias*

Timing	Geometric mean level of microfiladermia, (the associated 95% confidence interval) and {percentage reduction compared with baseline}*					
	Ivermectin		Albendazole		Ivermectin + albendazole	
Initial	148.5 (118.6–185.9)		151.2 (117.8–194.0)		196.6 (135.5–285.0)	
Day 4	21.6 (12.1–37.9)	{85.5}	121.9 (91.1–162.9)	{19.4}	35 (22.5–54.2)	{82.2}
Day 8	5.9 (2.6–12.3)	{96.0}	116.9 (91.2–149.8)	{22.7}	11.2 (4.8–24.3)	{94.3}
Day 30	1.3 (0.2–3.4)	{99.1}	118 (90.4—153.9)	{22.0}	1.9 (0.2–5.7)	{99.0}
Day 180	6.1 (3.2–10.9)	{95.9}	135 (98.2–185.6)	{10.7}	6.7 (2.9–14.0)	{96.6}
Day 270	7.8 (4.3–13.5)	{94.8}	126 (90.9–174.6)	{16.6}	15.6 (7.8–30.3)	{92.1}
Day 365	9.8 (18.3)	{93.4}	104.7 (71.9–152.3)	{30.8}	15.9 (7.6–32.2)	{91.9}

*Level of microfiladermia was estimated, for each subject at each time-point, as the sum of the microfilarial densities (microfilariae/mg skin) in skin snips taken from both iliac crests and both calves. The geometric means shown here are therefore the mean numbers of microfilariae/4 mg skin.

Counts of ocular mff were highly variable within and between groups (data not shown). The mean count (range) was 0.8 (one to four) in the ivermectin group, 4.1 (one to 14) in the albendazole group and 5.5 (one to 24) in the combination group. All ocular mff had been eliminated from the ivermectin group by day 365, when four subjects in the combination group still had a few ocular parasites (one to four/subject). During most of the follow-up period, however, the ocular counts in the albendazole group remained higher than seen pretreatment.

Clinical and Laboratory Evidence of Adverse Effects

Overall, the adverse effects observed were mild to moderate in severity and there were no serious effects in any treatment group. Examination of the scores for 13 types of adverse events together recognized as the Mazzotti reaction (Awadzi, 1980) indicated that the groups differed only in the severity of lymph-node tenderness and the total reaction score. Lymphadenitis was absent in the albendazole group (data not shown). Comparison of the two ivermectin-treated groups showed no significant differences in the severity of any of the individual types of adverse effect or in the total reaction. The combination, but not the ivermectin group, had significantly higher total-reaction scores than the albendazole group, with a median score of 42.5 ($\chi^2 = 5.14$; df = 1; $P = 0.02$). The severity of the Mazzotti reaction in the ivermectin group was correlated significantly with the level of microfiladermia pretreatment ($r^2 = 0.447$; $P < 0.05$). Other evidence of Mazzotti-type toxicity (swelling of the limb, face or groin) occurred in four patients treated with ivermectin alone, one treated with albendazole alone, and two treated with the combination. Swellings were mild and lasted for only a few hours or days. Various other adverse events not causally related to treatment occurred with similar frequency in the three groups. Ocular adverse effects were infrequent and mild. Two patients treated with the combination had eye pain and lacrimation on day 4, and one of them developed conjunctivitis and swollen eyelids that persisted until day 8. No anterior-segment inflammation was seen subsequently. Visual acuities, visual fields and pre-existing lesions of the posterior segment remained unchanged during the 30-day observation period. No clinically important ECG or laboratory abnormalities were recorded. Acetaminophen was given, mostly for moderately severe headache but occasionally for fever and gland pain, to five patients treated with ivermectin, three treated with albendazole and six treated with the combination.

