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COMPARISON OF MEGLUMINE ANTIMONIATE AND PENTAMIDINE FOR PERUVIAN CUTANEOUS LEISHMANIASIS

ELLEN M. ANDERSEN, MARIA CRUZ-SALDARRIAGA, ALEJANDRO LLANOS-CUENTAS, MARIA LUZ-CJUNO, JUAN ECHEVARRIA, CESAR MIRANDA-VERASTEGUI, OLGA COLINA, AND JONATHAN D. BERMAN

Navy Environmental and Preventive Medicine Unit No. 5, San Diego, California; Hospital Instituto Peruano Seguro Social, Cusco, Peru; Universidad Peruana Cayetano Heredia; Lima, Peru; National Center for Complementary and Alternative Medicine, National Institutes of Health, Bethesda, Maryland

Abstract. Pentamidine was compared with meglumine antimoniate (Glucantime) for 80 patients with cutaneous leishmaniasis due to *Leishmania braziliensis* in Peru. Of the 40 patients administered Glucantime (20 mg of antimony [Sb]/kg/day intravenously for 20 days), 31 cured (78%), 6 failed (15%), of which 5 were due to relapse, and 3 were lost to follow-up (7%). Of the 40 patients administered pentamidine (2 mg/kg every other day for seven injections), 14 were cured (35%), 23 failed (58%), and 3 were lost to follow-up (7%). Five pentamidine failures were due to relapse, and 14 failures were due to the presence of parasites two weeks after therapy. Both regimens were well tolerated. Gastrointestinal, musculoskeletal, and total adverse events were not statistically different in either group. Elevations in levels of liver enzymes and pancreatic enzymes were statistically higher in the Glucantime group, but no patient terminated therapy prematurely. In this study, Glucantime was more effective than pentamidine for treatment of *L. braziliensis* cutaneous leishmaniasis in Peru based on parasitologic as well as clinical criteria.

INTRODUCTION

In spite of major advances in the treatment of visceral leishmaniasis with liposomal amphotericin B and miltefosine, American cutaneous leishmaniasis is still primarily treated with pentavalent antimony (Sb). In South America, the form of Sb used is meglumine antimoniate (Glucantime). The standard regimen is 20 mg of Sb/kg/day parenterally for 20 days.[1] Chemotherapeutic agents are evaluated on the basis of efficacy, tolerance, and feasibility of administration, including ease of administration. Each of these parameters is problematic for Glucantime. Treatment may fail: the range of previously reported cure rates from large studies in Colombia is 79–93%.[2,3] Mild side effects such as myalgia, arthralgia, and elevation of levels of liver function enzymes can occur, but severe adverse events are rare.[4] In one report, 16 of 17 Pentostam-treated patients exhibited pancreatic enzyme abnormalities, and therapy was interrupted in 10 of the 17 patients because of abdominal complaints.[5] It bears mention that receiving injections for 20 consecutive days is onerous.

Colombian investigators, following initial reports from French Guiana,[6] have had success with pentamidine treatment of cutaneous leishmaniasis. Pentamidine is an excellent antileishmanial agent *in vitro*.[7] The rationale behind treatment of cutaneous leishmaniasis is to administer a dose far lower than the dose used for *Pneumocystis* pneumonia (4 mg/kg each day for 14–21 days)[8] so as to avoid significant pentamidine toxicity, but nevertheless be sufficiently high to provide efficacy. In Colombia against predominately *Leishmania panamensis* disease, the cure rates following treatment with 2 mg/kg administered every other day for seven injections was 23 of 24 evaluable patients (96%) with 3 patients lost to follow-up.[2] In that study, eight patients (30%) had mild-to-moderate adverse effects (myalgia, nausea, headache, lesion heat, pain, or metallic taste) and an additional four patients (15%) terminated prematurely because of hypotension (diastolic blood pressure < 45 mm of Hg), a low value for serum glucose (52 mg/dL), or severe myalgias and headaches.

Although pentamidine was compared with Glucantime in the Colombian pilot study, the comparison has not been repeated and the relative efficacies against different species of *Leishmania* are unknown. Furthermore, there is presently a greater concern about drug tolerance, necessitating a detailed examination of the relative toxicities of these two treatment regimens.

We compared the efficacy and tolerance of the standard regimen of Glucantime to this alternative regimen of pentamidine against cutaneous leishmaniasis due to *L. braziliensis* in Cusco, Peru in a trial conducted according to Good Clinical Practices.

