

Key messages

- Persistent abdominal pain in childhood is more common in families with high rates of reported physical illness and psychological symptoms
- The outcome for persistent abdominal pain is good in terms of mortality
- Children with persistent abdominal pain are not at greatly increased risk of developing physical symptoms in adulthood
- Abdominal pain in childhood is associated with considerably increased risk of psychiatric disorders in adulthood

belly-achers¹³ do not grow up to be big belly achers but do grow up to suffer from anxiety or depression.

We thank Warren Hilder and Erol Yusef for their assistance in data handling.

Contributors: MH is the guarantor for this paper. He was responsible for formulating initial hypotheses, collecting data on admission in childhood, analysing data, and writing early drafts. The other authors all participated in further refinement of hypotheses and study design. MW, as director of the Medical Research Council national survey of health and development, was responsible for recent data collection. SC rated data on the children's physical ailments. All authors commented on early results and considered additional analyses to perform. All commented on later drafts.

Funding: MH is a clinical training fellow funded by the Medical Research Council. The national survey of health and development is funded by the Medical Research Council.

Conflict of interest: None.

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(Accepted 22 December 1997)

Randomised controlled trial of aminosidine (paromomycin) *v* sodium stibogluconate for treating visceral leishmaniasis in North Bihar, India

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BMJ 1998;316:1200-5

Abstract

Objectives: To assess the efficacy and tolerability of aminosidine compared with sodium stibogluconate for treating visceral leishmaniasis.

Design: Randomised, unblinded, controlled trial with 180 day follow up.

Setting: Kala-Azar Research Centre, Brahmpura, Muzaffarpur, Bihar, India.

Subjects: People of either sex aged 6-50 years with symptoms and signs suggestive of visceral leishmaniasis (fever, loss of appetite, enlarged spleen) with leishmania amastigotes detected in Giemsa stained aspirates of spleen or bone marrow.

Interventions: Aminosidine at three daily doses (12, 16, and 20 mg/kg) for 21 days and sodium stibogluconate 20 mg/kg/day for 30 days.

Main outcome measures: Laboratory measures of efficacy: parasite count, haemoglobin concentration,

white cell count, platelet count, serum albumin concentration. Clinical measures of efficacy: spleen size, fever, body weight, and liver size. Measures of safety: liver and renal function tests, reports of adverse events.

Results: Of the 120 patients enrolled (30 per treatment arm), 119 completed treatment and follow up. Cure at end of follow up was achieved in 23 (77%), 28 (93%), and 29 (97%) patients treated with 12, 16, and 20 mg aminosidine/kg/day respectively, and in 19 (63%) patients given sodium stibogluconate. At 16 and 20 mg/kg/day, aminosidine was significantly more active than sodium stibogluconate in both clinical and laboratory measures of efficacy. No significant clinical or laboratory toxicity occurred in any treatment group.

Conclusions: A 21 day course of aminosidine 16 or 20 mg/kg/day should be considered as first line treatment for visceral leishmaniasis in Bihar.

Introduction

Bihar state, in the north east of India, carries the burden of about half of the world's annual cases of visceral leishmaniasis. In recent years these infections have become increasingly unresponsive to first line treatment with pentavalent antimony compounds. While a daily dose of 20 mg/kg sodium stibogluconate for 20-40 days was efficacious in the 1980s, up to 25% unresponsiveness is now reported even with high doses and longer administration.¹⁻⁸ In consequence, as well as increased morbidity and mortality, treatment costs have risen because of increased doses, prolonged hospitalisation, and need for retreatment. Alternative drug treatments for areas with endemic visceral leishmaniasis are badly needed.

Aminosidine is an aminoglycoside antibiotic identical to paromomycin.⁹ An injectable formulation of 500 mg aminosidine sulphate has been on the market in several countries for over 30 years for treating bacterial and parasitic infections. Aminosidine was first shown to have anti-leishmanial activity in the 1960s,¹⁰⁻¹¹ and it has been shown to act synergistically with antimony drugs.¹² Clinical trials with injectable aminosidine for treating visceral leishmaniasis have been conducted in Africa (Kenya and Sudan),¹³⁻¹⁴ India (Bihar),¹⁵⁻¹⁶ and in complicated cases imported into the United Kingdom.¹⁷ Most patients received aminosidine combined with antimony compounds, and the combinations were found to be highly efficacious and well tolerated. Minimal comparative data are available thus far on treatment with aminosidine alone.