Drug Concentrations and Pharmacokinetic Profiles

No drug was detectable in the plasma samples of three patients allocated to receive ivermectin alone. Plots of (detectable) plasma concentrations *v*. time are shown in Figures 1 and 2, for albendazole sulphoxide and ivermectin, respectively. Values of $AUC_{0-\infty}$ (ng.h/ml) for ivermectin were similar when the ivermectin was given alone or with albendazole (median difference = 44 ng.h/ml; 95% confidence interval for difference between medians = −386–+255 ng.h/ml; $P > 0.05$). Similarly, there was no difference in the $AUC_{0-\infty}$ for albendazole sulphoxide when albendazole was given alone or in the presence of ivermectin (median difference = 74 ng.h/ml; 95% confidence interval for difference between medians = −829–+1142 ng.h/ml; $P > 0.05$).

Ivermectin Dosage, Drug Exposure, Mazzotti Toxicity and Microfilaricidal Efficacy

Table 5 summarizes, for each patient and each treatment regimen, the dose of ivermectin administered, the degree of drug exposure (AUC), the initial level of microfiladermia, the Mazzotti-reaction score and the microfilaricidal effect achieved. Nearly all patients in the two ivermectin-treated groups received ivermectin in a dose close to the projected 200 μg/kg bodyweight; the exception was the heaviest subject — patient 12 in the combination group, who weighed 82.5 kg. There was, however, a marked inter-patient variation in the AUC for ivermectin, in both the ivermectin and combination groups. There was no apparent relationship between the AUC for ivermectin and the microfilaricidal activity. In the three patients in whom ivermectin could not be detected, one had a poor microfilaricidal response, another a moderate, and the third a good response. Curiously, patient 7 in the combination group showed a relatively low reduction in his skin counts of mff (<42%), despite an apparently adequate exposure to ivermectin.

Mazzotti scores were similarly unrelated to AUC or microfilaricidal efficacy. In the ivermectin-only group, for example, three

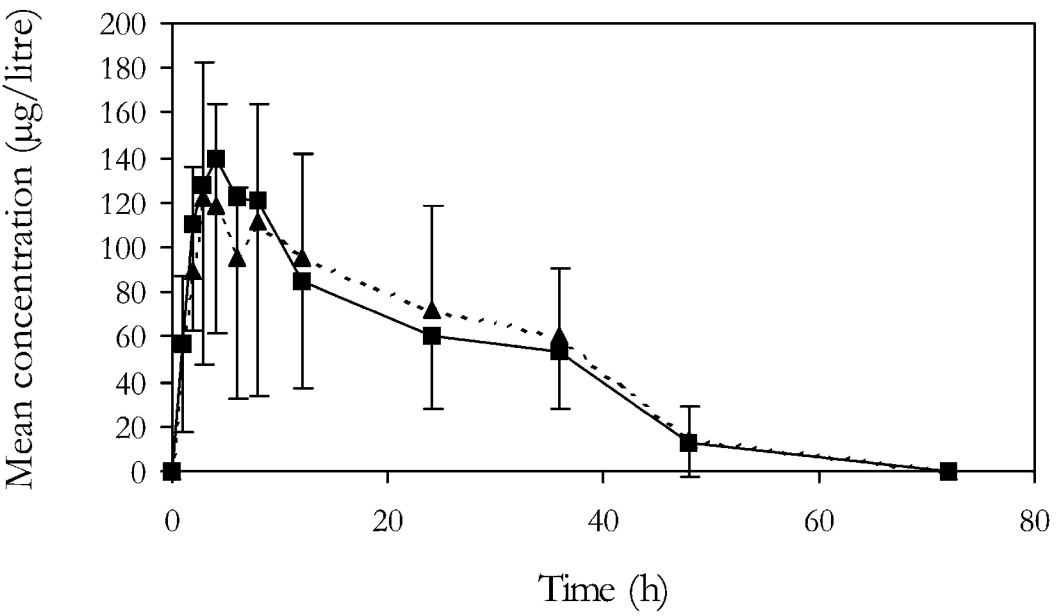

FIG. 1. Mean plasma concentrations of albendazole sulphoxide following oral administration of 400 mg albendazole with either placebo (▲) or 200 μg ivermectin/kg (■). Vertical lines indicate S.D.

