Comparison of generic and proprietary sodium stibogluconate for the treatment of visceral leishmaniasis in Kenya

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Objective To compare the use of generic and proprietary sodium stibogluconate for the treatment of visceral leishmaniasis (kala-azar).

Methods A total of 102 patients with confirmed kala-azar were treated in a mission hospital in West Pokot region, Kenya, with sodium stibogluconate (20 mg/kg/day for 30 days) — either as Pentostam® (PSM) or generic sodium stibogluconate (SSG); 51 patients were allocated alternately to each treatment group.

Findings There were no significant differences in baseline demographic characteristics or disease severity, or in events during treatment. There were 3 deaths in the PSM group and 1 in the SSG group; 2 patients defaulted in each group. Only 1 out of 80 test-of-cure splenic aspirates was positive for *Leishmania* spp.; this patient was in the SSG group. Follow-up after ⩾6 months showed that 6 out of 58 patients had relapsed, 5 in the SSG group and 1 in the PSM group. No outcome variable was significantly different between the two groups.

Conclusion The availability of cheaper generic sodium stibogluconate, subject to rigid quality controls, now makes it possible for the health authorities in kala-azar endemic areas to provide treatment to many more patients in Africa.

Keywords Leishmaniasis, Visceral/drug therapy; Antimony sodium gluconate/therapeutic use; Drugs, Generic/therapeutic use; Drug evaluation; Comparative study; Kenya (*source: MeSH*).

Mots clés Leishmaniose viscérale/chimiothérapie; Antimoine sodium, Gluconate/usage thérapeutique; Produits génériques/usage thérapeutique; Evaluation médicament; Etude comparative; Kenya (*source: INSERM*).

Palabras clave Leishmaniasis visceral/quimioterapia; Gluconato de sodio antimonio/uso terapéutico; Medicamentos genéricos/uso terapéutico; Evaluación de medicamentos; Estudio comparativo; Kenya (*fuente: BIREME*).

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Introduction

Kala-azar (visceral leishmaniasis), a debilitating disease caused by *Leishmania donovani*, poses a major health problem in East Africa, and since 1988, Médecins Sans Frontières–Holland (MSF–H) has treated over 45 000 patients in the region with the condition. The mainstay of this treatment remains pentavalent antimony compounds. Since the 1940s, Pentostam® (PSM) (GlaxoWellcome, London, England) (sodium stibogluconate) has been virtually the only substance used in English-speaking East Africa for the treatment of kala-azar and post-kala-azar dermal leishmaniasis (PKDL). In the former French and Italian colonies in Africa, meglumine antimoniate (Glucantime®) (Rhône-Poulenc-Rohrer, Paris) is used. However, the high cost of PSM (see below) makes it prohibitively expensive for both patients and the local health authorities in the affected areas. Furthermore, usually only small amounts of PSM are produced and the manufacturer often cannot cope with the fluctuating high demand for the drug. Shortfalls in supply have been encountered by MSF–H and a good-quality, but cheaper, treatment option for kala-azar is urgently required. Generic sodium stibogluconate B.P (SSG)) has been manufactured by Albert David Ltd in Calcutta, India, for several decades, and since 1997 it has been supplied by the International Dispensary Association (IDA), Amsterdam, Netherlands. Because of the 50-year virtual monopoly of PSM in East Africa for treatment

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of kala-azar, some individuals and institutions may be induced to change to generic SSG when it has been carefully evaluated with PSM. The content of pentavalent and trivalent antimony in generic SSG falls well within the batch-to-batch variability seen for PSM and Glucantime (*1*). Unacceptable toxicity has been reported with batches of some antimonials made in India (*2*); these batches have been found to have abnormally high osmolality. However, such toxicity has not been reported with SSG made by Albert David Ltd (Dr Shyam Sundar, personal communication, 1999). IDA and other laboratories — including the Drug Control Laboratory, Ministry of Health, Khartoum, Sudan — have found SSG to be of consistently high quality. IDA inspected the production plant in India in 1997, and found it to conform to Good Manufacturing Practices. MSF–H therefore undertook a series of evaluations of PSM versus SSG to establish whether the two compounds were similar in efficacy and tolerability under the field conditions where kala-azar is treated. This hospital-based study is the first evaluation in this series.

