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A randomized comparison of branded sodium stibogluconate and generic sodium stibogluconate for the treatment of visceral leishmaniasis under field conditions in Sudan

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Summary

OBJECTIVE To compare the outcome of treatment of Sudanese kala-azar patients treated under field conditions with either branded sodium stibogluconate (SSG) (Pentostam GlaxoWellcome) or generic SSG (Albert David Ltd, Calcutta, supplied by International Dispensary Association, Amsterdam).

METHOD Randomised comparison. 271 patients were treated with Pentostam and 245 with generic SSG.

RESULTS No statistically significant differences in cure rate or mortality were detected between Pentostam and generic SSG. No differences in side-effects between the two drugs were noted. The initial cure rate at the time of discharge was 93.7 and 97.6%, respectively; the death rate during treatment 5.9 and 2.4%. Six months follow up was achieved in 88.5% of the discharged patients. Two patients had died in the Pentostam group and two had died in the generic SSG group, giving a final death rate of 7.5 and 3.7%. The number of relapses in the Pentostam and generic SSG groups were 3 and 1, respectively. The final cure rates, calculated at 6 months after discharge, were 91.3% and 95.9%.

CONCLUSION No difference was observed in the performance of generic SSG compared to Pentostam for the treatment of visceral leishmaniasis in Sudan. Generic SSG can be routinely and safely used for the treatment of kala-azar. Generic SSG costs only 1/14 of the price of Pentostam. The use of generic SSG may make treatment of kala-azar affordable for national governments in Africa.

keywords Kala-azar, visceral leishmaniasis, treatment, randomised trial, pentavalent antimonials, sodium stibogluconate

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Introduction

Visceral leishmaniasis (kala-azar) is a fatal disease if not treated. About 500 000 new cases occur each year (UNDP *et al*. 1997), mainly in India. Sudan is another area of concern; precise incidence figures are not available, but it is estimated that in south Sudan, during the period 1989–94, 100000 people died in a kala-azar epidemic (Seaman *et al*. 1996a). Since 1988 Médecins Sans Frontières (MSF)-Holland has treated approximately 40000 kala-azar patients in the Sudan, initially in Upper Nile and subsequently in the Gedaref states.

The mainstay of the treatment of kala-azar remain the pentavalent antimony compounds. In East Africa, Pentostam, sodium stibogluconate (SSG), produced by GlaxoWellcome in the UK, is used. High cost (an average of 200 US dollars per patient), combined with output of the product which is exceeded at times by demand, make continuity in the supply of Pentostam uncertain. A cheaper, good quality drug is needed.

In India, sodium stibogluconate is manufactured by several companies, and used in large numbers of patients. Some batches of production have been found to be unexpectedly toxic (Sundar *et al*. 1998). Sodium stibogluconate has been manufactured by Albert David Ltd, Calcutta, for several decades and sold under the name Sodium Antimony Gluconate. The difference in name has led to generic SSG (Albert David) being regarded, erroneously, as a different drug to sodium stibogluconate. The International Dispensary Association (IDA, Amsterdam) inspected the manufacturing process and undertook independent quality testing of generic SSG (Albert David). Using an ongoing programme of inde-

pendent quality control, treated IDA provides generic SSG at around 13 US dollars per patient. Introducing generic SSG for the treatment of kala-azar in East Africa could make large-scale production of high-quality SSG available at low cost. However, MSF recognized that, having used solely Pentostam for visceral leishmaniasis for 50 years, individuals and institutions would have confidence in the use of generic SSG only when it has been carefully evaluated clinically. In a mission hospital setting, no differences in efficacy and tolerability between the two drugs were detected in a study of 102 kala-azar patients (Moore *et al*. 2000). We compared the efficacy and toxicity of generic SSG and Pentostam under field conditions.

Methods

The study was implemented in the MSF kala-azar treatment centres Um Kuraa and Kassab in Gedaref state, Sudan. The centres were established in 1996 and 1998 to treat the large number of kala-azar patients coming from this highly endemic focus. The trial was conducted with agreement, and in co-operation with, regional and federal health authorities and Sudanese kala-azar experts.

