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COMPARISON OF GENERIC TO BRANDED PENTAVALENT ANTIMONY FOR TREATMENT OF NEW WORLD CUTANEOUS LEISHMANIASIS

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Abstract. The cost of generic pentavalent antimony (generic stibogluconate) is approximately one-sixth that of branded pentavalent antimony (stibogluconate in the form of Pentostam® or meglumine antimoniate in the form of Glucantime®). We compared generic stibogluconate to Pentostam and Glucantime for the treatment of cutaneous leishmaniasis patients in Bolivia and Colombia. For all 114 patients, the per-protocol cure rates were 83–91% and the intent-to-treat cure rates were 75–83%. The highest values were in the generic stibogluconate group. The incidence of pancreatic enzyme abnormalities was 48–88% and the incidence of liver enzyme abnormalities was 48–87%. The lowest incidences were in the generic stibogluconate group. The efficacy and tolerance of inexpensive generic stibogluconate appears comparable to branded formulations for the treatment of cutaneous leishmaniasis in these endemic regions.

INTRODUCTION

In spite of major advances in the treatment of visceral leishmaniases with lipsosomal amphotericin B and miltefosine, American cutaneous leishmaniasis is still primarily treated with pentavalent antimony (Sb) in the form of meglumine antimoniate (Glucantime®) and sodium stibogluconate (Pentostam®).

Chemotherapeutic agents are evaluated on the basis of efficacy, tolerance, and feasibility of administration, including cost of goods. Concern about toxicity of the antimonials is particularly apt in light of the finding that 16 of 17 patients treated with Pentostam exhibited pancreatic enzyme abnormalities, and therapy was interrupted in 10 of the 17 patients because of abdominal complaints.[1]

The original aim of the present work was to compare the efficacy and tolerance of Pentostam to Glucantime (the standard Sb formulation in South America) for treatment of cutaneous leishmaniasis in Bolivia and Colombia. The study began with a comparison of Pentostam to Glucantime in Bolivian patients. Pentostam became unavailable midway in the study, and we became aware of the cost advantages of generic stibogluconate manufactured by Albert David Ltd (Kolkata, India): the proposed price was approximately $60 per treatment course, which was approximately 20% of that of branded pentavalent antimony. In South American countries such as Bolivia and Colombia, Glucantime, but not Pentostam, is marketed. Glucantime costs $4–6 per 5-mL ampule, and for a treatment course of 60 ampules, the cost of the drug is $240–360. For these reasons, additional Bolivian patients were randomized to receive either generic stibogluconate or Glucantime. In a subsequent Colombian study, patients were also randomized to receive generic stibogluconate, Pentostam, or Glucantime. Thus, the primary study aim evolved to be a comparison of the efficacy and toxicity of generic stibogluconate with branded Pentostam and Glucantime. If generic stibogluconate were to have pharmacodynamic parameters equivalent to or better than the branded formulations, its cost advantage would make its use attractive.

MATERIALS AND METHODS

Study design. The study was a randomized, double-blinded comparative trial of three formulations of pentavalent antimony at two South American sites with cutaneous leishmaniasis.

Patients. Forty-five consecutive Bolivian patients ≥ 18 years old from the province of La Paz who had parasitologically proven cutaneous leishmaniasis were randomized by playing cards to receive either Pentostam or Glucantime at an allocation ratio of 1:1. When branded Pentostam became unavailable after the first 17 patients (nine received Glucantime and eight received Pentostam), the next 28 patients were randomized to receive either generic stibogluconate and Glucantime at a ratio of 3:2 (17 received generic stibogluconate and 11 received Glucantime). Diagnosis and treatment were performed at the Hospital de Clinicas in La Paz.

Sixty-nine consecutive Colombian patients ≥ 18 years old from the provinces of Urabá and Carmen de Chucurí with parasitologically proven cutaneous leishmaniasis were randomized by playing cards to receive either generic stibogluconate, Pentostam, or Glucantime at an allocation ratio of 4:1:4. Diagnosis and treatment were performed in local hospitals in Apartade and Carmen de Chucuri, Colombia.