Methods

Study site

The study was carried out in a kala-azar endemic area of Kenya at the Ortum Mission Hospital in West Pokot (catchment area population of 80 000, consisting mainly of the semi-nomadic Pokot tribe), where approximately 100 kala-azar patients are treated a year. The hospital has 109 beds, is staffed by two doctors and two medical assistants, and has a well-established nurse training school. There is a laboratory with two trained technicians who are competent in carrying out microscopy of splenic and lymph-node aspirates. All kala-azar patients are admitted as inpatients for their treatment. The hospital is funded by private donations and the drugs for the trial were donated by MSF–H. The hospital's policy is for patients to make a financial contribution towards their care, and this policy was not altered during our study.

Ethics

The study was carried out with strict observance of the Declaration of Helsinki (1997). The protocol was internally reviewed at MSF–H for ethical and scientific validity. Informed verbal consent for the study was obtained from all patients or their parents/guardians.

Sample size calculations

Makuch & Simon's formula (*3, 4*) can be used to calculate sample sizes for comparative studies if the objective is to show that two treatments are equally effective. For this purpose, the difference in outcome that would lead one of the treatments to be discarded as inferior needs to be specified. For kala-azar treatment we judged this to be a 20% difference in cure rate. Since PSM has repeatedly been found to have a cure rate of about 95% for kala-azar in Africa, we considered that a 75% cure rate for generic sodium stibogluconate would be clinically unacceptable. Taking $\alpha = 0.05$ and $\beta = 0.1$, we required 25 patients per treatment group. We also tested a second set of assumptions suitable for an unpaired prospective study with a dichotomous outcome (cure versus failure). Assuming the drugs differ by 20% in their cure rate, 95% in one group versus 75% in the other ($\alpha = 0.05$; $\beta = 0.2$), we required 49 patients per treatment group.

Allocation of patients

From June 1997 until July 1998 all consecutive patients who were diagnosed for the first time as having kala-azar at the study hospital were referred to a clerk who assigned them alternately to one of the two treatment groups, SSG or PSM. The clerk operated independently of hospital staff, and was not given any medical details of the patients. Patients were unaware of which group they had been assigned to until the treatment started. Those who did not consent to be in the study received PSM in the normal manner. Trial patients were given a small incentive (a free mosquito net and blanket) to attend the follow-up at 6 months, but there was no incentive for them to participate in the study. All patients, whether in the study or not, were charged for bed and board, but the trial patients who received either SSG or PSM were not charged for the treatment, as is the usual practice at the hospital.

Diagnosis and inclusion criteria

Clinical suspicion of kala-azar was defined according to standard MSF–H guidelines: a history of fever lasting $\geqslant 2$ weeks (with exclusion of malaria), and either splenomegaly or wasting. Kala-azar was confirmed either by serology or by detection of *Leishmania* amastigotes in Giemsa-stained splenic aspirates. In addition, serology by the direct agglutination test (DAT) was performed in the MSF–H laboratory in Nairobi. Splenic aspirates were read at the hospital and later confirmed by an independent MSF–H microscopist. It may be noted that patients were included even if they had severe kala-azar, or comorbidity such as anaemia or cachexia. Pregnancy, breastfeeding, advanced age and infancy were not reasons for exclusion.

Exclusions

Patients with a past history of kala-azar or who had received any antimonials in the past were excluded. Patients who were clinically suffering from kala-azar but had both a negative DAT test and a negative splenic aspirate were also excluded.

Treatment

SSG was from batches 4P345, 5P169 and 5P233; PSM was from batches A66 29A, E66 29A, D66 29A,

E66 12A and A66 28A. A colour-coded treatment card was used to ensure that patients received either PSM or SSG by intramuscular injection daily for 30 days. For both groups the dose was 20 mg of pentavalent antimony (Sb^V) per kg body weight per day; the minimum dose was 2 ml (200 mg Sb^V) with no upper limit on the dose (*5–7*). Generic sodium stibogluconate is supplied in vials of 30 ml, and Pentostam® in 100-ml vials; both preparations are clear colourless solutions containing 100 mg Sb^V per ml. Injections of more than 10 ml were given in two aliquots, one in each buttock. Intercurrent illnesses were treated in according to the hospital's usual protocols. Blood transfusions were available for anaemic patients. Vitamin K was given to patients who had a history of bleeding.