Protocol

Patients, mostly self referred, were seen at the MSF kala-azar screening centres. The following clinical case definition was used: patients with fever for more than two weeks (with exclusion of malaria), in combination with either splenomegaly or wasting. In cases meeting the case definition, kala-azar was confirmed by a $\geq$ 1:6400 titre of antibodies against *Leishmania* by the Direct Agglutination Test (and a subsequent response to antimonial treatment); or by demonstration of *Leishmania* on aspirates of spleen or lymph node (WHO 1996). DAT antigen was obtained from the Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium. The DAT was standardized with freeze-dried positive sera of known titre.

In case of a borderline DAT titre of 1:400 to1:6400, aspiration of an inguinal lymph node or spleen was performed. In acutely ill patients, both DAT and aspiration were performed on the same day. If the results were negative but the clinical suspicion of kala-azar remained high, the DAT and/or aspiration were repeated. Giemsa-stained slides were read by MSF laboratory technicians, stored and checked (by JS) at a later date. Within 5 days of the end of treatment, a test of cure (TOC) lymph node aspiration was performed. The quality of a random sample of the slides was controlled by the Department of Biomedical Research of the Royal Tropical Institute, Amsterdam.

Patients who had received any treatment for kala-azar in the past were excluded. Nomadic patients, in whom follow up would be impossible, were excluded. Informed written consent was given by the patient or their guardian/parent. Participation in the study was voluntary, and those who did not participate were treated with Pentostam. Patients were not excluded from treatment on the basis of severe disease.

We calculated that, at a power of 90% and a significance level of $P = 0.05$ (two-tailed), to detect a difference of 10% in cure, death, or relapse rate between the two groups, a sample size of 207 patients in each arm was required. All consecutive kala-azar patients newly diagnosed from 30 November until 31 December 1998 were alternately assigned to either the Pentostam or the generic SSG treatment group. Allocation was on the basis of the DAT registration number, noted in a single ledger, with the number being allocated prior to enrolment in the study. Patients with odd DAT numbers received Pentostam, those with even numbers received generic SSG. The study was not blinded. Volume and colour of the drug was equal. The injection nurse knew which drug to give by colour coding of the patient treatment card. Nurses were trained and supervised in filling in the registration forms.

Data collection

The following data were collected at admission or soon thereafter: name, age, sex, address, previous treatment with pentavalent antimony compound, height, weight, spleen size (in cm, measured in the anterior axillary line to the furthest point during quiet breathing), liver size (in cm, measured in midclavicular line during quiet breathing), haemoglobin (Hb), walking status (normal, with assistance, carried on stretcher), DAT result (number, titre, and date tested) and parasitology result (tissue, parasite density, date). During treatment intermittent events and complications were noted daily. The signs and symptoms associated with death were recorded. At discharge, spleen size, liver size, Hb, weight, post kala-azar dermal leishmaniasis (PKDL), TOC aspirate (parasitology result, tissue, grade), and location of the chief for the next 6 months were noted. Six months after discharge we recorded history of fever, clinical symptoms, spleen size and PKDL. An aspiration was only performed in case of clinical features suggestive of a relapse.

Treatment

Treatment was given according to routine WHO and MSF schedules: 20 mg/kg/day for 30 days of either Pentostam or generic SSG intramuscularly. Both are colourless liquids, 1 mL contains 100 mg pentavalent antimony. The minimum dose was 2 mL (200 mg), no maximum upper limit was used. For injecting volumes $>$ 10 mL, the injection was given in two halves, in each buttock. All patients, whether in the study or

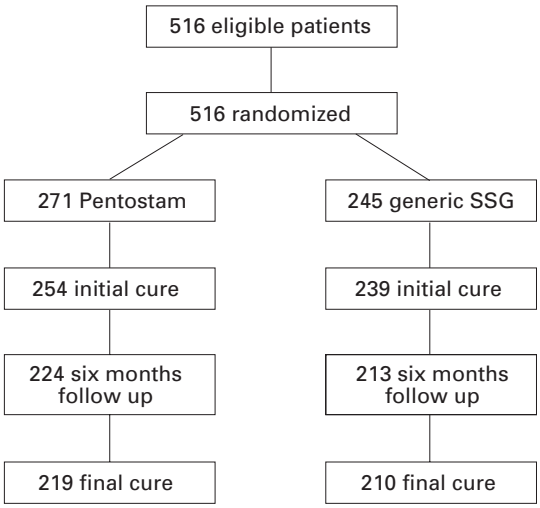

Figure 1 Flow chart describing the progress of patients through the randomised trial.

not, received free treatment and food. Intermittent illnesses were treated according to the standard protocols. Malnourished patients received supplemental or therapeutic feeding according to severity.