MATERIALS AND METHODS

Study design. This study was an open-label, randomized comparison of meglumine antimoniate (Glucantime) to pentamidine isethionate (pentamidine) in 80 patients with Peruvian cutaneous leishmaniasis with post-therapy follow up at two weeks, three months, and six months. The first patient was randomized on March 1, 2001, the last patient took his or her last dose on December 11, 2001, and the final six-month follow-up was performed on June 17, 2002.

Patients. The patients lived in and around the city of Cusco, Peru and presented with a clinical diagnosis of cutaneous leishmaniasis. Inclusion criteria were an age between 18 and 60 years old; a parasitologic diagnosis of cutaneous leishmaniasis from a lesion; no evidence of mucosal involvement of the oropharynx; no previous use of anti-leishmanial drugs; no previously confirmed leishmaniasis (by scar or clinically compatible history); no use of hypoglycemic, nephrotoxic, or pancreatitis-inducing drugs; no acute or chronic medical condition; and not being pregnant or not nursing.

Pre-enrollment procedures to verify inclusion criteria included a complete blood count (white blood cell count with differential, platelets, hemoglobin), clinical chemistries (creatinine, aspartate aminotransferase [AST], alanine aminotransferase [ALT], glucose, lipase, magnesium, calcium, potassium), human chorionic gonadotropin (for female volunteers); electrocardiogram (ECG); and a chest radiograph.

Parasitologic investigations upon study entry consisted of examination of Giemsa-stained smears of the lesion scrapings, and culture of lesion aspirates. Infection was confirmed by either the demonstration of motile promastigotes in aspirate cultures or microscopic identification of *Leishmania*

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amastigotes in stained smears. *Leishmania* growing in culture were speciated on the basis of isoenzyme electrophoresis.[9]

Drug administration. Volunteers were randomized to receive pentamidine isethionate (Pentam; Fujisawa, Deerfield IL) or meglumine antimoniate (Glucantime; Rhone Poulenc Rorer, Paris, France) in a 1:1 allocation. Pentamidine isethionate was given intravenously at a dose of 2 mg/kg on alternate days for seven doses. Pentamidine isethionate consisted of 300 mg of lyophilized powder that was dissolved in 5 mL of sterile water prior to administration to give a final concentration of 60 mg/mL. The proper dose depending on the weight (0.033 mL/kg) of the volunteer was added to 100 mL of 5% dextrose in water and the resulting solution was infused intravenously over a 60–120-minute period. To prevent possible hypotension, the volunteer received a bolus of 500 mL of 0.9% NaCl both prior to and post pentamidine infusion. Glucantime was given intravenously at a dose of 20 mg (Sb)/kg/day for 20 days. The correct dosage to achieve 20 mg (Sb)/kg was added to 250 mL of 5% dextrose in water and infused over a 120-minute period. Patients who failed were given rescue therapy with Glucantime.

Evaluation of toxicity. Patients were monitored each treatment day for any changes in vital signs, or any complaints of pain or discomfort. Blood collection for a repeat of complete blood counts, blood chemistries, and EKGs was performed on treatment days 4, 8, and 12 for those receiving pentamidine and on days 4, 8, and 20 for those receiving Glucantime. Subjective adverse events were graded on a 1 to 4 scale according to the Common Toxicity Criteria (CTC) scale of the National Cancer Institute.[10]

Evaluation of efficacy. Lesions were re-measured during follow-ups at two weeks, three months, and six months after the end of treatment. Lesions that had not completely re-epithelialized underwent repeat parasitologic investigation. Lesion sizes were measured in length and width using calipers, and lesion area was calculated at enrollment and at the three follow-up points by the same study physician throughout the duration of the trial. Complete clinical response was defined as 100% re-epithelialization of the lesion. Clinical improvement was defined as 75–99% re-epithelialization of the lesion compared with the previous measurement. Clinical failure was defined as a greater than 50% enlargement of the lesion at any time in comparison to the previous measurement. "Clinical relapse" was an enlargement of a previously clinically responsive or clinically improved lesion, a new lesion at the original site, or a new lesion along the lymphatic drainage of the original lesion. Parasitologic cure was defined as the inability to culture or stain parasites from the lesion and parasitologic failure was the presence of culturable or stainable parasites.

Definitions of lesion cure and failure were based on both clinical and parasitologic criteria. Failure was defined as lesions that demonstrated clinical failure, clinical improvement with parasitologic failure, clinical relapse, or the lack of complete clinical response at six months. Cure was the opposite of failure. Any lesion that did not meet the definition of failure prior to the six-month follow-up and was completely re-epithelialized by that time was considered to be cured. For a patient to be considered cured, all lesions on the patient had to be evaluated as cured.