Response

Our main outcome measure was the initial cure rate. We estimated that the relapse rate in antimonial-treated patients who were initially cured was <10%, and that the nomadic lifestyle of the patients would make follow-up difficult. At discharge, the patients were considered an *initial* cure if they had received injections for >28 days, were clinically well, and had a negative splenic aspirate at the end of treatment. If the spleen had completely regressed, the patient was discharged without an aspirate at the clinician's discretion. Patients who had a positive splenic aspirate at the end of treatment, or who were clinically unwell continued to receive treatment until two negative aspirates had been obtained, taken one week apart. If at the follow-up visit, 6 months after discharge, patients were clinically well, they were considered a *definitive* cure. A further splenic aspirate was performed only if the patient was unwell and the clinician was suspicious of relapsed kala-azar.

Evaluations

The nurses were trained to reduce bias in recording symptoms and treatment of intercurrent illness. At enrolment, the following data were recorded for each patient: name, age, sex, address, height (cm), weight (kg), spleen size (in cm from the costal margin in the anterior axillary line to the furthest point of the spleen during quiet breathing), haemoglobin level (g/dl), DAT result, and the number of months of illness. During treatment, any medical complaints were recorded in the patient's notes daily. Specific enquiries about possible side-effects and toxicity were not routinely asked by the staff to avoid possible bias. At discharge, the following parameters were recorded: spleen size, haemoglobin level, weight, and splenic aspirate result. At the 6-month follow-up, as many as possible of the following parameters were obtained from each patient (field visits restricted the collection of some data): weight, spleen size, haemoglobin level, whether the patient had a history of fevers that were unresponsive to antimalarials, the presence of post-kala-azar dermal leishmaniasis (PKDL) or PKDL-associated iritis, and the clinician's impression of the patient (well and cured, or unwell and relapse). A splenic aspirate was performed if there was suspicion of relapse. Owing to the distance and expense for the patients to attend follow-up at the hospital, outreach trips to distant villages were undertaken to locate the trial patients. Because of their semi-nomadic lifestyle it was difficult to trace many patients at the 6-month follow-up; local chiefs were then interviewed to obtain a verbal report on missing patients' health.

Results

A total of 102 patients were enrolled between 10 June 1996 and 30 July 1998, comprising all the patients treated in the hospital for kala-azar during this period; no other patients outside the study received the treatment. Splenic aspirates to diagnose kala-azar were taken from all 102 patients; 85 had a single aspirate and 17 had repeated aspirates, the first aspirate being negative for parasites despite strong clinical suspicion. Two patients had repeatedly negative splenic aspirates, and were diagnosed by a strongly positive DAT and clinical features: they were both in the SSG group, and responded to treatment. For the 93 patients who received DAT testing, 85 were strongly positive, 5 were borderline positive, and 3 were negative. All 8 patients with borderline or negative DAT results had positive splenic aspirates. A total of 51 patients were allocated to receive SSG and 51 to PSM. There were no significant differences in the baseline demographic characteristics or disease severity between the two groups (Table 1).

Outcome

None of the outcome measures was significantly different between the two treatment groups (see Table 2). In the PSM group, 2 patients defaulted (on days 27 and 30), and 3 died (on days 14 and 15, and 2 days after finishing treatment). In the SSG group, 2 patients defaulted (days 24, 30) and 1 died on day 10. There was no excessive vomiting, bleeding, or the need for transfusion in either group. To diagnose initial cure, we performed test-of-cure splenic aspirates at the end of treatment for 80 patients — 44 in the SSG group (43 negative and one positive) and 36 in the PSM group (all negative). The sole patient with a positive end-of-treatment aspirate received 15 further daily injections of SSG and had two further negative aspirates. Follow-up at 6 months was achieved with 58 patients; 30 were in the SSG group — 16 were examined and definitively cured, 9 were reported to be well by the chief or a close relative, 4 had relapsed (proven by splenic aspirate), and 1 had a clinical relapse (no aspirate available). In the PSM group, 28 patients were followed up — 18 were examined and definitively cured, 9 were reported to be well, and 1 patient had aspirate-confirmed relapse. There were no reports of PKDL.

