Generic sodium stibogluconate is as safe and effective as branded meglumine antimoniate, for the treatment of tegumentary leishmaniasis in Isiboro Secure Park, Bolivia

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Human cutaneous leishmaniasis (CL) and mucous leishmaniasis (ML) are highly endemic in Isiboro Secure Park, which lies in the Bolivian department of Cochabamba — an area where branded meglumine antimoniate (Glucantime®) is expensive and poorly distributed. The safety and efficacy of generic sodium stibogluconate (SSG), from Albert David Ltd, was therefore explored, in CL and ML cases from the park, who were treated with 20 mg/kg.day for 20 and 30 days, respectively. A questionnaire recording adverse effects was completed by a physician in each treatment centre. Efficacy of treatment was assessed at the end of treatment and at follow-ups 1 month and 3, 6 and 12 months later.

Overall, 146 patients completed treatment with SSG in 2003–2004. No fatalities or severe adverse effects were reported but mild to moderate adverse effects were noted in 41 (28%) of the patients. The incidence of adverse effects was significantly higher among the cases of ML than among the cases of CL.

Of the 86 patients with CL who completed 6 months of follow-up, 81 (94.2%) were considered to have been clinically cured; a comparable cohort of 69 CL cases who had been treated with Glucantime in 2001–2002 showed a similar frequency of clinical cure (90%). Generic SSG was shown to be safe and efficacious for the treatment of tegumentary leishmaniasis in Bolivia. Being several times cheaper than Glucantime, it could contribute to improving the access of CL and ML patients to treatment, not only in Bolivia but also in other countries of Latin America.

Tegumentary leishmaniasis is a significant public-health problem over large areas of Latin America (Grimaldi *et al.*, 1989). Despite numerous studies evaluating alternative drugs, such as ketoconazole (Navin *et al.*, 1992), paromomycin (Hepburn *et al.*, 1994), allopurinol (Llanos-Cuentas *et al.*, 1997; Velez *et al.*, 1997), pentamidine (Andersen *et al.*, 2005), amphotericin B (Sampaio *et al.*, 1971) and miltefosine (Soto *et al.*, 2004*a*), pentavalent antimonials remain the first-line treatment for cutaneous and mucosal leishmaniasis in most endemic countries of the region. The efficacy and safety of branded formulations of meglumine antimoniate (i.e. Glucantime®;

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Sanofi-Aventis, Paris) and sodium stibogluconate (i.e. Pentostam®; GlaxoSmithKline, Brentford, U.K.) have been extensively studied in patients with cutaneous (CL) and mucosal (ML) leishmaniasis acquired in the so-called 'New World' (Ballou *et al.*, 1987; Desjeux *et al.*, 1987; Franke *et al.*, 1990, 1994; Netto *et al.*, 1990; Guderian *et al.*, 1991; Saenz *et al.*, 1991; Navin *et al.*, 1992; Hepburn *et al.*, 1994; Llanos-Cuentas *et al.*, 1997; Velez *et al.*, 1997; Aronson *et al.*, 1998; Oliveira-Neto *et al.*, 2000; Palacios *et al.*, 2001; Romero *et al.*, 2001; Soto *et al.*, 2004*b*, 2005; Andersen *et al.*, 2005). The recommended pentavalent-antimonial treatment regimen for cases of CL and ML is 20 mg/kg.day (with no upper limit on the total daily dose) for 20 and 28 days, respectively (Herwaldt and Berman, 1992; Herwaldt, 1999). Unfortunately, the high prices of the branded antimonials are a serious obstacle to the completion of treatment. In Bolivia, for example, where Glucantime is the only drug marketed for use against leishmaniasis, a full course of treatment for a case of CL weighing 65 kg may cost as much as U.S.$360 (Soto *et al.*, 2004*b*). Consequently, most cases of CL do not receive any specific treatment and therefore suffer from skin lesions for long periods and are exposed to an increased risk of developing ML.