Ethical approval. The trial was reviewed and approved by the ethical committees of the Ministry of Health, Peru, and the University of Peru Cayetano Heredia. In addition, the study protocol was reviewed and approved by the Naval Medical Research Center Institutional Review Board (Protocol no. Naval Medical Research Center Detachment 2001.0012 (Department of Defense 31525) in compliance with all Federal regulations governing the protection of human subjects. The trial was monitored by the U.S. Army Medical Research and Material Command for conformity to Good Clinical Practices.

RESULTS

Patient characteristics. The characteristics of the 80 patients enrolled are shown in Table 1. The average patient was a 30-year-old man weighing 57 kg. The average number of lesions was two (one-third of which were on the arms and half of which were on the legs) that had been present for approximately four months. Cultures from 70 patients were typed. All were *Leishmania (Viannia) braziliensis.*

Efficacy. Efficacy data are shown in Table 2. In the Glucantime group, 31 (78%) patients cured, 6 patients failed, and 3 patients were lost to follow-up. The mean diminution in size of lesions by two weeks post-therapy was 72% (SD = 15%). Most of the six failures were due to relapse. For five patients, lesions that had initially improved or appeared healed then enlarged by 3–6-months post-therapy. In two of the five cases, clinical relapse was accompanied by the return of demonstrable parasites.

In the pentamidine group, 14 (35%) patients cured, 23 patients failed, and 3 patients were lost to follow-up. The difference between the Glucantime cure rate and the Pentamidine cure rate was highly statistically significant ($P < 0.001$, by chi-square test). The reason for the increased rate of failure for pentamidine was primarily the increased rate of lesions with demonstrable parasites when examined two weeks after therapy. Fourteen patients were parasitologically positive at this time and an additional 3 patients were parasitologically positive at the three-month follow-up, compared with none of the Glucantime patients. In contrast, the number of relapses in the pentamidine group (five) was identical to the number in the Glucantime group.

The pentamidine lesions that were parasitologically positive at two weeks had clinically responded to treatment to a lesser extent than did lesions that were parasitologically negative at that time. The mean diminution in size of parasitologically positive pentamidine lesions (52%) was less than the mean diminution in size of parasitologically negative pentamidine lesions (72%) and this difference was statistically significant ($P < 0.001$, by *t*-test). Nevertheless, all of the lesions

TABLE 1
Entrance characteristics of the study population

	Glucantime	Pentamidine
Age, years	28 (8.5)	31 (10)
Male/female	34/6	31/9
Weight, kg	56 (7.5)	57 (5.1)
No. of lesions	2.1 (1.7)	2.3 (1.8)
% on arms	35	34
% on legs	46	52
Duration of lesions (days)	134 (133)	119 (163)

* Values are the mean (SD) unless otherwise indicated.

TABLE 2
Efficacy of the two drugs tested*

	Glucantime	Pentamidine
No. randomized	40	40
No. cured (%)	31 (78)	14 (35)
No. failed (%)	6 (15)	23 (58)
Parasites at 2 weeks	0	14
Parasites at 3 months	0	3
Fail clinically at 3 months	1	1
Relapse at 3 months	1	1
Relapse at 3 months with parasites	2	1
Relapse at 6 months	2	2
Relapse at 6 months with parasites	0	1
No. lost (%)	3 (7)	3 (7)

* Values are number of patients in each outcome category.

that parasitologically failed at two weeks had diminished by at least 20% from their pre-therapy size, so none would have failed if judged solely by clinical criteria.

Tolerance. Tolerance data are shown in Tables 3 and 4. Subjective adverse events were evaluated by the National Cancer Institute NCI Common Toxicity Criteria (CTC) scale for which grades 1, 2, 3, and 4 essentially translate as mild, moderate, severe, and life-threatening.

Subjective events of grades 1–2 seen in this study are summarized in Table 3. These data are expressed in two ways: the number of patients experiencing the adverse event at any time, and the mean number of treatment days on which an adverse event occurred.

For example, 16 Glucantime patients and 23 pentamidine patients reported gastrointestinal events at some time during therapy. The average Glucantime patient experienced a gastrointestinal event on 0.50 of the 20 days during which Glucantime was given. To better compare side-effect incidence between pentamidine administered over a 12-day period and Glucantime administered over a 20-day period, the pentamidine incidence data was normalized to 20 days by multiplying the original data by 20/12, and the normalized data is presented in Table 3. Thus, if pentamidine had been given for 20 days, at least one adverse event would have occurred on 0.76 of 20 days in the pentamidine group.

