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Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for *Loa loa* infection

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Summary

Background In 1995, the World Bank launched an African Programme for Onchocerciasis Control to eliminate *Onchocerca volvulus* disease from 19 African countries by means of community-based ivermectin treatment (CBIT). Several cases of encephalopathy have been reported after ivermectin in people heavily infected with microfilariae of *Loa loa* (loiasis). We assessed the incidence of serious events in an area where onchocerciasis and loiasis are both endemic.

Methods Ivermectin (at 150 µg/kg) was given to 17 877 people living in the Lékié area of Cameroon. 50 µL samples of capillary blood were taken during the daytime before treatment from all adults (aged ≥15 years), and the numbers of *L loa* and *Mansonella perstans* microfilariae in them were counted. Patients were monitored for 7 days after treatment. Adverse reactions were classified as mild, marked, or serious. Serious reactions were defined as those associated with a functional impairment that required at least a week of full-time assistance to undertake normal activities. We calculated the relative risk of developing marked or serious reactions for increasing *L loa* microfilarial loads. Risk factors for serious reactions were identified and assessed with a logistic regression model.

Findings 20 patients (0.11%) developed serious reactions without neurological signs but associated with a functional impairment lasting more than a week. Two other patients were in coma for 2-3 days, associated with *L loa* microfilariae in cerebrospinal fluid. Occurrence of serious reactions was related to the intensity of pretreatment *L loa* microfilaraemia. The relative risk of developing marked or serious reactions was significantly higher when the *L loa* load exceeded 8000 microfilariae/mL; for serious reactions, the risk is very high (odds ratio >1000) for loads above 50 000 microfilariae/mL.

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Interpretation Epidemiological surveys aimed at assessing the intensity of infection with *L loa* microfilariae should be done before ivermectin is distributed for onchocerciasis control in areas where loiasis is endemic. In communities at risk, monitoring procedures should be established and adhered to during CBIT so that people developing serious reactions may receive appropriate treatment.

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Introduction

Onchocerciasis is a major public-health and socio-economic problem in many rural areas of Africa. In the 19 endemic countries outside the area of the Onchocerciasis Control Programme in West Africa (OCP), some 94.5 million people are exposed to the risk of infection with *Onchocerca volvulus*, and more than 15 million are infected.¹ In parts of 12 of these countries, *Loa loa* infections are also endemic.

Ivermectin has proven to be a safe microfilaricide and microfilarial suppressant, suitable for the mass treatment and control of onchocerciasis;²⁻⁶ and the manufacturer, now provides the drug free of charge for the treatment and control of onchocerciasis in endemic countries. Mass ivermectin distribution programmes are now being implemented in most endemic countries. In December, 1995, the World Bank, in cooperation with WHO, the ministries of health of the participating countries, and several non-governmental development organisations, launched the African Programme for Onchocerciasis Control (APOC), which aims to develop self-sustaining, countrywide, community-based ivermectin treatment (CBIT) programmes in the 19 endemic African countries outside the OCP.⁷

APOC's strategy is to deliver ivermectin by community-based distributors supervised only by monitoring teams. In areas where loiasis is also endemic, some cases of encephalopathy have been recorded after treatment with ivermectin.⁸⁻¹⁰ These patients had very high *L loa* microfilaraemia and *L loa* microfilariae in cerebrospinal fluid (CSF), suggesting that ivermectin may occasionally provoke an *L loa* encephalopathy similar to that seen after treatment of loiasis with diethylcarbamazine.¹¹

The aims of this study were to evaluate the incidence of serious reactions after treatment with ivermectin in an





Figure 1: Distribution of *Loa loa* and situation of study area and study villages

+ = study towns and villages. Dark green area is that endemic for *Onchocerca volvulus* and *Loa loa*. ? = endemicity not known.

area of Cameroon where onchocerciasis and loiasis are both endemic, and to record the relation between serious reactions and the intensity of pretreatment *L. loa* microfilaraemia.

