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EFFICACY OF 28-DAY AND 40-DAY REGIMENS OF SODIUM STIBOGLUCONATE (PENTOSTAM) IN THE TREATMENT OF MUCOSAL LEISHMANIASIS

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Abstract. The efficacy and toxicity of two regimens of antimony, 28 and 40 days of 20 mg of antimony/kg/day, were compared in the treatment of culture-positive mucosal leishmaniasis involving more than one anatomic site. Forty consecutive eligible Peruvians with infiltrative or ulcerative mucosal disease of the lips, nose, palate-uvula-pharynx, or larynx-epiglottis were randomized to receive either 28 days (P28) or 40 days (P40) of sodium stibogluconate (Pentostam). Treatment was prematurely terminated due to thrombocytopenia in three patients and two patients did not complete six months of follow-up. At one month post-treatment, 13% (2 of 16) of the P28 patients and 16% (3 of 19) of the P40 patients no longer had infiltrates or ulcers and were initially considered cured. During a further 11 months of follow-up, infiltrated lesions healed in eight more P28 patients and in 10 more P40 patients. The cure rate after 12 months of follow-up was therefore 63% for both groups (10 of 16 in the P28 group and 12 of 19 in the P40 group). The total of 13 patients who had infiltrates or ulcers at the 9–12-month follow-up were considered failures. All seven patients (three in the P28 group and four in the P40 group) whose lesions were culture-positive for *Leishmania* at some point in the 12 months after treatment, and who were thereby parasitologic failures, were also clinical failures. Since the cure rates did not differ between the two treatment regimens, there is no therapeutic advantage to increasing the length of treatment with Pentostam to 40 days in patients with mucosal leishmaniasis involving more than one anatomic site.

The World Health Organization recommended regimen for the treatment of mucosal leishmaniasis is 20 mg of antimony (sodium stibogluconate [Sb])/kilogram of body weight/day for a minimum period of 28 days.[1] A recent study by Franke and others showed that this regimen, although safe, is ineffective in the treatment of mucosal leishmaniasis involving both the nasal and oral mucosa.[2] Although 75% of the patients with nasal lesions only were cured, the cure rate in patients with both nasal and oral lesions was only 10%. In a study done in India on the treatment of visceral leishmaniasis, Thakur and others showed that a treatment regimen consisting of 20 mg of Sb/kg/day for 40 days resulted in a significantly higher cure rate than the same dose given for 20 days.[3] Side effects were minor and included pain or swelling at the injection site (six patients), arthralgia (three patients), and neuralgic pain (one patient). These results suggested that lengthening Sb therapy to 40 days in mucosal patients might result in a higher cure rate.

We compared the efficacy of the 28-day regimen of Pentostam (20 mg of Sb/kg/day) with the 40-day regimen in patients with mucosal leishmaniasis involving more than one anatomic site.

PATIENTS AND METHODS

Patients

Patients were from the villages of Ocongate and Sicuani in the Department of Cusco, Peru. Leishmaniasis is not endemic in these villages and men acquired their disease through occupational exposure in the jungles of the Department of Madre de Dios. All patients were males because it is more common for men to work in the jungles (e.g., panning for gold and cutting wood). Women from Ocongate and Sicuani usually do not travel down to the jungle to work; therefore, mucosal leishmaniasis is relatively rare in these women. Leishmaniasis patients from these two villages have formed an associ-

ation and it is from this group that patients were selected. Consecutive persons clinically suspected of having mucosal leishmaniasis involving more than one anatomic site were potentially eligible for the study. The four anatomic sites that could be infected with *Leishmania* were the lips, nose (septum and turbinates), palate-uvula-pharynx, and larynx-epiglottis. Each mucosal site in each of the patients was examined and classified as being either ulcerated, infiltrated, edematous, or erythematous. Patients were included in the study if cultures prepared by inoculating aspirates from mucosal lesions into Senekji's blood agar medium[4] were positive for *Leishmania*. Patients were excluded if they had received antimonials for treatment of leishmaniasis in the previous 12 months, had significant concomitant disease of any organ, or had abnormalities on subsequent baseline tests (complete blood count; serum levels of glucose, glutamate-oxaloacetate transaminase, glutamate-pyruvate transaminase, bilirubin, urea nitrogen, and creatinine; electrocardiogram; chest radiograph). Patients were randomized to receive either the 28- or 40-day regimen of Pentostam.

