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## EFFICACY AND TOXICITY OF PENTOSTAM AGAINST PANAMANIAN MUCOSAL LEISHMANIASIS

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**Abstract.** We tested the World Health Organization (WHO) recommended treatment for mucosal leishmaniasis in 16 Panamanians with disease due to *Leishmania braziliensis panamensis*. Disease was mild in this population because it was limited to the nasal mucosa and only one patient had septal perforation. The patients were administered 20 mg antimony (in the form of Pentostam) per kg intravenously each day for 28 days. Ten patients completed therapy and were cured at 12 month follow-up. Three patients completed therapy, healed their lesions, but relapsed at the six or 12 month follow-up. Three patients terminated therapy prematurely because of liver enzyme elevations in conjunction with either EKG abnormalities or musculoskeletal complaints; none of these patients were healed. This study indicates that in patients with mild mucosal leishmaniasis, the WHO regimen is curative in 77% patients who complete treatment and in 63% of all patients.

Infection of the oro-nasal mucosa with organisms of the *Leishmania braziliensis* complex (mucosal leishmaniasis) is a rare sequela to infection of the skin (cutaneous leishmaniasis). Most cases of mucosal leishmaniasis occur 2-10 years after a cutaneous lesion has self-healed, and are assumed to be due to hematogenous or lymphatic dissemination of organisms. In addition, the nasal mucosa can be involved by contiguous spread of cutaneous lesions on the face. Although the natural history of mucosal leishmaniasis is not clearly defined, "single nasal lesions often remain stationary for years, [but] multiple mucosal lesions may show relentless progression if treatment is not instituted."<sup>1</sup> Progression of disease in the nose results in septal perforation and/or anterior nares collapse. Involvement of more distal structures in the oro-pharynx can lead to loss of the uvula, gluing of the soft palate to the posterior oropharyngeal wall, and narrowing of the oral canal due to tonsillar fibrosis.

The World Health Organization's recommendations for the treatment of mucosal leishmaniasis are as follows: "Pentavalent antimony. . . is considered the drug of choice, being used in widely differing regimens. Single daily doses of Sb (antimony) of 20 mg/kg body weight are given. . . for a minimum period of four weeks. If toxic effects develop, or if the response is poor, an Sb dose of 10-15 mg/kg body weight may be given 12-hourly."<sup>2</sup> These recommendations convey the uncertainty about the efficacy and toxicity of recommended therapy for this disease.

We administered the WHO recommended regimen of Sb (20 mg Sb/kg/day for 28 days) to 16 patients with Panamanian mucosal leishmaniasis to determine the efficacy and toxicity of the recommended regimen.

### MATERIALS AND METHODS

#### *Patient eligibility*

Patients of either sex and at least 18 years of age were eligible for the study if they had a mucosal lesion from which *Leishmania* were seen or cultured, or if the patient was positive on the Montenegro skin test. Visualization of *Leishmania* was accomplished by Giemsa staining of impression smears of biopsy specimens. Culture of *Leishmania* was accomplished by applying biopsied material to Senckji's medium.<sup>3</sup> Cultured organisms were speciated by isoenzyme electrophoresis. The Montenegro skin test consists of subcutaneous inoculation of 0.1 ml of sonicated, sterilized *Leishmania braziliensis panamensis* promastigotes. Five (5) mm or more induration two days later signifies a positive test and that the patient has been sensitized to *Leishmania* antigen. Eligible patients were excluded from the study if they had received anti-leishmanial therapy in the prior six months, if they had significant disease other than leishmaniasis, or if they had significant abnormalities on subsequent laboratory tests [chest roentgenogram, EKG, hemoglobin, white cell count, platelet

count; urinalysis; blood urea nitrogen, serum glucose, serum glutamyl oxalate transferase (SGOT), serum glutamyl transferase (SGPT), and bilirubin]. Patients who were eligible and who signed informed consent were entered into the study. Patients were entered into the study between November, 1987 and June, 1989.

