ADVERSE REACTIONS TO IVERMECTIN TREATMENT IN SIMULIUM NEAVEI–TRANSMITTED ONCHOCERCIASIS

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Abstract. To assess adverse effects of ivermectin treatment in a Simulium neavei–transmitted focus of onchocerciasis, a study was conducted with 1,246 patients infected with Onchocerca volvulus in eight villages in western Uganda. Study participants were treated the first time with a single dose of 150 μg/kg of ivermectin. Adverse reactions to ivermectin were determined through questioning and clinical examination during house-to-house visits to the participants within 48 hours after ivermectin treatment. Overall adverse reactions were observed in 737 (59.1%) patients. Severe reactions were rare (10 patients, 1.4%). Our data show that adverse reactions to ivermectin in an S. neavei–transmitted onchocerciasis focus in western Uganda occur frequently. In spite of the fact that many patients showed adverse reactions to ivermectin, the drug was well accepted and appreciated by the population.

INTRODUCTION

The discovery of ivermectin for the treatment of onchocerciasis and the subsequent acceptance and registration of this drug in late 1987 has created new possibilities for the control of onchocerciasis. Ivermectin was successfully tested in large-scale trials in Ghana, Sierra Leone and Liberia. In addition to the efficacy, adverse reactions to ivermectin were also measured. Adverse reactions were generally rare and associated with the microfilaria density in the skin.

All of the studies on adverse effects of ivermectin have been carried out in areas of the Onchocerciasis Control Program (OCP) in west Africa, where Simulium damnosum s.l. is the transmitting vector. We conducted our study in an S. neavei–transmitted onchocerciasis focus because we had three reasons to believe that adverse reactions to ivermectin may be different in western Uganda: 1) S. neavei–transmitted onchocerciasis differs parasitologically and clinically from both the savanna and forest form of S. damnosum s.l.-transmitted onchocerciasis in west Africa, e.g., it has a higher burden of associated with the microfilaria density in the skin. DNA analysis showed that the strain of Onchocerca volvulus found in Kigoyera parish differed from the forest type strain of O. volvulus in west Africa; and 3) previous treatment of some onchocerciasis patients with ivermectin in western Uganda had shown unusually high rates of adverse reactions to ivermectin.

There is no published information available to answer the question if the frequency and severity of adverse reactions to ivermectin treatment in S. neavei–transmitted onchocerciasis areas differs from those reported from west Africa and the OCP areas where S. damnosum s.l. is the vector. This is somewhat surprising considering that the African Program for Onchocerciasis Control (APOC) focuses on ivermectin delivery in vast parts of central and eastern Africa where S. neavei often transmits O. volvulus. It is therefore crucial to know if ivermectin can be delivered safely to onchocerciasis patients or to the general population in mass treatment campaigns in the APOC areas where S. neavei transmits O. volvulus.

The objectives of this study were to 1) assess the frequency of adverse reactions in onchocerciasis patients treated for the first time with ivermectin; 2) determine the pattern of adverse reactions and their severity; and 3) compare the frequency of adverse reactions in western Uganda with those found in west Africa.

This study took place in Kigoyera parish a rural role district of western Uganda 60 km northeast of Fort Portal, the district capital. Details of study designs and other results are published elsewhere. Kigoyera is a rural parish with a population of 6,973 people living in 13 villages, according to the 1991 census. The population in the eight villages included in the study was 1,466, of which 1,246 (85.0%) were infected with O. volvulus. Our study was conducted in these eight villages in 1991.

Kigoyera parish lies within the onchocerciasis belt that stretches from north to south along the Ruwenzori Mountains where S. neavei is the main transmitting vector. In Kigoyera parish, the overall prevalence of infection with O. volvulus was 78% in 1991. The prevalence of onchocercal skin disease was found to be 26%. Levels of infections were high, with microfilaria (mf) loads up to 1,000 mf per skin snip. Onchocerciasis was viewed by most people in Kigoyera parish as an important health problem. Skin disease and itching was seen as especially troublesome by most parishioners infected with O. volvulus.

