Ivermectin treatment of mansonellosis in Blanchisseuse, Trinidad, West Indies

_Mansonella ozzardi_ is endemic in many parts of tropical Central and South America, including the Caribbean region (Ottesen, 1984). Although mansonellosis is generally thought to cause little or no disease in humans (Marinkelle and German, 1970), several reports have associated this infection with urticaria, lymphadenopathy, articular pains, pruritic skin eruptions, high-grade eosinophilia and headaches (Marinkelle and German, 1970; Nathan et al., 1982; Nutman et al., 1987).

No adequate treatment for mansonellosis is currently available; diethylcarbamazine (DEC) has been found ineffective in killing the microfilariae (mf) or the adult forms of the parasite (Bartholomew et al., 1978; Raccurt et al., 1980). However, ivermectin, a semisynthetic antibiotic derived from ivermectin B1, a macrocyclic lactone produced by the actinomycete _Streptomyces avermitilis_, is highly effective against a broad range of helminthic parasites in animals and has been used with great success in patients with onchocerciasis (Aziz et al., 1982) and bancroftian filariasis (Coutinho et al., 1994) and also in a single case of _M. ozzardi_ infection (Nutman et al., 1987).

A preliminary experiment preceded a medium-scale trial of ivermectin treatment of _M. ozzardi_ infections in Trinidad. A 3-ml blood sample was taken from each of four mansonellosis patients (two males and two females, admitted to the Port of Spain General Hospital) after each had been medically examined. Each patient was then given a 6-mg tablet of ivermectin (one male and one female patient) or calcium-carbonate placebo and then monitored continuously until discharged (24 h) and then every 12 h for 1 week, within the community of Blanchisseuse by the district nurse and the study group. The responses of the two patients given ivermectin indicated that there were relatively limited health risks associated with the treatment and that a community-treatment campaign was a reasonable idea (bed space at the hospital being very limited). Similar results have been found elsewhere (Moula-Pelat et al., 1993).

The subsequent, medium-scale, double-blind and placebo-controlled study involved 36 male and four female volunteers (aged 27–90 years, with 1–5679 mf/ml blood) from Blanchisseuse, who were selected after a 12-year follow-up study on the prevalence of _M. ozzardi_ microfilaraemia in the area (Chabee et al., 1994). Each subject gave his or her informed consent, and approval for the study was obtained from the Internal Review Board for Human Studies of the Insect Vector Control Division, Ministry of Health, Trinidad. Patients were randomly assigned to treatment or placebo groups. The protocol for the double-blind treatment and evaluation were similar to those used in ivermectin dose-finding studies for _M. perstans_ (Van den Enden et al., 1993) and _M. ozzardi_ (Nutman et al., 1987). Each subject was examined (at the Blanchisseuse Health Center) and given ivermectin (N=20) or placebo (N=20) like the subjects in the initial trial. Although all 40 were asked to return to the health centre 24 h post-treatment, 10 (four placebo and six treatment) failed to do so and refused to participate any further in the study. The remaining 30 subjects [with initial microfilaraemias ranging from 1–5679 (treatment group) and 4–5042 (placebo group) mf/ml, and means of 697 and 562 mf/ml, respectively] were visited by a team of physicians every 4 h and questioned about adverse reactions, which were graded 1 (mild—easily tolerated), 2 (moderate—discomfort insufficient to interfere with daily activity) or 3 (severe—preventing usual activities). In case of an emergency, five physicians were housed within the Blanchisseuse community for 48 h post-treatment to provide any medical care which may have been required. As expected, all 10 subjects (63% of
the remaining 16 subjects in the group) reporting adverse reactions (12 cases of fever, 12 of arthralgia, 11 of headache, eight of chills, five of malaise and three each with myalgia and pruritus) were in the treatment group: three subjects had grade-3 reactions (two of whom had the highest pre-treatment microfilaraemias seen in the group: 4490 and 5679 mf/ml), five had grade-2 and two had grade-1. All the reactions developed about 12 h post-treatment and had disappeared within 24 h.

For each subject, a venous blood sample (3 ml) was collected, vital signs were recorded, a recent medical history was obtained, and a physical examination (with emphasis on the genitalia, major lymph-node groups, extremities and cardiovascular system) was performed prior to treatment and 1, 7, 31 and 150 days post-treatment. Microfilaraemias, estimated from the blood samples using the standard, Nucleopore filtration and thick-blood-smear methods (Chadee et al., 1995; Fig.), fell rapidly in all the subjects given ivermectin and were either undetectable (11 subjects) or <5% of pre-treatment values (five subjects) within 24 h. Although all 15 treated subjects who were checked 1 week post-treatment were amicrofilaraemic, three became microfilaraemic within the 5 months of follow-up. One (RG) was microfilaraemic at the 1- and 5-month follow-ups (with 107 and 203 mf/ml, respectively) and two were microfilaraemic at 5 months (EG with 9 mf/ml and EJ with 2 mf/ml). These three cases of recrudescence were retreated at 5 months but two remained microfilaraemic at 6 months (RG with 105 mf/ml and EG with 11 mf/ml). Two treated subjects had died by the 5-month follow-up but there was nothing to link their deaths to the treatment or their mansonellosis.