Outcome variables

Initial cure at discharge, death during treatment, relapse and final cure (at 6 months after discharge) were the main outcome parameters. A patient was considered initially cured if clinically well at discharge and after at least 28 days of injections. If the TOC aspirate was positive, the patient continued treatment with the same drug and weekly TOCs were done until 2 consecutive TOCs were negative.

All patients were asked to return immediately, if any signs were experienced, to exclude relapse and to return for a standard clinical follow-up after 6 months. Aspiration was done only in case of symptoms suggestive for relapse (WHO 1996). Travel expenses were paid and a bednet was given as an incentive. If no relapse occurred within 6 months of discharge, the patient was considered cured. The clinical assessment at 6 months follow-up was made without knowledge of the treatment group.

Statistical analysis

Data were analysed with Excel (Microsoft) and Arcus-Quick stat. For parametric data, we used the Z score test for comparison of means was used; for nonparametric data, the Mann Whitney test; for categorical data, the χ^2 test for trend.

Results

Patients

During the trial period 978 clinically suspected cases were assessed; 516 were confirmed as kala-azar and entered in the trial (Figure 1). All 516 patients had been DAT-tested: 440 patients had a (high-titre) positive DAT result (85.6%) and the DAT results of two patients were missing, but both were parasitologically confirmed by lymph node aspirate. 189 patients underwent aspiration; 140 had a positive aspirate (123 positive in the first aspirate, 17 positive in the repeat

Table 1 Comparison of the baseline characteristics of 516 Sudanese patients with kala-azar after randomization to receive either Pentostam or generic SSG

	Pentostam		Generic SSG		
	Mean	Median	Mean	Median	*P*-value
Age (years)	12.5	9	12.2	10	0.90
Sex (m/f)	160/111		150/95		0.68 *
Duration of illness (months)	1.6	1	1.4	1	0.59
Ability to walk walking/stick/stretcher	229/3/18		216/4/15		0.85 †
Weight (kg)	26.6	21	27.0	21.7	0.61
Height (cm)	129.1	130.1	131.7	130.9	0.68
Hb (g/dl)	7.9	8	8.2	8.2	0.021 ‡
BMI (kg/m^2)	16.0	16.4	16.6	16.3	0.69
(in adults)	(n = 81)		(n = 66)		
Spleen size (cm)	6.1	6	6.6	7	0.12
Weight for height	80.0	79.5	80.2	80	0.73
(in children)	(n = 188)		(n = 179)		

Test used: Mann Whitney; except: *χ^2, †χ^2 for trend, ‡Z score comparison of the means.

Table 2 Initial outcome of 516 Sudanese patients with kala-azar who were treated either with Pentostam or generic SSG

	Pentostam		Generic SSG			
	no	(%)	no	(%)	*P*-value	Relative risk (95% confidence intervals)
Deaths during treatment	16	(5.9)	6	(2.4)	0.08	0.41 (0.16–1.04)
Initially cured:	254	(93.7)	239	(97.6)		
Negative 1st TOC	236	(87.1)	224	(91.4)	0.15	1.05 (0.99–1.11)
Positive 1st TOC; treatment extended until TOC negative	16	(5.9)	13	(5.3)	0.92	0.90 (0.44–1.83)
Negative TOC; treatment extended because of PKDL during treatment	2	(0.7)	2	(0.8)	1.0*	–
Defaulters	1	(0.4)	–		1.0*	
Total	271		245		–	–

Test used: χ^2; except: *-Fisher exact two-tailed.

aspirate). 185 aspirations were taken from inguinal lymph nodes, 4 from the spleen.

