Severe Adverse Reaction Risks during Mass Treatment with Ivermectin in Loiasis-endemic Areas

J-P. Chippaux, M. Boussinesq, J. Gardon, N. Gardon-Wendel and J-C. Ernould

The control of onchocerciasis remains a priority in sub-Saharan Africa. Jean-Philippe Chippaux, Michel Boussinesq, Jacques Gardon, Nathalie Gardon-Wendel and Jean-Christophe Ernould here outline studies concerning possible severe adverse reactions to ivermectin used to control onchocerciasis in areas where loiasis is also endemic, and discuss precautions that may be advisable during the implementation of such programmes.

Ivermectin treatment has drastically changed the approach of onchocerciasis control programmes in the past decade. First trials conducted in African savannah, where the severity of onchocerciasis is well established, showed the good tolerance of ivermectin and the feasibility of large-scale treatments against onchocerciasis in these areas[1]. The development of this strategy in Central Africa is in progress. The extension of these programmes in forest areas of Africa where onchocerciasis co-exists with loiasis brought into question the tolerance of ivermectin in patients infected with *Loa loa*. These studies are particularly important because severe adverse reactions following treatment with diethylcarbamazine (DEC) are observed in patients infected with *Loa loa*. First trials conducted in areas endemic for loiasis showed that ivermectin is well tolerated[2], even in patients with high level of *Loa loa* microfilariae (Mf) in their blood[3]. Following these results, large-scale treatment against onchocerciasis was implemented in areas endemic for loiasis. At the same time, trials for large-scale treatment against loiasis were done[4]. As these programmes progressed, several suspect cases were observed that led us to resume trials of ivermectin in loiasis patients with very high parasitaemia.

Assessing the situation

In South Cameroon, several patients presented severe problems days to weeks following ivermectin treatment. For eight of these patients, we failed to find any cause to explain their problems; these cases are documented in Table 1. One of these patients died 23 days after the dosing. It was impossible to attribute this death to ivermectin[5]. An accurate frequency for these severe problems, however, is difficult to obtain; the total number of people receiving ivermectin treatment is difficult to evaluate in areas endemic for loiasis because, in these areas, many teams are involved in ivermectin distribution. We assume that the number of subjects treated with ivermectin in South Cameroon exceeds 100 000. In addition, the procedure for surveillance of programmes varies from one programme to another, and so it is probable that not all cases of severe side effects have been reported.

The *Loa loa* microfilaraemia before treatment was known in four of the eight patients who presented severe neurological complaints (Table 1). Parasitaemia of these patients was particularly high. This led us to study the tolerance for ivermectin in patients with very high *Loa loa* microfilaraemia. Some 112 volunteers, whose parasitaemia before treatment was higher than 3000 Mf ml^{-1}, received ivermectin in Hôpital Central, Yaoundé[6]. The purpose of this study was twofold: (1) to determine the threshold of microfilaraemia above which adverse reaction risks could appear; and (2) to establish which indicators permit identification of people at risk. Clinical and biological examinations of patients were made daily. We observed clinical and biological inflammatory signs (fever, headache, myalgia, arthralgia, increase of C-reactive protein), renal impairment (proteinuria, haematuria) and neurological disorders (asthenia, reduction of the activity, stupor). The presence of *Loa loa* Mf was observed in cerebro-spinal fluid (CSF) of several patients after treatment. One of them presented a stage 2 coma, ie. he reacted to aching stimulation but was unable to reply to questions. He recovered three weeks later after a simple symptomatic treatment (analgesic, anti-inflammatory, anti-allergic and diuretic). The severity of the symptoms was closely related to the level of the parasitaemia before treatment. The fever seemed to be the first objective sign revealing the presence of severe adverse reactions. It appeared the day following treatment, and lasted two or three days. The passage of the Mf in the CSF was progressive from the first day, increasing until Days 4–6, and then decreasing slowly. In ten patients who underwent lumbar puncture (LP) before and after treatment, we confirmed that the passage of the Mf in CSF was linked to the treatment, whereas the density of Mf in CSF was proportional to the initial parasitaemia. The incidence of adverse reaction in patients with parasitaemia higher than 15 000 Mf ml^{-1} before treatment was significantly higher than for other patients. When parasitaemia before treatment was higher than 30 000 Mf ml^{-1}, severity of adverse reactions was obvious in most of the patients. The only patient showing a Karnofsky's index (a clinical score assessing the mobility and autonomy of patients presenting neurological disorders) below 70% presented more than 150 000 Mf ml^{-1} before treatment. This value of the Karnofsky's index indicates a loss of autonomy, necessitating hospitalization; for several days the patient needed assistance to feed and drink.

