Impact of repeated large scale ivermectin treatments on the transmission of Loa loa

J.-P. Chippaux, B. Bouchité, M. Bousinesq, S. Ranque, T. Balivet and M. Demanou

Abstract

We have studied the impact of large-scale treatment with ivermectin on the transmission of loiasis in a forest village in south Cameroon where loiasis was highly endemic, with a prevalence of 30%. After one year of parasitological and entomological surveillance without treatment, all consenting residents aged >5 years received ivermectin 200 µg/kg every 3 months. For ethical reasons, treatment was interrupted after 2 years, but parasitological and entomological surveillance continued for 18 months after the end of treatment. The prevalence of loiasis was reduced to <10% and the mean microfilaraemia decreased by 90% in 2 years. The prevalence and average intensity of infection remained stable during the 18 months after treatment ended. Two vector species were identified, Chrysops discida (representing about 90% of the fly population) and C. silacea. The infection rate (all stages) in Chrysops decreased by 75% and the infective rate (percentage of Chrysops harbouring third-stage larvae of Loa loa in the head) decreased by 85% in C. discida and became zero in C. silacea. After the end of treatment, the infection and infective rates increased gradually. Large-scale treatment seemed an efficient method for the control of L. loa transmission provided high drug coverage was achieved. Nevertheless, because of the high risk of adverse effects when using the current microfilaricidal drugs, such a strategy remains unacceptable.

Keywords: loiasis, Loa loa, Chrysops discida, Chrysops silacea, chemotherapy, ivermectin, Cameroon

Introduction

Loiasis is limited to the Central African rain forest from Nigeria to the former Zaire (Pender, 1988). Amongst the methods available for its control, larviciding breeding sites of the vector (Chrysops) or trapping adult insects are ineffective or impracticable on a large scale (Williams & Crewe, 1963; Noireau, 1990). The only means of controlling transmission of loiasis is to eliminate the human microfilarial reservoir through large-scale treatment with filaricidal drugs. To our knowledge, the only attempt to use such a strategy was made by Duke & Moore (1961) in a rubber estate at Sapele, Nigeria. The attempt was regarded as unsuccessful by the authors.

Because of this disappointing result, together with the difficulty of organizing large-scale treatment with diethylcarbamazine (DEC) over several days and the increasing evidence that this drug may induce encephalopathy in patients with very high Loa loa microfilaraemia (PA'N, 1981), no further attempt was made to control the transmission of loiasis with DEC. However, as emphasized by Duke & Moore (1961), the general strategy was theoretically promising and justified by the fact that the human population is probably the only reservoir of Loa, that the Chrysops population density is low, even in highly endemic areas (generally <1000/km²), and that the flight range of the vectors is short (generally <5 km) (Crewe & O'Rourke, 1951; Breslley & Crewe, 1963; Noireau et al., 1990; Chippaux et al., in press).

Over about 10 years, several studies have demonstrated that ivermectin may bring about a marked decrease in Loa microfilaraemia (Richard-Lenoir et al., 1988; Carme et al., 1991; Chippaux et al., 1992; Martin-Prével et al., 1993; Gardon et al., 1997). This, together with the fact that ivermectin, in contrast with DEC, is efficient as a single oral dose and can thus be much more easily used, and was considered at the outset of the study to be a safe treatment for loiasis, prompted us to re-investigate the principle of Duke & Moore (1961) and determine whether large-scale treatment with this drug would have an impact on the transmission of loiasis. The present paper reports the results of this investigation.

Patients and Methods

Study area and parasitological surveys

The study was conducted in Ngat (3°23'N, 11°34'E), a village in the Central Province of Cameroon, 70 km south of the capital Yaoundé, in an area of degraded forest. The area has been described in detail previously (Mommers et al., 1994; Garcia et al., 1995; Chippaux et al., in press). Briefly, Ngat lies at an altitude of 600-700 m; the climate is equatorial, with 2 rainy and 2 dry seasons; the mean annual rainfall is 1600 mm and the mean annual temperature is 28-1°C. The initial census revealed a total population of 788, of whom about 600 lived permanently in the village in small dwellings on both sides of an earth road 10 km long. The major occupations were subsistence agricultural farming and cultivation of cocoa. The fields, which extend 500-2000 m from the road, can be reached by a system of forest trails perpendicular to the main road. Muddy places fringing the numerous streams and swamps overgrown with rafia constitute very suitable breeding sites for Chrysops.