Densities of mf in the peripheral blood of the subjects in the placebo group fluctuated
IVERMECTIN TREATMENT OF MANSONELLOSIS

TABLE
Mansonella ozzardi microfilariaemias in those given the placebo, measured pre-treatment and at various times post-treatment (pt)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Pre-treatment</th>
<th>24 h pt</th>
<th>7 days pt</th>
<th>1 month pt</th>
<th>5 months pt</th>
</tr>
</thead>
<tbody>
<tr>
<td>EG</td>
<td>4</td>
<td>9</td>
<td>3</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>HJ</td>
<td>385</td>
<td>1866</td>
<td>71</td>
<td>1248</td>
<td>0*</td>
</tr>
<tr>
<td>LA</td>
<td>5042</td>
<td>2020</td>
<td>2371</td>
<td>5698</td>
<td>2949</td>
</tr>
<tr>
<td>TC</td>
<td>647</td>
<td>938</td>
<td>552</td>
<td>601</td>
<td>706</td>
</tr>
<tr>
<td>BM</td>
<td>925</td>
<td>1870</td>
<td>439</td>
<td>1990</td>
<td>2030</td>
</tr>
<tr>
<td>SD</td>
<td>406</td>
<td>699</td>
<td>601</td>
<td>700</td>
<td>684</td>
</tr>
<tr>
<td>CM</td>
<td>147</td>
<td>152</td>
<td>374</td>
<td>210</td>
<td>6</td>
</tr>
<tr>
<td>JA</td>
<td>248</td>
<td>34</td>
<td>10</td>
<td>89</td>
<td>162</td>
</tr>
<tr>
<td>LF</td>
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<td>347</td>
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</tr>
<tr>
<td>ER</td>
<td>4</td>
<td>0</td>
<td>9</td>
<td>0*</td>
<td></td>
</tr>
<tr>
<td>RM</td>
<td>1956</td>
<td>1237</td>
<td>609</td>
<td>1269</td>
<td>0*</td>
</tr>
<tr>
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<td>29</td>
<td>27</td>
<td>3</td>
<td>13</td>
<td>0*</td>
</tr>
<tr>
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<td>2001</td>
<td>2371</td>
<td>1983</td>
<td>2300</td>
<td>2275</td>
</tr>
<tr>
<td>SM</td>
<td>29</td>
<td>0</td>
<td>198</td>
<td>256</td>
<td>308</td>
</tr>
</tbody>
</table>

*Subjects were microfilaraemic when checked after the 5-month follow-up.

considerably, four of the 14 who were checked regularly appearing amicrofilaraemic at some time during the follow-up (Table and Fig.). Although Schulz-Key et al. (1993) found that ivermectin was more effective against low microfilaraemias than against high ones, in the present study the drug appeared equally effective at clearing high and low densities of M. ozzardi mf. Although there was a rapid decline in microfilaraemias in all those treated in the present study, the apparent cure rate 5 months post-treatment was only 78% (i.e. 11 of 14 surviving subjects still participating in the trial). However, this cure rate is much better than that achieved against M. perstans using DEC (Strohschneider, 1956), mebendazole (unless very expensive, high doses are used for prolonged periods) (Wahlgren and Frolov, 1983; Van Hoegaarden et al., 1987), mebendazole-levamisole (Maertens and Wery, 1975; Bernberg et al., 1979; Goldsmid and Rogers, 1979) or ivermectin (Richard-Lenoble, 1988, 1990; Schulz-Key et al., 1993; Van den Enden et al., 1993) and much better than that of DEC against M. ozzardi (Bartholomew et al., 1978; Weller et al., 1978; Raccurr et al., 1980). That M. ozzardi microfilaraemias (present study) are apparently easier to control with ivermectin than those of M. perstans (Schulz-Key et al., 1993) may reflect interspecific differences in response to the drug, or be the result of greater drug resistance in the African M. perstans used by Schulz-Key et al. (1993), possibly because of greater prior exposure to anti-filarial drugs.

In the present study, ivermectin cleared M. ozzardi microfilaraemias for several months in most cases, and may therefore affect the adult worms as well as the mf. The three subjects who were treated with ivermectin but re-developed microfilaraemias within the 5-month follow-up may be part of a group of ‘bad responders’ who continue to produce microfilariae after a single dose of ivermectin. Similar results were found during DEC treatment of M. ozzardi in Trinidad (Bartholomew et al., 1978) and ivermectin treatment of Wuchereria bancrofti in French Polynesia (Moula-Pelat et al., 1993) and M. perstans in Africa (Van den Enden et al., 1993). Variable levels of drug absorption among the treated patients, as demonstrated in ivermectin
treatment of *W. bancrofti* infections (Cartel et al., 1993), and/or sequestration of mf in the tissues may also have contributed to the three poor responses.

Ivermectin appears to be a safe and well-tolerated drug. Clinically, all the adverse effects seen in the present study were transient, and severe reactions only occurred in three subjects, two of whom had exceptionally high microfilaraemia. The most frequent adverse reactions (fever, arthralgia, headaches, chills, malaise and myalgia) were the same as those found using ivermectin against bancroftian filariasis in French Polynesia (Moulia-Pelat et al., 1993) and similar to those seen in Brazil (Coutinho et al., 1994), India (Ottesen et al., 1990) and Sri Lanka (Ismail et al., 1991).

The fluctuating densities of mf in the placebo group indicate that the mf may have a circadian rhythm of activity, although Nathan et al. (1978) failed to detect such periodicity in *M. ozzardi* from Blanchisseuse. Further studies are being conducted to check for periodicity in the local *M. ozzardi* and to determine the efficacy and long-term effects of an intervention programme based on ivermectin.

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