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Table 1. Severe adverse reactions following treatment with ivermectin

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Village	Ntui	Ntui	Pouma[a]	Elig Mfomo	Nkolassi	Mbakamo	Ngat[b]	Ngat[b]
Age /sex	20/M	40/F	37/M	69/M	44/M	42/M	27/M	59/F
Parasitaemia (Mf ml^{-1})	139 000	102 000	?	'Many' at Day 17 after treatment	'Few' at Day 7 after treatment	?	199 000	217 000
Associated parasites	*O. volvulus* (250 per skin-snip) *M. perstans* (1800 Mf ml^{-1})	*O. volvulus* (140 per skin-snip) *M. perstans* (650 Mf ml^{-1})	*O. volvulus* (?)	?	?	?	None	*O. volvulus* (7 per skin-snip)
Ivermectin[c] dose ($\mu g\ kg^{-1}$)	200	200	150	150	150	150	200	200
First symptoms (Day 1)	Asthenia?	Headache asthenia?	?	?	Asthenia anorexia	Asthenia	Headache asthenia	Headache asthenia
Time to report (h)	24	24	72	?	24	24	48	48
Fever (>38°C)	Yes	Yes	Yes	No at Day 17	Yes	Yes	Yes	No
Main symptom reported	Stupor (Day 1)	Stupor (Day 2)	Stupor (Day 4)	Stupor (Day 6)	?	?	Coma (Day 3)	Stupor (Day 4)
Main symptom observed	Lethargy	Lethargy		Stupor (Day 17)	Stupor			
% disability (Day 3/Day 8)	50	50	>80	?	?	?	70	50
Mf in CSF[d]	?	?	>100 Mf ml^{-1} (Day 4)	?	?	'Few' at Day 4	<1 Mf ml^{-1} (Day 4)	?
Evolution	Recovery (Day 21)	Recovery (Day 15)	Death (Day 23)	Recovery (Day 25)	Left hospital (Day 20)	Left hospital (Day 10)	Recovery (Day 21)	Recovery (Day 15)

[a] Ref. 5.
[b] Ref. 7.
[c] Day 0, day treatment (ivermectin dose) given.
[d] CSF, cerebrospinal fluid.

Collating available data

The frequency of severe adverse reactions occurring during large-scale treatment with ivermectin in areas endemic for loiasis can be estimated by combining observations collected during the clinical study[6] (reported above) and epidemiological data on the prevalence of people with high *Loa loa* parasitaemia. Surveys were performed in 46 selected villages according to a cline between savannah and forest zones in Cameroon (M. Boussinesq, unpublished). Blood samples (thick smears of 30 ml) were taken between 10.00 am and 3.00 pm. Prevalence of young people (under 15 years) with parasitaemia higher than 30 000 Mf ml^{-1} was negligible. The prevalence of adults presenting more than 30 000 Mf ml^{-1} ranged between 0.5% at the border of savannah to 4% in dense forest zone. The population at risk, therefore, essentially comprised adults, and represented about 50% of the general population.

The evaluation of the prevalence of severe neurological adverse reactions obtained from data collected during large-scale treatments corroborates the findings of the hospital trial. Population at risk can be estimated at about 200 subjects out of 10 000 people living in areas endemic for loiasis, and severe adverse reactions could occur in 5–10 of these people.

Recommendations

Therefore, severe adverse reaction risks should be considered during large-scale treatments with ivermectin in areas endemic for loiasis, and our observations indicate that precautions are advisable during the implementation of such programmes. On the one hand, it is necessary to define more accurately the criteria of choice for people who need ivermectin treatment. On the other hand, we think that it is desirable to modify implementation of large-scale treatment with ivermectin. We recommend the following measures:

(1) Information of treated population will have to specify risks of adverse reactions, clinical predictive signs of such reactions (fever, headache, myalgia, arthralgia) and to incite patients or their carers to report such symptoms immediately to surveillance teams in order to receive treatment (analgesic, anti-inflammatory, anti-allergic and diuretic) and advice concerning their food and beverage regimens.

(2) Post-treatment surveillance will have to be improved and, besides the recommended surveillance in

the 36 h following the treatment, a further visit in the treated community will be required on Day 3–4 to check patients presenting severe adverse reactions (fever, reduction of activity, stupor, coma) and to transport them to a place where dispensary or hospital therapeutic management will be ensured.

(3) A system of pharmacovigilance should be organized in areas endemic for loiasis to document these adverse reactions.

Because this is an important problem, it seemed useful to be aware of possible severe adverse reactions after treatment with ivermectin in Central Africa, and to take all possible precautionary measures during large-scale treatment programmes, instituting more efficient supervision.