Although cheaper, generic antimonials are produced in several countries, there have been serious problems with the toxicity of some batches of these drugs from several manufacturers (Sundar *et al.*, 1998; Deps *et al.*, 2000; Rijal *et al.*, 2003). There have been no such problems reported, however, with the generic sodium stibogluconate (hereafter called 'generic SSG') manufactured by Albert David Ltd in the Indian city of Calcutta, even though it has been widely used, in India, Nepal, Pakistan and Afghanistan, for the treatment of both visceral and cutaneous leishmaniasis. In East Africa, this generic SSG has been found to be as effective and as safe as Pentostam (Veeken *et al.*, 2000; Moore *et al.*, 2001; Ritmeijer *et al.*, 2001). Similarly, in a study involving 114 cases of CL in Colombia and Bolivia, it was found to be better tolerated and slightly more efficacious than Glucantime or Pentostam (Soto *et al.*, 2004*b*).

In Bolivia, tegumentary leishmaniasis is endemic in several tropical and sub-tropical regions (Grimaldi *et al.*, 1989), including the Isiboro Secure Park, in the department of Cochabamba. Almost all Bolivian cases of CL and ML are caused by *Leishmania braziliensis* (Desjeux *et al.*, 1987; Grimaldi *et al.*, 1989) although cases caused by *L. lainsoni* (Martinez *et al.*, 2001), *L. amazonensis* (Martinez *et al.*, 1998) and *L. guyanensis* (unpubl. obs.) have also been observed. During investigations within the framework of 'LeishNatDrug-R' (a 4-year-long multicentre observational study, on drug resistance in *Leishmania* parasites, that ended in 2005), it was found that most patients from Isiboro Secure Park who were prescribed Glucantime had no access to the drug, because of the drug's poor distribution and/or its high cost (unpubl. obs.). This unacceptable situation led the World Health Organization to donate 1700 vials of generic SSG, in January 2003. As little has been published on the use of generic SSG against tegumentary leishmaniasis, the present, retrospective analysis of the safety and efficacy of generic SSG, in the patients from the Isiboro Secure Park who were treated using these vials, was conducted.

PATIENTS AND METHODS

The present study was based at the Faculty of Medicine of the *Universidad Mayor San Simon* at Cochabamba, a partner in the LeishNatDrug-R consortium. The LeishNatDrug-R study protocol, which included the collection of the data discussed below, was approved by the ethical committees of both the *Universidad Mayor San Simon* (in April 2001) and the Prince

Leopold Institute of Tropical Medicine (Antwerp, Belgium, in August 2001).

Patients

All patients who presented at one of the five health facilities serving the Isidoro Secure Park — the Cayetano Hospital (a referral hospital located in the city of Cochabamba), the Villa Tunari District Hospital, or the Isinuta, Aroma or Villa Tunari health centres — with a disease that was clinically suspected to be CL and/or ML were enrolled on the study if they gave their written informed consent. Any skin and/or mucosal lesions were carefully examined clinically by a physician expert in tegumentary leishmaniasis (E.R.). A stained smear of at least one lesion/patient was then prepared, stained and checked microscopically for amastigotes, a lesion aspirate was collected from each patient and cultured on NNN medium, and each patient was given a leishmanin skin test (LST). All the isolated strains were unambiguously identified to species level using the Hsp70 PCR–restriction-fragment-length-polymorphism (PCR–RFLP) assay (Garcia *et al.*, 2004).

Confirmation of Diagnosis

A suspected case of CL or ML was considered confirmed when amastigotes were detected in a smear of a skin or mucosal lesion, respectively, or when promastigotes were detected in the corresponding aspirate cultures. In the absence of amastigotes in smears and promastigotes in culture, a suspected case was considered 'probable' if he or she gave a positive reaction in the LST (i.e. an induration, 48 h after injection, of at least 5 mm).

