Safety and Efficacy of Intravenous Sodium Stibogluconate in the Treatment of Leishmaniasis: Recent U.S. Military Experience

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The efficacy and toxicity of sodium stibogluconate (SSG) at a dosage of 20 mg/(kg·d) for either 20 days (for cutaneous disease) or 28 days (for visceral, mucosal, or viscerotropic disease) in the treatment of leishmaniasis is reported. Ninety-six U.S. Department of Defense health care beneficiaries with parasitologically confirmed leishmaniasis were prospectively followed for 1 year. One patient was infected with human immunodeficiency virus; otherwise, comorbidity was absent. Clinical cure occurred in 91% of 83 cases of cutaneous disease and 93% of 13 cases of visceral/viscerotropic disease. Adverse effects were common and necessitated interruption of treatment in 28% of cases, but they were generally reversible. These included arthralgias and myalgias (58%), pancreatitis (97%), transaminitis (67%), headache (22%), hematologic suppression (44%), and rash (9%). No subsequent mucosal leishmanial infection was identified, and there were no deaths attributable to SSG or leishmaniasis.

Methods

Selection of Patients

During the study period (1989–1996), all active-duty (and most reserve-component) U.S. military personnel with leishmaniasis who required IND pentavalent antimony treatment were referred to WRAMC. U.S. Department of Defense health care beneficiaries were eligible for this study if they had parasitologically confirmed leishmanial infection and gave written informed consent. Parasitological confirmation was defined as isolation of *Leishmania* promastigotes in culture [5–7] or demonstration of definitive tissue amastigotes in a Diff-Quik (Dade

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Diagnostics, Aguada, Puerto Rico) stained touch preparation or histopathologic section. Expandable cultures permitted identification of *Leishmania* species by cellulose acetate electrophoresis for isoenzyme analysis, with comparison to World Health Organization reference strains [8, 9]. Patients were excluded if they had serious concomitant cardiac, renal, or hepatic disease, had a history of hypersensitivity to antimonials, or were pregnant. Prior pancreatitis was not exclusionary. The protocol was approved by the WRAMC Human Use Committee and Triservice Scientific and Ethical Review Committee.

Cutaneous leishmaniasis was defined as chronic skin lesion(s) with parasites visible by the methods noted above. Visceroptropic leishmaniasis was defined as a subacute illness associated with a positive leishmanial culture of a bone marrow or lymph node specimen. These patients typically have mild symptoms, fairly normal physical examination findings, and few laboratory abnormalities [10]. Visceral leishmaniasis was a constellation of fever, cytopenias, and hepatosplenomegaly in association with parasites identified by biopsy of bone marrow or gastrointestinal or splenic specimens.

**Treatment and Follow-Up**

After enrollment in the study, patients were administered SSG at a dosage of 20 mg per kg (total body weight) per day. Treatment duration was 20 days for cutaneous leishmaniasis or 28 days for visceral, mucosal, or viscerotropic leishmaniasis. From 1989 to 1994, SSG was given for 30 days for visceral or viscerotropic leishmaniasis. SSG was diluted in 50 mL of 5% dextrose in water and infused intravenously via a peripheral butterfly needle over 10–15 minutes. Nine different lots of Pentostam were used during this period.

Enrolled patients had a detailed history recorded and physical examination performed initially and were seen by a physician daily during therapy. Before-treatment and after-treatment photographs of cutaneous lesions documented response to therapy. Electrocardiograms were obtained on treatment days 0, 4, 7, 14, and 20 (and 28 for visceral leishmaniasis). At baseline and twice weekly during therapy, urinalysis was performed and the complete blood cell count (with differential) and levels of glucose, blood urea nitrogen, creatinine, electrolytes, total protein, albumin, calcium, phosphorus, lactate dehydrogenase, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were determined.

After recognition of the frequent association between SSG therapy and pancreatitis [11], serum amylase and lipase levels were monitored daily for the first week and twice weekly thereafter. Patients were asked to refrain from alcohol use during therapy to avoid potentiation of possible hepatic or pancreatic toxicity (defined as an AST, ALT, lipase, or amylase serum level greater than the upper limit of normal [ULN]). Patients were reexamined at 2 months after initiation of therapy; those with visceral or viscerotropic leishmaniasis were seen again at 6 and 12 months. For patients with cutaneous leishmaniasis, follow-up by telephone at 6 and 12 months sufficed unless they described a change in the skin lesion or persistent nasal symptoms, in which case they were asked to return to WRAMC for evaluation. Fifty patients (52%) were contacted for longer follow-up to assess for late mucosal leishmaniasis or SSG-related adverse events.

