HIGH FREQUENCY OF SERIOUS SIDE EFFECTS FROM MEGLUMINE ANTIMONIATE GIVEN WITHOUT AN UPPER LIMIT DOSE FOR THE TREATMENT OF VISCERAL LEISHMANIASIS IN HUMAN IMMUNODEFICIENCY VIRUS TYPE-1-INFECTED PATIENTS

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Abstract. Organic pentavalent antimonials are one of the mainstays of treatment for visceral leishmaniasis (VL). Few data are available on the toxicity and efficacy of these drugs at the dosing schedule recommended by the Centers for Disease Control and Prevention (CDC) (Atlanta, GA). We analyzed 25 VL episodes in human immunodeficiency virus (HIV)-infected patients who were treated with meglumine antimoniate (MA) at the CDC-recommended dose in southern Spain. Adverse effects were observed in 14 (56%) VL episodes. In 7 (28%), treatment with MA was permanently discontinued due to serious adverse effects that included acute pancreatitis, acute renal failure, and leukopenia. Three (12%) patients died during therapy due to severe acute pancreatitis attributable to MA. The dosing regimen of MA currently recommended for treating VL is associated with a high rate of serious side effects in HIV-1-infected patients.

Visceral leishmaniasis (VL) caused by Leishmania infantum is endemic in countries bordering the Mediterranean basin. It has been increasingly recognized that it affects human immunodeficiency virus type-1 (HIV-1)-infected patients, not only in this endemic area, but also in non-endemic western countries. Organic pentavalent antimonials (SbV) are one of the first-line drugs recommended by the Word Health Organization (WHO) for treating VL in the Mediterranean area. In 1982, WHO (unpublished data) advocated treatment with 20 mg of SbV/kg of body weight, with a maximum dose of 850 mg/day. The Centers for Disease Control (CDC) (Atlanta, GA) recommended in 1992 to remove the upper limit dose. Data that supported this recommendation stemmed from clinical trials with patients not infected with HIV. It was reported that higher daily doses without an upper limit resulted in better responses. Side effects were regarded as reversible and rarely severe.

Patients with VL coinfected with HIV have a poor response to SbV therapy. Microbiologic cure is observed in less than half the cases and relapses are frequent. In this setting, toxic effects of SbV have seldom been reported in previous studies. However, the dose of SbV used in these patients was limited to a maximum of 850 mg/day. Therefore, we assume that a low dose was administered. Thus, few data are available on efficacy and safety of the currently recommended SbV dosing schedule to treat VL in HIV-1-infected individuals. We provide herein data on toxicity and efficacy of meglumine antimoniate (MA) at a dose of 20 mg/kg of body weight/day with no dose limit in HIV-1-infected patients with VL.

PATIENTS AND METHODS

Patients. Fifty-one episodes of VL were diagnosed in 46 HIV-1-infected patients attending 2 University Hospital Acquired Immunodeficiency Syndrome (AIDS) care units in Seville, Spain from October 1993 to December 1997. Based on the diagnosis of the responsible physician, 25 VL episodes (49%) were treated with MA following the dosing schedule recommended by CDC in 1992. Twenty-four were initial episodes and 1 was a relapse. We retrospectively analyzed these 25 episodes. The study was designed and conducted according to the Helsinki Declaration and was reviewed and approved by the Ethical Committee of the Hospital Universitario Virgen del Rocío.

Diagnosis of VL. All cases were diagnosed by examination of bone marrow aspirate smears. They were stained with Giemsa and examined at 1,000× magnification by an experienced parasitologist.

Treatment regimen. All episodes of VL were treated with MA, 20 mg/kg of body weight/day given in 2 separate intramuscular injections, without a maximum dose. The intended duration of the course of treatment with SbV was 28 days. Thirteen episodes were also treated with allopurinol, 300 mg three times a day.

Assessment of the effects of MA. The efficacy of MA therapy was assessed by clinical and microbiologic criteria. Clinical response was defined as the resolution of all symptoms and signs attributable to VL. A VL episode was considered microbiologically cured when a bone marrow aspirate obtained at the end of a course of treatment with MA yielded no demonstrable amastigotes by direct visualization. The number of relapses was recorded. The safety of treatment with MA was recorded by analyzing the number and grade of adverse effects directly attributed to MA. Asymptomatic hyperamylasemia was defined as serum amylase concentrations > 200 U/L or an elevation of 200 U/L above baseline levels, if they were greater than 200 U/L. Clinical pancreatitis was defined as an elevated amylase level with abdominal pain.