During the time of the study, 26 confirmed kala-azar patients did not fit the entry criteria and were treated outside the study. The reasons were previous treatment for kala-azar and nomadic lifestyle (no follow-up possible); no eligible adult patients, or guardians of eligible children refused to consent. 271 patients were assigned to receive Pentostam and 245 generic SSG. A review of drug allocation *vs*. DAT number showed none of the patients had been incorrectly allocated.

Base-line patient characteristics

Except for Hb, which was lower in the Pentostam group (Table 1), there were no significant differences between the two groups in base-line characteristics (age, sex, duration of illness, ability to walk, spleen size, weight, height, body mass index (BMI)(calculated for patients aged 16 years or older), weight-for-height (calculated for patients aged under 16 years). The patients had a range of disease severity, but many were in an advanced state of malnutrition and weakness. The true severity of malnutrition is worse than indicated by BMI and weight-for-height, because the weight of some patients includes the weight of oedema fluid and ascites.

Outcome

The initial outcome is presented in Table 2. The initial cure rate for the two treatment groups was 93.7 for Pentostam and 97.6% for generic SSG. Most had a negative TOC after treatment. In the Pentostam group 5.9% needed an extension of treatment due to a positive TOC at the end of treatment. In the SSG group this was necessary in 5.3% of the patients. In each group 2 patients were successfully treated with a schedule of longer duration due to PKDL.

The main causes of the 22 deaths (16 Pentostam, 6 generic SSG) were: anaemia and bleeding (Pentostam 5, generic SSG 3); gastro-enteritis (Pentostam 3, generic SSG 1); severe vomiting (Pentostam 3, generic SSG 1). The remaining deaths each occurred in one patient only and were, in the Pentostam group: severe kwashiorkor and sepsis; liver failure and pneumonia; febrile illness of unknown origin; coma; unknown; and in the generic SSG group: meningitis. There was no difference in death rates between patients treated in the two

Table 3 Comparison of the frequency of intercurrent events among 516 Sudanese patients with kala-azar treated with Pentostam or generic SSG

	Pentostam	Generic SSG	*P*-value	Relative risk (95% confidence intervals)
Diarrhoea	41.7%	37.7%	0.40	0.90 (0.73–1.12)
Vomiting	41.0%	33.5%	0.10	0.82 (0.65–1.03)
Respiratory tract infection	43.9%	41.8%	0.64	0.95 (0.78–1.16)
Bleeding	11.9%	16.8%	0.14	1.42 (0.92–2.18)

Test used: χ^2.

Table 4 Final outcome of 516 Sudanese patients with kala-azar, treated with Pentostam or generic SSG, as assessed 6 months after discharge

	Pentostam		Generic SSG		Total		
	no	(%)	no	(%)	no	(%)	*P*-value
Number treated	271		245		516		
Died during treatment	16	(5.9)	6	(2.4)	22	(4.3)	0.08
Survived treatment, eligible for follow up	255	(94.1)	239	(97.6)	494	(95.7)	
Not traced	31	(12.2)	26	(10.9)	57	(11.5)	0.76
Followed up at 6 months:	224	(87.8)	213	(89.1)	437	(88.5)	0.76
Clinical examination	206	(80.8)	199	(83.3)	405	(82.0)	0.55
History by close relative or chief	16	(6.3)	12	(5.0)	28	(5.7)	0.68
Died after discharge	2	(0.8)	2	(0.8)	4	(0.8)	1.00*
Relapse	3/224	(1.3)	1/213	(0.5)	4/437	(0.9)	0.62*
Severe PKDL	21/224	(9.4)	12/213	(5.6)	33/437	(7.6)	0.19
Total deaths	18/240	(7.5)	8/219	(3.7)	26/459	(5.7)	0.11
Final cure rate	219/240	(91.3)	210/219	(95.9)	429/459	(93.5)	0.07

Test used: χ^2; except: *Fisher exact two-tailed.

different treatment centres Um Kuraa (15 of 374) and Kassab (7 of 142), $P = 0.83$.

There was no statistically significant difference between the two groups for the following changes during treatment: increase of Hb (Pentostam 2.1 g/dL; generic SSG 2.0 g/dL); increase in weight (Pentostam 2.1 kg; generic SSG 2.1 kg); decrease in spleen size (Pentostam 5.1 cm; generic SSG 5.4). The frequency of intercurrent events (diarrhoea, vomiting, bleeding and respiratory tract infections) is shown in Table 3.

