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Pharmacokinetics of Experimental Pentavalent Antimony After Intramuscular Administration in Adult Volunteers

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ABSTRACT

Background: Pentavalent antimony (SbV) has demonstrated therapeutic effectiveness against clinical manifestations of leishmaniasis, an infection caused by *Leishmania*, a genus of flagellate protozoa comprising parasites of worldwide distribution. Approximately 1.8 million new cases are reported annually.

Objective: The aim of this study was to assess the pharmacokinetics of the investigational generic SbV, Ulamina (pentachloride of antimony + *N*-methyl-glucamine), in healthy adult volunteers.

Methods: In this study, SbV was administered IM as a single 5-mg/kg dose. Blood samples were collected at 0.25, 0.75, 1, 2, 4, 8, 12, and 24 hours after administration; urine samples were collected at 6-hour intervals during the 24-hour postadministration period. Determination of trivalent antimony, SbV, and total antimony concentrations in blood and urine samples was carried out using atomic absorption spectrometry. Clinical history was reviewed and the subjects were monitored before and after administration of SbV using physical examination, weight, and hepatic- and renal-function studies. The pharmacokinetic parameters calculated were C_{max}, T_{max}, absorption constant (Ka), elimination constant (K_{el}), AUC_{0-24h}, $AUC_{0-\infty}$, elimination phase ($t_{1/2\beta}$), volume of distribution (V_d), and urinary excretion rate.

Results: Five subjects (3 men, 2 women; mean age, 28 years [range, 18–34 years]) were included in the study. One hour after drug administration the following values were obtained: C_{max}, 1.1 µg/mL; T_{max}, 1.3 hours; Ka, 1.87 hours;

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K_{el}, 0.043 hours; AUC_{0-24h}, 12.26 μg/mL · h; $AUC_{0-\infty}$, 19.84 μg/mL · h; $t_{1/2\beta}$, 17.45 hours; V_d, 6.6 L/kg; and urinary excretion rate, 2.8 μg/h; these were mean values for the entire study group. The single dose was well tolerated by all subjects.

Conclusions: The investigational generic SbV, Ulamina, was associated with linear elimination after IM administration of a single 5-mg/kg dose. A 2-compartment pharmacokinetic model was observed in these volunteers; the mean $t_{1/2\beta}$ was 17.45 hours and the mean V_d was 6.6 L/kg. (*Curr Ther Res Clin Exp.* 2006;67: 193–203)

Key words: pharmacokinetic, antimony, Ulamina, humans, antileishmania drugs.

INTRODUCTION

Pentavalent antimony (SbV) is a compound derived from the heavy metal antimony (Sb). In the form of sodium stibogluconate* or meglumine antimoniate,† these SbVs have demonstrated effectiveness against the clinical manifestations of leishmaniasis, an infection caused by *Leishmania*.[1–3] This disease is a top priority for the tropical disease program of the World Health Organization and has a worldwide incidence of ~1.8 million new cases annually.[4]

The mechanism of the antileishmanial action of sodium stibogluconate remains to be clarified. Exposure to this compound compromises the bioenergetics, which diminishes net generation of adenosine triphosphate and guanosine triphosphate of the parasites.[5] The drugs may be administered IM or IV, usually as SbV 20 mg/kg · d for 20 to 30 days.[6] The drug causes mild to moderate adverse events, such as myalgias, arthralgias, abdominal symptoms, headache, elevation of aminotransferases and amylases, and electrocardiographic changes affecting the ST segment and corrected QT interval, all of which rarely lead to treatment suspension. Rarely, severe toxicity occurs, such as acute renal and hepatic failure, thrombocytopenia, and even sudden death, probably due to cardiac rhythm disturbances.[6,7]