#### *Treatment of patients*

Patients were hospitalized in the Ear-Nose-Throat service of Santo Tomas Hospital, in Panama City, Panama. Each was treated with 20 mg Sb (antimony) in the form of Pentostam (sodium stibogluconate)/kg/day, intravenously, for 28 days. Patients were evaluated daily during treatment for vital signs and for the subjective complaints of arthralgia, myalgia, headache, nausea, abdominal pain, diarrhea, and anorexia; twice a week for EKG changes; and weekly for changes in laboratory parameters. Patients were seen at follow-up approximately 1, 3, 6, 9, and 12 months after the end of the one-month period of treatment. Three patients prematurely terminated therapy due to apparent drug toxicity. One of these, #13, removed himself from the study and was lost to follow-up.

#### *Definition of lesion healing, cure, and failure*

A stringent definition of lesion healing was used: the ulcerative or infiltrative lesion had to completely re-epithelialize or completely flatten to be defined as healed. A cured lesion was a healed lesion that did not relapse during follow-up. A failed lesion was a lesion that never initially healed, or that relapsed.

### RESULTS

#### *Patient characteristics*

There were 16 patients in the study (Table 1). Of the 16, 9 were female and 7 were male. Thirteen of the 16 were 18–33 years of age; one patient each was 53, 61, and 74 years old. Their mean weight was  $57 \pm 8$  kg (mean  $\pm$  SD).

#### *Presenting lesions*

All patients had ulcerative or infiltrative lesions and all except two had disease that primarily involved the nasal septum. Patient #3 had

an nasal alae ulcer, and patient #6 had a turbinate infiltrate that did not involve the septum. Only one patient (#5) demonstrated septal perforation. None had disease of the pharynx or larynx. Although four patients had concomitant infection of the skin, in two of these cases (patients #2 and #16) the skin on the tip of the nose was infiltrated, and such lesions may simply have been extensions of the underlying septal infiltration. There were two cases, however, in which there was simultaneous cutaneous disease, in one case (patient #3) of the cheek, and in the second case (patient #11) of the thigh.

Seven patients had scars on the extremities signifying cutaneous lesions that had previously healed. The time between the cutaneous disease and the onset of mucosal symptoms in these patients (#s 4, 5, 6, 7, 8, 9, and 12) was reported to be 2, 25, 6, 7, 7, 27, and 4 years, respectively.

#### *Presenting symptoms*

All patients reported nasal obstruction. Approximately half reported rhinorrhea, epistaxis, and pruritis; and approximately one-quarter had nasal pain and bleeding. In 14 patients, these symptoms had been present a mean of 14 months (range 2–36 months). In the two oldest patients, symptoms were reported for 14 and 30 years.

#### *Parasitology*

All 16 patients were positive by the Montenegro skin test. In 13 patients, *Leishmania* amastigotes were visualized in Giemsa-stained lesion biopsies. In three cases, *Leishmania* promastigotes were grown from lesion material, and all promastigotes were characterized by isoenzyme electrophoresis to be *L. b. panamensis*.

#### *Efficacy of treatment*

All 20 mucosal and skin lesions on the 16 patients healed or improved at the end of the one month period of Pentostam therapy. Specifically, two of the mucosal lesions healed and the other 14 mucosal lesions improved; the cheek and thigh skin lesions healed and the two nasal skin lesions improved. Of the 16 improved mucosal or nasal skin lesions, 14 continued to improve over the next nine months. Because the criteria for healing in this study, complete re-epithelialization of the ulcer and loss of all infiltrates, were stringent,

