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Adverse systemic reactions to treatment of onchocerciasis with ivermectin at normal and high doses given annually or three-monthly

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Summary In Cameroon, a 3-year randomized, double-blind controlled trial was conducted to determine if ivermectin, given at 3-monthly intervals and/or at high doses (800 μg/kg), had a greater effect on adult *Onchocerca volvulus* than standard annual doses of 150 μg/kg. Adverse reactions were recorded and analysed in a logistic regression model with random effects to assess the influence of the dose and rhythm of treatment on their occurrence. After the first dose, 3-monthly treatment was associated with a clearly reduced risk of reactions, especially oedematous swellings, pruritus and back-pain. Oedematous swellings and subjective ocular troubles were found to be associated with high doses of ivermectin. These results reinforce former parasitological conclusions that it would be desirable to evaluate the feasibility and effects on transmission of large-scale 3-monthly treatments with standard doses of ivermectin for onchocerciasis control. Owing to the unexpected ocular reactions, the use of high doses to counteract any future resistance of *O. volvulus* to ivermectin should be considered with caution.

1. Introduction

In 1993, the WHO estimated that 18 million people suffered from onchocerciasis, over 95% of them in sub-Saharan Africa and the rest in six Latin American countries and the Yemen (WHO, 1995). Control of onchocerciasis in Africa is currently based on mass administration of ivermectin (Mectizan®, Merck & Co., Inc., Whitehouse Station, NJ, USA) at an annual dose of 150 μg/kg to all eligible persons in communities where the disease is hyper or

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mesoendemic. In Latin America, the same dosage is given on a 6-monthly basis.

At 150 μg/kg annually, ivermectin does not kill the adult *Onchocerca volvulus* which, after 3—6 months of embryostasis, resume production of microfilariae (mf) (Duke et al., 1991). When repeated the treatments seem to cause an irreversible decline in mf production of 30% per treatment (Plaisier et al., 1995), but this would not prevent the intensity of transmission from increasing again some time after the distribution, thus preventing control of the parasite (Winnen et al., 2002).

We undertook a double-blind, randomized controlled trial in Cameroon, to evaluate if higher and/or more frequent doses of ivermectin would have a greater effect on the adult worms and mf of *O. volvulus* than standard doses. Of four groups of patients, the reference group received the standard dose of 150 μg/kg annually (Group 150 × 1); the other three received respectively: 150 μg/kg 3-monthly (Group 150 × 4); high doses (400 μg/kg then 800 μg/kg) annually (Group 800 × 1); and the same high doses 3-monthly (Group 800 × 4). We aimed to investigate if more frequent or higher doses would have greater impact on the adult worms and mf thus leading to a shortening of treatment campaigns.

The design and parasitological results of this trial have been published elsewhere (Gardon et al., 2002) with the conclusion that 3-monthly treatments, whether at 150 μg/kg or at high doses, increased the mortality of adult *O. volvulus* by some 30% and diminished considerably the fertility of the females; and that 3-monthly treatments reduced the concentrations of mf in the skin much more than did annual treatments. The present paper describes the adverse systemic reactions that were encountered during this trial.

2. Methods

2.1. Study area and design

The study took place in the Republic of Cameroon, in 20 villages in the Mbam River valley (a tributary of the Sanaga River), where onchocerciasis was hyperendemic (Macé et al., 1997). Initially it involved 657 men aged 18—60 years, each presenting at least two palpable, presumably *O. volvulus* nodules, but otherwise in good health.

In May 1994, a pre-treatment nodule was excised from each man followed by a suppressive dose of 150 μg/kg ivermectin to avoid the possibility of severe reactions developing after the first dose in those on the high-dose schedules. Each patient was then randomly allotted to one of the four treatment groups. The trial proper began in August 1994 and ended in August 1997, when a second nodule was removed from each patient to assess the effect of the each regimen on the adult worms. As no treatment was given in August 1997, the 3 year follow-up corresponded to three doses of ivermectin (and nine of placebo) for the groups treated annually, and 12 doses of ivermectin for the groups treated 3-monthly.