Patients and methods

The study protocol, which was approved by the Ministry of Public Health of Cameroon and by WHO, involved 1-week follow-up of a cohort of people treated with ivermectin. The study was conducted in 106 villages of the Lékié Division (Central Province, Cameroon; figure 1), where 40–95% of the residents were infected with *O. volvulus*, and 10–33% had *L. loa* microfilaraemia (MB, unpublished data). The area was also endemic for the minimally pathogenic *Mansonella perstans*. The age and sex distribution of the population was known from the 1987 Cameroon population census. The name, sex, age, and information on previous filaricidal treatment were recorded for all participants. Capillary blood smears (50 μ L) were taken between 1000 h and 1600 h from all individuals aged 15 years or older. Blood samples were not taken from children because previous epidemiological surveys in the study area have shown that they had low *L. loa* microfilaraemia. After giemsa staining, the slides were stored and examined for microfilariae after 1–2 weeks. Microfilarial loads for each filarial species were expressed per mL blood. No skin snips were taken. Ivermectin was given at a standard dose of 150 μ g/kg, after the usual exclusion criteria had been applied.⁶

During the distribution of ivermectin, patients were informed that any reactions would be recorded from the next day to day 7, and would be treated free of charge. Monitoring was performed

by physicians, with the assistance of selected residents who were asked to visit all the households, especially the remote ones, in order to record eventual serious reactions.

Reactions to treatment were classified according to the existence of functional impairment: no complaint, patients who did not report any reaction; mild reaction, patients who complained of reactions (headache, joint pains, itching, oedema) not accompanied by any functional impairment; marked reaction, patients who showed reactions similar to those developed by patients with mild reactions, but whose intensity was such that they were accompanied by functional impairment requiring, for several days, assistance in performing some everyday natural functions and household activities; serious non-neurological reactions, patients who showed a functional impairment that required for at least 1 week full-time assistance, these patients usually stayed in bed or in armchairs, and had difficulty in standing up or walking, but no neurological signs were found; and serious neurological reactions, patients who developed disorders of consciousness and objective neurological signs and admitted to hospital.

Incidence of serious reactions was calculated on the total number of treated patients, and CIs calculated according to the Poisson distribution.¹² We calculated the relative risk of marked or serious reactions for increasing *L. loa* microfilarial loads. The reference group included all patients who did not show *L. loa* microfilaraemia, and the *L. loa* load in the microfilaraemic patients was expressed as $mfl = \log(x)$, where (x) is the microfilarial count per mL. The CIs of the relative risks were calculated with Taylor series approximation. The reason why the patients with marked reactions were added in this step of the analysis is explained below (see Results). The third step of the

analysis aimed at identifying risk factors for developing serious reactions. In this analysis, the microfilarial load was expressed as $\text{mfL} = \log_e(x+1)$ to include those individuals who were amicrofilaraemic. A univariate analysis was first done to identify whether sex, age, and *M perstans* microfilarial load were significantly associated with the occurrence of serious reactions. A multivariate analysis, using the logistic regression model,¹³ was then done to evaluate the relation between the *L loa* microfilarial load and the occurrence of serious reactions, taking into account the above covariates.

In the univariate analysis, the χ^2 test and the Fisher's exact test were used for assessing the significance of differences in proportions. The comparison of means was done by analysis of variance, or the Kruskal-Wallis test when the variances had been found significantly different by the Bartlett's test. In the logistic regression model, the significance of the coefficients was tested with the likelihood ratio test and the Wald test. Analyses were done with Epi Info (version 5), and EGRET (version 0.26.6), software packages.

Results

17 877 people were treated; age and sex distributions were close to those of the total population, although there was a slight over-representation of children aged 10–14 years, and a slight under-representation of women aged 15–39 and of men aged 20–54. 6415 (35.9%) adults and 8261 children (46.2%) received their first filaricidal treatment; 2823 adults (15.8%) and 378 children (2.1%) had a history of previous filaricidal treatment (ie, either ivermectin or, for 154 of the adults, diethylcarbamazine). For technical reasons, 865 blood smears could not be examined and the number of patients included in the analysis of microfilarial loads was thus 5550.