Treatment

From March 2001 to December 2002, patients with proven or probable tegumentary leishmaniasis were prescribed intramuscular meglumine antimoniate (Glucantime) at 20 mg/kg.day, for 20 days (CL) or 30 days (ML). The patients were treated as outpatients, with daily medical supervision. From January 2003 to December 2004, however, the first-line treatment was switched to generic SSG from Albert David Ltd (batch number 2P08005), administered, at the same dosages and for the same periods as the Glucantime, by slow intravenous injection. All patients treated with generic SSG were hospitalized throughout their treatment.

Evaluation of Toxicity

A semi-structured questionnaire recording the occurrence and grade of adverse effects was prepared. The clinician in charge at each health facility recorded newly occurring complaints daily in all patients treated with generic SSG. Adverse effects were only graded 'severe' if they interfered with the patient's daily activities and/or required a temporary or permanent interruption of treatment. The difference between 'mild' and 'moderate' effects was based on the clinician's subjective assessment. All patients with proven or probable CL or ML who completed treatment with generic SSG were included in the safety analysis. A univariate analysis of individual risk factors for the occurrence of adverse effects was also carried out.

Evaluation of Efficacy

All patients with CL or ML treated with Glucantime or generic SSG were asked to attend follow-up visits 1 month and 3, 6 and 12 months after treatment ended. At each visit, the same physician (E.R.) assessed the clinical appearance of the lesion(s), in terms of size, presence of signs of inflammation, and the presence of scarring. The status of the lesion(s) was evaluated by comparison with pre-treatment digital pictures and drawings of the lesion(s), and graded from M0 (no change or worsening of the lesion) to M4 (complete scarring of the lesion). The efficacy analysis was restricted to the CL and ML patients who had both parasitologically

proven disease and follow-up data for at least 6 months after the end of treatment. The efficacies of generic SSG and Glucantime were only compared for the CL cases; there were too few ML cases to allow a valid comparison of the efficacies of the two drugs in the treatment of ML.

Definition of Clinical Outcome

Outcomes were categorized as: (1) 'initial cure' (ulcers showing complete scarring and disappearance of inflammatory signs within 3 months of completing treatment, or nodular lesions showing flattening and absence of infiltration or other signs of inflammation within same period); (2) 'unresponsiveness' [no or incomplete scarring of lesion(s) and/or persistence of inflammatory signs 3 months after completing treatment, or either worsening of existing lesion(s) or appearance of new lesion(s) within 3 months of completing treatment]; or (3) 'relapse' (reappearance of an ulcer/nodule and/or local signs of inflammation after initial cure). Any patient showing unresponsiveness or a relapse was considered a 'treatment failure' whereas those showing initial cure and no relapse within 12 months of the end of treatment were considered 'definite cures'.

Data Management and Statistical Analysis

Demographic, clinical, laboratory, treatment and outcome data were entered in an Excel (Microsoft) database by the same physician (E.R.). During several data-monitoring visits by a second investigator (F.C.), all of these data were cross-checked with the information held in the routine medical records of the patients. Statistical analysis was performed using the SPSS 11.0 for Windows software package (SPSS Inc, Chicago, IL). Numerical variables were summarized as means with (S.D.) if normally distributed, and as medians and quartiles if not. Categorical variables were compared using cross-tabulations and χ^2 tests, and numerical variables (means) with Student's *t*-tests, at a critical α-level of 0.05. All *P*-values were two-sided.

RESULTS

Baseline Assessment

A total of 146 patients, 118 with CL and 28 with ML, completed treatment with generic SSG during the study period. Diagnosis was parasitologically proven in 95 (81%) of the CL patients and 18 (64%) of the ML, and was considered as probable in the remaining cases. The species-typing of strains by Hsp70 PCR–RFLP was successful in 50 (42%) of the 118 CL patients, with *L. braziliensis* (88% of identified isolates), *L. lainsoni* (6%), *L. guyanensis* (4%) and *L. amazonensis* (2%) identified. As expected, all seven identified isolates from the ML patients were *L. braziliensis*. The mean (S.D.) age of the 146 patients given generic SSG was 28.2 (14.8) years, and most (87%) were male. The number of lesions per CL patient ranged from one to six, with a mean (S.D.) of 1.7 (1.1). The mean (S.D.) total doses of generic SSG administered were 405 (58) mg/kg for the CL cases and 560 (75) mg/kg for the ML patients.