**Definition of Clinical Cure**

Leishmanial cutaneous ulcers were considered clinically cured if complete reepithelialization was evident by 2 months following the initiation of SSG treatment. Papulonodular or verrucous cutaneous lesions were considered cured if they were flattened, were not indurated (unless a cicatrix or keloid had formed), and showed no signs of new activity over the same period. When initial improvement of lesions with therapy was followed by new ulcerative or infiltrative clinical findings after completion of SSG treatment, the lesions were considered to have relapsed. Those lesions that did not completely reepithelialize by 2 months following initiation of treatment were considered nonresponders (partially responding to treatment [12]). Treatment failure was defined by little response of skin lesions to treatment (<25% epithelialization).

Visceroptropic leishmaniasis was considered cured if the majority of symptoms diminished in temporal relationship with SSG treatment and/or if culture of a bone marrow biopsy specimen at the end of treatment yielded no growth. Visceral leishmaniasis was considered to be clinically cured if symptoms resolved and if hepatosplenomegaly and hematologic parameters normalized by the 6-month follow-up.

**Statistical Methods**

Data were abstracted from patient records with use of a standardized form. These data were doubly entered into a database with the program Epi-Info (version 6; CDC), and descriptive data analyses were performed. In the calculation of efficacy, the denominator included the total number of patients who started SSG treatment. The numerator included the patients who were considered clinically cured and completed at least 10 days of treatment with SSG.

For statistical comparison of medians between groups of patients with cutaneous, visceral, and viscerotropic leishmaniasis, the Kruskal-Wallis test was used. Proportions of treatment responders to nonresponders were compared with the two-tailed Fisher’s exact test, and medians between these two groups were compared with the Mann-Whitney *U* test. All *P* values were considered significant at a level of *P* < .05.

**Results**

**Characteristics of Patients**

Ninety-six patients with parasitologically confirmed leishmaniasis were treated with SSG and evaluated in this study. Their demographic characteristics are shown in table 1.
Table 1. Demographic characteristics of the 96 patients with leishmaniasis treated between 1989 and 1996.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cutaneous (n = 82)</th>
<th>Mucocutaneous (n = 1)</th>
<th>Visceral (n = 5)</th>
<th>Viscerotropic (n = 8)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years of age, median (range)</td>
<td>24 (18–53)</td>
<td>23</td>
<td>18 (0.6–46)</td>
<td>32 (20–43)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>82</td>
<td>1</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>White</td>
<td>68 (83)</td>
<td>0</td>
<td>3 (60)</td>
<td>8 (100)</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>7 (9)</td>
<td>0</td>
<td>1 (20)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
<td>6 (7)</td>
<td>1 (100)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (20)</td>
<td>0</td>
</tr>
<tr>
<td>History of travel to</td>
<td>Panama</td>
<td>53 (65)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>French Guiana</td>
<td>15 (18)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Saudi Arabia</td>
<td>11 (13)</td>
<td>0</td>
<td>0</td>
<td>7 (88)</td>
</tr>
<tr>
<td></td>
<td>Belize</td>
<td>9 (11)</td>
<td>1 (100)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Sicily</td>
<td>0</td>
<td>0</td>
<td>3 (60)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Spain</td>
<td>0</td>
<td>0</td>
<td>2 (40)</td>
<td>1 (12)</td>
</tr>
<tr>
<td></td>
<td>Central/South America</td>
<td>12 (14)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Days of potential exposure in areas of endemicity, median (range)</td>
<td>88 (30–360)</td>
<td>8,030</td>
<td>395 (45–600)</td>
<td>200 (60–1,460)</td>
<td>.048*</td>
</tr>
<tr>
<td>Days from onset of symptoms to treatment, median (range)</td>
<td>118 (30–360)</td>
<td>360</td>
<td>35 (16–300)</td>
<td>177 (13–723)</td>
<td>.792*</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients unless otherwise indicated.
* The case of mucosal disease was not included in the Kruskal-Wallis test.

All patients were in excellent health at baseline, with the exception of one patient with visceral leishmaniasis who had AIDS. Three HIV-negative patients with visceral leishmaniasis were children <4 years of age; otherwise, the patients were young men. One patient with cutaneous leishmaniasis reported a history of unsuccessful meglumine antimoniate therapy; the remaining patients had no history of antimonial treatment. All patients had traveled to an area in which *Leishmania* is known to be endemic.