The Colombian allocation ratios were chosen to achieve a final allocation ratio for both sites for generic stibogluconate, Pentostam, and Glucantime of approximately 3:1:3.

Parasitology. Lesion samples were taken by slit skin smear or by biopsy. Proof of infection prior to treatment or of continued infection after treatment consisted of microscopic identification of *Leishmania* amastigotes in a direct Giemsa stain of the smear. In Colombia, lesion aspirates were also performed and when motile promastigotes were seen, the species was determined by monoclonal antibody binding.[2]

Drug administration. A generic form of sodium stibogluconate was kindly provided by the manufacturer (Albert David Ltd). This formulation is referred to as generic stibogluconate in the text and stibogluconate in the tables. Sodium stibogluconate in the form of Pentostam was obtained from GlaxoSmithKline (Asuncion, Paraguay). Meglumine antimonate in the form of Glucantime was provided by the Ministry of Health for Colombia.

Each agent was administered at a dose of 20 mg of Sb/kg/day (there was no upper limit on the daily dose) intramuscularly for 20 consecutive days. Exclusion criteria were mucosal disease, previous treatment with antimonials, concurrent treatment with hepatotoxic, pancreaticotoxic, or cardiotoxic drugs, and any concurrent systemic medications except com-

mon drugs for symptomatic relief. Neither patient, administering medical personnel, or evaluator knew the identity of the agent. The patient code was broken only after all efficacy and toxicity evaluations had been completed.

Efficacy evaluation. Lesion failure was defined by clinical criteria: enlargement of lesion area by more than 100% during therapy, no diminution (Colombia) or < 50% diminution (Bolivia) of lesion area by 1.5 months after the end of therapy, lack of complete healing of the lesion by three months after therapy, or relapse of an initially healed lesion by six months after the end of treatment. Lesion cure was the absence of lesion failure. Additionally, non-healed lesions were parasitologically examined as per prior to therapy. For a patient to be cured, each lesion had to have cured.

Toxicity evaluation. At screening and on each day of therapy, patients were asked about the subjective side effects of arthralgias, myalgia, headache, dizziness, tiredness, nausea, diarrhea, abdominal pain, or other complaints. The responses were graded with adherence to the Common Toxicity Criteria (CTC) of the U.S. National Cancer Institute[3] for subjective adverse events: 0 = no significant complaints, 1 = mild complaints (not limit normal function), 2 = moderate complaints (did limit normal function), 3 = significant complaints (resulting in termination of antimonial treatment).

At screening, on day 10 of therapy, at the end of therapy on day 20, and 15 days after therapy, blood was drawn for determination of a complete blood count and plasma levels of lipase, amylase, aspartate aminotransferase (AST), and creatinine. Levels of alanine aminotransferase (ALT) were also assessed in Bolivia. An electrocardiogram (ECG) was also performed on these four occasions. Each value was graded according to the CTC criteria for laboratory adverse events.[3] For amylase and lipase, the upper limit of normal values are < 120 U/L and < 150 U/L, respectively. The CTC Grade 1, 2, and 3 abnormalities are up to 1.5, up to 2.0, and up to 5.0 times the upper limit of normal. For AST and ALT, the upper limits of normal values are < 40 U/L and < 38 U/L, respectively. The CTC Grade 1, 2, and 3 abnormalities are up to 2.5, up to 5, and up to 20 times the upper limit of normal. For creatinine, the upper limit of normal is 1.2 mg/dL. The lower limits of normal and of CTC grade 1 abnormalities are 4,500/mm^3 and 2,000/mm^3, respectively, for the white blood cell counts, 120,000/mm^3 and 75,000/mm^3, respectively, for platelets, and 13.5 g/dL and 10 g/dL, respectively, for hemoglobin levels. For ECGs, CTC grade 1 signifies non-specific T- wave flattening.

Ethics. The study protocol and amendments were reviewed and approved by the responsible authorities at the Bolivian and Colombian study sites: Colegio Medico in Bolivia and Comite de Etica en Investigacion, Hospital Militar Central, Bogota for Colombia. All patients provided informed consent. The first visit of the first patient was in October 2001. The last visit of the last patient was in February 2003.