When the trial started, the highest dose permitted by Merck & Co., Inc. was 400 μg/kg. Six months later, when the results of Awadzi et al. (1995, 1999) became available, we were allowed to increase the high-dose regimens from 400 to 800 μg/kg. Thus our high-dose patients treated annually received one dose of 400 μg/kg and two doses of 800 μg/kg, and those on the 3-monthly regimen received two doses at 400 μg/kg and ten doses of 800 μg/kg. Including the clearing dose (150 μg/kg) given 3 months before the trial proper began, the patients treated annually at 150 μg/kg received a total of 600 μg/kg; and those on high dosage a total of 2150 μg/kg. In the groups treated 3-monthly, those on 150 μg/kg received a total of 1950 μg/kg, and those on high dosage 8950 μg/kg.

2.2. Treatment given and adverse reactions recorded

The trial was conducted double-blind, thanks to Merck & Co. which provided indistinguishable gelatin capsules, containing either ivermectin or placebo. At the outset, each patient was given a plastic name card, identifying him to the medical team for ivermectin treatment or consultation about reactions. Ivermectin was given in the morning under the strict control of one of the investigators. Each patient received his correct dose of ivermectin or placebo given in five gelatin capsules, pre-prepared by the pharmacist in a packet with the patient's name and photograph attached. Neither the patients nor those giving out the drug knew what dose any patient was receiving.

In the afternoon of each treatment day (D0) and on each of the following three days (D1—D3), a medical team moved from village to village, at appointed times, to be at the disposal of patients who presented adverse reactions. The patients were asked to come to well-defined places for free palliative treatment as necessary. Each was instructed to seek another consultation if his reaction to treatment had not settled within 24—48 hours. A member of each treated patient's family was

instructed to inform the team in the event of a domiciliary visit being necessary.

During the first six treatment rounds, full details of all reactions were 'narratively' recorded; but, from the treatment round in November 1995, experience allowed us to keep records on the basis of a list of 12 reactive symptoms and signs or groups thereof (see Tables 1—3). Fever was diagnosed by touch. For analysis, all the complaints recorded before November 1995 were recoded so as to be included in one or other of these 12 symptoms.

2.3. Statistical analysis

When a patient complained of more than one type of reaction at any given round, each reaction was included for analysis. This was so either when a patient showed $\geq$2 reactions on a given day, or when he came more than once (i.e. on different days), each time with a different sign or symptom. When the patient came more than once for the same sign, only one complaint was considered for analysis.

The first step in the analysis involved comparing the mean number of consultations as a whole, and the mean number of consultations for a given symptom, using the non-parametric test of Kruskal—Wallis. Then, a logistic regression analysis was performed, in which the risk of occurrence of each adverse reaction in the 'non-standard' treatment groups was compared with the risk in the reference group (150 $\times$ 1). In this analysis, we took into account the fact that the adverse reactions presented by any one patient at any one treatment round, or over the whole course of the trial, could not be considered as independent events. To take account of the excess variation introduced by this 'individual effect', we used a logistic regression model with random effects. Odds ratios (OR), with their 95% CIs, were calculated for each group and each reaction.

The next step in the analysis was to evaluate the way in which the risk of occurrence of a given symptom at a given round was dependent on the rhythm of treatment, and on the dose. In this analysis, the reference categories were the annual ivermectin treatment and the doses of placebo. As in the previous analysis, we used a logistic regression model with random effects. This analysis allowed us to evaluate, simultaneously and within a single model, the relationship between the dosage level and the interval between dosings, and to adjust the one in relation to the other.

Finally, to focus the analysis on the effect of high doses of ivermectin, we compared the impact of the dose given, after having discarded the treatment rounds in which the patients received placebo; thus no longer using the placebo as the reference, but instead using the standard 150 μg/kg dose.

3. Results

3.1. General information

Of the 657 patients allocated initially to one of the four treatment groups, only 643 actually participated in the first treatment in August 1994. Comparisons of the means of their ages, heights, weights, numbers of palpable nodules and *O. volvulus* microfilarial densities showed that the four groups did not differ significantly (Gardon et al., 2002). After 3 years, 572 patients completed the protocol and received the twelfth and last treatment in May 1997. Three months later, 541 of them submitted to further skin snips and the excision of a second palpable nodule. Over the whole trial, 7237 treatments were given, i.e. 2808 doses of placebo; 2226 of ivermectin at 150 μg/kg; and 2203 of high-level ivermectin (475 at 400 μg/kg and 1728 at 800 μg/kg).