The level of endemicity of loiasis in the village was assessed before the first ivermectin distribution. Capillary blood smears (30 µL) were taken between 10:00 and 15:00 from 667 volunteers aged 6 months or more, stained with Giemsa's stain, and examined under a microscope (Mommers et al., 1994; Garcia et al., 1995). Ngat was highly endemic for loiasis; in the total population, the prevalence of Loa microfilaraemia was 30-1%, and the Williams geometric mean Loa microfilarial load was 81.4 microfilariae per 30 µL of blood.

Ivermectin efficacy was assessed by parasitological surveys one week after the first distribution (April 1993) and just before both the second (July 1993) and third (October 1993) treatment rounds. The next 2 surveys (in July and October 1993) were carried out on microfilaraemic persons only. Further parasitological surveys were spaced to avoid withdrawal from treatment; they were performed in April 1994, April 1993, and finally in April 1996, and involved the whole population.

Entomological studies were also conducted to determine the dispersal of Chrysops in the study area, and to evaluate the annual fluctuation in the density of the fly population and in the Loa infection rates.

Treatment schedule

At the outset of the study, the long-term effect of ivermectin on Loa microfilaraemia was not documented,
and it was assumed, wrongly (GARDON et al., 1997), that the level of parasitemia would have increased considerably 6 and 12 months after a single dose. As our objective was to obtain the optimum effect of treatment on transmission, we decided to treat the population at intervals of 3 months over 2 years, from April 1993 to April 1995. It was also planned to limit the first treatment to individuals who had undergone a parasitological examination previously; from the second treatment round, however, ivermectin would be distributed to all the volunteers attending for the treatment, whether they had undergone an initial parasitological examination or not. This strategy was modified because serious reactions, including disorders of consciousness, were recorded after the first dose in 2 patients who had very high Loa microfilaraemia (1990000/mL and 2170000/mL, respectively) (CHIPPAX et al., 1995). Assuming that the risk of developing such reactions was related to the intensity of infection, and because a single dose of ivermectin brings about a marked decrease in microfilaraemia, even in patients with very high initial values, we decided to limit the subsequent distribution to those individuals who had received a first treatment. New residents, who had settled in the treatment area between April 1993 and July 1994, were thus excluded from the treatment, because some of them were assumed to harbour high infections and to be at risk of serious reactions. However, after having noticed that these new residents constituted an increasing proportion of the population, and thus a significant microfilarial reservoir, we decided, in November 1994 and April 1995, to examine parasitologically those new residents who expressed their wish to receive ivermectin, and to treat them if their microfilaraemia was <10000/mL.

At each treatment round, the drug was administered at a dose of 200 μg/kg of body weight, taking into account the usual exclusion criteria in children <3 years of age, weight <15 kg, pregnancy, first month of lactation, and severe illness. The dose of 200 μg/kg was chosen because RICHARD-LENÖBBLE et al. (1988) demonstrated that it was much more effective on Loa microfilaraemia than a dose of 150 μg/kg (the latter being presently the standard dose for the treatment of onchocerciasis). The rounds lasted one week: on each of the first 3 d, the distribution team was installed at a different place, in the house of the village chief or in that of a quarter chief; these 3 distribution points had been selected so that the insecticide to limit the entomological study to the periods of transmission, and thus a significant microfilarial reservoir, we decided, in November 1994 and April 1995, to examine parasitologically those new residents who expressed their wish to receive ivermectin, and to treat them if their microfilaraemia was <10000/mL.

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1996 (and, unusually, in April–May 1993). This suggests that the population density for this species is higher at the beginning of the short rainy season than at the end of the main rainy season. In contrast, the population density of C. silacea tended to be higher in October–November (biting rates between 4.7 and 9.0 bites per person–day) than in April–May (biting rates between 1.2 and 7.9 bites per person–day).