Incidence of reactions

Of 17 877 patients treated, 4700 (26.3%; 2030 male and 2670 female) reported at least one reaction (table 1). 20 patients developed serious non-neurological reactions (incidence rate: 11.2/10 000; [95% CI 6.8–17.3]); 19 had never received any filaricidal treatment previously, and one was a woman, aged 70, who had been treated with diethylcarbamazine in 1990 and whose *L loa* and *M perstans* microfilarial loads before ivermectin treatment were 142 400 and 0 mf/mL, respectively. In all but one case, the reaction was recorded before day 5. The reaction of one man, aged 80, was recorded on day 7; according to his family, after having had a mild reaction, he developed functional impairment on day 5, developed acute

	No complaint	Mild reaction	Marked reaction	Serious non-neurological reaction
Number of people treated	13 177	4636	42	20
Adults (≥ 15 years)	5770	3415	31	20
Adults never treated	3872	2497	25	19
Median age (years)	13	30	33	37
M/F	0.93	0.75	1.47	3
Number of people examined	3378	2130	22	18
Prevalence of <i>L loa</i> mf (%)	27.4	32.7	72.7	100
Geometric mean <i>L loa</i> microfilaraemia (mf/mL)	7	12	848	83 448
Prevalence of <i>M perstans</i> mf (%)	18.7	21.1	59.1	66.7
Geometric mean <i>M perstans</i> microfilaraemia (mf/mL)	1	2	24	38

mf=microfilariae.

*Data on two patients who developed serious neurological reactions are given in the text. The median age and the sex ratio were calculated on the number of persons treated. The persons examined were those adults who received their first filaricidal treatment and from whom blood smears were prepared before treatment.

Table 1: Pretreatment characteristics*

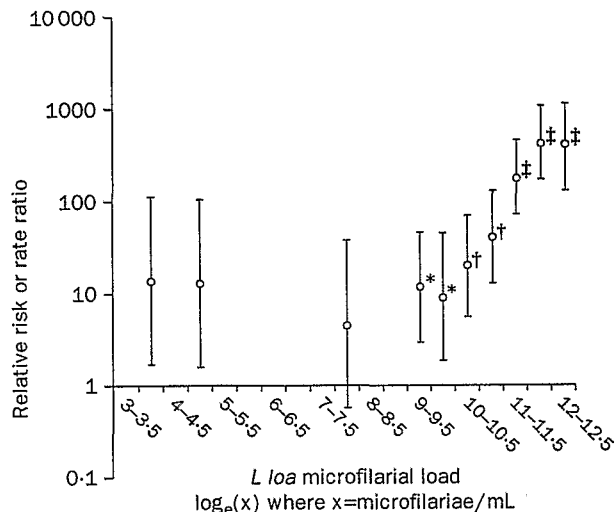


Figure 2: Relative risk of developing a marked or serious reaction for increasing *L loa* microfilarial loads

Reference group: patients without *L loa* mf. *L loa* microfilarial load = $\text{mfL} = \log_e(x)$, where x is the microfilarial count per mL. Bars indicate 95% CI. For difference from reference group: * = $p < 0.05$; † = $p < 0.001$; ‡ = $p < 10^{-6}$; other differences are not significant.

diarrhoea on day 7, was admitted to hospital on day 11, became hemiplegic, and died on day 22. Since the pretreatment *L loa* microfilaraemia of this patient was 86 900 mf/mL, ivermectin may have been responsible.

Two patients developed serious neurological reactions, one 18-year-old man and one 32-year-old man, whose pretreatment *L loa* microfilarial counts were 152 940 mf/mL and 50 520 mf/mL, and *M perstans* counts 100 mf/mL and 420 mf/mL. Both developed disorders of consciousness on days 3–4 and then became comatose for 2–3 days. Both were incontinent of urine, and had motor and sensory deficits and hypertonia. The first patient had no tendon reflexes and, when he became conscious, complained of paraesthesia. The second patient was agitated, and showed involuntary movements, a transient grasping reflex, and brisk tendon reflexes. In both cases *L loa* microfilariae were found on day 4 in the CSF and urine. The condition of both improved with symptomatic treatment and clinical examination was normal after 1 month. The incidence of serious neurological reactions was thus two of 17 877 (ie, 1.1 per 10 000 treated patients [upper limit of one-sided 95% CI 3.5 per 10 000]).