RESULTS

Efficacy. The efficacy of the three antimony formulations tested is shown in Table 1.

Bolivian patients. In 45 patients, the mean number of lesions per patient was 1.8 and the mean lesion size was 397 mm^2. For all antimony groups, 33 patients were cured with the six-month follow-up and four more were cured at three months but not seen at six months.

TABLE 1
Efficacy of various antimony formulations tested*

	Glucantime	Pentostam	Stibogluconate
Bolivian data			
No. of patients	20	8	17
Males	100%	87%	88%
Age: mean (range), years	34 (18–65)	20 (20–61)	37 (18–63)
Weight: mean (range), kg	53 (42–80)	58 (49–80)	55 (45–85)
No. of lesions	43	14	37
Ulcer size: mean (SD)	281 (304)	633 (1,122)	406 (442)
Cure at six months	16	6	11
Cure at three months	1	0	3
Fail	1	1	1
Lost	2	1	2
PP cure rate	17/18 = 94%	6/7 = 86%	14/15 = 93%
ITT cure rate	17/20 = 85%	6/8 = 75%	14/17 = 82%
Colombian data			
No. of patients	30	8	31
Males	70%	75%	81%
Age: mean (range), years	25 (18–70)	28 (22–65)	31 (19–71)
Weight: mean (range), kg	62 (52–92)	60 (56–80)	59 (44–90)
No. of lesions	53	14	62
Ulcer size: mean (SD)	333 (314)	316 (195)	327 (292)
Cure at six months	21	6	26
Cure at three months	0	0	0
Fail	7	1	3
Lost	2	1	2
PP cure rate	21/28 = 75%	6/7 = 86%	26/29 = 90%
ITT cure rate	21/30 = 70%	6/8 = 75%	26/30 = 87%
Both sites			
No. of patients	50	16	48
Cure	38	12	40
Fail	8	2	4
Lost	4	2	4
PP cure rate	38/46 = 83%	12/14 = 86%	40/44 = 91%
ITT cure rate	38/50 = 76%	12/16 = 75%	40/48 = 83%

* PP = per protocol; ITT = intent to treat.

There were three treatment failures, one in each of the three treatment groups. Although clinical criteria alone were to be used in determining failure, in a protocol violation, two of the failures were so judged at 1.5 months because their lesions were approximately 50% smaller than at pre-therapy and also were parasite positive. The third failure was due to relapse at three months. There were three other patients (two in the Glucantime group and one in the generic stibogluconate group) whose lesions at 1.5 months were approximately 50% smaller but were parasite negative were not declared to be failures, were not rescued, and eventually met our clinical criteria for cure. Five patients were lost between the end of treatment and the 1.5-month follow-up.

The cure rates were similar in the three treatment groups for per-protocol (PP) analysis of evaluable patients, and for intent-to-treat (ITT) analysis for which all patients are included.

Colombian patients. In 69 patients, the mean number of lesions per patient was 1.9 and the mean lesion size was 328 mm^2. The aspirates of seven lesions were cultured and speciated by monoclonal antibody binding. All seven parasites were *L. panamensis*. For all antimony groups, 53 patients were cured with the six-month follow-up.

A total of 11 patients failed treatment. Six of the seven Glucantime failures occurred at the 1.5-month follow-up and one failed at the three-month follow-up; the one Pentostam failure occurred by two weeks after therapy; and the two stibogluconate failures occurred at 1.5 months after therapy and at three months after therapy. In each case, the lesions were at least as large as prior to therapy, and most of the lesions had markedly enlarged compared with their pretherapy size. For 8 of the 11 failures, the lesions were parasitologically positive at the time of failure.

Both sites. Of the 114 patients treated with all pentavalent antimonials formulations at both sites, 104 patients were evaluable and 90 of these cured. Thus, the PP cure rate for all formulations was 86% (90 of 104) (95% confidence interval [CI] = 79–93%) and the ITT cure rate was 79% (90 of 114) (95% CI = 73–83%). Generic stibogluconate had a slightly higher absolute value of cure rate on both a PP and an ITT basis.