This study was therefore undertaken to determine the efficacy and safety of aminosidine alone in treating visceral leishmaniasis and to establish the optimum dose for a fixed duration of 21 days in comparison with standard treatment. This study is part of the aminosidine development project of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, the aim of which is to produce data to support the registration and use of aminosidine in control programmes for visceral leishmaniasis.

Methods

Protocol

Study design

This randomised, unblinded, controlled trial was designed to evaluate the ratio of risk to benefit of three doses of aminosidine compared with the standard dose of antimony. This study was undertaken at the Kala-Azar Research Centre in Muzaffarpur, Bihar, which is situated in the centre of the hyperendemic area spread over a radius of 70 km. Patients were randomly assigned to one of four treatment arms: aminosidine (Gabbromycin, Farmitalia-Carlo Erba, Milan, Italy, now Pharmacia-Upjohn) given intramuscularly at a dose of 12, 16, or 20 mg/kg/day for 21 days, or sodium stibogluconate 20 mg/kg/day (Albert David, Calcutta, India, 30 ml vial containing 100 mg/ml) to a maximum of 8.5 ml/day for 30 days. Patients were hospitalised for treatment and, after discharge, were followed up at 30, 90, and 180 days after treatment was completed.

At initial assessment, at end of treatment, and at each follow up, subjects were examined by means of parasitology on Giemsa stained aspirates of spleen or bone marrow to assess the parasite burden (measured in accordance with the WHO Technical Series No 793¹⁸), electrocardiography, and audiometry. At initial assessment, at weekly intervals during treatment, and at each follow up, subjects were also assessed by means of measurement of spleen and liver size (from the costal margin along the anterior axillary line of supine patients); blood chemistry (liver and renal function tests); haematology (complete blood count, including haemoglobin concentration, white cell count, and platelet count); prothrombin and bleeding time; and urine analysis.

Inclusion and exclusion criteria

Patients aged 6-50 years with symptoms and signs suggestive of visceral leishmaniasis and aspirates of spleen or bone marrow positive for leishmania amastigotes were eligible for inclusion in the study if they gave signed informed consent. Exclusion criteria were a known allergy to aminoglycosides, treatment in the previous 12 months with a drug with recognised or presumed anti-leishmanial action, serious concomitant diseases, pregnancy or lactation (women underwent a pregnancy test at initial assessment), failure to agree to return for all follow up evaluations, and being critically ill from leishmaniasis. Definitions for critical illness from leishmaniasis included the spleen reaching to the pelvic crest, haemoglobin concentration <50 g/l, white cell count <2 × 10⁹/L,³ platelet count <80 × 10⁹/L,³ aspartate aminotransferase concentration >4 × upper limit of normal, serum albumin concentration <20 g/l, and urine urea or creatinine concentration >2 × upper limit of normal.

Ethics

The study received formal clearance from the drug controller of the Indian government, the local ethics committee, and the WHO Secretarial Committee on Research Involving Human Subjects and was conducted in accordance with the Declaration of Helsinki. Patients were informed of the purpose of the trial and had to give their signed informed consent before being enrolled.

Efficacy variables

The primary parameter of efficacy was final cure (clinical improvement and parasitological cure persisting at 180 days after treatment completed). Parasitological definitions of efficacy were cure (negative aspirates for leishmania amastigotes after treatment completed), improvement (reduction of parasitic load ≥2 grades after treatment completed), failure (reduction of parasitic load by <2 grades), and relapse (positive aspirates after initial conversion to negative aspirate). Clinical improvement was defined as defervescence and improvement in one or more clinical sign—that is, increase in body weight by 2 kg, in haemoglobin concentration by 20 g/l, in white cell count by 1 × 10⁹/L, and in albumin concentration by 5 g/l and reduction in spleen size by 40%.

Statistical methods

We decided that 30 patients with visceral leishmaniasis should be enrolled into each treatment arm (total 120

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Table 1 Selected baseline characteristics of patients with visceral leishmaniasis by treatment. Values are means (SD) unless stated otherwise