Safety of Generic SSG

Forty-one (28.1%) of the patients given generic SSG each developed at least one adverse effect — arthralgias and/or myalgias (8%), headache (7%), phlebitis (4%), pain at injection site (3%), malaise (3%), insomnia (3%), bradycardia (2%), fever (2%), vertigo (1%), weight loss (1%), nausea (1%), vomiting (1%), pruritus (1%) or anorexia (1%). Ten (6.8%) of the patients given generic SSG were considered to have had moderate adverse effect(s) but no fatalities or other severe adverse effects occurred. Compared with the CL patients, the ML patients were significantly more likely to have presented with one or more adverse effects ($P=0.016$), with an odds ratio and

[95% confidence interval (CI)] of 2.8 [1.2–6.6]. A higher total dose of generic SSG (454 *v.* 426 mg/kg; $P=0.078$) and a larger induration in the LST (13.1 *v.* 10.5 mm; $P=0.019$) were also associated with increased risk of adverse effect(s), whereas gender, age, number of skin lesions, and presence of lymph nodes were not.

Efficacy of Generic SSG against CL

Of the 95 patients with parasitologically proven CL who completed treatment with generic SSG, 86 (91%) were included in the efficacy analysis [the other nine (9%) being excluded because they were lost to follow-up <6 months after the end of treatment]. The demographic and medical data of these 86 patients are shown in the Table. Eighty-one (94.2%, with a CI of 87.1%–97.5%) showed a definite cure. The other five CL patients, who were categorized as treatment failures, showed unresponsiveness (three) or relapse (two). Four of the treatment failures were each given a second course of generic SSG (20 mg/kg.day for 20–30 days) and then showed definite cure (one) or

TABLE. *Comparison of demographic, clinical, treatment and outcome data between patients with cutaneous leishmaniasis treated with generic sodium stibogluconate (SSG) and those treated with Glucantime, in Isiboro Secure Park, Bolivia*

	Treatment:		
	Generic SSG	Glucantime	*P*
No. of patients investigated	86	69	
NO. AND (%) OF PATIENTS:			
Male	71 (83)	60 (87)	0.45
Female	15 (17)	9 (13)	
With superimposed bacterial infection	39 (45)	42 (61)	0.06
With lymphadenopathy	69 (80)	60 (87)	0.27
Infected with:			0.32
Leishmania braziliensis	42 (88)	31 (86)	
L. lainsoni	3 (6)	5 (14)	
L. guyanensis	2 (4)	0	
L. amazonensis	1 (2)	0	
With initial outcome:			
Cured (M4) at end of treatment	29 (34)	39 (57)	0.004
Cured (M4) at 1-month follow-up	63 (73)	56 (81)	0.25
Cured (M4) at 3-month follow-up	81 (96)	62 (91)	0.3
With final outcome:			0.32
Definite cure	81 (94)	62 (90)	
Treatment failure	5 (6)	7 (10)	
Unresponsiveness	3 (4)	5 (7)	
Relapse	2 (2)	2 (3)	
Mean (S.D.) age (years)	25.6 (14.0)	25.9 (13.3)	0.9
Mean (S.D.) no. of lesions	1.8 (1.8)	1.7 (1.8)	0.78
NO. AND (%) OF LESIONS:			0.79
Ulcer	72 (84)	60 (87)	
Nodular	11 (13)	5 (7)	
Infiltrative or proliferative	3 (4)	4 (6)	
NO. AND (%) OF LESIONS ON:			0.34
Head	9 (11)	12 (17)	
Upper limb	21 (24)	20 (29)	
Lower limb	54 (63)	34 (49)	
Trunk	2 (2)	3 (4)	
Mean (S.D.) total dose (mg/kg)	409.6 (44.2)	402.2 (26.4)	0.24

unresponsiveness (one, subsequently cured with a third course of generic SSG) or were lost to follow-up (two).