L loa microfilarial load and reactions

Among the 5550 patients included in the analysis of *L loa* microfilarial load, the relative risk of presenting with a reaction of any type when the patients showed *L loa* microfilaraemia was 1.20 (95% CI 1.12–1.28; $p < 0.001$). The relative risks of developing serious reactions for increasing *L loa* microfilaraemia could not be calculated because all patients who had such reactions were microfilaraemic for *L loa*. The relative risks of developing marked or serious reactions for increasing *L loa* microfilaraemia are shown in figure 2. The relative risk of developing marked or serious reactions was significantly higher as soon as *L loa* microfilarial load exceeded 8100 mf/mL.

Risk factors for serious reactions

Univariate analysis showed that age, and pretreatment *L loa* and *M perstans* microfilarial loads were significantly

Variables	Regression coefficient	SE	p	Odds ratio (95% CI)
Constant	-54.84	10.90	<0.001	
Age (30-44 years)	2.18	1.02	0.032	8.8 (1.2-64.7)
Age (45-59 years)	-1.29	1.51	0.392	0.27 (0.01-5.30)
Age (≥ 60 years)	1.89	1.22	0.120	6.64 (0.61-72.20)
<i>L loa</i> mfL†	4.74	0.97	<0.001	114.7 (17.2-764.0)
<i>M persans</i> mfL†	0.29	0.15	0.054	1.33 (0.99-1.78)

*The odds ratios for *L loa* and *M persans* mfL correspond to an increase of 1 on a logarithmic scale. †mfL=log_e(x+1), where x is the microfilarial count per mL.

Table 2: Logistic regression of factors associated with serious reactions to ivermectin

higher in those with more serious reactions (table 1). Four variables were included in the logistic regression model: *L loa* microfilarial load (as the presumed risk factor) and sex, age, and *M persans* microfilarial load (as covariates). Age was divided into four classes: 15-29 (reference), 30-44, 45-59, and over 60 years. The model (table 2) confirmed that the occurrence of serious reactions was closely related to the *L loa* microfilarial load (odds ratio 114.7). People aged 30-44 were found to develop serious reactions significantly more often than those in the reference class.

Discussion

Ivermectin has proven to be a safe drug for onchocerciasis control, and can be delivered by small monitoring teams in most endemic areas. In 1995, more than 7 million people exposed to *O volvulus* were treated. Treated populations are well aware that reactions may occur, but the drug's popularity is high. However, the fall-off in attendance we noticed during the present study after the occurrence of several serious reactions suggests that such events might modify the target populations' attitude toward the drug. In addition, the treated population soon came to believe (as did we) that there is a continuum between mild side-effects and the serious neurological reactions. This might affect the future development of distribution programmes.

In a recent unpublished document, the Mectizan Expert Committee defined a "probable case of *L loa* encephalopathy temporally related to ivermectin treatment" (PLERI) as having to satisfy four criteria: coma occurring in a person previously healthy and without other underlying cause for the coma; onset of central nervous system symptoms within 5 days of treatment, and illness progressing to coma without remission; pretreatment *L loa* microfilaraemia 10 000 mf/mL or more (or >1000 mf/mL if sample obtained within 2 months after treatment); and *L loa* microfilariae present in CSF. Before September, 1995, three cases of PLERI had been reported, all in Cameroon.⁸⁻¹⁰ During the present study, two other cases have been recorded and the incidence of serious neurological reactions has been estimated to be about 1.1 per 10 000 people. The upper limit of 95% CI (3.5 per 10 000) is consistent with the estimation calculated previously by combining epidemiological data and results of a clinical trial (5-10 per 10 000).¹⁰