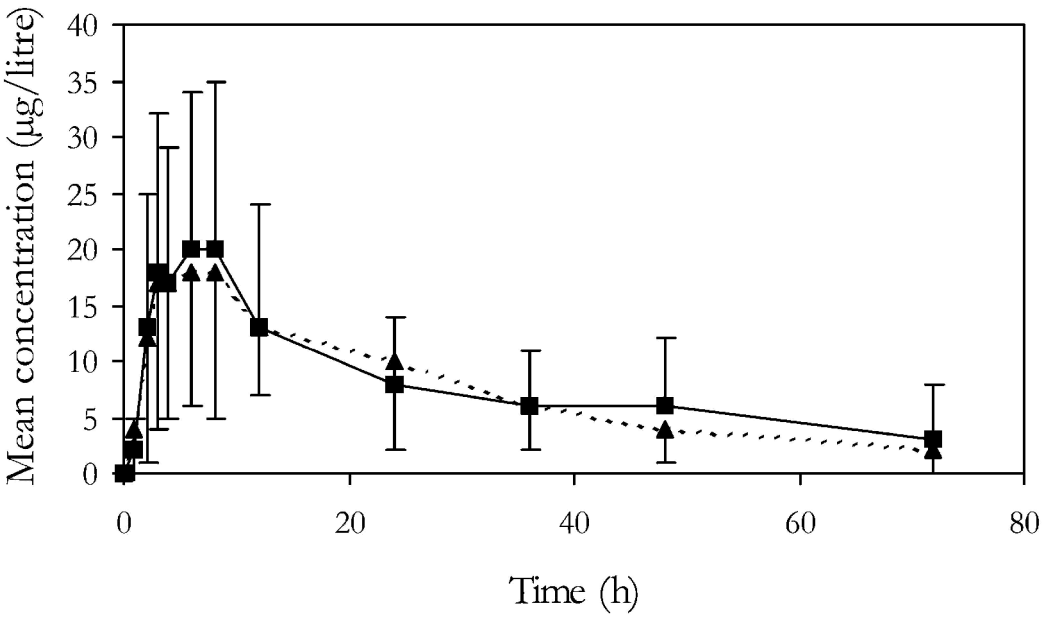

FIG. 2. Mean plasma concentrations of ivermectin following oral administration of 200 µg ivermectin/kg with either placebo (▲) or 400 mg albendazole (■). Vertical lines indicate S.D.

patients with moderately heavy infections at baseline achieved a 97%–100% reduction in their levels of microfiladermia yet had zero Mazzotti-reaction scores.

DISCUSSION

The successful control of human onchocerciasis by chemotherapy requires drugs that are suitable for use in endemic areas, given the characteristics of the populations at risk. The 'end-user' population is often poor, not readily accessible and plagued by several communicable diseases, and lacks basic medical infrastructure and storage facilities. Ideally, any drugs used should be safe to the point that little medical expertise is required in distribution, monitoring, or the treatment of adverse effects. They should either kill the adult worms or permanently inhibit their ability to produce or release mff, thus limiting the duration of treatment to the time required to effect adequate distribution. Simplicity of dosage (a single dose, or a small number of doses), efficacy in all endemic areas, especially in Africa, minimal cost, and stability under adverse environmental conditions are other important considerations. Ivermectin meets most but not all these requirements. Drug combinations are indicated when one drug is insufficient. Clinically useful combinations may result in an augmented therapeutic response. The main aim of the present study was to see whether an improved efficacy against *O. volvulus* could be achieved using a single-dose combination of ivermectin with albendazole, without jeopardising the central role of ivermectin in onchocerciasis control.