MATERIALS AND METHODS

In eight villages in Kigoyera parish, 1,246 confirmed mf carriers, who were a subset of an ongoing research program, were included in the study. All patients infected with O. volvulus who did not receive ivermectin prior to the examination date were treated with a single dose of 150 μg/kg of ivermectin according to the protocol of the Mectizan Expert Committee. Children less than five years old, pregnant women, women during the first week of breast feeding, and persons with severe acute and chronic illnesses other than onchocerciasis were excluded from the study. Treated patients were informed about adverse reactions of ivermectin and were told that they would be visited at home after 48 hours to assess any possible adverse reactions to the ivermectin treatment. Adverse reactions were assessed by taking a history and performing a clinical examination. Adverse reactions were recorded according to their location and their severity (two categories: light/moderate and severe). In all patients with adverse reactions, the temperature (axillary) was taken and
blood pressure was measured in lying and sitting positions. Adverse reactions were treated with analgesics and antihistamines and with corticosteroids for patients with severe reactions.

All data were entered into Stata version 5.0 (Stata Corporation, College Station, TX) for analysis. All persons received an explanation of the study in the local Rutooro language. Informed consent was read in the local language and persons who participated in the study gave their verbal consent. Parents gave their consent on behalf of study participants less than 18 years old. In addition to individual consent, the village chiefs of the eight villages in Kigoyera parish gave their consent on behalf of their communities. All procedures met the requirements of the Ugandan Ministry of Health. The study protocol was submitted to the Ethical Review Board and the Ministry of Health and formal approval was given by the Permanent Secretary of the Ugandan Ministry of Health.

RESULTS

Of the 1,246 study participants who were treated with ivermectin for the first time, 737 (59.1%) showed signs of adverse reactions to ivermectin upon examination during the visit of the research team after treatment. The mean ± SD age of the patients with adverse reactions was 28.2 ± 15.6 years (range 5–79 years) (376 were male and 361 were female). Details on the adverse reactions of the patients after ivermectin treatment are shown in Table 1.

Fifty-seven (7.8%) patients had a fever (temperature greater than 38°C), with 45 (6.2%) between 38°C and 39°C, nine (1.2%) between 39°C and 40°C, and three (0.4%) greater than 40°C. Those patients with a temperature ≥ 40°C complained of being severely ill with headaches. They had only light swellings of the upper body. Nine patients had a decrease in the systolic and/or diastolic blood pressure of 20 mm of Hg when they changed from a lying to a sitting position; three had a decrease of more than 30 mm of Hg. On average, the systolic blood pressure decreased by 25 mm of Hg, and the diastolic blood pressure decreased by 10 mm of Hg. All of these patients complained of dizziness. The severity of dizziness was somewhat related to the magnitude of the decrease in blood pressure. Swelling most frequently involved the buttocks, chest, and lower back. Seven (0.9%) patients complained about blurred vision and had difficulty reading. Four (0.5%) individuals reported photophobia and said that they could not leave the house. Twelve (1.6%) patients reported that they had to lie down after ivermectin treatment. These patients were found lying in bed or on the floor when the research team members arrived at their houses.

Pain, conditions, swellings, and cutaneous reactions were the three most dominant symptoms of adverse effects. Ten (1.4%) patients had severe adverse reactions. Most patients with severe adverse reactions and severe symptomatic postural hypotension (SSPH) had high fever.

During the examinations of patients with adverse reactions, few expressed concerns about the safety of the ivermectin treatment to the research team or did they complain about it. No formal complaint about ivermectin treatment was received in the District Health Department in Fort Portal. Most of the participants said that they would be happy to participate in future ivermectin treatment rounds.

DISCUSSION

In western Uganda, adverse reactions to ivermectin are much more frequent compared with reports from West Africa. Since we actively followed-up treated onchocerciasis patients in their homes within 48 hours after ivermectin treatment, we are confident that we have reliable information regarding adverse reactions to ivermectin treatment from this focus, and we believe that we did not miss patients with adverse reactions. This approach differs from some other studies, in which patients with adverse reactions only self-reported to a health clinic for the assessment and treatment of their adverse reactions. In this case, it can be assumed that patients with mild adverse reactions may not have reported their adverse reactions after receiving treatment, resulting in under-reporting of adverse reactions.