The protocol for this study was approved by the Peruvian Ministry of Health, by the scientific and ethical review committees of the U.S. Naval Medical Research Institute Detachment, and by the U.S. Food and Drug Administration. Each patient gave informed consent.

Treatment course

After inclusion into the study, patients were admitted to Cusco Regional Hospital (Cusco, Peru) and administered Pentostam (20 mg of Sb/kg of body weight/day with no upper limit on the daily dose) for 28 days or for 40 days. Eight lots of Pentostam (Wellcome, Dartford, UK) were used; the lot numbers were B9664A, A9946A, A0676A, A0678A, D0282A, E0282A, A0925A, and A0677A. The daily dose of Pentostam was administered in 50 ml of 5% dextrose in water by intravenous infusion over a 30–45-min period. Patients were asked daily during treatment for symptomatic complaints including headache, dizziness, insomnia, nervousness, palpitations, abdominal pain, nausea, vomiting, diarrhea, anorexia, itching, backache, arthralgias, and myalgias. Electrocardiograms were obtained twice a week, and blood for complete blood counts and serum chemistries was obtained weekly.

Follow-up

The nasal, oral, pharyngeal, and laryngeal areas were examined at the end of therapy and the lesions were recultured at this time. The patients were re-examined at one, three, six, nine, and 12 months after the end of therapy, at which times cultures were taken when clinically indicated.

Definition of cure and failure

The ulcerated or infiltrated lesions were defined as healed if they re-epithelialized or became noninfiltrated, respectively, during the 12-month follow-up period. A nonhealed lesion was one that had not re-epithelialized or had not lost its infiltrate. A person was defined to be cured of mucosal leishmaniasis only if all of his lesions healed. A patient was defined to have failed therapy if any lesion did not heal, or relapsed, or if a new lesion appeared during the follow-up period. Lesions that were edematous or erythematous after treatment were considered healed if they did not become infiltrated or ulcerated during the follow-up period.

Identification of Leishmania

If cultures yielded a sufficient number of promastigotes, identification by isoenzyme analysis was done using cellulose acetate electrophoresis. The isolates were characterized for the following enzymes: phosphogluconate dehydrogenase, glucose phosphate isomerase, mannose phosphate isomerase, glucose-6-phosphate dehydrogenase, phosphoglucomutase, glutamate-pyruvate transaminase, and glutamate-oxaloacetate transaminase. The enzyme profile of each isolate was compared with those of the World Health Organization reference strains of *Leishmania braziliensis*, *L. guyanensis*, *L. panamensis*, *L. amazonensis*, and *L. mexicana*.

RESULTS

Patient characteristics and history of leishmaniasis

The characteristics and history of cutaneous and mucosal leishmaniasis in the 40 patients are summarized in Table 1.

TABLE 1

Patient characteristics by treatment regimen

	P28	P40
No. of patients	20 males	20 males
Age (years)	33.7 ± 7.3* (24–47)	30.7 ± 6.3* (22–42)
Weight (kg)	53.3 ± 4.7* (45–65)	53.3 ± 4.2* (47–61)
Cutaneous disease		
No. of patients with		
Lesion scars	19	18
Active lesions	0	1
Scars/lesions above the waist	10	7
Scars/lesions below the waist	14	13
No. years since appearance of first cutaneous lesion	7.4 ± 3.23* (0–12.8)	8.7 ± 5.8* (0–29)
No. who received prior Sb therapy	11	13
Mean total dose of Sb (grams)	4.64 ± 3.25* (1.28–12.75)	9.35 ± 13.2* (1.28–51.0)
Mucosal disease		
Duration in years	2.9 ± 2.1* (0.3–8.5)	2.9 ± 2.6* (0.2–10)
No. who received prior Sb therapy	6	2
Mean total dose of Sb (grams)	7.51 ± 5.24* (2.13–17.0)	4.47 ± 4.04* (0.43–8.5)

* Values are the mean ± SD (range)

Parasitology

Culture of at least one mucosal lesion on each patient was positive for *Leishmania* prior to therapy. Cultures from 35 patients grew sufficient numbers of promastigotes to be characterized by isoenzyme analysis. All 35 strains were *L. braziliensis*.