SbV attains much higher plasma concentrations than trivalent antimony (SbIII). Most of a single dose of sodium stibogluconate is excreted in the urine within 24 hours.[5] The agent is rapidly absorbed: T_{max}, 2 hours; C_{max}, 9.35 μg/mL[8]; volume of distribution (V_d), ~0.22 L/kg; and is eliminated in 2 phases. The first phase has a short elimination phase ($t_{1/2\beta}$) of ~2 hours, while the second phase is much slower (33–76 hours).[5,8] The prolonged terminal $t_{1/2\beta}$ might reflect conversion of SbV to the more toxic and effective SbIII form, which accumulates in macrophages and is slowly released from tissues.[5,9] The pharmacokinetics of branded drugs, such as sodium stibogluconate and meglumine antimoniate, are similar with a $t_{1/2\beta}$ of 2.17 and 1.92 hours, a T_{max} of 2 and 2 hours, and a C_{max} of 9.35 and 11.23 μg/mL, respectively.[8]

*Trademark: Pentostam® (GlaxoSmithKline, Research Triangle Park, North Carolina).[10]
†Trademark: Glucantime® (Rhone-Poulenc, Paris, France, and Aventis, São Paulo, Brazil).[11]

Recent interest in this drug class has focused largely on confirming the efficacy of low-cost generic drugs.[3] The generic formulations of SbV are valuable alternative treatments in countries with a high mortality due to *Leishmania* parasites.[2,7] Individual and comparative studies have found that some of the generic formulations of Sb are as effective as the registered formulations.[12] However, it should be pointed out that some generic formulations have been reported to exhibit higher cardiotoxicity.[13,14] In Venezuela, the branded meglumine antimoniate is expensive and has limited availability due to import costs and a lack of local synthesis. A generic formulation of SbV, Ulamina, has been synthesized at the Laboratory of Chemotherapy and Control in the José Witremundo Torrealba Center of Parasitology Investigations of the University of The Andes (Trujillo, Venezuela). Local synthesis of Ulamina has diminished the cost and has been associated with clinical response and tolerability similar to that of the branded drug.[15]

We previously conducted a retrospective review of the medical records of 416 patients with cutaneous leishmaniasis who were treated exclusively with either meglumine antimoniate or Ulamina as the investigational agent to compare their tolerability.[15] A local cutaneous reaction (induration, edema, and erythema) was reported in the medical records of 22 (13.3%) of the 166 patients treated with meglumine antimoniate and in 18 (7.2%) of the 250 patients treated with Ulamina. Systemic reactions, such as hypertension, tachycardia, dyspnea, hepatitis, fever, headache, dizziness, asthenia, and systemic allergic reaction were reported in 5 (3.0%) meglumine antimoniate-treated patients and in 5 (2.0%) of the patients who received Ulamina. The positive results of the cutaneous hypersensibility test were significantly higher with Ulamina. The Ulamina group also showed a significantly lower density ($P = 0.024$), osmolarity ($P = 0.036$), and concentration of chlorates ($P = 0.038$).

The objective of the present study was to assess the pharmacokinetics of Ulamina after IM administration of a single 5-mg/kg dose to healthy adult human volunteers.

SUBJECTS AND METHODS

Volunteers and Ethics

Only healthy adult human volunteers were included in the study. The procedures and the possible risks associated with the use of Ulamina were explained to the volunteers in detail. Written consent to participate in the study, as required by the guidelines of the bioethics committee of the José Witremundo Torrealba Center of Parasitology Investigations, was obtained from all participants before study initiation. The volunteers were compensated for their participation.

Volunteers were excluded from the study if they were allergic to Sb, if female volunteers were pregnant, if their hemoglobin concentration was <12 mg/L, if they had renal dysfunction or hepatic abnormalities (elevated parameters or enzymatic modifications), or if they were taking pharmacologic treatment before study initiation.

Clinical history was reviewed and the following procedures were used for assessment of the volunteers before and after administration of Ulamina: physical examination, weight, hematology, and hepatic- and renal-function studies that included blood glucose, serum creatinine, blood urea nitrogen, serum alanine aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin, alkaline phosphatase, and gamma-glutamyl transpeptidase levels.

