SHORT- AND LONG-TERM ACTION OF MULTIPLE DOSES OF IVERMECTIN ON LOIASIS MICROFILAREMIA

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Abstract. One hundred nine Gabonese patients infected with Loa loa microfilariae were treated with ivermectin (200 µg/kg of body weight) at the Parasitology, Mycology and Tropical Medicine Department (Faculte de Medecine et des Sciences de la Sante, Libreville, Gabon). Each was given one dose per month for six consecutive months. The peripheral blood microfilaria (mf) count before and after each dose showed an average decrease in the microfilaremia of 87.3% (short-term–single dose). An annual single-dose mass treatment with 200 µg/kg of ivermectin was sufficient to control the parasite in populations with low (<400/ml) L. loa mf counts. One month after the sixth dose (short-term–multiple doses), the average microfilaria rate had decreased by 99.2% compared with the initial infection (35 patients). Samples were taken from 28 patients one month after the first dose and one month after the sixth dose. The average mf count decreased by 96.4% after the first dose and by 99.6% after the sixth dose (average residual mf counts = 13.7 and 1.5 mf/ml, respectively). The mf count after the sixth dose was only 11.2% of the count at the first dose. The low mf count persisted for more than six months after the sixth treatment (long-term–multiple doses). Thus, mass treatment with multiple doses is more appropriate for areas where the blood mf count is very high. These results show that the number of the annual treatments used in mass chemotherapy with ivermectin can be adapted to each population to provide efficient protection.

The parasitic disease loiasis occurs throughout the Congolese forest area of central and west Africa.1 Stoll2 estimated the number of microfilariae carriers to be 13 million in 1947 while a more recent study by Fain3 in 1981 reduced the number to 2–3 million. However, analyses of the symptomatology due to the Loa loa adult filariae and the specific immunologic responses of patients without microfilaria (mf) indicate that the real prevalence is somewhat higher,4 and could involve more than 75% of the residents in these forest areas. Ivermectin has been shown to decrease the transmission of the onchocerciasis when given as an annual mass treatment of 150 µg/kg of body weight repeated over a period of 3–5 years.5 As single dose of 200 µg/kg of ivermectin resulted in a massive decrease in the occurrence of circulating Wuchereria bancrofti mf two years after treatment.6 Another study7 showed that one dose of ivermectin (20–200 µg/kg) reduced the infection rate of Brugia malayi mf by 25% within six months.

The initial evaluations of the action of ivermectin on loiasis8–10 showed decreases in the blood mf count of 80–93% 10–14 days after a single dose of 200 µg/kg, with no major side effects. The parasitemia rate was reduced to 10% of the starting load for three months by a single dose of ivermectin (200 or 400 µg/kg).11 The first trials with multiple doses of ivermectin was carried out in southern Cameroon.12 Ivermectin (200 µg/kg) was given 2–3 times at three-month intervals to two groups of patients. The microfilaremia rate had decreased by 80–90% six months after the last treatment.

This study was carried out to evaluate the changes in the microfilaremia rates and the persistence of ivermectin efficacy. Ivermectin (200 µg/kg) was given once each month for six consecutive months to Gabonese patients who were carriers of L. loa microfilariae. Blood samples were taken and analyzed one month after a single dose ivermectin (short term–single dose), one month after the sixth monthly dose (short-term–multiple doses), and six months or more after the sixth monthly dose (long-term–multiple doses).

PATIENTS AND METHODS

A total of 109 Gabonese patients were recruited from several areas where loiasis is endemic, after agreement of the Ethics Committee of the National Mectizan® Program (Ministry of Public Health, Gabon). All subjects provided written informed consent for participation in the study. They all had symptoms of loiasis (pruritus, calabar swelling, subcutaneous and eye migration of the adult worm, pain, and arthritis) but none had serious disease. Pregnant or nursing women and children less than five years old were excluded. The youngest patient was seven years old and the oldest was 78 years old (mean ± SD age = 40 ± 20 years). Samples of venous blood (4 ml) were taken from the forearm into anticoagulant between 9:00 am and 1:00 pm. The microfilariae in a 10-µl aliquot were counted directly under the microscope; if negative, the samples were checked by treating the whole blood sample with saponin, centrifuging the white blood cells, and counting these mf.

Each dose of ivermectin was accompanied by anti-histamine anti-H1 (loratadine) treatment for one week. The patients were examined one month later, at which time a blood sample was taken for parasite counting and they were given the next ivermectin treatment. This process was continued for six months. Parasite counts were performed between six and nine months after the last ivermectin treatment. The initial microfilaria before treatment was compared with the microfilaremia one month after the first dose, one month after the sixth dose, and six months after the sixth dose. Of 109 participants, 84 were examined after the first dose (84 serum samples). Fifty-seven serum samples were obtained from patients controlled after one of the six doses (141 samples). The mf count per milliliter of blood was expressed as the

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geometric mean with 95% confidence levels. A Student's paired *t*-test was used to analyze the data.