Response to therapy with Pentostam

Toxicity. Table 2 summarizes the subjective complaints of four or more days duration during treatment in the 40 patients. None of the subjective complaints was severe enough to warrant cessation of treatment. Although more P40 patients than P28 patients complained of arthral-

TABLE 2

Adverse effects of four or more days duration during treatment in the 20 P28 patients and the 20 P40 patients

	P28			P40		
		Day of onset			Day of onset	
Adverse effect	No.	Mean	Range	No.*	Mean	Range
Arthralgia	10	15	(2–24)	18 (2)	19	(1–29)
Myalgia	11	19	(10–25)	19 (3)	20	(1–32)
Pruritis	1	17	(17)	4 (2)	22	(13–29)
Rash	2	9	(6–11)	4 (2)	25	(6–34)
Nausea	6	11	(6–21)	6 (0)	13	(2–28)
Anorexia	3	14	(5–22)	5 (1)	12	(3–32)
Abdominal pain	3	17	(5–26)	4 (1)	20	(6–33)
Cough	5	15	(2–26)	4 (0)	8	(2–23)
Headache	7	14	(2–26)	3 (0)	8	(2–21)

* The number of patients who complained of side effects after day 28 is in parentheses

TABLE 3

History of leishmaniasis in patients by treatment group and outcome

	P28		P40	
	Cure	Fail	Cure	Fail
No. of patients	10	6	12	7
Cutaneous disease				
No. of years since appearance of first cutaneous lesion	6.6 ± 3.5* (0–11)	7.9 ± 3.4* (3.3–12.8)	7.4 ± 3.3* (0–29)	11.9 ± 8.2* (5–29)
No. (%) who received prior Sb therapy	3 (33)	4 (67)	9 (75)	4 (57)
Mean total dose of Sb (grams)	0.81 ± 1.5* (0–4.3)	4.6 ± 4.9* (0–12.8)	4.6 ± 4.9* (0–51)	8.8 ± 18.8* (0–51)
Mucosal disease				
Duration in years	2.6 ± 2.4* (0.3–8.5)	3.9 ± 2.2* (1–6.8)	2.7 ± 2.9* (0.2–10)	3.6 ± 2.5* (1.4–9)
No. (%) who received prior Sb therapy	3 (33)	3 (50)	0 (0)	2 (29)
Mean total dose of Sb (grams)	3.2 ± 5.9* (0–17)	2.2 ± 3.3* (0–8.5)	0.0* (0–17)	1.3 ± 3.2* (0–8.5)

* Values are the mean ± SD (range).

gias and myalgias, most complaints began before day 28.

Treatment was suspended prior to the end of therapy in two P28 patients (#377 and 763) patients and one P40 patient (#493) due to thrombocytopenia. Treatment was stopped on day 6 in patient #377 (pretherapy platelet count = 155,000/mm^3, day 6 count = 46,000), on day 12 in patient #763 (pretherapy count = 395,000, count on day 12 = 88,000), and on day 34 in patient #493 (pretherapy count = 295,000, count on day 34 = 20,000).

Treatment was suspended for two days in one patient due to an abnormally high potassium level measured on day 7. Another sample of the patient's blood was taken on day 8 and all blood chemistry results were normal; treatment was resumed on day 9 and this patient received the full 40-day course of therapy.

Clinical and parasitologic response

Of the 37 patients who completed all therapy, two were not seen at the 6–12-month follow-up examinations. One month after the end of therapy, ulcerative or infiltrative lesions had healed in two patients in each group. After 11 months of further follow-up, infiltrative lesions healed in seven more of the P28 patients and in 10 more P40 patients. One patient in the P28 group not seen at the one-month follow-up also healed by the end of the 12-month follow-up. Therefore, 10 of the 16 patients (63%) that completed the 28-day course of therapy and 12 of the 19 patients (63%) that completed the 40-day regimen had no ulcers or infiltrates at the end of the 12-month follow-up period and were considered cured.