Pharmacologic Material and Doses

Ulamina (pentachloride of Sb + *N*-methyl-glucamine) was synthesized at an initial dose of 0.3 g/mL of SbV. Mean (SD) results of the Ulamina used in this study produced total Sb, 78.25 (23.01) µg/mL; SbV, 77.95 (23.05) µg/mL; SbIII, 0.20 (0.23) µg/mL; chlorates, 1.61 (0.28) mg/mL; pH, 5.01 (1.57); density, 1.01 (0.0578) g/mL; and osmolarity, 266 (141.43) mmol/Kg$H_2$0.[15] The drug was administered IM as a single 5-mg/kg dose.

Experimental Design

An initial blood sample was collected from the volunteers before administration of Ulamina; 2-mL blood samples were collected at 0.25, 0.75, 1, 2, 4, 8, 12, and 24 hours after treatment. Urine was collected throughout the 24-hour postadministration period at intervals of 0 to 6, 6 to 12, 12 to 18, and 18 to 24 hours. Urine volume was determined for each of those periods, and an aliquot of each sample was saved. The blood and urine samples were kept at –6°C, lyophilized, and stored for later analysis.

Analytical Methods

The concentrations of total Sb and of its species (SbIII and SbV) were determined by flow-injection hybrid-generation atomic absorption spectrometry. The limits of detection obtained were 2.8 ng/L for SbIII and 3.2 ng/L for SbV. Total Sb was calculated as the sum of the concentrations of both species.[16,17]

Pharmacokinetic Analysis

The following pharmacokinetic parameters were calculated: absorption constant (Ka); AUC_{0-24h}, which was calculated using the trapezoidal rule for the interval of 0 to 24 hours; $AUC_{0-\infty}$; $t_{1/2\beta}$, determined as ln2/β, with β being calculated from the slope of the linear, least-squares regression line; the elimination constant (K_{el}); and the V_d, calculated using the formula dose/AUC × β.[18] C_{max} and T_{max} were calculated directly from the individual curves.

The urinary excretion rate of dose over time was calculated by dividing the total Sb concentration reported (µg) between 6 (interval duration of urine collected in hours).[19,20]

Statistical Analysis

Plasma concentration versus time curves were determined for each volunteer and were analyzed using a noncompartmental model based on the statistical

moments theory[18] and using PK Solutions version 2.0 software (Summit Research Services, Montrose, Colorado). Differences by sex were analyzed statistically using the Wilcoxon rank sum test, a nonparametric test. $P \leq 0.05$ was considered significant.

RESULTS

Five healthy adult human volunteers (3 men, 2 women; mean age, 28 years [range, 18–34 years]) were included in the study. **Table I** summarizes the levels of total Sb, SbIII, and SbV (μg/mL) in blood after IM administration of Ulamina 5 mg/kg.

Total Antimony

The plasma concentration of total Sb and its species as a function of time is shown in the **figure**. The mean plasma Ulamina concentration at 15 minutes postadministration was 0.59 μg/mL, C_{max} was 1.1 μg/mL, and T_{max} was 1.3 hours (**Table II**). From that moment on, Sb concentrations decreased in 2 phases. The first phase of rapid elimination lasted for 4 hours postadministration. The second phase of slower elimination (β) extended beyond the 24-hour postadministration period, with a $t_{1/2\beta}$ of 17.45 hours. The difference between the value of AUC_{0-24h} (12.26 μg/mL · h) and $AUC_{0-\infty}$ (19.84 μg/mL · h) was 38.2%, indicating that ~60% of the drug remained to be eliminated.

Other pharmacokinetic parameters of total Sb and the mean values obtained from the analysis of the curves of each volunteer are shown in **Table II**. The Ka was 1.88 hours, the K_{el} was 0.043 hour, and V_d was 6.66 L/kg.

Pentavalent Antimony

The profile of SbV was similar to that of total Sb. The phases of rapid elimination and slow elimination were observed: K_{el} was 0.056 hour, V_d was 8.55 L/kg, and AUC_{0-24h} was 12.76 μg/mL · h (**Table III**).

Trivalent Antimony

The profile of SbIII had a significantly lower K_{el} (0.014 hour, $P = 0.043$) compared with SbV, was associated with a significantly greater V_d (29.3 L/kg, $P = 0.043$) than SbV, and had an AUC_{0-24h} of 0.18 μg/mL · h.