3.2. Causes of exclusion from the cohorts and serious reactions

By August 1997, 24/643 patients, who took their first treatment in August 1994, had died in the interval (seven in Group 150 $\times$ 1; eight in Group 800 $\times$ 1; two in Group 150 $\times$ 4; and seven in Group 800 $\times$ 4). None of these deaths was related to treatment (see details in Gardon et al., 2002). Between August 1994 and August 1997, 78 other patients were excluded from the trial: 17 on medical grounds and 61 because they had moved away or missed one treatment round. The proportions of patients lost (overall or for each of the above three specific reasons) did not differ significantly between groups.

No patient developed a serious adverse reaction, none required hospitalization, and, no-one withdrew from the trial because of an adverse reaction.

3.3. Risk of mild adverse reactions in the trial as a whole

Mild adverse reactions began very soon after taking the gelatin capsules. Of 1129 consultations for adverse reactions, 367 (32.5%) took place in the afternoon following treatment the same morning (D0); and 449 (39.8%), 195 (17.3%) and 118 (10.5%) took place on the following three days (D1—D3). This distribution over time was similar in all four treatment groups ($P = 0.69$).

Table 1 Number of consultations for, and risk of occurrence of, various adverse reactions in each of the four treatment groups

Dosage group	150 × 1	800 × 1	150 × 4	800 × 4
Total no. of doses	1878	1965	1783	1750
Occurrence of at least one symptom	283	292 0.96 (0.64–1.44)	255 0.91 (0.59–1.40)	299 1.17 (0.74–1.85)
Total no. of symptoms	456	513	402	452
Sundry aches and pains	23	25 1.07 (0.52–2.18)	13 0.61 (0.27–1.37)	18 0.85 (0.4–1.83)
Joint pains	34	18 0.44* (0.21–0.94)	29 0.85 (0.42–1.70)	32 1.03 (0.52–2.04)
Back and waist pain	42	44 0.79 (0.39–1.60)	22 0.49 (0.23–1.06)	26 0.58 (0.27–1.23)
Headache	89	93 0.88 (0.48–1.62)	79 0.87 (0.48–1.57)	93 0.98 (0.54–1.80)
Sensation of fever	31	46 1.39 (0.72–2.69)	31 0.96 (0.48–1.91)	28 0.89 (0.44–1.79)
Pruritus	95	125 1.24 (0.79–1.95)	103 1.13 (0.70–1.81)	100 1.09 (0.68–1.73)
Oedematous swellings	31	50 1.55 (0.86–2.81)	15 0.49 (0.24–1.02)	25 0.87 (0.45–1.68)
Cutaneous eruptions	15	17 1.07 (0.44–2.60)	23 1.61 (0.69–3.76)	25 1.79 (0.77–4.14)
Subjective ocular troubles	18	31 1.62 (0.72–3.64)	18 1.04 (0.45–2.42)	50 3.30** (1.58–6.96)
Asthenia	33	24 0.71 (0.36–1.42)	34 1.16 (0.59–2.76)	26 0.84 (0.42–1.69)
Abdominal troubles	15	15 0.95 (0.41–2.18)	6 0.42 (0.15–1.20)	4 0.29* (0.09–0.95)
Giddiness	18	8 0.44 (0.16–1.17)	15 0.91 (0.39–2.17)	17 1.03 (0.43–2.46)
Others	12	17 1.34 (0.60–3.02)	14 1.24 (0.53–2.87)	8 0.71 (0.27–1.84)

The odds ratios (95% CI) were calculated using treatment with 150 μg/kg as the reference category.
* $P < 0.05$.
** $P = 0.0017$.