Efficacy Comparison between Generic SSG and Glucantime against CL

Between March 2001 and December 2002, 75 patients with parasitologically proven CL were treated with Glucantime, including 69 (92%) from whom complete follow-up data were subsequently collected. Among the patients with adequate follow-up data, the 69 treated with Glucantime were similar, in terms of their demographic baseline data, the clinical characteristics of their lesions and the total dosages of antimonials administered, to the 86 patients treated with generic SSG (see Table).

At the end of treatment, patients in the Glucantime cohort were more likely to show complete healing of their lesions than patients given generic SSG [56.5% (CI=44.8%–67.6%) *v.* 34.0% (CI=24.6%–44.2%); $P=0.004$]. By the 1-month and 3-month follow-ups, however, response to treatment was similar in the two groups. The frequency of definite cure was also similar in the two cohorts: 94% (CI=87.1%–97.5%) with generic SSG *v.* 90% (CI=80.5%–95%) with Glucantime ($P=0.32$). All 11 patients known to be infected with a *Leishmania* species other than *L. braziliensis* strains were definitely cured with generic SSG (six) or Glucantime (five).

Efficacy of Generic SSG for ML

Eleven (61%) of the 18 patients with parasitologically proven ML had sufficient follow-up data to be included in the efficacy analysis. All 11 were male, with a mean (S.D.) age of 37.1 (13.8) years. Ten (91%) had a previous history of CL (which, in five of the patients, had been left untreated) and one had concomitant skin lesions. A mean (S.D.) total dose of 506 (100) mg generic SSG/kg was administered. Eight of the 11 patients (72.7%; CI=43.4%–90.3%) showed definite cure, whereas the other three (27.3%; CI=9.7%–56.5%) showed unresponsiveness. The three treatment failures each had severe mucosal disease, involving five to seven mucosal areas including the pharynx, epiglottis and vocal cords. In contrast, only one of the eight patients with definite cure had lesions extending beyond the nose and the oral cavity ($P=0.02$).

DISCUSSION

The present results indicate that, at least in the Bolivian department of Cochabamba, generic SSG from Albert David Ltd (Calcutta, India) is safe and efficacious in the treatment of patients with CL caused, predominantly, by *L. braziliensis*. Drug tolerance and efficacy were lower in patients with ML.

None of the 146 patients given generic SSG died or suffered from severe adverse effects during treatment. Mild to moderate adverse effects were reported in 28% of these patients. Although such effects were more frequent in the patients with ML than in the CL cases, the former were treated for longer and therefore received higher total doses. The risk of adverse effects following treatment with any antimonial drug is probably dose-dependent (Palacios *et al.*, 2001). Encouragingly, the frequencies of the adverse effects generally associated with pentavalent antimonials (such as myalgia, arthralgia and headaches) were lower in the present study than previously reported (Ballou *et al.*, 1987; Franke *et al.*, 1990, 1994; Saenz *et al.*, 1991; Hepburn *et al.*, 1994; Llanos-Cuentas *et al.*, 1997; Aronson *et al.*, 1998; Palacios *et al.*, 2001; Soto *et al.*, 2004*b*; Andersen *et al.*, 2005). Although some under-reporting of adverse effects might have occurred in the present study, for socio–cultural reasons, it seems possible that generic SSG is better tolerated than the branded antimonial drugs (Soto *et al.*, 2004*b*). As the concentration of the pentavalent antimonial drug in the formulation of

generic SSG marketed by Albert David (100 mg/ml) is higher than that in Glucantime, a lower injection volume is required with SSG, and this is an important benefit when treatment is given intramuscularly. The present results must be treated with some caution, however, since, in the present study, no attempt was made to explore the cardiac, liver, pancreatic and haematological toxicities of the generic SSG, even though such toxicities are frequently associated with antimonial use (Ballou *et al.*, 1987; Franke *et al.*, 1994; Llanos-Cuentas *et al.*, 1997; Aronson *et al.*, 1998; Andersen *et al.*, 2005).