A decrease in SbV concentration was observed 2 hours after administration, with systemic conversion in SbIII of 23.3%. The mean urinary excretion rate of Ulamina was determined to be 2.8 μg/h.

No significant difference was found in pharmacokinetic parameters between sexes.

The findings with regard to the demographic data (ie, age, sex, weight) and safety monitoring (renal and hepatic function and hematology) before and 24 hours after administration of Ulamina for the 5 volunteers are shown in **Table IV**. No adverse events were reported after this single dose.

Table I. Trivalent antimony (SbIII), pentavalent Sb (SbV), and total Sb, in blood after IM administration of Ulamina 5 mg/kg to healthy adult human volunteers.

		Time (h)							
Volunteer	Sb	0.25	0.75	1.0	2.0	4.0	8.0	12.0	24.0
1	III	0.026	0.156	0.246	0.146	0.250	0.166	0.136	0.113
	V	0.470	0.640	0.726	0.690	0.480	0.448	0.329	0.280
	Total	0.496	0.796	0.927	0.736	0.730	0.514	0.465	0.393
2	III	0.209	0.273	0.170	0.240	0.220	0.142	0.152	0.152
	V	0.623	0.841	0.769	0.759	0.568	0.560	0.522	0.196
	Total	0.832	1.114	0.939	0.999	0.788	0.702	0.674	0.348
3	III	0.232	0.236	0.252	0.168	0.123	0.093	0.100	0.093
	V	0.543	0.830	0.674	0.212	0.298	0.254	0.262	0.112
	Total	0.775	1.066	0.926	0.380	0.421	0.347	0.362	0.205
4	III	0.165	0.280	0.328	0.313	0.228	0.160	0.164	0.160
	V	0.482	0.628	0.817	1.024	0.574	0.438	0.436	0.177
	Total	0.647	0.908	1.145	1.337	0.802	0.598	0.600	0.337
5	III	0.210	0.255	0.352	0.272	0.123	0.130	0.131	0.068
	V	0.013	0.580	0.702	0.713	0.359	0.213	0.240	0.092
	Total	0.223	0.855	1.054	0.985	0.482	0.343	0.371	0.160

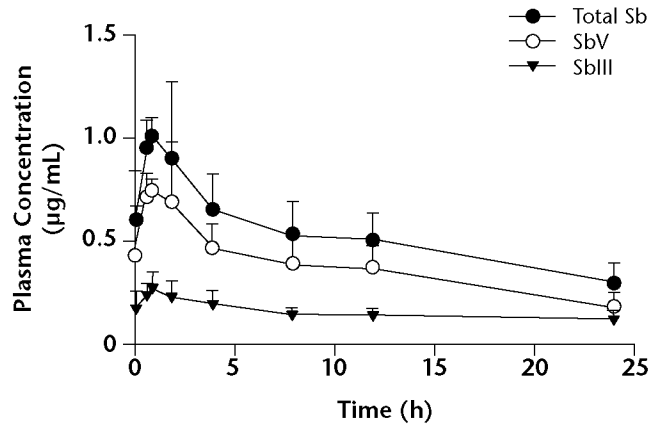

Figure. Mean concentration of total antimony (Sb) and its species (pentavalent Sb [SbV] and trivalent Sb [SbIII]) in healthy adult volunteers (N = 5) who received a single 5-mg/kg IM dose of Ulamina.

DISCUSSION

Ulamina is an experimental SbV for the treatment of leishmaniasis in Venezuela.[15] A C_{max} of 1.12 µg/mL, with a T_{max} of 1 hour and a Ka of 1.87 hours, suggests a fast and complete absorption for Ulamina.

In the present study, metabolism of the drug resulted in a decrease in SbV concentration 2 hours after administration, with systemic conversion of 23.3%. For the next 12 hours this percentage was maintained. The drug was distributed at the tissue level, at a rate of V_d 6.66 L/kg. The concentration of SbIII depended on the reduction process of SbV converting into SbIII.[21] As reported with the

Table II. Pharmacokinetic parameters of total antimony after IM administration of Ulamina 5-mg/kg to healthy adult human subjects.