During the 3 years of treatment, the mean number of consultations per patient was the same in each of the four treatment groups: i.e. 1.8 (SE = 2.4) for 150 × 1; 1.8 (SE = 2.9) for 800 × 1; 1.7 (SE = 2.3) for 150 × 4; and 1.9 (SE = 3.0) for 800 × 4 ($P = 0.92$). Over the whole trial, the risk in the non-standard treatment groups of presenting at least one adverse symptom or sign after taking the treatment, was comparable to that observed in the reference group (Table 1), with ORs of 0.96, 0.91, and 1.17. The same applied to each of the individual symptoms, almost all of which appeared with similar frequencies in all four groups. Only arthralgia seemed slightly less frequent in the group 800 × 1 (OR = 0.44, 95% CI 0.21–0.94); whereas abdominal pains were less frequent (OR = 0.29, 95% CI 0.09–0.95), and subjective ocular troubles (transitory blurring of vision, itching or pain of the eye, and in several cases dyschromatopsia) more frequent (OR = 3.30, 95% CI 1.58–6.96) in the group 800 × 4 than in the reference group.

3.4. Changes in the risk of mild adverse reactions over time

Although the results presented above demonstrate only small differences between the four groups, taking the 3 year trial as a whole, things were very different when each treatment round is considered separately. The incidence of adverse reactions diminished steadily over the course of the trial. Overall, they affected 28.6% of patients after the first round of treatment, 20.0% during the course of the first year of treatment, 12.5% in the course of the second year and 8.0% during the third year.

Table 2 Symptoms recorded and the risk of their happening as a function of the ivermectin dosage regimen

	No. of events	Dosage interval		Dose			
		3-monthly[a]		150 μg/kg[b]		800 μg/kg[b]	
		OR (*P*)	95% CI	OR (*P*)	95% CI	OR (*P*)	95% CI
Any one symptom	1129	0.36 (<0.001)	0.25—0.52	4.27 (<0.001)	3.21—5.67	6.30 (<0.001)	4.69—8.46
Sundry pains	79	0.46 (0.021)	0.24—0.89	1.60 (0.19)	0.79—3.23	2.22 (0.018)	1.14—4.30
Joint pains	113	0.88 (0.70)	0.47—1.66	1.57 (0.18)	0.81—3.02	2.09 (0.028)	1.08—4.02
Back and waist pain	134	0.33 (<0.001)	0.18—0.61	2.36 (0.002)	1.36—4.10	2.53 (<0.001)	1.48—4.33
Headache	354	0.64 (0.066)	0.40—1.03	1.95 (0.001)	1.30—2.91	1.84 (0.003)	1.24—2.74
Fever	136	0.38 (<0.001)	0.22—0.66	2.85 (<0.001)	1.62—4.98	3.31 (<0.001)	1.95—5.61
Pruritus	423	0.34 (<0.001)	0.24—0.49	6.04 (<0.001)	4.20—8.68	6.55 (<0.001)	4.63—9.28
Oedematous swellings	121	0.11 (<0.001)	0.067—0.20	77.08 (<0.001)	23.0—257.9	131.4 (<0.001)	39.6—436.0
Cutaneous eruptions	80	0.58 (0.10)	0.31—1.12	6.42 (<0.001)	2.78—14.84	3.19 (<0.001)	3.19—16.55
Subjective ocular troubles	117	0.61 (0.11)	0.34—1.11	2.67 (0.008)	1.29—5.56	8.57 (<0.001)	4.46—16.47
Asthenia	117	0.69 (0.23)	0.38—1.26	2.54 (0.003)	1.39—4.66	1.85 (0.059)	0.98—3.52
Abdominal troubles	40	0.42 (0.093)	0.15—1.16	0.78 (0.63)	0.28—2.17	0.92 (0.86)	0.35—2.43
Giddiness	58	1.15 (0.75)	0.47—2.81	1.46 (0.41)	0.59—3.63	1.07 (0.89)	0.40—2.85
Others[c]	51	0.47 (0.042)	0.22—0.97	2.77 (0.015)	1.22—6.26	2.00 (0.10)	0.87—4.63

The odds ratios (OR) and their 95% confidence intervals (95% CI) were calculated using regression models with random effects.
[a] Reference category: annual interval.
[b] Reference category: dose of placebo.
[c] Insomnia, feeling cold, cramps, nausea, anorexia, paresthesiae, pains in the chest, etc.