In the present study, the incidence of serious reactions that required careful medical attention was about 0.12%. However, biases related to the study design should be taken into account when considering this estimate. First, previous filaricides taken by about 18% of the patients might have lowered their *L loa* microfilarial load, so that they were less likely to develop serious reactions. Second, although most of the patients who had serious non-

neurological reactions had high *L loa* microfilarial loads, their illness may have been related not to their *L loa* infection or to the effect of ivermectin but to the death of *O volvulus* or to other causes. Third, since it was impossible to examine all the patients after treatment, some patients with serious reactions may have been missed. Because age was found to be a risk factor for the development of serious reactions, the under-representation of adults in the treated population, as compared with the whole population, might have led to an under-estimation.

This study shows that the initial *L loa* microfilarial load was the main risk factor for the development of serious reactions, and that the risk increased with the intensity of microfilaraemia. The association between *L loa* load and the occurrence of marked or serious reactions was found significant above 8000 mf/mL. For higher values, the association was very close and stable. All patients who developed serious reactions were microfilaraemic for *L loa*. No case of a serious reaction has been previously reported during clinical trials of ivermectin against loiasis in Congo and Gabon,¹⁴⁻¹⁶ perhaps because these studies involved a relatively small number of patients, all of whom showed *L loa* microfilarial loads below 50 000 mf/mL. This may also explain why PLERIs have been recorded only in Cameroon, because the intensity of infection with *L loa* may well be lower in the neighbouring countries (Central African Republic, Congo, Gabon, Nigeria), than in the Central Province of Cameroon. However, in Zaire many cases of *L loa* encephalopathy had been recorded after treatment with diethylcarbamazine.¹⁷ The threshold value of *L loa* microfilaraemia, above which a pronounced risk exists for the development of serious neurological reactions appears to be similar for ivermectin and diethylcarbamazine. Fain has suggested¹⁷ that patients harbouring more than 50 000 *L loa* mf/mL are at risk of encephalopathy, but no precise incidence rate could be calculated.

Our assumption that the serious disorders recorded were induced by ivermectin, and did not arise spontaneously, is supported by several arguments: there was a strong temporal relation and a similar time interval (3-4 days) between the treatment and the appearance of the serious condition; ivermectin has been shown to provoke the passage of *L loa* microfilariae into the CSF of patients harbouring very high *L loa* microfilaraemia;⁹ and in agreement with Fain,¹⁷ we assume that most cases of *L loa* encephalopathy apparently unrelated to previous filaricidal treatment are not spontaneous. All cases of neurological disorders attributed to *L loa* before 1947, when diethylcarbamazine became available, were not encephalopathies but motor deficits,¹⁸⁻²⁰ or meningitis.²¹ Moreover, in the present study, the incidence rate of serious neurological reactions with a follow-up of 7 days was 2/17 877, corresponding to an incidence of 1 per 171 person-years. Of the 50 000 residents of the study villages, we would expect 292 cases of encephalopathy per year. No such endemic encephalopathy has ever been reported from the study area, and hence we believe that the possibility that the cases recorded during the present study occurred spontaneously is unlikely.

The risk of serious reactions associated with *L loa* infection, has considerable importance as part of the development of APOC in areas where infections with this parasite are of high prevalence and intensity. More extensive epidemiological research on the distribution of

loiasis, and the relation between prevalence and intensity of infection is needed. In areas where loiasis coexists with onchocerciasis, the ivermectin treatment should be carefully considered if the onchocerciasis found therein is not a serious public-health problem. In areas where blinding or severely disabling onchocerciasis coexists with loiasis, specific strategies, based on the identification of patients at risk, need to be developed. Specific health educational messages and monitoring strategies will also be needed. Every case of a serious reaction should be reported as recommended by the Mectizan Expert Committee.

Contributors

All the authors played a part in the design and execution of the study, and in data analysis. J Gardon, N Gardon-Wendel, J P Chippaux, and M Boussinesq wrote the paper.

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