	Volunteer					
Parameters	1	2	3	4	5	Mean (SD)
C_{max}, µg/mL	1.0	1.1	1.1	1.3	1.1	1.1 (0.070)
T_{max}, h	1.0	0.8	0.8	3.0	1.1	1.3 (0.501)
Ka, h	2.70	0.27	2.90	1.35	2.17	1.88 (1.08)
AUC_{0-24h}, µg/mL · h	13.1	15.5	8.5	14.9	9.3	12.3 (2.866)
$AUC_{0-\infty}$, µg/mL · h	29.0	21.8	14.2	21.9	12.3	19.8 (6.72)
$t_{1/2\beta}$, h	8.07	12.58	19.12	14.41	13.11	13.46 (6.46)
K_{el}, h	0.024	0.055	0.036	0.048	0.052	0.043 (0.012)
V_d, L/kg	6.98	4.16	9.74	4.74	7.67	6.66 (2.26)

Ka = absorption constant; $t_{1/2\beta}$ = elimination phase; K_{el} = elimination constant; V_d = volume of distribution.

Table III. Elimination level observations for trivalent antimony (SbIII), pentavalent Sb (SbV), and total Sb in 5 healthy adult subjects after IM administration of Ulamina 5-mg/kg.

	SbIII	SbV	Total Sb
K_{el}, h	0.014*	0.056	0.043
V_d, L/kg	29.30†	8.55	6.66
AUC_{0-24h}, μg/mL · h	0.18	12.76	12.26

K_{el} = elimination constant; V_d = volume of distribution.
*P = 0.043 versus SbV.
†P = 0.043 versus SbV.

sodium stibogluconate,[5] Ulamina was associated with ~20% of the plasmatic Sb remaining in the trivalent form. A positive balance of SbIII resulted from the conversion of SbV to SbIII, possibly at the hepatic or systemic level.[5,8]

The pharmacokinetics of Ulamina in these subjects was consistent with a 2-compartment model of elimination, with a V_d of total Sb (6.6 L/kg), which was larger than described for other formulations. The V_d for sodium stibogluconate was found to be ~0.22 L/kg in other studies.[5,8] Ulamina was completely absorbed, and it was thought that the drug was retained in the tissues and eliminated slowly. Because the difference between C_{max} (1.12 μg/mL) and minimum concentration at 24 hours (0.28 μg/mL) was small and the difference between $AUC_{0-\infty}$ and AUC_{0-24h} was 38.2%, this suggested that a large percentage of the drug had not been eliminated after 24 hours. The capacity of the macrophages to accumulate Sb has been described to be at least 3 days.[8,9] This might explain, in part, the low plasma Ulamina concentrations in humans. Binding of the drug to tissues and to intracellular proteins might also be involved.[5] SbIII had a greater V_d than SbV in this study, possibly owing to its greater ability to react electrochemically.[22] These pharmacokinetic characteristics are shared with arsenic, whose trivalent species have been described as interacting with the thiol groups of proteins[21]; a mechanism that contributes to increased tissue retention.[22] Indeed, this has been suggested to be one of the mechanisms accounting for the leishmanicidal effects of Sb.[9]

Ulamina followed a kinetic of linear elimination after administration in a single 5-mg/kg dose. The last phase of elimination appeared dependent on the release of the drug from the tissues. The measured $t_{1/2\beta}$ of Ulamina was 17.45 hours, whereas $t_{1/2\beta}$ for branded formulations has been reported to be 33 to 76 hours.[5] The principal route of elimination of SbV was renal.[5,8,23,24] Urinary excretion of Ulamina occurred at a mean rate of 2.8 μg/h, which was probably dependent on low plasma concentrations.

The present study was limited by its small sample size. In addition, these results might not be generalizable to all patients with leishmaniasis or renal disease, in whom it is necessary to characterize the pharmacokinetics of Ulamina.

Table IV. Demographic data and laboratory values before and at 24 hours after IM administration of a single 5-mg/kg dose of Ulamina to healthy adult volunteers.