RESULTS

The dose of 200 µg/kg was used because a previous trial in which 11,036 doses of ivermectin (200 µg/kg) had been given for mass therapy against onchocerciasis and loiasis in Gabon (donation to the Mectizan® Program; Merck, Sharp and Dohme, La-Celle-Saint-Cloud, France) was without adverse effects that required hospitalization (Kombila M, Duong TH, Richard-Lenoble D, unpublished data).

The geometric mean initial mf count per ml blood was 1,692.8–5,190.4. The population was divided into two groups. One group of 25 patients had counts < 100 mf/ml (6.5–24.7) while the other 84 patients had > 100 mf/ml (2,237.4–6,684.6); 37 of these 84 patients had > 1,000 mf/ml (5,211.0–14,239.0), and 13 had > 10,000 mf/ml (12,248.9–31,668.7). The short-term action (single dose) of ivermectin on parasitemia was evaluated from the results of 141 samples (the microfilariaemia of some patients was examined several times during repeated treatments) taken before any treatment (and one month after one dose of ivermectin given to randomly selected patients). The mean decrease in the mf count (from 129.2 mf/ml to 16.3 mf/ml) was 87.3% (*P* < 0.002).

One-third (35) of the 109 patients who took part in the trial were given all six monthly treatments on consecutive months, and blood samples were taken one month after the sixth dose (short-term–multiple doses). The average number of blood mf was reduced (from 353.5 mf/ml to 2.6 mf/ml) by 99.2% (*P* < 0.005). Blood samples were taken from 15 of these 35 patients over a six-month period after the sixth dose (long-term efficacy–multiple doses) (Figure 1a). The average blood mf count was still decreased (from 272.7 mf/ml to 2.7 mf/ml) by 99.0% (*P* < 0.05).

The influence of the number of ivermectin doses on the microfilaremia rate was evaluated on the 35 patients who were given six doses of drug. Blood parasite counts were done on 28 of them one month after the first treatment and one month after the sixth treatment (Figure 1b). The one month microfilariaemia rate (13.7 mf/ml) was 96.4% (*P* < 0.02) below the pretreatment rate (390.1 mf/ml), and the one-month mf count after the sixth dose (1.5 mf/ml) was 99.6% (*P* < 0.02) below the pretreatment rate (390.1 mf/ml). The mf count one month after the six doses of ivermectin (1.5 mf/ml) was 88.8% (*P* < 0.03) below the mf count one month after the first dose (13.7 mf/ml). One month after the first dose, seven of 28 patients were negative and one month after the six doses, 17 of 28 patients were negative.

DISCUSSION

The ivermectin was well tolerated provided it was given in conjunction with an anti-histamine anti-H1 for one week. A few patients with fewer than 10,000 mf/ml had side effects such as pruritus and weakness, but they were relatively well tolerated. These clinical manifestations appeared the day following ivermectin treatment and persisted for 24–36 hr. Only one of the 13 patients with a microfilariaemia rate > 10,000 mf/ml developed a skin rash, fever, arthralgia, an intense asthenia, and headache. These severe side effects were attenuated by an intramuscular injection of 1 mg of tetracosactide (Synacthene®; Ciba-Geigy Laboratories, Rueil-Malmaison, France). Hospitalization was not required.

Ivermectin caused a large significant (*P* < 0.002) decrease (short-term–single dose) in the number of the *L. loa* mf (87.3%) in the peripheral blood one month after each dose. These results are in agreement with those of earlier reports. The greatest decrease in the blood mf count occurred in the patients who received all six monthly treatments. The mf count was reduced by 99.2% (*P* < 0.005), compared with the count before treatment, one month after the sixth dose (short-term–multiple doses). The reduction in mf count after six doses (short-term–multiple doses) was greater (*P* < 0.03) than the reduction after the first dose (short-term–single dose). One month after the sixth dose, the mean mf count was 1.5 mf/ml, while the mf count one month after the first dose was 13.7 mf/ml, showing that multiple doses give a greater reduction in microfilariaemia. Six months after the sixth dose (long-term–multiple doses), the parasite count was still 99.0% below the pretreatment count. Chavasse and others studied the action of ivermectin on *Onchocerca volvulus* and found that it altered the fertility of the adult female.
worms. The long-term action of ivermectin on loiasis could be due to it having a similar action on the *L. loa* adult female worms.

Ivermectin is well tolerated by all the patients with relatively low parasite counts. Patients with a high microfilarial load who are not given anti-histaminic treatment can have severe reactions, including severe neurologic disturbance with asthenia, disturbed consciousness, and renal impairment that may require hospitalization. Only one patient with a very high blood mf count (62,300 mf/ml) in our study had a major secondary reaction despite the anti-histaminic treatment and this was reduced by an injection of corticosteroid.

This study shows that any future filariasis control campaigns with ivermectin in multifilarian areas of central Africa must take into account the short-term efficacy of the ivermectin; each dose reduced the blood parasite count by 87.3%. The short-term efficacy was amplified by repeated doses, so that the mf count had decreased by 99.0% one month after the sixth dose. There is a persistent low mf count six months after the last treatment, regardless of the number (1–6) of doses given. Finally, the reduction in the mf count produced by any treatment persists for more than six months.

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