	Aminosidine			Sodium stibogluconate 20 mg/kg/day (n=30)	Comparison (P value)*
	12 mg/kg/day (n=30)	16 mg/kg/day (n=30)	20 mg/kg/day (n=30)		
Male:female ratio	18:12	18:12	23:7	24:6	0.19
Age (years)	29.83 (14.77)	23.73 (12.02)	29.10 (14.67)	26.07 (12.58)	0.28
Weight (kg)	37.85 (12.80)	35.87 (11.39)	37.63 (12.53)	37.25 (12.44)	0.60
Duration of illness (No of days with fever)	73.57 (57.07)	69.73 (49.28)	90.47 (59.20)	62.33 (40.50)	0.2
Spleen size (cm)	5.96 (3.59)	6.44 (3.70)	6.36 (4.70)	5.55 (3.45)	0.80
Haemoglobin concentration (g/l)	86 (14.2)	76 (20.1)†	82.5 (10.3)	89.2 (13.1)†	0.0064
White cell count (10 ⁹ /l)	4.05 (1.16)	3.59 (0.89)	4.04 (1.07)	4.15 (1.13)	0.19
Platelet count (10 ⁹ /l)	210 (66)†	178 (34)	168 (56)†	178 (50)	0.016
Albumin concentration (g/l)	30.7 (5.0)	30.7 (3.8)	29.9 (4.0)†	33.2 (5.2)†	0.015
Parasite burden (grade)	2.20 (0.96)	2.03 (0.96)	2.40 (0.81)	1.93 (0.74)	0.18

*Calculated from one way analysis of variance, except for male:female ratio calculated from χ^2 test.

†Significant on Tukey's honest significance difference.

patients). With this number, we thought it unlikely that we would be able to demonstrate significant differences in efficacy, but it was considered a satisfactory balance between scientific purposes and practical constraints.

All 120 patients enrolled were included in the analyses on the basis of intention to treat. We used descriptive statistics to summarise baseline values, and we used the χ^2 test to compare dichotomous variables between groups and one way analysis of variance for continuous variables. We assessed changes in continuous variables from baseline over time by using paired *t* tests within groups and, for comparisons between groups, used the one way analysis of variance with post hoc multiple comparison using Tukey's honest significance difference. Both actual values and changes from baseline were compared across the groups. All results were assessed at a significance level of $P = 0.05$.

Values were compared at each follow up visit. Since patients given antimony were treated for 30 days while those given aminosidine were treated for 21 days, we created the category "end of treatment" (day 30 for antimony, day 21 for aminosidine). In this paper we present detailed comparisons only for day 21 and end of treatment.

Data quality assurance

The sources of data were verified, values were keyed in using DataBase III and double checked at the clinical site. Further checks with spss for Windows were made after transferring the data to Geneva for analyses.

Assignment

Treatment was unblinded. Patient eligibility was evaluated before randomisation to treatment with a compu-

ter generated randomisation list. Treatment was administered by nurses at the hospital. The doctor assessing clinical efficacy was unaware of the dose of aminosidine given, and technicians assessing laboratory measures of efficacy were unaware of the treatment administered.

Results

Subjects

Patient disposition—Between June 1993 and August 1995, 2007 patients who attended the centre with complaints of fever were screened for visceral leishmaniasis. Visceral leishmaniasis was diagnosed in 507 patients, of whom 120 met the inclusion criteria.

Baseline characteristics—Table 1 shows that the baseline characteristics of the four groups allocated to different treatment arms did not differ significantly except for haemoglobin concentration (higher in the group allocated antimony compared with those allocated aminosidine 16 mg/kg/day), platelet counts (higher in those allocated aminosidine 12 mg/kg/day than in those allocated 20 mg/kg/day), and albumin concentration (higher in the antimony group than in those allocated aminosidine 20 mg/kg/day).

Efficacy evaluation

Overall assessment—Table 2 shows that a final cure (clinical cure, clinical improvement, and parasitological cure at 180 days after end of treatment) was achieved in 23, 28, and 29 patients given aminosidine 12, 16, and 20 mg/kg/day respectively, compared with 19 of the patients given antimony (χ^2 test, $P = 0.003$). Of the three doses of aminosidine, only treatment with 12 mg/kg/day did not differ significantly from antimony treatment ($P = 0.26$).

Parasitological outcome—At the end of treatment tissue aspirates were negative for leishmania amastigotes in 27, 28, and 27 patients given aminosidine 12, 16, and 20 mg/kg/day respectively, compared with 22 patients given antimony (table 3). All three doses of aminosidine were significantly more effective than antimony (χ^2 test, $P = 0.002$). Only two failures were recorded in the group given aminosidine 12 mg/kg/day compared with eight in the antimony group. During follow up, a total of 10 patients relapsed after apparent clearance of parasites (5, 1, and 1 given aminosidine 12, 16, and 20 mg/kg/day respectively,

Table 2 Overall efficacy of treatments for visceral leishmaniasis. Values are number (percentage) of patients

Treatment	Final cure (at end of follow up)	Failure (at end of treatment)	Relapse (during follow up)	Defaulters
Aminosidine*:				
12 mg/kg/day (n=30)	23(77)	2	5	0
16 mg/kg/day (n=30)	28(93)	0	1	1
20 mg/kg/day (n=30)	29(97)	0	1	0
Sodium stibogluconate 20 mg/kg/day (n=30)†	19(63)	8	3	0

*Treatment given for 21 days. †Treatment given for 30 days.