This fall-off was observed in all the groups, but in those that received ivermectin annually, it was associated with a recrudescence only when the patients received ivermectin, i.e. at rounds 5 and 9. In both groups treated annually, the frequency of adverse reactions was higher after round 5 than after round 9. After round 5, the proportions of consultations in the groups 150 × 1 and 800 × 1 were 24.5 and 30.9%, respectively; in the groups 150 × 4 and 800 × 4, they were 17.8 and 22.6% (comparison between the four groups: $P = 0.060$). Likewise, after round 9, the proportions of consultations in the groups 150 × 1 and 800 × 1 were 18.0 and 21.5% respectively; in the groups 150 × 4 and 800 × 4, they were only 9.0 and 12.5% (comparison between the four groups: $P = 0.014$).

When the various symptoms are considered separately, this variability over time was particularly noticeable with regard to itching, which was also the most frequent secondary symptom encountered. Taking the study as a whole, the risk of itching developing after a round of treatment seemed to be almost the same in all groups including the reference group, with ORs of 1.24, 1.13, and 1.09 in the groups 800 × 1, 150 × 4 and 800 × 4, whereas in reality the frequency of itching varied greatly as a function of the dosage rhythm (Figure 1). In fact, in the groups treated annually there was a strong recrudescence of itching after rounds 5 and 9, which was the price to be paid for the much lower number of consultations requested after those rounds at which the placebo was administered.

3.5. Study of the respective effects of dosage and of the rhythm of ivermectin treatment on the occurrence of reactions

Analysis shows that taking ivermectin every 3 months was associated with a clearly reduced risk of adverse reactions (OR = 0.36, 95% CI 0.25—0.52), regardless of the dose (Table 2). When considering the various symptoms separately, the analysis shows that the reduction of risk associated with 3-monthly treatments was especially noticeable with regard to oedema (OR = 0.11, 95% CI 0.07—0.20), pruritus (OR = 0.34, 95% CI 0.24—0.49) and back- or waist-pain (OR = 0.33, 95% CI 0.18—0.61). In addition, the risk of joint pains, headache, rash, subjective ocular troubles, asthenia, intestinal troubles and giddiness seemed to be independent of the rhythm of ivermectin treatment.

When compared to treatment with placebo, ivermectin dosage was associated with a marked increase in adverse reactions, whether it was given at the standard dose of 150 μg/kg (OR = 4.3, 95% CI 3.2—5.7) or at high doses (OR = 6.3, 95% CI 4.7—8.5). The manifestations with the highest occurrence after ivermectin treatment were itching, rash, oedematous swellings and fever; and, amongst them, swellings appeared to be more frequently associated with high-dose treatment (OR = 131.4, 95% CI 39.6—436.0) than with standard doses (OR = 77.1, 95% CI 23.0—257.9). Besides these signs, which are classically reported in many studies, the analysis showed that ivermectin treatment was also associated with a risk of occurrence of subjective ocular problems (blurring of vision, changes in colour vision, etc.). In contrast, giddiness and abdominal problems seemed to be independent of the treatment regimen. Throughout the three years of the trial, 2808 doses of placebo were given and the adverse reactions most frequently observed after these treatments were headache (3.7%), pruritus (3.0%), back and waist pain (1.6%), sensation of fever (1.4%), asthenia (1.1%) and joint pain (1.1%).

If one eliminates the placebo dosings from the analysis, one can compare the impact of high

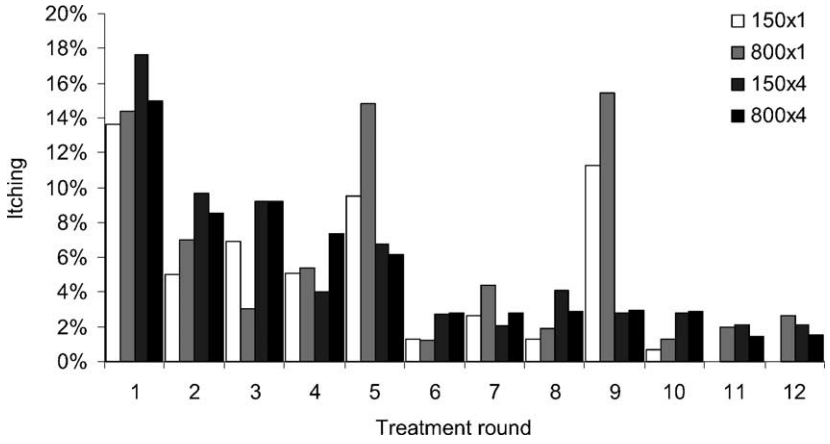

Figure 1 Development over time of the frequency of itching after treatment in the four treatment groups.