Table 2 delineates the diagnostic findings in this series. Parasites were visualized in specimens from at least one lesion/site in each patient. Leishmanial cultures confirmed the diagnosis in 73 (76%) of the 96 cases. The remaining cases were diagnosed by expert review of histopathology at the Armed Forces Institute of Pathology (Washington, D.C.). The cause of our few cases of visceral leishmaniasis was identified as *Leishmania (Leishmania) infantum* by the Istituto Superiore Di Sanita (Rome), with use of the Montpellier zymodeme classification [13].

Toxicity with Sodium Stibogluconate Therapy

Details of SSG dosing and adverse effects are shown in table 3. An arbitrary absolute upper limit to the daily SSG dose was not implemented. No patients were considered obese or significantly malnourished.

Daily unstructured physician interviews were conducted during therapy (table 4). The most common symptoms were ar-

Table 2. Diagnostic findings in the study cases of leishmaniasis.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cutaneous*</th>
<th>Visceral</th>
<th>Viscerotropic</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Leishmania</em> amastigotes visualized</td>
<td>51/67 (76)</td>
<td>5/5 (100)</td>
<td>0/6 (0)</td>
</tr>
<tr>
<td><em>Leishmania</em> culture positive</td>
<td>62/83 (75)</td>
<td>3/3 (100)</td>
<td>8/8 (100)</td>
</tr>
<tr>
<td><em>Leishmania</em> species isolated</td>
<td>(n = 48)</td>
<td>(n = 3)</td>
<td>(n = 7)</td>
</tr>
<tr>
<td><em>L. (Viannia) panamensis</em></td>
<td>18 (38)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>L. (V.) braziliensis</em></td>
<td>10 (21)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>L. (Leishmania) major</em></td>
<td>6 (12)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>L. (L.) mexicana</em></td>
<td>5 (11)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>L. (V.) guyanensis</em></td>
<td>5 (11)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>L. (L.) tropica</em></td>
<td>3 (6)</td>
<td>0</td>
<td>7 (100)</td>
</tr>
<tr>
<td><em>L. donovani sensu lato</em></td>
<td>1 (2)</td>
<td>3 (100)</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients.
* One patient with mucocutaneous leishmaniasis also had cutaneous leishmaniasis. This patient is included in the cutaneous group, unless otherwise noted.
Table 3. Characteristics of patients’ \( (n = 96) \) clinical courses with sodium stibogluconate therapy according to type of leishmaniasis.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cutaneous ( (n = 83) )</th>
<th>Visceral/viscerotropic ( (n = 13) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose in mg/d, median (range)</td>
<td>1,620 (1,300–2,140)</td>
<td>1,700 (200–1,890)</td>
</tr>
<tr>
<td>No. of doses, median (range)</td>
<td>20 (3–20)</td>
<td>30 (2–30)</td>
</tr>
<tr>
<td>No. (%) of patients requiring interruption of treatment</td>
<td>22 (27)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Days off treatment, median (range)</td>
<td>3 (1–17)</td>
<td>10 (4–28)</td>
</tr>
<tr>
<td></td>
<td>Symptomatic pancreatitis 5/4 3/10</td>
<td>Elevated transaminase levels 1/2 . . .</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia . . . 1/12</td>
<td>Left against medical advice 2/5 1/1</td>
</tr>
<tr>
<td></td>
<td>Not specified . . . . . .</td>
<td></td>
</tr>
</tbody>
</table>

thralgias and myalgias, which developed in the latter half of therapy. These complaints varied from mild discomfort to activity-limiting effects and were managed by the limiting of physical exercise and use of nonsteroidal antiinflammatory agents. Abdominal pain, nausea, and vomiting were generally noted in the first week and were usually associated with elevated serum amylase and lipase levels. Most cutaneous reactions were few, generalized, erythematous papules. Several patients had small vesicular, pruritic lesions on the palmar or interdigital aspects of their hands. Four patients (4%) developed herpes zoster near the end of treatment or in the early convalescent period [14].

Electrocardiographic changes were noted in 20 patients (21%), principally T-wave inversion or flattening in comparison with baseline findings. The patient with AIDS and visceral leishmaniasis, who was receiving SSG at a dosage of 1,640 mg/d, developed a prolonged corrected Q-T interval (Q-Tc) of .551 on day 28.