Direct assessment of efficacy against the adult worms was based on the interpretation of histology slides by two, blinded, independent observers. In a previous collaboration between the same observers (Awadzi *et al.*, 1997), only the data from one observer (Reader 2) were presented. In this study, both datasets are shown, mainly to illustrate the variability that occurs between observers and to determine if this leads to any important differences in the overall conclusions. Despite the fact that the two observers differed in the absolute numbers and proportions of some features

TABLE 5. *Ivermectin dosages (ID), AUC (areas under the curves of plasma concentration* v. *time), Mazzotti toxicity scores (MTS) and microfilaricidal activity, in terms of the reduction in the level of microfiladermia between that recorded pretreatment (PT) and that observed on day 30, in patients treated with ivermectin alone, albendazole alone or ivermectin plus albendazole*

	Ivermectin only					Albendazole only				Ivermectin + albendazole					
Patient no.*	AUC_{IVM} (ng.h/ml)	ID (μg/kg)	PT (mff/4 mg)	Reduction (%)	MTS	AUC_{ABS} (ng.h/ml)	PT (mff/4 mg)	Reduction (%)	MTS	AUC_{IVM} (ng.h/ml)	ID (μg/kg)	AUC_{ABS} (ng.h/ml)	PT (mff/4 mg)	Reduction (%)	MTS
1	1122	207	128.7	99.2	15	2846	233.3	27.9	20	1268	207	2530	62.7	99.4	40
2	1095	226	287.7	98.4	95.9	2054	177.2	36.9	45	1191	182	3158	161.2	100	86.8
3	848	183	90.6	96.8	0	2602	67.9	−15.9	105	1134	194	2790	94.6	100	20
4	636	194	83.1	99.2	101	4329	100.5	44.4	20	1098	231	3948	309.4	99.6	90
5	487	186	182	99.3	56.8	1773	122.3	36	10	599	203	1606	271.7	98.2	113
6	455	240	215.7	100	140	6900	167.3	−11.4	15	545	194	3309	647.6	99.9	78
7	435	200	234.5	100	100	2173	110.9	−12.3	0	225	182	3238	332.2	41.9	45
8	372	207	123.2	95.5	30	2155	115.6	19.7	70	223	226	2902	282.7	100	127
9	336	207	182.9	100	20	4166	118.9	11.6	15	196	211	4008	335.3	100	50
10	293	261	83.3	100	0	3498	314.7	22.6	30	180	200	5158	133.9	100	162
11	283	273	238.6	100	171	5038	110.4	−86.5	68.2	137	211	7604	73.5	98.6	55
12	274	207	104	100	0	5374	212.5	70.1	35	136	145	3230	409.3	99.9	65
13	213	222	182.1	99.6	20	3305	137.5	39	35	0	207	2166	172.4	75.6	29.5
14	0	200	115.7	38.7	5	3918	363.1	30	35	0	176	2776	111	98.4	25

*Data are presented for individual patients and rearranged in descending order of AUC for ivermectin, in the two ivermectin-treated groups. AUC_{IVM}, AUC for ivermectin; AUC_{ABS}, AUC for albendazole sulphoxide; mff, microfilariae.

of the adult worms, most of the conclusions as to the efficacy of the treatment regimens, based on the analysis of the data presented for the treated groups, were very similar, except for the suppression of embryogenesis (Table 2). In the comparison between ivermectin and the combination, Reader 1 found the two regimens to be equally efficacious whereas Reader 2 observed that the combination had a greater suppressive effect on embryogenesis and hence, potentially, on the production of mff. Since the mff hold the key to the pathology and to the transmission of onchocerciasis, for any effect on the adult worms to be of practical value, mff must be prevented from repopulating the skin after their initial elimination. A study of the microfilarial kinetics in skin snips collected after day 30 did not show any advantage of the combination over ivermectin alone. It therefore appears that any difference between ivermectin alone and the combination, in terms of their effect on the reproductive activity of the adult worms, was not clinically important. Additionally, the combination was no more effective than ivermectin alone in eliminating skin mff. The treatment regimens employed during a field trial in Ghanaian patients with *Wuchereria bancrofti* infections (Dunyo *et al.*, 2000*a*, *b*) were the same as those used in the present study. As in the present study, both ivermectin and the combination were found to be safe and efficacious but any differences observed between the two regimens were minor, and there was no clear evidence to show that the combination was superior (Dunyo *et al.*, 2000*a*, *b*).