Table 3 Symptoms recorded and the risk of their happening as a function of the treatment regimens

	3-monthly treatment[a]		Dose 800 μg/kg[b]	
	OR (*P*)	95% CI	OR (*P*)	95% CI
Any one symptom	0.35 (<0.001)	0.25–0.50	1.24 (0.22)	0.88–1.75
Sundry pains	0.44 (0.012)	0.24–0.83	1.37 (0.32)	0.74–2.55
Joint pains	0.87 (0.65)	0.47–1.61	1.19 (0.56)	0.67–2.10
Back and waist pain	0.32 (<0.001)	0.19–0.56	1.12 (0.68)	0.65–1.94
Headache	0.63 (0.040)	0.41–0.98	1.03 (0.89)	0.67–1.58
Fever	0.38 (<0.001)	0.22–0.65	1.18 (0.53)	0.70–2.02
Pruritus	0.33 (<0.001)	0.24–0.47	1.14 (0.47)	0.81–1.60
Oedematous swellings	0.012 (<0.001)	0.067–0.19	1.76 (0.039)	1.03–2.96
Cutaneous eruptions	0.60 (0.15)	0.30–1.21	1.14 (0.70)	0.58–2.23
Subjective ocular troubles	0.58 (0.070)	0.32–1.05	3.22 (<0.001)	1.76–5.87
Asthenia	0.69 (0.18)	0.40–1.19	0.72 (0.22)	0.43–1.21
Abdominal troubles	0.40 (0.066)	0.15–1.06	1.11 (0.83)	0.43–2.89
Giddiness	1.13 (0.78)	0.47–2.73	0.72 (0.41)	0.33–1.57
Others[c]	0.47 (0.039)	0.23–0.96	0.74 (0.41)	0.37–1.51

The odds ratios (OR) and their 95% confidence intervals (95% CI) were calculated using regression models with random effects.
[a] Reference category: annual interval.
[b] Reference category: dose of ivermectin at 150 μg/kg.
[c] Insomnia, feeling cold, cramps, nausea, anorexia, paresthesiae, pains in the chest, etc.

versus normal dosings (Table 3). In these circumstances, 3-monthly dosage was still associated with a marked decrease in the risk of developing adverse reactions, when compared with annual treatments (OR = 0.35, 95% CI 0.25–0.50). Of the different adverse manifestations, only oedematous swellings (OR = 1.8, 95% CI 1.0–3.0) and subjective ocular problems (OR = 3.2, 95% CI 1.8–5.9) were more frequent after high doses than after the standard dose.

4. Discussion

The safety of ivermectin treatment has allowed it to be used by the African Programme for Onchocerciasis Control (APOC) in mass community-directed treatment with ivermectin (CDTI). The only areas where mass ivermectin treatments against onchocerciasis are associated with problems concerning the management of adverse reactions are those where onchocerciasis is co-endemic with loiasis. In communities where the prevalence of *Loa loa* microfilaraemia is >20%, and the proportion of persons at high risk of severe *Loa*-encephalopathic reactions is sufficiently high, specific measures to prevent and control such unfortunate eventualities are essential (Boussinesq et al., 2001; Gardon et al., 1997). In the present trial, we avoided recruiting persons from communities with such high prevalence of *Loa* microfilaraemia.