Laboratory abnormalities associated with SSG treatment were also analyzed (table 5). Pancreatic abnormalities tended to occur very early in therapy and to decline despite continued SSG treatment. Our practice was to withdraw SSG if serum amylase levels became >4 times the ULN or lipase levels became >15 times the ULN, regardless of symptoms. We resumed therapy once these values trended significantly toward normal levels [11]. Fifteen patients’ serum triglyceride levels were followed but were unremarkable. Elevations in transaminase levels tended to occur later in the treatment course than the pancreatic enzyme changes.

SSG caused some hematologic toxicity. In viscerotropic or cutaneous leishmaniasis, peripheral blood cell counts declined during treatment. In one case thrombocytopenia (platelets,
Table 5. Laboratory results: elevation in pancreatic and hepatic enzyme levels associated with sodium stibogluconate therapy for leishmaniasis.

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>No. (%) of patients with elevated value</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day of onset</td>
<td>Day of peak value</td>
</tr>
<tr>
<td>Cutaneous leishmaniasis (n = 83)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylase*</td>
<td>43/51 (84)</td>
<td>3 (0–14)</td>
</tr>
<tr>
<td>Lipase*</td>
<td>49/51 (96)</td>
<td>3 (2–19)</td>
</tr>
<tr>
<td>AST</td>
<td>51/83 (61)</td>
<td>9 (0–21)</td>
</tr>
<tr>
<td>ALT</td>
<td>52/83 (63)</td>
<td>8 (0–20)</td>
</tr>
<tr>
<td>Visceral/viscerotropic (n = 13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylase*</td>
<td>6/7 (86)</td>
<td>3 (1–4)</td>
</tr>
<tr>
<td>Lipase*</td>
<td>7/7 (100)</td>
<td>2 (1–4)</td>
</tr>
<tr>
<td>AST</td>
<td>8/12 (67)</td>
<td>4 (0–27)</td>
</tr>
<tr>
<td>ALT</td>
<td>7/12 (58)</td>
<td>3 (0–8)</td>
</tr>
</tbody>
</table>

NOTE. ALT = alanine aminotransferase; AST = aspartate aminotransferase.
* Since amylase and lipase levels were systematically measured starting in 1992, denominators include only patients for whom data were available. Normal ranges in our laboratory: amylase, 30–110 U/L; lipase, 23–300 U/L; AST, 17–59 U/L; ALT, 17–59 U/L.

Toxicity was increased during the second course of antimony. Arthralgias were noted with earlier onset (day 2–3). Two of five patients stopped the second course early, one because of severe musculoskeletal symptoms. Three patients’ therapy was stopped (on days 2, 3, and 12) for symptomatic pancreatitis. One required support with parenteral hyperalimentation for 1 week.

Clinical Outcome

Table 6 summarizes the results of SSG treatment. The IND protocol required a 1-year follow-up. However, to identify possible late mucosal leishmaniasis and adverse effects of medication, longer-term follow-up was initiated; 85 (88%) of the patients were contacted, with an overall median follow-up of 1.3 years (range, 0–9 years). During follow-up, no SSG-treated patient with New World cutaneous leishmaniasis developed mucosal leishmaniasis.

Three deaths occurred: 1 patient was killed in combat, 1 committed suicide 4 years after SSG treatment, and 1 died of AIDS complicated by toxoplasma encephalitis.

Five patients (6%) showed some initial improvement but then relapsed (table 6). Each was given a second 20-day course of SSG. Of the five patients treated with a second course of SSG, four (80%) were then clinically cured. One patient required a third course of SSG. This patient had also been previously treated with meglumine antimoniate. The small number of clinical nonresponders limited the conclusions that can be drawn about them (table 7). Nonresponders were treated with SSG from multiple lots. Since resistance in vitro has been identified after intermittent antimony exposure [15], we analyzed the nonresponders for interrupted treatment courses (33%) and found no significant difference from the responders (26%).

Toxicity was increased during the second course of antimony. Arthralgias were noted with earlier onset (day 2–3). Two of five patients stopped the second course early, one because of severe musculoskeletal symptoms and the other for abdominal symptoms with elevated transaminase levels. Two patients had conjunctival edema and facial puffiness or swelling.