Subjective side effects. The subjective side effects reported are shown in Table 2. Side effects reported during this study that were not present on day 0 were myalgias, headache, metallic taste, and abdominal pain. The severity grade of all side effects was 1 or 2, and therapy was not stopped in any patient. As shown in Table 2, the percentage of all patients (Colombian and Bolivian combined) with each subjective side effect was less for generic stibogluconate than for the other forms of pentavalent antimony. 16–56% of the Glucantime and Pentostam patients reported subjective side effects, compared with 4–29% of the generic stibogluconate patients.

Laboratory data. Individual instances of laboratory abnormalities that were seen at the midpoint or the end of the study for patients with normal baseline values are shown in Table 3. The information in this table includes the total number and percentage of patients (Colombian and Bolivian combined) who had abnormalities in levels of amylase, lipase, AST, or ALT, formed elements of the blood, or ECG. Data are given for both mild-to-moderate abnormalities (CTC grades 1–2) and for more significant abnormalities (CTC grade 3).

Decrements in the formed elements of the blood were CTC grade 1 except in one instance. Twelve patients had CTC grade 1 decrements in platelet counts and one Glucantime patient had a CTC grade 2 decrement of platelets to 68,000/mm^3. Ten patients had a CTC grade 1 decrement in white blood count counts and three patients had a CTC grade 1 decrement in hemoglobin values. Alterations in the ECG were uniformly grade 1.

Elevation of liver enzyme levels to CTC grades 1 and 2 was common (44–75% of the patients) and increases to CTC grade 3 also occurred (4–12% of the patients). Additionally, elevation of pancreatic enzyme levels to CTC grades 1–2 was common (46–69%) and there were increases to CTC grade 3 (2–19% of the patients). The percentage of generic stibogluconate patients with each grade of abnormality was less than or equal to the percentage of the branded Sb patients.

Group values for a pancreatic enzyme (amylase) and a liver enzyme (AST) are shown in Table 4. For amylase, the mean values at the middle to end of therapy increased 2–3-fold compared with entrance values, and were greater than the upper limit of normal in all groups except for the generic stibogluconate group. Thus the mean increase for pancreatic enzymes was less for the generic stibogluconate group than for the other groups. Although the multiple comparisons makes statistical evaluation unreliable, it should be noted that for the three sets of values, the means for the generic stibogluconate group were less ($P < 0.01$) than for the means for another group. For AST, increases were approximately threefold and were greater than the upper limit of normal for all groups. Mean values of all laboratory parameters in each group regressed so as to be less than the upper limit of normal by 15 days after therapy.

DISCUSSION

Pentavalent antimonials remain the primary therapy for New World cutaneous leishmaniasis. The purpose of the present investigations was to compare generic stibogluconate with the branded formulations (Glucantime and Pentostam) in an attempt to demonstrate therapeutic equivalence. Because generic stibogluconate was the novel agent and Glucantime is the formulation registered in South America, most patients were randomized into these two groups rather than to receive Pentostam. At the end of the study, there were approximately equal numbers of patients (48–50) in the generic stibogluconate and Glucantime groups, and one-third this number of patients (16) in the Pentostam group.

The 114 patients who received the standard dose of 20 mg of Sb/kg/day for 20 days constitute the largest reported series

TABLE 2
Subjective side effects reported in the study

Group	No. of patients	No. with myalgias (grade)	No. with headache (grade)	No. with metal taste (grade)	No. with abdominal pain (grade)
Bolivian data*					
Glucantime	20	9 (1–2)	1 (2)	3 (1)	0
Pentostam	8	4 (1–2)	1 (2)	2 (1)	0
Stibogluconate	17	1 (2)	3 (1–2)	0	0
Colombian data*					
Glucantime	30	14 (1)	15 (1–2)	16 (1)	8 (1–2)
Pentostam	8	5 (1–2)	4 (1–2)	3 (1)	4 (1)
Stibogluconate	31	13 (1–2)	6 (1–2)	7 (1)	2 (1)
Both sites†					
Glucantime	50	23 (46%)	16 (32%)	19 (38%)	8 (16%)
Pentostam	16	9 (56%)	5 (31%)	5 (31%)	4 (25%)
Stibogluconate	48	14 (29%)	9 (19%)	7 (15%)	2 (4%)

* Data represent the number of patients with an abnormal value during therapy (common toxicity criteria grade of abnormality), who had normal values at baseline.
† Data represent the number of patients with an abnormal value during therapy (% total patients).