TABLE  
Patient clinical data

Patient no.	Anatomic region	Lesion pre-RX	Lesion post-RX	Lesion 1 m	Lesion 6 m	Lesion 9 m	Lesion 12 m	Final result
Patients who cured								
1	Septum	ulcer	Heal	NC	—	NC	NC	Heal RX
3	Alae	ulcer	Heal	NC	NC	—	NC	Heal RX
	Cheek	ulcer	Heal	NC	NC	—	NC	Heal RX
5	Septum	perforation erythema	Improve	Improve	Heal	NC	NC	Heal 6 m
6	Turbinates	infiltrate	Improve	Heal	NC	NC	NC	Heal 1 m
7	Septum-turbinates	infiltrate	Improve	Heal	NC	NC	NC	Heal 1 m
8	Septum-turbinates	infiltrate	Improve	Improve	NC	Heal	NC	Heal 9 m
9	Septum	ulcer	Improve	NC	Heal	—	NC	Heal 6 m
10	Septum	infiltrate	Improve	NC	NC	Heal	NC	Heal 9 m
14	Septum	infiltrate	Improve	Heal	NC	NC	erythema	Heal 1 m
16	Septum	infiltrate	Improve	NC	Heal	—	—	Heal 6 m
	Nasal skin	infiltrate	Improve	NC	Heal	—	—	Heal 6 m
Patients who failed								
2	Septum-turbinates	infiltrate	Improve	Heal	Relapse (P)	—	NC	Relapse 6 m
4	Nasal skin	infiltrate	Improve	Heal	NC	—	NC	Heal 1 m <sup>†</sup>
	Septum	ulcer	Improve	Heal (at 3M)	NC	—	Crust (P)	Relapse 12 m
12	Septum	infiltrate	Improve	Improve	Heal	NC	Crust	Relapse 12 m
11*	Septum	ulcer	Improve	Worse	NC	NC	—	Not Heal
	Thigh	ulcer?	Heal	NC	NC	NC	—	Heal RX
13**	Septum-turbinates	infiltrate	Improve	—	—	—	—	(lost to follow up)
15***	Septum	infiltrate	Improve	Heal	NC	Relapse	—	Relapse 9 m

NC signifies no change from previous examination.

(P) signifies that parasites were seen in relapsed lesion.

\* 13 days of therapy.

\*\* 21 days of therapy.

\*\*\* 14 days of therapy.

Termination of healing was officially delayed until the six or nine month follow-up examinations in many cases.

Two improved mucosal lesions that did not progress to healing were in patients #11 and #13 who terminated therapy after 13 and 21 days, respectively.

There were four lesions that relapsed. One lesion was on the third patient (#15) who prematurely terminated therapy. Three lesions were on patients #2, #4, and #12. In patient #2 and #4 clinical relapse was confirmed by the presence of parasites in lesion material.

#### Toxicity of treatment

Subjective musculoskeletal complaints were common in this study: 10 of the 16 patients (62%) had arthralgias and nine of 16 (56%) had myalgias. Abdominal complaints were less frequent in that only 2 patients had either nausea, abdominal pain, diarrhea, or anorexia.

Six of the 16 patients (37%) had abnormalities of liver function tests signified by elevations of both SGOT and SGPT. Patient #5 had elevated values at weeks 1 and 2 of therapy (SGPT = 115), but the values normalized by week 3 (SGPT = 36) in spite of continued therapy. Patient #8 demonstrated a striking rise of values in week 3 of therapy (SGPT = 219), but this too decreased one week later in spite of continued therapy (SGPT = 110). In patient #16, the SGPT rose to 88 in week 2, but then decreased to 55 by week 4 in spite of continued therapy.

There were three patients in whom therapy was prematurely terminated because of high liver function tests in conjunction with other evidence of drug toxicity. Patient #11 had a significant increase in SGOT (= 82) by week 2. This patient also experienced severe arthralgias, myalgias, and headaches, and her white blood cell count had decreased from 5, 100/mm<sup>3</sup> pre-therapy to 2, 300/mm<sup>3</sup> at week two. Therapy was stopped on day 13. The SGOT rose to 126 by week 3 but decreased to 84 by week 4 after the beginning of therapy. The white count recovered to 4,000/mm<sup>3</sup> by week 3. Patient #13 had only modest elevations of liver function tests by week 3 (SGPT = 59), but premature ventricular contractions seen on EKG caused therapy to be terminated on day 21. The third patient in whom therapy was terminated prematurely was #15, in whom modest changes in liver function tests (SGOT =

71) and in T-wave height on EKG coupled with significant nausea, diarrhea, and fever caused therapy to be discontinued on day 14.