	Volunteer 1		Volunteer 2		Volunteer 3		Volunteer 4		Volunteer 5	
Demographics										
Sex	Female		Female		Male		Male		Male	
Age, y	26		30		18		34		31	
Weight, kg	53		52		76		75		78	
Whole blood data	Before	After	Before	After	Before	After	Before	After	Before	After
Leukocyte count, $\times 10^3/mm^3$	7.5	7.1	9.2	8.7	6.1	7.2	8.1	8.8	7.0	7.6
Erythrocyte count, $\times 10^6/mm^3$	3.94	3.94	3.83	3.83	4.57	4.57	4.99	4.99	4.57	4.57
Hemoglobin, g/dL	12.3	12.0	12.1	12.1	13.9	13.9	15.4	15.4	14.7	14.7
Hematocrit, %	40.5	41.0	40.1	42.0	46.7	46.7	48.8	48.8	48.0	48.0
Platelet count, $\times 10^3/mm^3$	215	226	331	278	283	303	261	250	331	320
Lymphocytes, %	27.6	27.6	31.1	31.1	21.7	21.7	20.8	20.8	18.4	18.4
Lymphocytes, $\times 10^3/mm^3$	2.0	2.8	2.9	1.9	1.4	2.2	1.7	1.9	1.3	1.4
Blood glucose, mg/dL	61	90	64	64	91	89	87	90	64	87
Blood urea nitrogen, mg/dL	11.4	11.0	10.5	9.5	7.3	7.0	11.7	9.7	14.5	14.5
Serum creatinine, mg/dL	0.4	0.5	0.6	0.6	0.8	0.9	0.7	0.9	0.7	0.7
Serum alanine aminotransferase, U/L	12	12	11	11	27	27	44	44	36	36
Serum aspartate aminotransferase, U/L	16	16	18	18	16	16	46	46	26	26
Serum total bilirubin, mg/dL	0.91	0.70	0.45	0.45	0.64	0.54	1.04	1.04	0.59	0.78
Serum direct bilirubin, mg/dL	0.20	0.20	0.21	0.21	0.26	0.26	0.82	0.82	0.22	0.20
Serum alkaline phosphatase, U/L	93	98	103	103	134	134	130	130	102	102
Serum GGTP, mg/dL	9	12	12	17	13	20	23	33	25	22

GGTP = gamma-glutamyl transpeptidase.

CONCLUSIONS

Ulamina followed linear elimination kinetics after its administration in a single 5-mg/kg dose. In these 5 volunteers, the drug followed a 2-compartment pharmacokinetic model, with a $t_{1/2\beta}$ of 17.45 hours and V_d of 6.6 L/kg. These properties suggested that Sb might accumulate after multiple administrations.

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REFERENCES

1. Palacios R, Osorio LE, Grajalew LF, Ochoa MT. Treatment failure in children in a randomized clinical trial with 10 and 20 days of meglumine antimonate for cutaneous leishmaniasis due to *Leishmania viannia* species. *Am J Trop Med Hyg.* 2001;64:187–193.
2. Berman J. Current treatment approaches to leishmaniasis. *Curr Opin Infect Dis.* 2003;16:397–401.
3. Croft SL, Coombs GH. Leishmaniasis—current chemotherapy and recent advances in the search for novel drugs. *Trends Parasitol.* 2003;19:502–508.
4. Alrajhi AA, Ibrahim EA, De Vol EB, et al. Fluconazole for the treatment of cutaneous leishmaniasis caused by *Leishmania major. N Engl J Med.* 2002;346:891–895.
5. Tracy JW, Webster LT. Drugs used in the chemotherapy of protozoal infections. In: Hardman JG, Limbird LE, Molinoff PB, et al, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics.* 10th ed. New York, NY: McGraw-Hill; 2001: 1097–1120.
6. Romero GA, Guerra MV, Paes MG, Macedo VO. Comparison of cutaneous leishmaniasis due to *Leishmania (viannia) braziliensis* and *L. (v.) guyanensis* in Brazil: Therapeutic response to meglumine antimoniate. *Am J Trop Med Hyg.* 2001;65: 456–465.
7. Romero GA, Flores MR, Noronha EF, Macedo VO. High frequency of skin reactions in patients with leishmaniasis treated with meglumine antimoniate contaminated with heavy metals: A comparative approach using historical controls. *Mem Inst Oswaldo Cruz.* 2003;98:145–149.
8. Chulay JD, Fleckenstein L, Smith DH. Pharmacokinetics of antimony during treatment of visceral leishmaniasis with sodium stibogluconate and meglumine antimoniate. *Trans R Soc Trop Med Hyg.* 1988;82:69–72.
9. Roberts WL, Berman JD, Rainey PM. In vitro antileishmanial properties of tri- and pentavalent antimonial preparations. *Antimicrob Agents Chemother.* 1995;39:1234–1239.
10. GlaxoSmithKline. Patient information leaflet: Pentostam injection. Available at: http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?documentid=4423. Accessed June 8, 2006.