Discussion

We found no important clinical differences between the use of generic sodium stibogluconate and Pentostam® in Kenyan patients with kala-azar. There are, however, certain shortcomings of this study that should be noted. First, though the study ranks among the larger prospective evaluations of drugs for kala-azar (*8*), our sample size only permitted detection of statistically significant differences of efficacy between the drugs of about 20%. We are currently conducting larger studies in Ethiopia and the Sudan to strengthen the conclusions of the present study. Second, the allocation of patients to treatment groups was alternate and not random, and the hospital staff were not blinded to the treatment given. However, the slides of splenic aspirates were read "blind", and the main outcome measures (death, initial cure, or definitive cure) are unlikely to have been affected by a knowledge of the treatment received.

Generic SSG and Pentostam® should be recognized as being the same drug. Like other pentavalent antimonials, generic SSG is a mixture of organometallic compounds (M_r = 100–4000) (*9*). All fractions of the mixtures have similar *in vitro* antileishmanial activity against amastigotes (*10*). The lower price of generic SSG is a major advantage and it is currently available from IDA for approximately US$ 2.21 per 30-ml bottle, equivalent to US$ 10.60 per patient in our study (median body weight = 24 kg, corresponding to a median of 144 ml of

Table 1. **Baseline characteristics of kala-azar study patients treated with generic sodium stibogluconate (SSG) and Pentostam® (PSM)**

	Total (*n* = 102)	SSG group (*n* = 51)	PSM group (*n* = 51)	*P*-value[a]
Mean age (years)	9 (2–40)[b]	7 (2–40)	9.5 (2–28)	0.34
No. of patients aged ⩽5/<16/>16 years	25/55/32	16/19/16	9/26/16	0.22*
Sex (M/F)	72/30	35/16	37/14	0.83**
Mean weight (kg)	23.6 (7.4–55)	20.8 (7.4–55)	24.4 (11–52)	0.37
Mean height (cm)	123 (37–184)	117 (37–182)	131 (49–184)	0.39
Mean spleen size (cm)	13.5 (5–23)	13 (5–23)	14.3 (6.7–20)	0.1
Mean haemoglobin level (g/dl)	6.6 (3.6–10.8)	6.3 (3.8–10)	7 (3.6–10.8)	0.99
DAT[c] postive/borderline/ negative/not done	85/5/3/9	42/4/3/2	43/1/0/7	0.19*
Splenic aspirate: Positive/negative	100/2	49/2	51/0	0.5**
Mean duration of illness (months)	3 (1–48)	3 (1–48)	3 (1–12)	0.6

[a] Mann–Whitney U-test, except * = χ^2 test and ** = Fisher's exact test.

[b] Figures in parentheses are the range.

[c] DAT = direct agglutination test for *Leishmania* antibodies.

Table 2. **Events during and after treatment of kala-azar patients with generic sodium stibogluconate (SSG) and Pentostam® (PSM)**

	Total (*n* = 102)	SSG group (*n* = 51)	PSM group (*n* = 51)	*P*-value[a]	Odds ratio
Mean no. of injections received	30 (12–45)[b]	30 (12–45)	30 (14–30)	0.7*	–
No. of patients vomiting	12	7	5	0.8	1.46; *0.37–6.29*[c]
No. of patients with rash	27	14	13	>0.9	1.11; *0.42–2.94*
No. of patients with jaundice	2	1	1	>0.9	1.0; *0.01–80.05*
No. of patients transfused/ units of blood given	43 / 60	23/32	20 / 28	0.7	1.27; *0.54–3.02*
TOC[d] negative/positive/not done	79/1/22	43/1/7	36/0/15	>0.9	–
No. initially cured	93	47	46	>0.9	1.27; *0.26–6.84*
No. who died	4	1/ on day 10	3/on days 14, 15, 32	>0.9	0.32; *0.01–4.19*
No. who defaulted	4	2/on days 24, 30	2/on days 27, 30	>0.9	–
No. followed up at or beyond 6 months	58	30	28	0.84	1.07; *0.43–2.67*
Relapses at or beyond 6 months	6/58; 10%[e]	5/30; 17%[e]	1/28; 4%[e]	0.19	5.4; *0.54–265*
Definitively cured	52/58; 90%[e]	25/30; 83%[e]	27/28; 96%[e]	0.19	0.19; *0.004–1.87*

[a] Fisher's exact test, except * = Mann-Whitney U-test.

[b] Figures in parentheses are the range.

[c] Figures in italics are the 95% confidence intervals.