Table 3 Parasitological measures of efficacy of treatments for visceral leishmaniasis. Values are number of patients

Treatment	Time after start of treatment													
	21 days		30 days			60 days			90 days		120 days		180 days	
	Cured	Improved	Cured	Improved	Failed	Cured	Failed	Relapsed	Cured	Relapsed	Cured	Relapsed	Cured	Relapsed
Aminosidine*:														
12 mg/kg/day (n=30)	27	3	28	0	2	28	0	0	27	1	26	1	23	3
16 mg/kg/day (n=30)	28	2	30	0	0	30	0	0	30	0	30	0	29	1
20 mg/kg/day (n=30)	27	3	30	0	0	30	0	0	29	1	29	0	29	0
Sodium stibogluconate 20 mg/kg/day (n=30)†	19	2	22	2	6	21	2	1	21	0	20	1	19	1

*Treatment given for 21 days. †Treatment given for 30 days.

and 3 given antimony). Parasitological outcome was independent of initial parasite burden.

Changes from baseline

Comparisons within groups—With few exceptions, the parasite burden, spleen and liver size, and body temperature were significantly lower and body weight, haemoglobin concentration, and platelet counts were significantly higher than baseline values at every assessment during treatment with all four treatment regimens (paired *t* tests). Compared with baseline, albumin concentration was significantly higher at all assessments in the patients given aminosidine 20 mg/kg/day, on days 14 and 21 in the patients given aminosidine 12 and 16 mg/kg/day, and on days 14, 21, and 30 in those given antimony.

Comparisons between groups—At the end of treatment (21 days for aminosidine and 30 days for antimony), aminosidine was significantly more effective than antimony for most of the variables considered (table 4). At both day 21 and end of treatment, the changes from baseline values of parasite counts and white cell counts were significantly greater for all

groups given aminosidine than for those given antimony. For other parameters, only the patients given the two higher doses of aminosidine showed significantly greater changes from baseline than did those who were given antimony.

Safety evaluation

No clinically relevant differences in laboratory values were recorded in any of the treatment groups, and no renal toxicity was apparent with any of the doses of aminosidine (table 5). During the study, six patients experienced adverse events that did not require discontinuation of treatment (see box). Overall, both drugs were well tolerated. Aminosidine did not produce any substantial degree of ototoxicity or renal toxicity.

Discussion

Although the activity of aminosidine (paromomycin) against *Leishmania* has been known since the 1960s,^{10–11} the drug was not clinically evaluated for treating human leishmaniasis until the late 1980s.^{13–16} Two stud-

Table 4 Changes from baseline value in measures of efficacy of treatments for visceral leishmaniasis on day 21 (end of aminosidine treatment) and day 30 (end of sodium stibogluconate treatment) after start of treatment. Values are mean (SD) unless stated otherwise

	Aminosidine on day 21			Sodium stibogluconate 20 mg/kg/day (n=30)		Comparison (P value)*	
	12 mg/kg/day (n=30)	16 mg/kg/day (n=30)	20 mg/kg/day (n=30)	Day 21	Day 30	Day 21	End of treatment
Body weight (kg)	2.10 (1.82)	2.40 (1.90)	2.00 (1.57)	2.03 (1.84)	2.55 (1.82)	0.82	0.60
Fever (°C)	-1.64 (0.47)	-1.82 (0.60)†	-1.75 (0.42)	-1.33 (0.94)†	-1.46 (0.91)	0.023	0.14
Spleen size (cm)	-4.12 (1.91)	-4.75 (2.56)†	-5.1 (3.83)†‡	-2.5 (2.57)†	-2.88 (3.12)‡	0.0032	0.023
Haemoglobin concentration (g/l)	17.9 (10.2)	24.1 (16.1)†	21.0 (8.9)†	12.5 (12.6)†	16.3 (15.8)	0.003	0.11
White cell count (10 ⁹ /l)	3.05 (1.50)†‡	3.44 (1.48)†‡	3.12 (1.30)†‡	1.79 (1.48)†	1.90 (1.85)‡	0.001	0.001
Platelet count (10 ⁹ /l)	110 (96)	122 (74)	142 (79)†	82 (70)†	100 (89)	0.037	0.25
Albumin concentration (g/l)	9.1 (3.8)†	8.9 (3.7)†	9.8 (3.5)†	5.8 (6.3)†	7.8 (8.1)	0.004	0.54
Parasite burden (grade)	-2.07 (0.87)†‡	-1.97 (0.93)†‡	-2.30 (0.75)†‡	-1.30 (0.91)†	-1.23 (1.14)‡	0.0002	0.002