When both species were considered together, the maximum densities and infection rates, and thus the maximum intensity of transmission, were recorded in April–May and October–November (CHIPPAAUX et al., in press). During the whole study, C. silacea represented only 4–8% of the human-biting Chrysops population in April–May and 16–26% in October–November.

Infection and infective rates of Chrysops

The total numbers of C. dimidiata and C. silacea dissected were 26947 and 3294, respectively (Table 2). For both species, the parous rates did not differ markedly from one catching round to another: they generally ranged from 24% to 28% for C. dimidiata and from 23% to 30% for C. silacea.

At the same time, the infection rate of C. silacea had decreased, with a P value (0.053) close to the limit of significance; in addition, none of the infected flies of this species was infective. The infection rates recorded in April–May 1994 and April–May 1995 were not significantly different for each of the 2 species. However, the infective rate of C. dimidiata continued to decrease significantly (P<0.05).

The last ivermectin treatment was given in April–May 1995; at this time, the infection and infective rates for both species of Chrysops were at a minimum. They then tended to increase gradually until November 1996. The increases in the infection and infective rates of C. dimidiata, and in the infection rate of C. silacea, were not significant between April–May and October–November 1995, but they were significant between April–May 1995 and April–May 1996 (P<0.05). In November 1996, i.e., 18 months after the last ivermectin distribution, the infection rates of both species were still lower than their respective initial values: they were about 70% of the rates recorded just before the first treatment in April 1993. The infective rates were 50–54% of the initial values.

### Table 2. Infection rate of Loa loa in Chrysops, Ngat (Cameroon)

<table>
<thead>
<tr>
<th>Dates</th>
<th>Dissected</th>
<th>Total no. of L3 larvae</th>
<th>No. of Insects</th>
<th>Total no. of L3 larvae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nov. 92</td>
<td>47</td>
<td>5 (10.8)</td>
<td>1 (20)</td>
<td>37 (7.4)</td>
</tr>
<tr>
<td>Apr. 93</td>
<td>87</td>
<td>9 (10.9)</td>
<td>3 (33)</td>
<td>97 (10.8)</td>
</tr>
<tr>
<td>Nov. 93</td>
<td>103</td>
<td>9 (9.7)</td>
<td>4 (40)</td>
<td>596 (59.6)</td>
</tr>
<tr>
<td>Apr. 94</td>
<td>75</td>
<td>1 (2.7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nov. 94</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Apr. 95</td>
<td>364</td>
<td>9 (2.5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nov. 95</td>
<td>932</td>
<td>3 (4.1)</td>
<td>17 (45)</td>
<td>792 (20.8)</td>
</tr>
<tr>
<td>Apr. 96</td>
<td>1039</td>
<td>13 (4.9)</td>
<td>13 (25)</td>
<td>724 (14.2)</td>
</tr>
<tr>
<td>Nov. 96</td>
<td>647</td>
<td>7 (2.1)</td>
<td>12 (25)</td>
<td>560 (11.9)</td>
</tr>
</tbody>
</table>

**Note:** Numbers in parentheses show the number infected as a percentage of those dissected. Numbers in parentheses show the number with third-stage (L3) larvae as a percentage of those infected with any stage. Numbers in parentheses are the mean number of third-stage (L3) larvae per infected fly.