RESULTS

Characteristics of the study population. The mean (range) age of the patients was 30.2 (19–39) years; and 20 (83%) subjects were men. Twenty (83%) patients were intravenous drug addicts; 3 had sexual predisposing factors and 1 had an unknown predisposing factor for transmission.
of HIV-1 infection. The mean (range) CD4+ cell count when VL was diagnosed was 66.2 (2–307) cells/μl. Diseases defining AIDS had been diagnosed previously in 17 (68%) VL episodes.

**Side effects.** All 25 VL episodes were evaluable with regard to antimony-related side effects. Adverse effects were observed in 14 (56%) VL episodes (Table 1). Moreover, SbV therapy was permanently discontinued in 7 (28%) VL episodes due to serious adverse effects: acute pancreatitis in 5 episodes, acute renal failure in 1, and leukopenia in 1. Three patients that died received allopurinol. The proportion of previous AIDS diagnoses was not statistically different between the VL episodes with and without MA-related side effects: 8 (57%) of 14 compared with 9 (81%) of 11, respectively (P = 0.2, by Fisher’s exact test).

**Efficacy.** Ten (40%) of 25 VL episodes did not complete a course of MA for the following reasons: 7 patients had serious side effects; 2 patients died of lymphoma before completing the course of MA, and treatment for 1 patient was changed to amphotericin B due to concomitant esophageal azole-resistant candidiasis.

A clinical response was observed in the 5 (33%) of 15 evaluable episodes of VL. Clinical responses were not evaluable in 10 (66%) episodes of VL because other diseases could have been responsible for persistent symptoms and signs.

Bone marrow aspiration was performed in 9 (60%) of 15 VL episodes following completion of the course of MA. Amastigotes were not detected in 8 (89%) and were observed in 1 (11%). Six (40%) VL episodes were not evaluable because a bone marrow aspirate was not performed following treatment. Allopurinol was added to the regimen of MA in 5 of the 9 evaluable VL episodes (55%), all of which show a microbiologic cure.

Amastigotes were not demonstrable in bone marrow aspirates after treatment in the 5 episodes of VL that showed clinical responses. The only episode of VL with amastigotes in the bone marrow aspirate after treatment was not evaluable with regard to a clinical response because of concomitant tuberculosis.

The 15 VL episodes that completed SbV treatment for 28 days were followed-up for a mean (range) period of 53.9 (1–104) weeks. Three (20%) of these VL episodes relapsed. Five (37%) of 14 patients that completed a course of MA died, as did 4 patients with an initial episode of VL, and 1 patient who relapsed. One (7%) of these 14 patients was lost to follow-up.

**DISCUSSION**

The dosing regimen of MA currently recommended for treating VL in the Mediterranean area is associated with a high rate of adverse effects in HIV-1-infected patients; acute pancreatitis is most common. In addition, these side effects are frequently serious enough to require interruptions of treatment.

The present study was limited due to a relatively small sample size and a retrospective design. Adequately designed clinical trials would more accurately assess recommended

### Table 1

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Total number, n = 25</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperamylasemia</td>
<td>10 (40)</td>
<td></td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>5 (20)</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine &gt; 2 mg/dl</td>
<td>3 (12)</td>
<td></td>
</tr>
<tr>
<td>Leukocyte count &lt; 1,500 cells/μl</td>
<td>2 (8)</td>
<td></td>
</tr>
<tr>
<td>T wave inversion</td>
<td>2 (8)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (4)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2

Characteristics of the patients with acute clinical pancreatitis due to meglumine antimoniate (MA)*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Risk group</th>
<th>CDC stage</th>
<th>CD4 cell counts (cells/μl)</th>
<th>Concomitant opportunistic diseases</th>
<th>Potential pancreatotoxic drugs given simultaneously</th>
<th>Exposure to MA (days)</th>
<th>Outcome of acute pancreatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29</td>
<td>Male</td>
<td>IDU</td>
<td>C</td>
<td>60</td>
<td>None</td>
<td>None</td>
<td>5</td>
<td>Death</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>Female</td>
<td>Heterosexual</td>
<td>A</td>
<td>84</td>
<td>None</td>
<td>None</td>
<td>4</td>
<td>Cure</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>Male</td>
<td>IDU</td>
<td>C</td>
<td>49</td>
<td>Pneumocystis carinii pneumonia</td>
<td>TMP-SMX</td>
<td>12</td>
<td>Death</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>Male</td>
<td>IDU</td>
<td>C</td>
<td>42</td>
<td>None</td>
<td>None</td>
<td>8</td>
<td>Cure</td>
</tr>
<tr>
<td>5</td>
<td>32</td>
<td>Male</td>
<td>Homosexual</td>
<td>B</td>
<td>30</td>
<td>None</td>
<td>None</td>
<td>7</td>
<td>Death</td>
</tr>
</tbody>
</table>