Overall, 93 (97%) of the 96 patients were clinically cured with SSG, four required a second treatment course, and one even needed a third course. Two patients received only 2–3 doses of SSG, and the likelihood of significant drug effect was questionable in assessment of outcome, as they received no further therapy.

Discussion

We determined the efficacy and toxicity of the SSG dosing regimen currently recommended for the treatment of leishmaniasis [4]. Since SSG is available in the United States under an IND protocol, requirements for monitoring its use are stringent. Most of our patients did not reside in areas of endemicity during follow-up, a circumstance decreasing the likelihood of reinfection.

The demographic characteristics of our patients were dictated by exposures to *Leishmania* from military operations.
Table 6. Sodium stibogluconate (SSG) therapy for leishmaniasis: outcome measures for the 96 cases studied according to type of leishmaniasis.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Cutaneous (n = 82)</th>
<th>Mucocutaneous (n = 1)</th>
<th>Visceral (n = 5)</th>
<th>Viscerotropic (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median no. of years (range)</td>
<td>1.3 (0–9)</td>
<td>5 (…)</td>
<td>1 (0.5–1)</td>
<td>2 (1–6)</td>
</tr>
<tr>
<td>&gt;1 y</td>
<td>43 (52)</td>
<td>1 (100)</td>
<td>0</td>
<td>6/7 (86)</td>
</tr>
<tr>
<td>Clinical cure</td>
<td>76/82 (93)*</td>
<td>1/1 (100)</td>
<td>5/5 (100)³</td>
<td>8/8 (100)²</td>
</tr>
<tr>
<td>Relapse</td>
<td>5/82 (6)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Response to 2nd SSG course</td>
<td>4/5 (80)</td>
<td>. . . . . . . . .</td>
<td>. . . . . . . . .</td>
<td>. . . . . . . . .</td>
</tr>
<tr>
<td>Response to 3rd SSG course</td>
<td>1/1 (100)</td>
<td>. . . . . . . . .</td>
<td>. . . . . . . . .</td>
<td>. . . . . . . . .</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Subsequent mucosal infection (to date)</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Discontinuation of SSG therapy at &lt;10 d</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Death (unrelated to SSG)</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE. NA = not available.
* One patient received SSG for only 3 days.
*² One patient died at month 5.
*³ One patient received SSG for only 2 days.

Table 7. Data concerning nonresponders to sodium stibogluconate (SSG) therapy, among patients with cutaneous leishmaniasis.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonresponders (n = 6)</th>
<th>Remaining patients with cutaneous disease (n = 76)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, in years (range)</td>
<td>24 (18–34)</td>
<td>24 (18–53)</td>
<td>.165</td>
</tr>
<tr>
<td>SSG dosage in mg/d, median (range)</td>
<td>1,620 (1,400–1,900)</td>
<td>1,620 (1,300–2,140)</td>
<td>1.0</td>
</tr>
<tr>
<td>Median no. of SSG doses</td>
<td>20</td>
<td>20</td>
<td>.734</td>
</tr>
<tr>
<td>Days from onset of symptoms to treatment initiation, median (range)</td>
<td>62 (60–150)</td>
<td>118 (30–360)</td>
<td>.370</td>
</tr>
<tr>
<td>No. of lesions per patient, median (range)</td>
<td>4 (1–9)</td>
<td>2 (1–12)</td>
<td>.157</td>
</tr>
<tr>
<td>Area of cutaneous lesion (mm²), median (range)</td>
<td>315 (40–2,100)</td>
<td>300 (20–3,600)</td>
<td>.952</td>
</tr>
<tr>
<td>Total no. of lesions</td>
<td>9</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>Location of lesions*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck/Head</td>
<td>1 (4)</td>
<td>31 (25)</td>
<td>.028⁷</td>
</tr>
<tr>
<td>Arm</td>
<td>4 (17)</td>
<td>30 (24)</td>
<td>.597</td>
</tr>
<tr>
<td>Leg</td>
<td>10 (43)</td>
<td>20 (16)</td>
<td>.01¹</td>
</tr>
<tr>
<td>Hand</td>
<td>0</td>
<td>17 (13)</td>
<td>.076</td>
</tr>
<tr>
<td>Foot</td>
<td>2 (9)</td>
<td>8 (6)</td>
<td>.666</td>
</tr>
<tr>
<td>Back</td>
<td>1 (4)</td>
<td>8 (6)</td>
<td>1.0</td>
</tr>
<tr>
<td>Abdomen</td>
<td>3 (13)</td>
<td>5 (4)</td>
<td>.12</td>
</tr>
<tr>
<td>Torso</td>
<td>2 (9)</td>
<td>5 (4)</td>
<td>.317</td>
</tr>
<tr>
<td>Character of skin lesion*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulcer</td>
<td>10 (42)</td>
<td>66 (53)</td>
<td>.374</td>
</tr>
<tr>
<td>Papulonodular</td>
<td>14 (58)</td>
<td>30 (24)</td>
<td>.002⁷</td>
</tr>
<tr>
<td>Eschar</td>
<td>0</td>
<td>13 (11)</td>
<td>.128</td>
</tr>
<tr>
<td>Verrucous</td>
<td>0</td>
<td>2 (1)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* Not noted for all lesions.
¹ A P value of <.05 was considered significant.
Most cases were of New World cutaneous leishmaniasis associated with jungle training; Old World cutaneous (Leishmania [L.] major) and Leishmania (L.) tropica visceral leishmaniasis was acquired in Saudi Arabia (1990–1992). Consistent with these opportunities for exposure to Leishmania, most patients were male infantry soldiers, Special Forces, Rangers, or SEAL team members. The predominance of whites (83%) in the leishmaniasis case population is somewhat higher than in the active-duty U.S. Army (62%) (personnel data from the Defense Manpower data center). The distribution of Leishmania species identified in culture is consistent with previously published British and U.S. military experience [16–21].