In our study population, the frequency of adverse reactions after ivermectin treatment was much higher (59%) than that reported in other similar studies: De Sole and others found a rate of 9% for adverse reactions to ivermectin in their trial in Ghana, while Whitworth and others reported 28% of the patients with adverse reactions after ivermectin treatment in Sierra Leone. In Liberia, it was found that the rate of adverse reactions was quite low, ranging between 0.6% and 1.3%. One explanation for the much higher occurrence of adverse reactions after ivermectin treatment in Kigoyera parish could be that the community microfilarial load (CMFL) was much lower in Ghana, where only 4.9% of the villages had a CMFL higher than 35 mf/skin snip, while in our eight villages, the CMFL was always greater than 35 mf/skin snip, with an average CMFL of 79 mf/skin snip (range = 39–128 mf/skin snip). Since the frequency of adverse reactions in onchocerciasis patients depends mostly on the intensity of infection (as reported in the literature), one would expect higher levels of adverse reactions to ivermectin in areas with a higher CMFL.

Other investigators have found similarly high levels of adverse reactions to ivermectin. Njoo and others observed that 64% of a small sample of 71 onchocerciasis patients displayed adverse reactions. Mwetta and Hills found in the Usambara mountains in Tanzania that 98% of 743 onchocerciasis patients treated with ivermectin reported some adverse reactions.

The pattern of adverse reactions to ivermectin in our sample is similar to results from other studies. De Sole and

<table>
<thead>
<tr>
<th>Type of reaction</th>
<th>All reactions</th>
<th>Severe reactions</th>
</tr>
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<tbody>
<tr>
<td>Pain</td>
<td>420 (57.0)</td>
<td></td>
</tr>
<tr>
<td>Swellings</td>
<td>368 (49.9)</td>
<td></td>
</tr>
<tr>
<td>Cutaneous</td>
<td>281 (38.1)</td>
<td></td>
</tr>
<tr>
<td>Gland</td>
<td>168 (22.8)</td>
<td></td>
</tr>
<tr>
<td>Fever and chills</td>
<td>133 (18.0)</td>
<td>8 (1.1)</td>
</tr>
<tr>
<td>Eye</td>
<td>49 (6.6)</td>
<td></td>
</tr>
<tr>
<td>SSPH or severe dizziness</td>
<td>9 (1.2)</td>
<td>9 (1.2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Other complaints</td>
<td>80 (10.9)</td>
<td></td>
</tr>
</tbody>
</table>

* Values in parentheses are percentages (n = 737). SSPH = severe symptomatic postural hypotension.
others also listed pain, cutaneous reactions, fever, chills, and swelling as the main complaints. Febrile reactions were less frequent in our sample compared with the findings of De Sole and others. Burnham found in Malawi that swelling of the face is the most common symptom, which is similar to what we have reported.

One important finding of our study is that severe adverse reactions were rare. We had nine (1.2%) patients with severe fever and/or severe dizziness that required bed rest. The overall number of patients with severe reactions was nine (1.2%, with one additional patient with severe dyspnea). This is slightly higher than what was found in Ghana, where 0.24% of the participants had severe reactions to ivermectin. In spite of the high rate of adverse reactions, ivermectin was overwhelmingly accepted and appreciated in the communities and the reactions did not deter people from taking ivermectin. This is also shown by the high participation rate of the population in subsequent ivermectin mass treatment campaigns that increased in the 13 villages of Kigoyera parish from 76% in 1992 to 85% in 1994.

There are two limitations in our study. First, our study was not placebo controlled. Therefore our estimation of the frequency and severity of adverse reactions to ivermectin treatment may have been overestimated. However, taking this into account and considering the very high number of onchocerciasis patients (59%) found to have had adverse reactions to ivermectin, we still can conclude with some confidence that there is a significant difference in adverse reactions of onchocerciasis patients living in areas where *S. damnosum* is the vector compared with those living in areas where *S. neavei* is the vector. Second, the medical assistants who assessed the adverse reactions in our patients were part of the OCP in the district and were very familiar with all aspects of onchocerciasis control and the clinical features of onchocerciasis. They were trained regarding ivermectin and its adverse reactions. However, since they did not have specific research training, it is possible that some adverse reactions were wrongly classified because they occurred due to other reasons. This also would have overestimated our findings.

In conclusion, adverse reactions to first-dose ivermectin were common in the Kigoyera focus in western Uganda compared with those in west Africa. Fortunately, severe adverse reactions such as SSPH, high fever, and asthma were rare and comparable with results in west Africa. In spite of the high rate of mild and moderate adverse reactions, ivermectin was well accepted and did not deter people from participating in ivermectin treatment campaigns. The beneficial effect of ivermectin obviously outweighed the adverse reactions in the opinion of the population. This finding is important for the ivermectin treatment activities within the APOC area in central and eastern Africa, where species of the *S. neavei* group transmit *O. volvulus*.

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