Comparison of the number of patients who experienced side effects and the incidence of side effects for pentamidine to Glucantime shows that by both measures, the two drug regimens were comparable. Although total gastrointestinal symptoms and the individual symptoms of abdominal pain, vomiting, and diarrhea were greater on an absolute basis in the pentamidine group, the differences were not statistically significant in this study with n = 40 per group. The increase in total and individual musculoskeletal symptoms in the Glucantime group were not statistically higher than in the pentamidine group, although the increase in arthralgia incidence approached statistical significance ($P = 0.07$).

Common Toxicity Criteria grade 3 adverse events were rare. Two pentamidine patients reported grade 3 abdominal pain lasting 1 day, and one Glucantime patient experienced grade 3 abdominal pain lasting 2 days.

Laboratory values pretreatment and post-treatment are summarized in Table 4. There were no significant differences in mean values between the Glucantime or pentamidine groups in the formed elements of the blood, electrolytes, or creatinine, and no clinically significant abnormalities in individual patients.

For blood glucose, mean values at the end of therapy did not differ between the groups and no individual value was outside the range of 61–107 mg/mL. Similar data were seen on days 4 and 8 of therapy. On day 4 of therapy, the mean glucose level was 79 mg/dL with no value < 60 mg/dL for pentamidine, and 81 mg/dL with no value < 62 mg/dL for Glucantime. On day 8 of therapy, values were 77 mg/dL with no value < 63 mg/dL for pentamidine, and 79 mg/dL with no value < 64 mg/dL for Glucantime.

Levels of AST were significantly elevated in Glucantime patients compared with pentamidine patients, although no value at the end of therapy exceeded 174 IU and levels of ALT was not statistically elevated. In the Glucantime group, pancreatic lipase values increased to a mean of 61 on day 4, to

TABLE 3
Subjective adverse events

Adverse event	No. of glucantime patients*	Incidence in glucantime group, per 20 days†	No. of pentamidine patients*	Incidence in pentamidine group, normalized to 20 days†
All adverse events	36	0.77 (0.74)	35	0.77 (0.87)
All gastrointestinal events	16	0.50 (1.9)	23	0.76 (2.2)
Nausea	3	0.2 (0.97)	4	0.17 (0.86)
Abdominal pain	15	1.4 (3)	22	2.1 (2.6)
Vomiting	1	0.02 (0.16)	3	0.13 (.45)
Diarrhea	4	0.35 (1.6)	5	0.67 (3.2)
All musculoskeletal events	20	1.0 (2.2)	16	0.65 (2.0)
Arthralgia	6	0.82 (1.9)	3	0.21 (0.77)
Myalgia	8	0.47 (1.6)	2	0.21 (0.86)
Sciatica	15	1.7 (2.7)	12	1.5 (3.0)
Lesion pain	4	1.0 (3.6)	6	1.4 (4.4)
Paresthesia	7	0.25 (0.59)	2	0.38 (2.1)
Fever or chills	7	0.25 (0.58)	3	0.13 (0.45)
Bad taste	8	0.6 (1.7)	7	1.2 (3.6)
Headache	33‡	2.5 (2.4)	20‡	2.5 (4.2)
Cough	7	1.2 (3.2)	2	0.21 (1.1)

* Values are the number of patients reporting the adverse event at some time during the treatment course.
† Values are the mean (SD) of the number of days during treatment that the adverse event occurred. Because Glucantime was given for 20 days but pentamidine was given for 12 days, the values for the pentamidine group based on 12 days were normalized to 20 days by multiplying by 20/12 = 1.67. All comparisons between Glucantime and pentamidine had P values > 0.05 (by t-test). For arthralgia and for cough, $P = 0.07$.
‡ $P < 0.01$, by chi-square test.