Previous reports of SSG toxicity at a dosage of 20 mg/(kg \cdot d) have been limited and varied [4, 12]. Reported symptoms have included anorexia, nausea, and/or abdominal pain in 7%–28% [22–28] and arthralgias and myalgias in 15%–83% [22–24, 26–28, 29]. Depression of various hematologic cell lines has been found in 2%–37% of patients [26–28, 30]. Echocardiographic changes have been noted with 4%–50% of SSG treatment courses [23, 25, 26, 29]. Severe and even fatal necrotizing pancreatitis occurring with antimony therapy has been described [31, 32]. Our experience suggests that patients with clinical or chemical evidence of pancreatitis tolerate rechallenge without recurrence of symptoms or chronic sequelae.

The efficacy of SSG at a dosage of 20 mg/(kg \cdot d) for 20 days in cases of New World leishmaniasis has varied from 88% to 100%, with most failures occurring in cases of disease caused by Leishmania (L.) mexicana [22, 23, 29, 30]. A similar dose used for 14–15 days has been shown to have 34%–64% efficacy in cases of New World leishmaniasis [24, 25].

This study did not have a control arm of untreated patients, but the natural history of untreated cutaneous leishmaniasis is well documented [23, 30, 33, 34]. As self-healing can occur, our results may represent the best possible outcome. With clinical cure as the endpoint, treatment rates among the types and species of Leishmania represented indicate high efficacy (88 of 96; 92%) and manageable toxicity for a single course of the 20-mg/(kg \cdot d) regimen of SSG.

There are advantages and disadvantages to note in recommending SSG for cutaneous disease. The natural history of New World cutaneous leishmaniasis suggested that many lesions (22%–88%) may heal without intervention in 14 weeks but that those due to Leishmania (V.) braziliensis were less likely to do so [3]. The risk of late mucosal disease in cases due to L. (V.) braziliensis has been reported as 2%–10% among untreated cases [35, 36], and there remains some risk despite completion of a course of antimony for localized cutaneous disease. Antimonials accelerate healing and may decrease the likelihood of late mucosal disease. Use of SSG involves prolonged parenteral treatment, expense ($105/100-mL bottle; N. Ahle, personal communication), costly intensive monitoring, data collection for (United States) IND status, restricted access, and significant, albeit usually reversible, toxicity. More than one-quarter of patients must temporarily interrupt SSG treatment because of toxicity, and 6% terminate therapy prematurely. Serious rheumatologic, pancreatic, and cardiac toxicity has been observed with SSG. Given these drawbacks, a better-tolerated, nonparenteral, approved therapy is needed for cutaneous leishmaniasis.

In conclusion, we found SSG administered intravenously at a dosage of 20 mg/(kg \cdot d) to have excellent efficacy in the treatment of nearly 100 patients with leishmaniasis. New World cutaneous leishmaniasis was most prevalent in our series, but visceral and viscerotropic leishmaniasis cases were also treated with good results.

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References