The present results for albendazole are disappointing. The degeneration of all intrauterine stages — observed previously (Awadzi *et al.*, 1991) and apparently justifying the drug's combination with ivermectin — was not manifest. Embryogenesis in nodules taken from the patients treated with albendazole alone was carefully compared with that in control nodules (excised previously from untreated subjects from the same communities as the patients). Even in this comparison, neither Reader 1 nor Reader 2 saw anything to indicate that albendazole was superior to 'no treatment' in its effects on the reproductive activity of the adult worms. Other evidence (Awadzi *et al.*, 1991) does not support the apparent effect of albendazole on the vitality of the adult worms reported by Reader 1.

The adverse effects examined included the Mazzotti complex of reactions, other Mazzotti toxicity, other systemic adverse effects, ocular toxicity, and ECG and laboratory-test abnormalities. The addition of albendazole to ivermectin treatment had no effect on the frequency and severity of each type of adverse effect recorded, or on the perceived need for additional medication (such as acetaminophen for headache). Although the combination, but not ivermectin alone, produced a significantly higher total Mazzotti-reaction score than albendazole, the clinical significance of this difference was minor. Thus, the co-administration of ivermectin with albendazole did not alter the safety profile of ivermectin.

The large inter-individual variation seen in the plasma concentrations of the drugs in the present series of investigations has been reported before (Awadzi *et al.*, 1994). There is no evidence from this study to indicate that albendazole alters the systemic exposure to ivermectin or that ivermectin alters systemic exposure to albendazole, even though both drugs are metabolised by the same isoenzymes of cytochrome P450 (Zeng *et al.*, 1998; Rawden *et al.*, 2000). Ivermectin does not normally cross the blood–brain barrier because p-glycoprotein restricts it passage. Severe central-nervous-system side-effects following ivermectin treatment are likely only in the absence, or functional deficiency, of p-glycoprotein (Kwei *et al.*, 1999). As albendazole appears not to be a substrate for human p-glycoprotein (Merino *et al.*, 2002), it seems unlikely that there would be competition between albendazole and ivermectin for binding sites. The combination of ivermectin with albendazole does not require an alteration in the dosage of either component to compensate for such competition.

The present study allowed the relationships between a fixed dose of ivermectin, the extent of drug exposure (AUC), the number of mff killed and the clinical reaction to be explored. The lack of a relationship between drug exposure and microfilaricidal activity in ivermectin-treated individuals was very evident. One explanation could be that the lowest measurable AUC recorded was already in excess of that required for microfilarial elimination and hence higher values produced no additional effect. This study also demonstrates that ivermectin is able to eliminate moderate to heavy microfilarial loads with few, if any, adverse effects. In one subject in the combination group, treatment appeared to have little significant effect on his levels of microfiladermia. It seems unlikely that malabsorption of the ivermectin was to blame, as the trial was conducted under standard hospital conditions. A relatively unsusceptible population of *O. volvulus* mff in this previously ivermectin-naive patient needs to be considered.

In summary, the combination was safe and well tolerated, and is unlikely to jeopardise the role of ivermectin in onchocerciasis control or require an alteration in the dosage of either component. However, the co-administration of ivermectin with albendazole offered no advantage over ivermectin alone in terms of efficacy against *O. volvulus*. Hence, the additional benefit to onchocerciasis patients in the use of this regimen (e.g. in programmes for the elimination of lymphatic filariasis from onchocerciasis-endemic areas of Africa) is limited to the effect of albendazole on intestinal helminths.

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