TABLE 4
Laboratory values at baseline and the end of treatment*

	Baseline		End of treatment	
	Glucantime	Pentamidine	Glucantime (on day 20)	Pentamidine (on day 12)
Hb g/dL	16	16	17 (≥ 13)	17 (≥ 12)
WBCs × 10^3/mL	7.7	7.9	6.9 (≥ 3.4)	8.0 (≥ 4.8)
Platelets × 10^6/mL	352	341	338 (≥ 91)	368 (≥ 297)
AST, U/L	24	27	42 (≤ 174)†	27 (≥ 59)†
ALT, U/L	28	31	59 (≤ 294)‡	43 (≤ 115)‡
Lipase, U/L	38	40	71 (≤ 231)§	38 (≤ 127)§
Glucose, mg/dL	77	79	78 (63–107)	76 (61–94)
K, mmol/L	4.4	4.2	4.1 (≥ 3.4)	4.3 (≥ 3.7)
Ca, mmol/dL	2.4	2.3	2.4 (≥ 2.0)	2.3 (≥ 1.9)
Mg, mmol/L	0.84	0.83	0.86 (≥ 0.70)	0.80 (≥ 0.67)
Creatinine, mg/dL	0.72	0.70	0.70 (≤ 1.0)	0.74 (≤ 1.0)

* Data are the mean values at baseline, and the mean (relevant range) of values at the end of therapy. Hb = hemoglobin; WBCs = white blood cells; AST = aspartate aminotransferase; ALT = alanine aminotransferase.
† $P = 0.03$.
‡ $P = 0.14$.
§ $P = 0.003$. Lipase on day 4 was 61 (≤ 141) in the Glucantime group versus 37 in the pentamidine group; $P = 0.001$. Lipase on day 8 was 73 (≤ 141) in the Glucantime group versus 40 in the pentamidine group; $P = 0.005$.

73 on day 8, and were then maintained at 71 at the end of therapy. All these values were significantly greater than those in the pentamidine group, which had not changed from the pre-therapy values.

Electrocardiograms in the Glucantime group did not change significantly due to therapy. On each occasion during which ECGs were performed, there were 2–3 patients with insignificant right bundle branch conduction abnormalities, and 2–3 patients with transitory t-wave abnormalities.

The pentamidine patients had mean (SD) blood pressures of 108 (12) systolic and 66 (9) diastolic upon study entry. Subsequently, blood pressure was measured four times for each infusion of drug: prior to the procedure, after the 500 mL of intravenous (IV) saline that preceded pentamidine infusion, after pentamidine infusion, and after an additional 500 mL of IV saline. When the blood pressure after pentamidine infusion was subtracted from the blood pressure just prior to pentamidine infusion, the mean (SD) change in systolic and diastolic blood pressures were as follows: first infusion: 0 (18) systolic and 3 (8) diastolic; second infusion: –1 (9) systolic and 4 (11) diastolic; third infusion: 1 (11) systolic and 2 (10) diastolic; fourth infusion: –1 (9) systolic and –1 (10) diastolic; fifth infusion: –2 (9) systolic and 1 (11) diastolic; sixth infusion: 1 (16) systolic and 1 (9) diastolic; seventh infusion: –1 (8) systolic and 0 (8) diastolic. Thus the infusion procedure of saline, followed by pentamidine, followed by more saline, resulted in no significant changes in blood pressure due to drug administration.

DISCUSSION

Cutaneous leishmaniasis in and around Cusco, Peru is known to be caused by *L. braziliensis*. In a previous study, Lucas and others reported that of 66 organisms speciated, 64 were *L. braziliensis.*[11] All 70 organisms speciated in this trial were *L. braziliensis*. In the present study, the standard regimen of Glucantime was acceptably effective in patients with this disease. The Glucantime cure rate was 31 (78%) of 40 randomized patients and 31 (84%) of 37 evaluable patients. The rate of cure for Glucantime against presumed *L. braziliensis* in Peru was similar to that of Glucantime against *L. panamensis* in Colombia: 79–84% of all patients and 84–93% of evaluable patients.[2,3]

In contrast, pentamidine at 2 mg/kg on each of seven alternative day injections was surprisingly ineffective in our study. The pentamidine cure rate was 14 of 40 (35%) randomized patients and 14 of 37 (38%) evaluable patients. Most of the pentamidine failures were due to the demonstration of parasites two weeks after therapy. Although these lesions were statistically larger than those on parasitologically negative patients, each of the parasitologically positive lesions were smaller than their pre-therapy size and would not have been judged failures on clinical grounds alone. If rescue therapy were not given to patients with parasitologically positive lesions at the two-week time point and these lesions had been followed clinically, and the lesions might have eventually reepithelialized and be declared cured. The scars of clinically cured *L. braziliensis* lesions in Brazil contain polymerase chain reaction–detectible parasite DNA in 94% of the cases.[12] If a few live parasites are present years after treatment in lesion scars, it is likely that live parasites in sufficient numbers to be seen by conventional parasitologic techniques are present soon after treatment in many lesions destined to cure. In clinical practice, patients are often evaluated according to clinical criteria alone, and many of the pentamidine patients that were declared failures at two weeks in the present study would not have been rescued at that time under clinical practice conditions.

