RESPONSE OF CUTANEOUS LEISHMANIASIS (CHICLERO’S ULCER) TO TREATMENT WITH MEGLUMINE ANTIMONIATE IN SOUTHEAST MEXICO

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Abstract. Cutaneous leishmaniasis, known as chiclero’s ulcer in southeastern Mexico, is characterized by a predominantly single, painless, ulcerated lesion, without lymphangitis or adenopathy. When located on the ear, it tends to become chronic, causing destruction of the pinna and disfigurement. It is caused predominantly by Leishmania (L.) mexicana. Although pentavalent antimonials (Sb5⁺) are the mainstay of leishmanial therapy and have been used for more than 50 years, dosage regimens have been repeatedly modified and the best one has not been fully identified. The main purpose of the present study was to investigate the response of chiclero’s ulcer to treatment with meglumine antimoniate. One hundred five patients were treated with meglumine antimoniate at a daily dose of 1 ampule per day (425 mg of Sb5⁺) until healing. The lesions healed after a mean of 25 days (range = 5–60 days).

Cutaneous leishmaniasis (CL), known as chiclero’s ulcer in southeast Mexico, was described by Seidelin in 1912. Since then, the sylvatic region of the Yucatan peninsula has been determined to be an endemic focus of CL.2–4 Leishmania (L.) mexicana Biagi, 1953, emend. Garnham, 1962, is the main agent causing CL in this focus; however, L. (Viannia) braziliensis has also been isolated from a few cases. Four species of wild rodents, Otomys phyllotis, Peromyscus yucatanicus, Oryzomys melanotis, and Sigmodon hispidus, have been found naturally infected by L. (L.) mexicana.5 6 7 Lutzomyia olmeca and Lu. cruciata have been incriminated as vectors of L. (L.) mexicana.5 8–10 The clinical picture is characterized by a predominantly single, painless, ulcerated lesion, without lymphangitis or adenopathy, and when located on the ear (the most common presentation) tends to become chronic, causing destruction of the pinna and disfigurement.1 2 11 An annual incidence rate of 5.08 per 1,000 inhabitants has been reported in the state of Campeche in the Yucatan peninsula.12 The time required for natural cure is poorly defined, as in other New World cutaneous leishmaniasis. It is generally thought that the disease due to L. (L.) mexicana heals spontaneously in a time varying from a few months to several years.13 14

The only chemotherapeutic agent with a clearly favorable therapeutic index against Leishmania is pentavalent antimony (Sb5⁺) complexed to carbohydrate in the form of sodium stibogluconate (Pentostam®; Wellcome, Hartfordshire, United Kingdom) or meglumine antimoniate (Glucantime®; Rhône-Poulenc, Lyon, France).15 In 1988 the “Program for Study, Surveillance, and Control of the Leishmaniasis in the Yucatan Peninsula, Mexico” was approved by the Mexican Health Secretariat and it was decided to investigate the response of CL to treatment with Sb5⁺. This study was not designed to be a controlled clinical trial, but rather an evaluation of the response of chiclero’s ulcer to treatment with meglumine antimoniate.

PATIENTS, MATERIALS, AND METHODS

Patient population. Patients with a clinical picture suggestive of CL from the state of Campeche, Yucatan Peninsula, Mexico who sought treatment at any of the Rural Health Posts of the Instituto Mexicano del Seguro Social (IMSS) and the Secretaría de Salud (SSA) between January 1990 and December 1994 were evaluated. This study was reviewed and approved by the Ethical Committee of the Universidad Autónoma de Yucatán, in agreement with international ethical guidelines for biomedical research involving human subjects, Ley General de Salud, Mexico. Written informed consent to participate was obtained from all patients. Eligibility for the study included a confirmed diagnosis of acute (time of evolution less than 12 months) localized CL based on both clinical diagnosis and visualization of the parasite by smear, biopsy, and/or isolation-culture,16 no previous treatment with any antileishmanial drug, no serious concomitant disease, and availability to be followed-up for 12 months. A complete clinical history was obtained in all cases that included age, sex, occupation, and clinical state of the lesion (number, size, location, and duration).

Characterization of parasites. Parasites isolated by needle aspirates from the edge of the lesion were inoculated into a tube of Senekjie’s modified medium and kept at 22°C. After initial growth in culture tubes, the parasites were mass cultivated for isoenzyme electrophoresis and analyzed with monoclonal antibodies.5 7

Regimen of meglumine antimoniate. Glucantime® is marketed in 5-ml ampules containing 1.5 grams of N-methyl-glucamine antimoniate, which corresponds to 425 mg of Sb5⁺. Treatment was initiated at least 1 month after the diagnosis was established. Administration of a daily intramuscular dose of 1 ampule until healing was based on the following rationale: chiclero’s ulcer has been considered a simple form of CL causing predominantly a single, localized lesion, without lymphatic and mucosal involvement, and the recommended dose for treatment of infection with L. (L.) mexicana with pentavalent antimonials is the lowest in the literature.17–19 Baseline and weekly laboratory data, including serum alanine transferase, aspartate aminotransferase, bilirubin, creatinine, blood urea nitrogen, serum albumin, and an electrocardiogram, were obtained in 42 hospitalized patients monitored in a previous study to evaluate safety of administering 1 ampule (425 mg of Sb5⁺) per day for 35 days. There was no adverse reaction to this dosage and no changes in the results of laboratory studies.20

Assessment of response. A complete response to treatment was defined as a complete re-epithelization of all le-
sions with no residual erythema and no relapses during monthly follow-ups for a period of 1 year. Relapse was defined as ulceration or positive cultures developing in a lesion that had previously healed.