Our trial was designed to evaluate the potential macrofilaricidal activity of ivermectin against *O. volvulus*, and the safety of normal and higher doses of ivermectin given at shorter intervals than in the regimen currently used as part of APOC. The examinations of nodules and skin snips after 3 years of repeated treatments led to two main results. The first was that 3-monthly treatments increase the mortality of adult female worms and have an increased sterilizing effect on those females that remain alive. Because of these effects, as well as the direct microfilaricidal action of ivermectin, 3-monthly treatments maintain the concentrations of mf in the skin at much lower levels than annual treatments. The second, and perhaps surprising, result was that high doses (800 μg/kg) produce little marginal parasitological benefit as compared with standard doses of 150 μg/kg. These observations lead us to recommend the use of ivermectin at 150 μg/kg 3-monthly rather than once a year.

Our results regarding adverse reactions reinforce the former conclusions, mainly based on parasitological arguments. First, throughout the 3 year trial, no severe adverse reaction was recorded; nor did we observe any case of orthostatic hypotension such as those reported from West Africa by Awadzi et al. (1990). The adverse reactions recorded during our trial were always transitory and responded readily to symptomatic treatment with analgaesics or antihistamines over 24–72 h. Only occasionally were corticosteroids necessary. Second, analysis

of the respective roles of dosage level and rhythm of treatment have demonstrated that taking ivermectin every 3 months is associated with a clearly reduced risk of adverse reactions, and that this decrease is particularly marked for the frequent and inconvenient reactions of oedema, itching and backache. Lastly, although we have shown that the dosage level seems to have little or no impact on the majority of reactions, two worrying manifestations, namely oedematous swellings and subjective ocular troubles, were more frequent after high doses than after the standard dose of 150 μg/kg.

In onchocerciasis the adverse reactions of ivermectin are linked to the death of mf in the skin or in the network of lymphatic capillaries, vessels and nodes, and to the resulting inflammatory reactions. Many studies have shown that the severity of such reactions is proportional to the degree of microfilaridermia (e.g. De Sole et al., 1989; Prod'hon et al., 1991), and that, under treatment, they tend to diminish year by year along with the *O. volvulus* microfilarial skin load. In our trial, this was particularly obvious in those groups treated with ivermectin at 3-monthly intervals.

One may wonder why, in our trial, the risk of occurrence of some reactions was related to the dose received, whereas others were not. The pathophysiology of post-ivermectin reactions is not fully understood, but is clearly associated with various immune responses (Njoo et al., 1993, 1994), including, particularly, eosinophil sequestration and activation/degranulation (Cooper et al., 1999, 2000). Recent results have also suggested that the *Wolbachia* bacterial endosymbiont of *O. volvulus* plays a role in mediating the inflammatory responses after treatment (Brattig et al., 2001; Keiser et al., 2002). In the present study, most of the symptoms seemed to occur at similar frequency, whatever the dose of ivermectin given. As indicated by Awadzi et al. (1995), this is probably because 'the Mazzotti reaction is a response to the death of microfilariae; and as near complete elimination is achieved with the standard dose, additional reaction is unlikely at higher doses'. However, we observed that the oedematous swellings were more frequent after high doses; this may possibly have resulted from the action of ivermectin on worms (probably males or possibly third or fourth-stage larvae or immature females) moving about outside the nodules. The issue of the higher frequency of subjective ocular symptoms after high doses will be addressed elsewhere, together with the results of two series of detailed ophthalmological examinations; but at present we have no explanation for these phenomena.

We have shown that high doses may be the cause of unexpected oedematous swellings, and especially of subjective ocular side reactions. In future, these findings should be taken into account if increasing the dose of ivermectin, to counteract any tendency of *O. volvulus* to develop a resistance to this drug, is considered. It should also be kept in mind, with regard to current trials evaluating the effects and safety of moxidectin, a close structural relative of ivermectin, but one, which has a considerably longer persistence in plasma.

All these results are consistent with our former conclusions (Gardon et al., 2002) that 3-monthly treatments with standard doses of ivermectin would have a great beneficial effect on communities suffering from onchocerciasis, and that this regimen should be further tested in the field to evaluate its feasibility under CDTI and its effect in reducing transmission of *O. volvulus*.

Ethical clearance

Ethical agreement to the trial was received from the Cameroonian Ministry of Public Health and from Merck & Co., Inc.

Conflicts of interest statement

The authors have no conflicts of interest concerning the work reported in this paper.

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