The low cure rate for pentamidine in Peru can be compared with the high cure rates (96% per protocol and 85% intent-to-cure) in Colombia[2] and to a 87% cure rate in a retrospective study in Surinam in which 120 mg was administered on 7 consecutive days.[13] Solely clinical criteria were used in the Colombian and Surinam studies. The difference in cure rate between *L. panamensis* in Colombia and *L. guyanensis* in Surinam versus *L. braziliensis* in Peru could be due to the use of different efficacy criteria, to the different *Leishmania* species, or to a combination of both factors.

Irrespective of the absolute cure rate that would be expected for pentamidine in different circumstances, the relative cure rate for pentamidine compared with Glucantime was investigated in the present study. This trial demonstrates that

pentamidine is less effective than Glucantime under identical trial conditions.

Considerable effort was expended in investigating subjective and laboratory side effects under the conditions of Good Clinical Practices. Because this trial was not placebo controlled, side effects for each drug can be compared with the other drug but not to the effect of a placebo. Although this trial was open label, we believe that the patients were unlikely to exaggerate the side effects of one drug relative to the other because both drugs have the reputation of intolerance.

We were unable to identify significant differences between the Glucantime and pentamidine groups in subjective side effects with respect to their total number, the number of gastrointestinal side effects, or the number of musculoskeletal side effects. The particular reputation of antimonials for causing musculoskeletal side effects was not statistically confirmed in comparison to pentamidine with n = 40 per group, and in this perhaps stoic patient population. The high doses of pentamidine used for *Pneumocystis* pneumonia causes "significant azotemia, pancreatitis, hypoglycemia followed by hyperglycemia, leukopenia, thrombocytopenia, nausea, vomiting, orthostatic hypotension, and a bitter taste…",[8] but with the lesser dosage used here, nausea, vomiting, and altered taste were not statistically more frequent than for the Glucantime comparator.

In terms of laboratory values for pentavalent antimony, only lipase was statistically elevated compared with pentamidine. For pentamidine, the dose used here successfully obviated the laboratory abnormalities seen in *Pneumocystis* patients treated with this drug. No azotemia, pancreatitis, hypoglycemia or hyperglycemia, leukopenia, or thrombocytopenia was found in any of our patients. It is worth noting that no patient in either drug group prematurely terminated therapy because of adverse effects.

This study demonstrates that Glucantime, at 20 mg of Sb/kg/day intravenously for 20 days, can be confidently used for treatment of *L. braziliensis* cutaneous leishmaniasis in Peru. Patients will tolerate this regimen and the efficacy will approach 90%. Pentamidine, at the dose of 2 mg/kg every other day for seven injections, will also be tolerated. However, the efficacy of this regimen will be unacceptably low (< 40%) if parasitologic criteria are used to define failure. The difference between this cure rate and the high cure rate in Colombia could be due to the differing failure criteria used, or to an inherent difference in clinical responsiveness to pentamidine between *L. panamensis* and *L. braziliensis*. For *L. braziliensis* in Peru, pentamidine is more appropriate for rescue therapy after Glucantime failure than as an initial therapy to replace Glucantime.

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Authors' addresses: Ellen M. Andersen, Navy Environmental and Preventive Medicine Unit No. 5, Naval Station, 3235 Albacore Alley, San Diego, CA 92136, Maria Cruz-Saldarriaga, Hospital Instituto Peruano Seguro Social, Cusco, Peru. Alejandro Llanos Cuentas, Juan Echevarria, and Cesar Miranda-Verastegui, Universidad Peruana Cayetano Heredia, Casilla Postal 4314, Lima 100, Peru. Maria Luz Cjuno and Olga Colina, Naval Medical Research Center Detachment, Unit 3800, APO AA, 34031, Lima, Peru. Jonathan D. Berman, National Center for Complementary and Alternative Medicine, National Institutes of Health, Bethesda, MD 20892, E-mail: JBe9320457@aol.com.

Reprint requests: Ellen M. Andersen, Navy Environmental and Preventive Medicine Unit No. 5, Naval Station, 3235 Albacore Alley, San Diego, CA 92136, E-mail: eandersen@nepmu5.med.navy.mil.

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