#### DISCUSSION

The object of this study was to determine the efficacy and toxicity of the treatment regimen recommended by the World Health Organization to treat mucosal leishmaniasis: 20 mg Sb (in this case in the form of Pentostam)/kg/day for 28 days. The etiologic cause of mucosal leishmaniasis in this series of Panamanian patients was almost certainly *L.b. panamensis*. In all three cases in which parasites were grown from biopsy material, the organisms were typed by isoenzyme electrophoresis as *L. b. panamensis*. In addition, in previous cases of mucosal leishmaniasis that we have diagnosed in Panama, *L. b. panamensis* grew from all of seven lesions from which parasites could be cultured.<sup>4</sup> Also, during this time period *L. b. panamensis* grew from 36 of 37 cutaneous lesions from which parasites were cultured.<sup>5</sup>

A common presentation of mucosal leishmaniasis is mucosal infiltrates or ulcers in a person with scars indicative of cutaneous disease, which is self-reported to have healed 2-10 years previously.<sup>1-6</sup> Our patients were somewhat unusual in that only seven of 16 patients had cutaneous scars, and two patients had concomitant active cutaneous disease. The etiology of mucosal disease in these two cases could either be sand-fly bites of the skin and nasal mucosa simultaneously, or very rapid spread of organisms from a primary cutaneous site of disease. Our series confirms the literature in that the time between previous cutaneous disease and mucosal disease generally varied from two to seven years.

The electrocardiographic, hepatic, and symptomatic adverse effects of the WHO regimen are to some extent known. Pentostam treatment results in EKG abnormalities (generally T-wave depression or inversion) whose incidence is proportional to the total amount of Sb administered,<sup>7</sup> and Marsden and others have reported that 30% of their 12 patients experienced EKG abnormalities.<sup>6</sup> Although several of our patients experienced T-wave depression, the only major EKG abnormality evidenced in this study was premature ventricular contractions in one patient. It is unclear if this EKG finding was related to therapy, but treatment was stopped as a pre-

caution. Our experience of a 37.5% incidence of hepatic enzyme abnormalities was confirmatory of the work of Marsden and others, who reported a 26% incidence of abnormalities in Brazilian patients,<sup>6,8</sup> and of Franke and others, who reported a 35% incidence in Peruvian patients.<sup>9</sup> It is clinically useful to note that in three patients in which liver function test abnormalities were unaccompanied by other toxic manifestations we continued therapy, and the values either leveled off or decreased in spite of further therapy, also confirming the Peruvian experience.<sup>9</sup> Our demonstration of an approximately 60% incidence of subjective musculoskeletal complaints also confirms the Brazilian experience in which a 90% incidence of arthralgia, a 45% incidence of myalgia, and a 30% incidence of anorexia was found.<sup>6</sup> The combination of liver function abnormalities and subjective complaints led to discontinuation of therapy in two patients.

Mild mucosal disease may be defined as disease that only involves the nasal mucosa, whereas moderate disease would signify nasal disease with septal perforation and severe disease would signify disease involving more distal parts of the oropharynx. Since almost all (15 of 16) patients had non-perforating disease of the nasal mucosa, this was a study of mild mucosal disease. Ten of the 16 patients (63%) were cured in the sense that their mucosal lesions healed and remained healed throughout follow-up. Because three of the 16 patients prematurely terminated therapy due to drug toxicity, the cure rate in those who completed 28 days of therapy was 10/13, or 77%.

We are only able to locate two series in the English literature that address the question of the cure rate of the WHO recommended regimen. In Brazil, 11 of 12 patients (92%), administered either Glucantime or Pentostam, 20 mg/kg/day of Sb for a mean of 30 days, were cured within a mean follow-up period of 8 months.<sup>6</sup> The lack of details of case presentation and follow-up in the Brazilian work makes a comparison with our work difficult. In addition, Franke and others have recently published a study using the exact regimen of Pentostam used here, but on a patient population infected with *L. b. braziliensis* in which eight patients had mild disease and 21 patients had severe disease. In the Peruvian study, six of the eight patients with mild disease, but only two of the 21 patients with severe disease,

were cured.<sup>9</sup> The present report indicates that the WHO recommended Sb regimen is quite effective for patients with mild disease due to *L. b. panamensis*. The clinical failure of all patients in our series who received an abbreviated regimen because of drug toxicity suggests that the full 28 days of therapy may be needed to cure mild disease. The work by Franke and others suggests that more Sb than that provided by the 28 day regimen is needed to cure severe disease.

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Ethical Review: This protocol was approved by the human use committees of the respective institutions and by the the US FDA. Each patient in the study signed informed consent.

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