The frequency of definite cure of the CL patients treated with generic SSG was excellent (94%). It compares well with the 91% efficacy recently found with the same drug in Colombia and Bolivia (Soto *et al.*, 2004*b*), and lies at the upper end of the range of efficacies (51%–96%) observed when branded antimonial drugs were used against CL (caused by *L. braziliensis*) in Bolivia and other countries of Latin America (Desjeux *et al.*, 1987; Netto *et al.*, 1990; Navin *et al.*, 1992; Hepburn *et al.*, 1994; Romero *et al.*, 2001; Andersen *et al.*, 2005). It also compares well with the 90% frequency of definite cure observed, at the present study sites, when Glucantime was used. Interestingly, Glucantime appeared better than SSG when patients were assessed at the end of treatment but no better by the time of the 1- or 3-month follow-ups. It appears that, compared with Glucantime, generic SSG has a marginally lower potency on both target and host cells, so that it acts more slowly on the skin lesions but is better tolerated. The results of the present comparison between Glucantime and generic SSG have to be treated with caution, however, as they come from a non-randomized study and residual confounding cannot be excluded. Some degree of selection bias may have occurred, for example, as access to the drug and treatment surveillance were better for generic SSG than for Glucantime.

In Brazilian and Peruvian patients with CL, the *Leishmania* species causing the disease appears to be an essential determinant of antimonial-drug efficacy (Romero *et al.*, 2001). It is currently impossible to say if the same inter-specific differences in drug susceptibility occur in Bolivia, as, in the present study, only six of the 48 parasite isolates from CL patients treated with generic SSG belonged to a species other than *L. braziliensis*. Further studies are needed to assess the efficacy of generic SSG, or other antimonial drugs, on the CL caused by *L. guyanensis*, *L. lainsoni* or *L. amazonensis* in Bolivia.

In the present study, which involved only a small sample of ML cases, the efficacy of generic SSG against ML was found to be 73% overall and only 25% in patients with severe ML involving the pharynx, epiglottis and vocal cords. The branded antimonial drugs are also, however, less effective against ML than against CL and particularly poor against the severe forms of ML (Franke *et al.*, 1990; Saenz *et al.*, 1991; Berman, 1997; Llanos-Cuentas *et al.*, 1997; Herwaldt, 1999). Prolonging the use of antimonials for up to 40 days did not result in higher frequencies of cure among ML cases (Franke *et al.*, 1994). For the treatment of ML, there is clear and urgent need to explore potentially more efficient alternatives, such as conventional amphotericin B (Sampaio *et al.*, 1971; Berman, 1997), particularly in patients with lesions extending beyond the nose.

A full, 20-day course of generic SSG for a 50-kg adult case of CL costs about U.S.$29 when bought from the International Dispensary Association in Amsterdam. The costs of international and local transport of the drug, medical consultations and daily injections must be added to the direct costs of the drug. Sadly, although they are much lower than those of Glucantime (Soto *et al.*, 2004*b*), the true costs of treatment with generic SSG are still too high for most Bolivians seeking treatment for leishmaniasis, who are

generally impoverished farmers. The recent announcement by Sanofi-Aventis that the price of Glucantime is to be reduced is an encouraging step that could not only promote a wider use of this drug but also, through competitive pricing, decrease the price of generic SSG.

Conclusion and Recommendations

The generic SSG from Albert David Ltd is a safe and efficacious alternative to branded antimonials for the treatment of Bolivian tegumentary leishmaniasis. Other clinical studies elsewhere have confirmed its safety and efficacy, for both CL and visceral leishmaniasis (Veeken *et al.*, 2000; Moore *et al.*, 2001; Ritmeijer *et al.*, 2001; Soto *et al.*, 2004*b*). Its relatively low cost could contribute to better patient access to treatment. It is therefore recommended that the Bolivian Ministry of Health and Sports includes this generic SSG in its list of essential drugs, and builds up an efficient system of subsidy and delivery for this formulation, in all areas with endemic leishmaniasis.

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