### Discussion

DEC, albendazole and ivermectin are filaricidal drugs which bring about a marked decrease in Loa microfilaraemia, but have little direct effect on the adult stage of the parasite, which is assumed to be the cause of most of the signs of the disease. The current individual treatment of loiasis is thus not satisfactory. It is possible that large scale treatment with a microfilaricidal drug may reduce the microfilaricidal reservoir, and therefore the intensity of transmission of Loa, the population of adult worms, and the prevalence or severity of symptoms related to the latter. The only evaluation of the possibility of reducing the transmission of Loa...
through large scale treatment has been carried out by DUKE & MOORE (1961) in an area of Nigeria where the main vector was C. silacea. The objective was to treat, with a 20 d course of DEC, all individuals, among a total population of 5120 persons at risk, who harboured Loa microfilariae. However, about 35% of the population did not attend for the pre-treatment blood examination. The authors assumed that the proportion of microfilariaemic persons, and their microfilarial loads, would be similar in the subjects who attended for examination and those who did not. They thus estimated that 35% of the microfilaria carriers had not been treated, and that the treatment brought about a reduction of the infection potential of the whole population at risk to only 30% of the pre-treatment level. After treatment, the infection rate of C. silacea was reduced to 50% of the pre-treatment values in contrast, no reduction was observed in the infection rate of C. dimidiat. The authors concluded that these fairly disappointing results were mainly related to the unsatisfactory drug coverage.

The general principles of the present study were similar to those of DUKE & MOORE (1961). However, besides the fact that the drug distribution was repeated every 3 months, we made 2 other alterations. First, we decided to treat the total population of the study area, and not only those subjects who carried Loa microfilariae, because we were certain that to exclude from treatment some microfilaria carriers who had not been detected at the outset of the study because their microfilaraemia was very low. This strategy was also ethically justified because Ascaris infection was common in the area; ivermectin is very effective against this parasite, it was thought that even persons who were not microfilaraemic would take advantage of the treatment. The second alteration concerned the location of the catching siteme. Instead of using the village as the distance between them and the nearest untreated community exceeded 5 km, the maximum flight range of C. silacea and C. dimidiatata (see BEESLEY & CREWE, 1963; CHITPAUX et al., in press). It was hoped that the flies caught would not, therefore, have taken a potentially infective blood meal on individuals living outside the treatment area.

The most surprising observation was the fact that the infection and infective rates in April and November 1993, i.e., after the first and third treatment rounds, were reduced only very slightly, if at all. As the entomological surveys were carried out at the same time as the treatment round, we assumed that, in April 1993, most of the flies had become infected either before ivermectin distribution or before the drug had had an effect on microfilaraemia. In November 1993, the unexpected result was less easily explained. Two possible reasons are: (i) infected flies originated from outside the treated area, and (ii) untreated infected residents (about 15–20% of the microfilaria carriers at this time) and infected visitors constituted an adequate parasite reservoir. The first hypothesis can be rejected as the flight range was less than the distance between the catching zone and untreated communities, and because of the marked decrease in infection rates in April 1994 and April 1995.

The reductions in infection and infective rates, and in the average number of L3 per infected fly, from April 1994, could be attributed to the drug treatment. A direct impact of ivermectin on Loa larvae should reduce the percentage of Chrysops harbouring L3, which was not observed (Table 2). In April 1994 (fifth treatment round), more than 85% of the entire population, and 95% of microfilaria carriers, participated at least one ivermectin course, which is enough to reduce the parasite load for one year or more (GARDON et al., 1997). The low infection and infective rates remained stable until April 1995, due to the parasite reservoir remaining reduced, and microfilaria carriers in April 1995 was 6.7% (RANQUE et al., 1996). Treatment was stopped in April 1995 because of the risk of reactions in areas highly endemic for loiasis (CHITPAUX et al., 1996), even though those already treated could have continued to receive the drug without risk. In April 1995, a number of pregnant women with potentially infective flies. Nevertheless, considering the risks of severe adverse effects in patients with high microfilaraemia and treated with ivermectin (CHITPAUX et al., 1996), large-scale treatment cannot be recommended.

Conclusion

This study confirmed that the human parasite reservoir can be drastically reduced by large-scale treatment (RANQUE et al., 1996). There was also a notable reduction of the infection rate in Chrysops, especially in the number of infective larvae in the heads of the insects. Large-scale treatment therefore seems to be efficient and is a potential control strategy providing that drug coverage exceeds 90% of the microfilaria carriers. Nevertheless, considering the risks of severe adverse effects in patients with high microfilaraemia and treated with ivermectin (CHITPAUX et al., 1996), large-scale treatment cannot be recommended.

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