Statistical analysis. Possible associations between the number of ampules required for complete re-epithelization and lesion characteristics (number, size, location, and duration), age and sex of patients, and Leishmania spp. were tested for statistical significance by analysis of variance and multiple regressions.

### RESULTS

#### Patients characteristics.
A total of 131 patients were eligible to be included in this study. Only 105 (80.15%) completed the 1-year follow-up. Ninety-five (90.47%) were males and 10 (9.53%) were females. Ages varied from 4 to 74 years old (mean = 25.2). Duration of lesions prior treatment varied from 21 days to 7 months (mean = 2.56 months). A single lesion was observed in 82 (78%) of 105 patients. All lesions were of the ulcerative type and the areas varied from 0.04 cm² to 37.44 cm² (mean = 3.40 cm²). Lesions were located predominantly on the ear and face (Table 1).

#### Demonstration and characterization of parasites.
Demonstration of parasites was positive with at least 1 of the methods used in all cases (Table 2). Fifty isolates were successfully cultivated. Forty-eight (96%) were identified as *L. (L.) mexicana* and only 2 (4%) as *L. (V.) braziliensis*.

#### Response to treatment.
The 105 cases included in this study were cured in response to treatment with meglumine antimoniate. The dose required to obtain complete healing of lesions varied from 5 to 60 ampules (mean = 25.1), as shown in Figure 1. In all cases healing in response to Sb5+ was shorter than the duration of lesions recorded before treatment. Patients were followed-up for at least 12 months after healing and none showed a relapse. We looked for possible associations between the number of ampules required

### Figure 1
Distribution of the number of ampules required for complete re-epithelization of chiclero’s ulcer patients treated with meglumine antimoniate in southeast Mexico.
for complete re-epithelization and characteristics of lesions (number, size, location, and duration), age and sex of patients, and Leishmania spp. The only association that approached statistical significance was that between number of ampules required and age in patients less than 15 years old (mean = 17 ampules). With reference to a possible difference in response due to Leishmania spp., no statistically significant difference was observed between patients infected with L. (L.) mexicana (mean = 25.9 ampules), and those infected with L. (V.) braziliensis (mean = 24 ampules). However, only 2 cases infected with L. (V.) braziliensis were treated. The daily dose of 425 mg of Sb5+/day was well tolerated in all cases and no subjective complaints were recorded.

**DISCUSSION**

Leishmaniasis remains one of the major communicable diseases in tropical and subtropical regions of the world, and CL leishmaniasis is the most abundant form, with an estimated prevalence of 1.5 million new cases per year.21 Undoubtedly, pentavalent antimonial compounds are the mainstay of the leishmanial therapy. Although they have been used for more than 50 years, dosage regimens have been repeatedly modified and the best one has not been fully identified. Substantial confusion exists about optimum dosage regimen, ranging from less than 10 mg to a high of 20 mg of pentavalent antimony per kilogram of body weight. Moreover, recommendations for duration of treatment have equally varied, ranging from a minimum of a few days to a maximum of 40 days. Regardless of the value of antimonial compounds in the treatment of leishmanial infections, response to treatment may be variable depending on the species of parasite.22,23

It is generally accepted that American cutaneous leishmaniasis (ACL), especially when caused by L. (L.) braziliensis, should be treated with a dose of 20 mg of Sb5+/kg/day for 20 days to prevent the late development of disfiguring mucosal lesions.24-26 Nevertheless, Oliveira-Neto and others studied 15 patients with ACL from Rio de Janeiro who were treated with 1 ampule of meglumine antimoniate per day for 30 consecutive days, and they reported clinical cure in all about 2 months after therapy.27 Moreover, Oliveira-Neto and others compared doses of 5 mg/kg/day and 20 mg/kg/day for 30 days and the results in both groups were essentially the same.28

On the other hand, knowledge of the treatment of chiclero’s ulcer caused by L. (L.) mexicana with pentavalent antimonials is scarce. In a placebo-controlled clinical trial of meglumine antimoniate versus localized controlled heat in the treatment of CL in Guatemala, Navin and others observed clinical cure rate of 25% (1 of 4) in cases caused by L. (L.) mexicana when treated with 850 mg of Sb5+/day for 15 days.29 In another clinical trial comparing sodium stibogluconate versus ketoconazole for treating CL in the same endemic area, they reported a clinical cure rate of 57% (4 of 7) in L. (L.) mexicana-infected patients treated with sodium stibogluconate at a dose of 20 mg/kg/day intravenously for 20 days.30 However, they recognized that the sample size did not allow reliable evaluation of treatment of CL caused by L. (L.) mexicana. In the present study, clinical cure rates in CL patients from southeast Mexico, an endemic focus caused predominantly by L. (L.) mexicana, was 100% (105 of 105) using a mean dose of 25.1 ampules (range = 5–60) and a daily dose of 1 ampule as that used by Oliveira-Neto and others to treat CL caused by L. (V.) braziliensis.27

In the state of Campeche where patients seek treatment and where medical facilities are available, management of chiclero’s ulcer must achieve 2 immediate goals: healing of cutaneous lesions and prevention of disfigurement observed in chronic lesions located on the ears. Since it is generally accepted that re-epithelization of lesions continues after therapy has ended, administration of Sb5+ until complete clinical and parasitologic cure has been achieved constitutes considerable overtreatment.15 Therefore, the optimal treatment regimen for chiclero’s ulcer still remains to be specified based on the fact that a cure rate of 100% has been achieved without relapse in this area. Trials of a lower daily dose or of a shorter duration should be undertaken.

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