TABLE 3
Individual laboratory abnormalities in the groups studied*

Group	No. of patients	Amylase or lipase (CTC grade)	AST or ALT† (CTC grade)	White blood cells or platelets or hemoglobin	ECG (CTC grade)
Bolivian data					
Glucantime	20	10 (1), 4 (2), 1 (3)	7 (1), 2 (2)	0	6 (1)
Pentostam	8	3 (1), 2 (2), 3 (3)	7 (1), 1 (3)	0	2 (1)
Stibogluconate	17	7 (1), 3 (2), 1 (3)	8 (1), 2 (2), 1 (3)	0	10 (1)
Colombian data					
Glucantime	30	12 (1), 6 (2), 3 (3)	13 (1), 5 (2), 2 (3)	14 (1), 1 (2)	13 (1)
Pentostam	8	4 (1), 2 (2)	4 (1), 1 (2), 1 (3)	3 (1)	3 (1)
Stibogluconate	31	8 (1), 4 (2)	8 (1), 3 (2), 1 (3)	8 (1)	6 (1)
Both sites					
Glucantime	50	32 (1–2), 4 (3)	27 (1–2), 2 (3)	11 (1), 1 (2)	19 (1)
% patients‡		64% (1–2), 8% (3)	54% (1–2), 4% (3)	22% (1), 2% (2)	38% (1)
Pentostam	16	11 (1–2), 3 (3)	12 (1), 2 (3)	3 (1)	5 (1)
% patients‡		69% (1–2), 19% (3)	75% (1–2), 12% (3)	19% (1)	31% (1)
Stibogluconate	48	22 (1–2), 1 (3)	21 (1–2), 2 (3)	5 (1)	16 (1)
patients‡		46% (1–2), 2% (3)	44% (1–2), 4% (3)	10% (1)	33% (1)

* Data represent the number of patients with an abnormal value during therapy (CTC grade of abnormality) who had normal values at baseline. CTC = Common Toxicity Criteria; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ECG = electrocardiogram.
† AST and ALT assessed in Bolivia. Only AST was assessed in Colombia.
‡ Row show percentage of patients with an abnormal value (CTC grade of abnormality).

of such patients. Velez and others had previously reported 66 Colombian patients,[4] Aronson and others reported 83 patients seen over a 10-year period in the United States,[5] and Desjeux and others reported 168 patients from Bolivia treated with the older regimen of 10-day courses of antimony.[6]

The PP and ITT cure rates for all pentavalent antimonials formulations were 86% and 79%, respectively. The range of previously reported values from large studies in Colombia are 84–93% for PP analyses and 79–84% for ITT analyses.[4,7] In Bolivia, Desjeux and others reported a cure rate of 88% after 2–4 10-day courses of Glucantime.[6] The *Leishmania* species represented by the present and previous Colombian studies is *L. panamensis*.[4,7] Since it is believed that *L. braziliensis* is endemic in the region of La Paz, Bolivia from which the present patients originated,[6,8] infection by other species was considered to be unlikely in our study. The cure rates reported here are in conformity with previous reports, and because of the size of the study are likely to be the standards for future investigations of chemotherapy for these populations.