Follow-up

The final outcome of those patients who were discharged alive, and who could be traced for follow-up at 6 months is summarized in Table 4. In total 437 (88.5%) of the surviving patients were followed up, either through clinical examination (82.0%) or history of their well-being taken from a family member (5.7%). There were 4 relapses, 4 deaths, and 33 cases of severe PKDL (grade 2 and 3) after discharge. The final cure rate, calculated for all patients minus those who could not be traced for follow-up, was 91.3% (Pentostam) and 95.9% (generic SSG). There were no significant differences between treatment groups.

Discussion

This is the largest randomised drug evaluation ever undertaken in kala-azar patients. The study was done in remote areas under basic conditions: the treatment centres consisted mainly of shelters built of mud and grass. Investigations available to diagnose and treat complications were restricted to urine microscopy and dipstick, colourometric Hb estimation, and slides for malaria and *Leishmania*. Randomization by DAT ledger number produced two comparable groups. The study could not be blinded due to the fact that the drugs were in different types of vials. However, our main outcome parameter, death, is not susceptible to information bias, and does not require blinding. Although the patients could learn which drug they received, the volume and colour of the drugs given was equal, and neither patients nor nurses expressed a preference of one drug over another during the study. The nurses were trained and had ample experience in treating kala-azar patients; they knew which of the two treatments was given. Empty ampoules were collected to double check that the right drugs were prescribed.

We followed the routine MSF kala-azar diagnostic schedule for a high patient load during an epidemic, in agreement with WHO guidelines for field situations (WHO 1996). Accordingly, in patients fulfilling the case definition, kala-azar was confirmed either by a strongly positive DAT titre (and subsequent response to antimonial treatment), or a positive aspirate. Diagnostic aspirations were taken from an inguinal lymph node by paramedical staff. Few diagnostic spleen aspirates were needed. The high number of children in the study (mean age 12 years) is caused by the location within a known endemic focus of kala-azar.

Although the difference in the number of deaths during treatment between the two groups was not statistically significant, deaths among the Pentostam recipients (16) were more than twice as frequent as those among the generic SSG group (6). We have no explanation for this, but saw a similar trend in our smaller, hospital-based study in Kenya (4) (Moore *et al*. 2000). At 6 months follow-up we were able to locate 82% of patients and examine them clinically. For another 5.7% we obtained a history from relatives or their village chief of the patient being well. Relapses, severe PKDL and death after dis-

charge were infrequent, and equally distributed between the two groups. The 57 patients who could not be traced during the follow-up were excluded from the calculations of final cure and final death rates. Reasons for failed follow-up were moved to another state (Sennar) or inaccessibility (road conditions). It is reasonable to assume that their final outcome will not be different from those who could be traced. The final cure rate includes one defaulter (a child who received 18 injections) who was clinically investigated after 6 months and considered cured.

The final death rate in the study was 5.7%. This is lower than the death rate among patients treated during the epidemic in south Sudan, where 11% died (Seaman *et al*. 1996b), but similar to the 6% mortality we found during an evaluation of treatment with Pentostam with or without aminosidine in south Sudan (Seaman *et al*. 1993). None of the deaths had the clinical features of cardiac arrythmias, which have been considered by others (Sundar *et al*. 1998) to be the cause of unexpected deaths during treatment with antimonials.

We conclude that generic SSG (as manufactured by Albert David and quality tested by IDA) can be used safely and routinely for the treatment of kala-azar patients. Generic SSG costs only 1/14 of the price of Pentostam. The use of generic SSG may make treatment of kala-azar affordable for national governments. However, we add a note of caution: production of antimonials is notorious for its batch-to-batch variation. Continuous quality control of each batch produced is essential to guarantee safe treatment. At present, despite its high price, we find that Pentostam is sometimes available informally in East Africa, and used in inadequate doses and duration by the villagers themselves. The availability of cheaper sodium stibogluconate could increase unregulated self-medication with inadequate regimens. Eventually, this might lead to antimonial-resistant leishmaniasis. We therefore hope to continue our field evaluations of antileishmanial drugs such as aminosidine and miltefosine, to identify affordable second-line treatment for kala-azar in Africa.

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