* CDC = Centers for Disease Control and Prevention; IDU = intravenous drug user; TMP-SMX = trimethoprim-sulfamethoxazole.
drug regimens. Nevertheless, trials involving VL therapy in HIV-1-infected patients are lacking.\textsuperscript{1} Data on the effect of Sb\textsuperscript{V} on HIV-1-infected patients with VL come mostly from retrospective series that describe clinical aspects of the co-infection.\textsuperscript{6-12} However, none of these studies follow the dose recommendations of the CDC\textsuperscript{5} with respect to the schedule of treatment with Sb\textsuperscript{V}. Thus, the present study provides information on the effect of Sb\textsuperscript{V} administered at the currently recommended doses to HIV-1-infected patients with VL.

Treatment with Sb\textsuperscript{V} has been regarded as safe for treatment of leishmaniasis in clinical trials of otherwise healthy subjects,\textsuperscript{14} although adverse effects have been increasingly reported.\textsuperscript{3,10,11,14-16} Acute pancreatitis has been identified as a rare side effect associated with treatment with Sb\textsuperscript{V} among renal transplant recipients.\textsuperscript{17-19} Anecdotal reports of immunocompetent\textsuperscript{20} and HIV-1-infected patients\textsuperscript{21} have been published. Hyperamylasemia was found in individuals in a case series of non-HIV-infected patients, most of whom had cutaneous or mucosal leishmaniasis that were treated with the CDC-recommended doses of currently advised Sb\textsuperscript{V} regimens.\textsuperscript{22} Nearly half of the patients in this series developed acute pancreatitis. Therapy was interrupted in 10 of the 17 patients, 9 of them because of acute pancreatitis or elevated amylase levels. In the present study, MA was discontinued in 28% of the VL episodes due to side effects, most commonly acute pancreatitis. We may have underestimated the frequency of asymptomatic elevated amylase levels due to the retrospective design of the study.

There is no obvious explanation for the high frequency of acute pancreatitis in HIV-1-infected patients treated with MA. It has been reported that the amount of antimony found in different batches of Glucantime\textsuperscript{58} (Rhone-Poulenc Rorer, Madrid, Spain) and Pentostam\textsuperscript{59} (Wellcome Farmaceutica, Madrid, Spain) was more than the amount reported by the manufacturers.\textsuperscript{23} If this was true, the episodes of VL could have been treated with higher doses of Sb\textsuperscript{V} than intended. Conversely, trivalent antimony was present in all ampules tested in this study,\textsuperscript{23} ranging from 10.5% to 15.8% of the total antimony. Formulations of Sb\textsuperscript{V} have been developed to minimize the side effects associated with trivalent antimonal drugs.\textsuperscript{20} Thus, high levels of the latter could partly explain the severity of toxicity found in this and other studies.\textsuperscript{22}

Patients infected with HIV-1 frequently receive drugs that are toxic for the pancreas and kidneys. When given concomitantly with Sb\textsuperscript{V}, the likelihood of toxicity increases. In the present study, didanosine and stavudine were associated with asymptomatic hyperamylasemia and indinavir was associated with renal failure. Trimethoprim-sulfamethoxazole was administered to a patient who developed severe acute pancreatitis and died. Subclinical pancreatitis frequently occurs in patients with AIDS.\textsuperscript{24} This could predispose them to pancreatic disease.\textsuperscript{24,25} Finally, HIV-1-infected patients frequently develop side effects when treated with drugs that are usually well-tolerated.\textsuperscript{26} This is more prevalent in advanced HIV-1 disease, as in the heavily immunosuppressed patients reported in this study.\textsuperscript{26}

Although definitive conclusions cannot be made from the current study, the data suggest that doses exceeding 850 mg/day are more efficacious than those reported with an upper limit of 850 mg/day.\textsuperscript{6-9,11,12} but this should be tempered by this higher toxicity. It is possible that the efficacy observed in this study is due at least in part to having used allopurinol along with MA since this therapy seems to show greater efficacy than MA alone.\textsuperscript{27}

In conclusion, Sb\textsuperscript{V} at currently recommended doses has a high level of toxicity. Alternative treatments, such as amphotericin B, are also highly toxic. Therefore, clinical trials are urgently needed to evaluate drugs for treating VL in HIV-infected patients. If MA is administered at the recommended CDC dosing schedule, toxic effects, especially pancreatitis, should be carefully monitored. In addition, drugs with known pancreatic toxicity should not be used when possible.

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TOXICITY OF MEGLUMINE ANTIMONIATE 769