The 13 patients who failed treatment had a total of 30 ulcerative or infiltrative lesions at the completion of follow-up (9–12 months after therapy, except patients #113, 189, and 411 who became culture-positive after therapy and were not followed beyond six months). Of these 30 lesions, 18 (60%) had never healed, 11 (37%) healed soon after therapy but then relapsed, and one (3%) lesion was new. Cultures positive for *Leishmania* were obtained from one patient in the P40 group immediately after treatment, and during the follow-up period from three patients in the P28 group (one each at three, six, and 12 months) and three patients in the P40 group (one at six months and two at nine months). All seven patients demonstrated clinical failure as well as parasitologic failure.

We attempted to identify patient characteristics that might account for, and be used to predict, cure or failure to cure. Table 3 summarizes the history of leishmaniasis in patients by treatment group and outcome. Although there were no statistically significant differences in the amount of Sb received prior to entrance into the study or in the duration of disease in the patients that cured versus those that failed, patients that failed therapy tended to have received more Sb

prior to therapy and to have had leishmaniasis for a greater length of time.

DISCUSSION

Our previous study showed that the 28-day regimen of Pentostam was ineffective in the treatment of severe mucosal leishmaniasis (disease involving the oral cavity as well as the nose).[2] A study by Thakur and others in India on the treatment of visceral leishmaniasis indicated that a regimen of 40-days of Pentostam resulted in a higher cure rate than a 28-day regimen.[3] The objective of the present study was to determine whether a 40-day regimen of sodium stibogluconate (Pentostam) would similarly be more effective than a 28-day regimen in the treatment of severe mucosal leishmaniasis. Results at the 12-month follow-up examination indicated that the cure rate in the two groups was the same, 63% (10 of 16 in the P28 group and 12 of 19 in the P40 group). There was no therapeutic advantage to increasing the length of treatment with Pentostam to 40 days in patients with disease involving more than one mucosal site.

The percent cure in both treatment groups in this study, 63%, is greater than the percent cure in patients administered 20 mg of Sb/kg/day for 28 days in our previous study (2 of 21 [10%]).[2] The previous study cohort did not differ from the present patients in time since initiation of cutaneous disease (mean of 8.1 years in the previous study versus 8.0 years in the present study) or in duration of mucosal lesions before treatment (mean of 3.0 years in the previous study versus 2.9 years in the present study). Phenomenologically, in the previous study, lesions that had apparently cured at the end of therapy frequently relapsed by the end of follow-up. Forty-nine apparently cured lesions relapsed, whereas only four lesions that improved after therapy continued to heal during follow-up. In contrast, in the present study, only eight initially healed lesions relapsed, but 23 lesions that improved soon after therapy continued to heal with further follow-up. We have no explanation for the tendency towards relapse in the previous study and the tendency towards continued improvement after therapy in the present study. However, the protocols for both studies were similar, the only difference being that in the present study, follow-up examinations were done at one, three, six, nine, and 12 months, whereas in the previous study, there was no one-month follow-up examination.

The most common side effects that did not require cessation of treatment were arthralgias and myalgias, which affected 70% (28 of 40) and 75% (30 of 40) of the patients, respectively. Arthralgias and myalgias are well-known side effects of antimony therapy, and were also common in our previous study in which 83% (24 of 29) of the patients who received the 28-day regimen of Pentostam complained of arthralgias and myalgias.[2] Treatment was also suspended prior to the end of therapy due to thrombocytopenia in three patients (2 of 20 P8 patients and 1 of 20 P40 patients). In our previous study, therapy was discontinued in one of 29 patients due to thrombocytopenia.[2]

Our data show that patients who failed therapy tended to have received more Sb prior to therapy and to have had leishmaniasis for a longer period of time. Greater exposure to antimony could lead to a greater possibility of parasite resistance to the drug;[5] longer duration of disease could lead to greater extent of disease within an anatomic site.

The combination of the results of the previous study with those of the present study indicates that in severe (multi-anatomic) mucosal leishmaniasis, the cure rate with 28 days of Pentostam may vary from 10% to 63%. Increasing the duration of therapy to 40 days does not appear to improve this cure rate. Cure, when it occurs, will be due both to an initial response to therapy and to continued amelioration of lesions during a year of follow-up. It is important to treat mucosal lesions as soon as they are recognized, since the longer the duration of mucosal lesions, the higher the chance for failure. Because of widely different rates of cure in different studies, close observation of the patient during 12 months of follow-up is essential to verify that treatment is effective.

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