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References

1 Prod'Hon, J. *et al.* (1991) **Lutte contre l'onchocercose par ivermectine: résultat d'une campagne de masse au nord-Cameroun.** *Bull. OMS* 69, 443–450

2 Richard-Lenoble, D. *et al.* (1988) **Ivermectin in loiasis associated with or without concomitant *O. volvulus* and *M. perstans* infections.** *Am. J. Trop. Med. Hyg.* 39, 480–483

3 Carme, B. *et al.* (1991) **Essai thérapeutique de l'ivermectine au cours de la loase à moyenne et forte microfilarémie.** *Ann. Soc. Belge Méd. Trop.* 71, 47–50

4 Chippaux, J-P. *et al.* (1992) **Ivermectin treatment of loiasis.** *Trans. R. Soc Trop. Med. Hyg.* 86, 289

5 WHO (1991) **Encephalitis following treatment of loiasis.** *WHO Drug Information* 5, 113–114

6 Ducorps, M. *et al.* (1995) **Effets secondaires du traitement de la loase hypermicrofilarémique par l'ivermectine.** *Bull. Soc. Pathol. Exot.* 88, 105–112

7 Chippaux, J-P. *et al.* (1993) **Adverse reactions following ivermectin treatment in hyperendemic loiasis area.** *Am. J. Trop. Med. Hyg.* 49, 161

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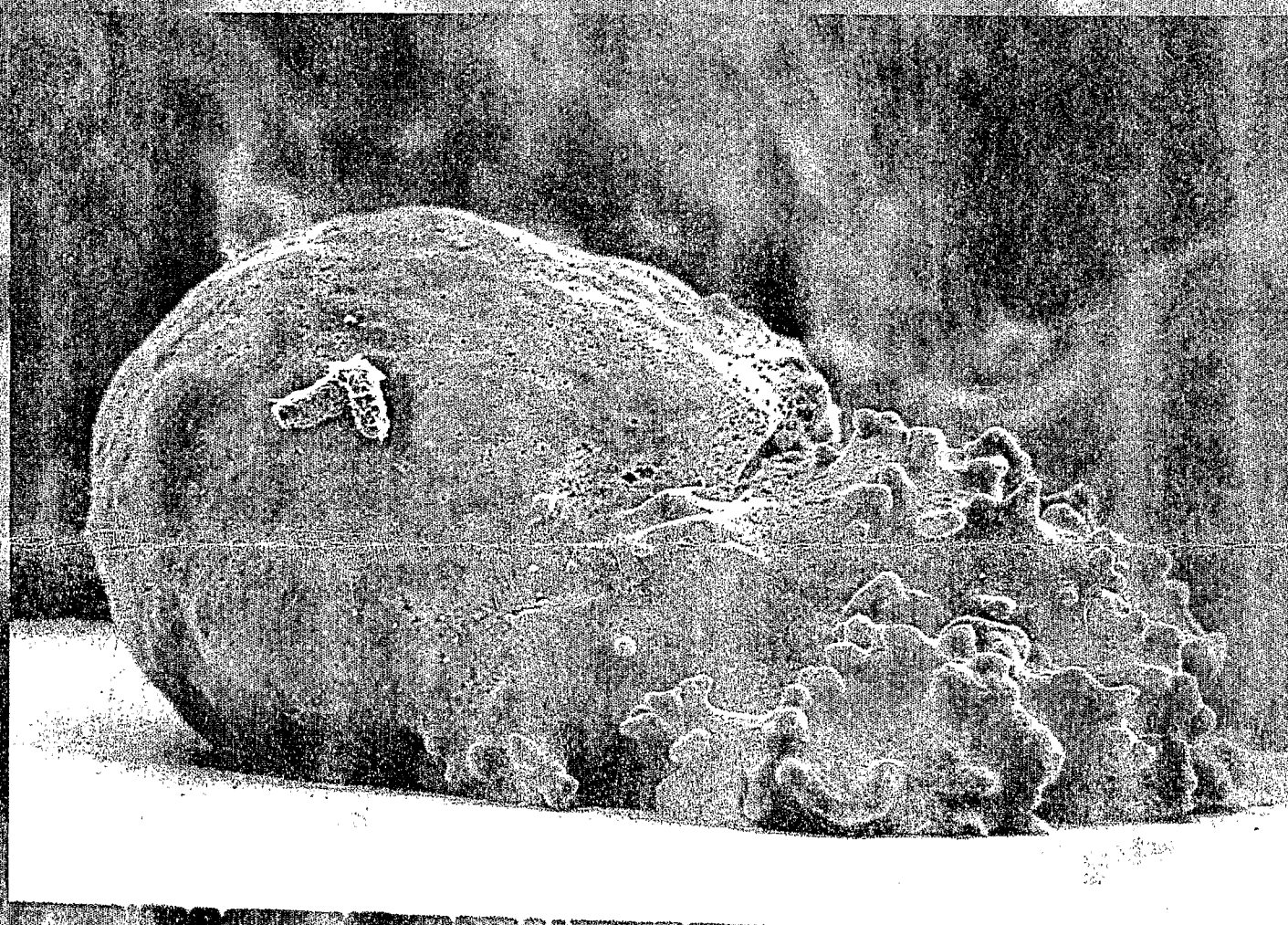

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