11. Medical information: Glucantime, injectable solution: Envase 5 amp 1.5g/5mL. E.F.222. Guia Spilva de las Especialidades Farmaceuticas. XXIX Edición. Caracas, Venezuela: Aventis Pharma; 2005.
12. Veeken H, Ritmeijer K, Seaman J, Davidson R. A randomized comparison of branded sodium stibogluconate and generic sodium stibogluconate for the treatment of visceral leishmaniasis under field conditions in Sudan. *Trop Med Int Health.* 2000;5: 312–317.
13. Sundar S, Sinha PR, Agrawal NK, et al. A cluster of cases of severe cardiotoxicity among kala-azar patients treated with a high-osmolarity lot of sodium antimony gluconate. *Am J Trop Med Hyg.* 1998;59:139–143.
14. Rijal S, Chappuis F, Singh R, et al. Sodium stibogluconate cardiotoxicity and safety of generics. *Trans R Soc Trop Med Hyg.* 2003;97:597–598.
15. Vásquez L, Scorza JV, Vicuña-Fernández N, et al. Comparación de tolerabilidad y fisico-química entre lotes de antimonial comercial y no comercializado (Glucantime® Vs. Ulamina) en el tratamiento de la leishmaniasis cutánea. *MedULA.* 2005;11:1–4.
16. Petit de Peña Y, Vielma O, Burguera JL, et al. On-line determination of antimony (III) and antimony (V) in liver tissue and whole blood by flow injection—hydride generation—atomic absorption spectrometry. *Talanta.* 2001;55:743–754.
17. Petit de Peña Y, Vicuña-Fernández N, López S, et al. Antimony speciation in human blood samples from patients treated with Ulamina; a novel experimental drug for leishmaniasis. *Metal Ions Biol Med.* 2004;8:560–563.
18. Farrier D. PK Solutions 2.0. Noncompartmental pharmacokinetics data analysis. Montrose, CO: Summit Research Services; 2003.
19. Wagner JG. *Pharmacokinetics for the Pharmaceutical Scientist.* Lancaster, Penn: Technomic Publishing Company; 1993.
20. Villodre A, Plá J. Curvas de excreción urinari. In: Doménech J, Martínez J, Plá J, eds. *Biofarmacia y Farmacocinética. Vol I: Farmaocinética.* Editorial Síntesis Madrid; 2001:251–276.
21. Frezard F, Demicheli C, Ferreira CS, Costa MA. Glutathione-induced conversion of pentavalent antimony to trivalent antimony in maglumine antimoniate. *Antimicrob Agents Chemother.* 2001;45:913–916.
22. McKinney JD. Metabolism and disposition of inorganic arsenic in laboratory animals and humans. *Environ Geochem Health.* 1992;14:43–48.
23. Rees PH, Keating MI, Kager PA, Hockmeyer WT. Renal clearance of pentavalent antimony (sodium stibogluconate). *Lancet.* 1980;2:226–229.
24. Belloli C, Ceci L, Carli S, et al. Disposition of antimony and aminosidine in dogs after administration separately and together: Implications for therapy of leishmaniasis. *Res Vet Sci.* 1995;58:123–127.

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