The most prominent symptomatic complaints, myalgia and abdominal pain, were reported by 29–56% and 4–25% of the patients, respectively. The highest values, which were in the Pentostam group, duplicate almost exactly the values found in patients at Walter Reed Hospital who received Pentostam intravenously (55% for myalgia and 29% for abdominal pain).[5]

TABLE 4
Group values for laboratory parameters*

Parameter	Group	No. of patients	Pre RX	Mid RX	End RX	15 days post RX
Bolivian data						
Amylase	Glucantime	20	77 (25)	134 (51)	128 (40)	108 (44)
	Pentostam	8	97 (42)	265 (150)	246 (129)	114 (36)
	Stibogluconate	17	80 (26)	134 (71)	134 (69)	78 (22)
AST	Glucantime	20	24 (6)	42 (26)	47 (31)	34 (12)
	Pentostam	8	21 (4)	90 (101)	56 (28)	47 (39)
	Stibogluconate	17	23 (7)	62 (40)	48 (27)	28 (6)
Colombian data						
Amylase	Glucantime	30	57 (26)	124 (92)	214 (163)	94 (72)
	Pentostam	8	52 (26)	170 (95)	195 (60)	82 (36)
	Stibogluconate	31	62 (25)	100 (75)	141 (96)	69 (32)
AST	Glucantime	30	12 (5)	32 (27)	52 (63)	21 (12)
	Pentostam	8	10 (4)	23 (11)	52 (33)	25 (15)
	Stibogluconate	31	12 (5)	20 (16)	42 (64)	22 (20)
Both sites						
Amylase	Glucantime	50	65 (27)	128 (77)	181 (136)	100 (63)†
	Pentostam	16	74 (41)	217 (131)†	221 (103)†	97 (36)
	Stibogluconate	48	68 (26)	113 (75)†	139 (88)†	72 (29)†
AST	Glucantime	50	17 (8)	36 (27)	50 (53)	26 (14)
	Pentostam	16	16 (7)	56 (78)	54 (30)	34 (28)
	Stibogluconate	48	16 (8)	35 (33)	44 (44)	24 (17)

* Data are the mean (SD) value prior to treatment (Pre RX), after 10 days of treatment (mid RX), at the end of treatment (End RX), and 15 days after the end of treatment (15 days post RX). Normal values: amylase < 150 U/L; AST < 40 U/L. AST = aspartate aminotransferase.
† For vertically-paired means: $P < 0.01$, by t-test.

Significant abnormalities of pancreatic and liver enzyme levels occurred frequently. For pancreatic enzymes, 46–69% had mild-to-moderate elevations and 2–19% had grade 3 elevations. For liver enzymes, 44–75% had mild-to-moderate elevations and 4–12% had grade 3 elevations. Again, the highest values were in Pentostam patients and these are comparable with those for Walter Reed Hospital patients: 96% had elevations in levels of at least one pancreatic enzyme and 63% had some elevation in the level of ALT.[5]

In our study, 10–24% of the patients had mild decrements of formed elements of the blood, and approximately half of these cases reflected thrombocytopenia. Instances of thrombocytopenia have been previously reported in the literature. Franke and others reported thrombocytopenia in 3 of 35 cases, including one case in which the platelet count was reduced to 20,000/mm^3.[9] Aronson and others reported one case in whom the platelet count decreased to 46,000/mm^3.[5]

Generic stibogluconate has been previously shown to be as effective as branded Pentostam for visceral leishmaniasis in Africa. The comparative cure rates for generic stibogluconate versus Pentostam were 83% versus 96% in Kenya,[10] 74% versus 62% in Ethiopia,[11] and 96% versus 91% in Sudan.[12] In those studies of systemically ill visceral leishmaniasis patients, some concomitantly infected with human immunodeficiency virus, information on mild-to-moderate subjective and laboratory side effects could not be easily obtained.

In our study of South American cutaneous leishmaniasis patients, the efficacy of generic stibogluconate was slightly greater on an absolute basis than that of either Glucantime or Pentostam. Cutaneous leishmaniasis patients have only a skin lesion and are systemically well. Investigation of the tolerance in the cutaneous leishmaniasis population serves to determine the inherent tolerability of drugs in physiologically normal populations. For most of the many parameters we examined, generic stibogluconate was better tolerated than the branded formulations. Our sizable evaluation of this formulation of generic stibogluconate in Colombian and Bolivian cutaneous leishmaniasis patients indicates that this product is effective and inherently well tolerated, and can be recommended as a low-cost alternative to the branded products for treatment of American cutaneous leishmaniasis.

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