[d] TOC = test-of-cure aspirate at the end of treatment.

[e] Proportion.

SSG or PSM). By comparison, Pentostam® can be bought from IDA for US$ 115.18 per 100 ml bottle, i.e US$ 165.86 per patient in our study. All batches of generic sodium stibogluconate provided by IDA undergo a second round of quality control at the association, where the assessment includes the proportion of trivalent and pentavalent antimony and the osmolality (M. de Goeje, personal communication). Generic SSG has been used to treat hundreds of thousands of cases of kala-azar in Bangladesh and India, with cure rates of ca. 95% having been reported in a very large series (*11*). The availability of cheaper generic sodium stibogluconate, subject to rigid quality controls, now makes it possible for the health authorities in endemic areas to provide affordable treatment to many more patients with kala-azar in Africa. ■

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Conflicts of interest: none declared.

Résumé

Comparaison entre une spécialité et un générique de stibogluconate de sodium pour le traitement de la leishmaniose viscérale au Kenya

Objectif Comparer l'utilisation d'une spécialité et d'un générique de stibogluconate de sodium pour le traitement de la leishmaniose viscérale (kala-azar).

Méthodes Au total, 102 patients atteints de kala-azar confirmé ont été traités par le stibogluconate de sodium (20 mg/kg par jour pendant 30 jours) dans un hôpital de mission de la région de West Pokot au Kenya. Le stibogluconate de sodium était administré soit sous forme de Pentostam® (PSM), soit sous la forme générique correspondante (SSG) ; les patients étaient répartis à tour de rôle dans chacun des groupes de traitement (51 patients par groupe).

Résultats Aucune différence significative n'a été observée, que ce soit au niveau des données démographiques de base, de la gravité de la maladie ou des faits survenus en cours de traitement. Trois décès ont été enregistrés dans le groupe PSM et un dans le groupe SSG, et deux patients de chaque groupe ont été perdus de vue. Sur 80 ponctions de rate effectuées pour évaluer la guérison, une seule était positive pour *Leishmania* spp. (chez un patient traité par SSG). Un suivi réalisé au bout de 6 mois au minimum a montré que 6 patients sur 58 avaient rechuté (5 dans le groupe SSG et 1 dans le groupe PSM). Aucun paramètre relatif à l'issue du traitement n'était significativement différent d'un groupe à l'autre.

Conclusion La possibilité de disposer à moindre coût de stibogluconate de sodium générique soumis à des contrôles de qualité rigoureux permet maintenant aux autorités sanitaires des régions d'Afrique où le kala-azar est endémique de fournir un traitement à un nombre beaucoup plus grand de patients.

Resumen

Comparación de las formas genérica y patentada de estibogluconato sódico como tratamiento de la leishmaniasis visceral en Kenya

Objetivo Comparar el uso del estibogluconato sódico genérico y patentado como tratamiento de la leishmaniasis visceral (kala-azar).

Método Un total de 102 pacientes con kala-azar confirmado fueron tratados en un hospital de misión en la región de West Pokot (Kenya) con estibogluconato sódico (20 mg/kg/día durante 30 días), bien en forma de Pentostam® (PSM) o bien como preparado genérico (EGS). De forma alternativa, se asignó a 51 pacientes a cada grupo de tratamiento.

Resultados No se observaron diferencias significativas en lo tocante a las características demográficas basales o la gravedad de la enfermedad, así como tampoco en lo que respecta a los eventos registrados durante el tratamiento. Hubo 3 defunciones en el grupo PSM y una en el grupo EGS; en cada grupo hubo dos pacientes que abandonaron el tratamiento. Sólo uno de los 80 aspirados esplénicos de confirmación de la curación fue positivo para *Leishmania* spp., y se trataba de un paciente del grupo EGS. El seguimiento realizado al cabo de un periodo mínimo de seis meses mostró que habían recaído seis de 58 pacientes: cinco en el grupo tratado con EGS y uno en el grupo tratado con PSM. No se observaron diferencias significativas en ninguna variable de resultado final entre los dos grupos.

Conclusión Gracias a la disponibilidad de estibogluconato sódico genérico más barato, y siempre que se aplique un control de calidad estricto, las autoridades sanitarias de las zonas con kala-azar endémico pueden hoy suministrar tratamiento a muchos más pacientes en África.

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