*Comparison between groups done by one way analysis of variance with post hoc Tukey's honest significance difference.

†Significant differences between groups on day 21. ‡Significant differences between groups at end of treatment.

Table 5 Changes from baseline value in measures of safety of treatments for visceral leishmaniasis on day 21 (end of aminosidine treatment) and day 30 (end of sodium stibogluconate treatment) after start of treatment. Values are mean (SD) unless stated otherwise

	Aminosidine on day 21			Sodium stibogluconate 20 mg/kg/day (n=30)		Comparison (P value)*	
	12 mg/kg/day (n=30)	16 mg/kg/day (n=30)	20 mg/kg/day (n=30)	Day 21	Day 30	Day 21	End of treatment
Creatinine concentration (μmol/l)	-11.5 (29.2)	-10.6 (23.9)	-10.6 (15.9)	-10.6 (26.5)	-13.3 (23.9)	0.99	0.97
Blood urea nitrogen (mmol/l)	0.43 (2.05)	0.39 (1.61)	0.32 (1.81)	-0.62 (1.56)	-0.54 (1.52)	0.071	0.11
Bilirubin (μmol/l)	47.0 (260.1)	-1.0 (222.3)	-0.2 (2.1)	-0.5 (2.7)	-0.5 (2.2)	0.40	0.40
Aspartate aminotransferase (U/l)	-16.43 (32.57)	-7.00 (40.30)	-18.73 (39.15)	-1.67 (50.03)	-8.37 (45.51)	0.33	0.59

*Comparison between groups done by one way analysis of variance with post hoc Tukey's honest significance difference.

ies were conducted in African patients (Kenya and Sudan),^{13 14} in which aminosidine was administered at 14 or 16 mg/kg/day for 14-19 days, either alone or in combination with sodium stibogluconate 20 mg/kg/day administered for 21 days, and compared with sodium stibogluconate 20 mg/kg/day given for 30 days. In both studies the combinations of aminosidine plus antimony were at least 95% effective at end of treatment and were significantly more effective than sodium stibogluconate alone. The combination of aminosidine plus antimony was evaluated in two trials in Bihar, India.^{15 16} The highest dose, aminosidine 12 mg/kg/day in combination with sodium stibogluconate 20 mg/kg/day for 21 days, was 82-88% effective. However, these studies produced limited data on the efficacy of aminosidine used alone.

This prompted us to compare the efficacy of aminosidine alone with that of the standard treatment with antimony. At 180 days after end of treatment, the final cure rate with sodium stibogluconate given for 30 days was 63%, confirming that antimony can no longer be considered the drug of choice in this region. Aminosidine given at 12 mg/kg/day for 21 days produced a final cure rate of 77%; although this was not significantly better than the rate with sodium stibogluconate, it was achieved one week earlier. The higher doses of aminosidine, 16 and 20 mg/kg/day for 21 days, were significantly more effective than antimony, with final cure rates of 93% and 97% respectively. No significant difference was detected between these two doses. These two regimens proved significantly more effective than antimony on almost all measures of efficacy that we evaluated.

Our results are substantially better than those obtained earlier in Bihar with the combination of aminosidine 12 mg/kg/day plus sodium stibogluconate 20 mg/kg/day for 21 days, suggesting that antimony played a minor role in this regimen.^{15 16}

We actively sought our patients for follow up visits, and only one patient defaulted. Statistical analyses were done on an intention to treat basis. One potential limitation of our study design was that it was conducted in an unblinded fashion. However, measures of concealment were applied to both clinical and laboratory evaluations to limit potential bias.

Adverse events recorded during study

Aminosidine 12 mg/kg/day

- One case of vomiting, possibly drug related, relieved with symptomatic treatment

Aminosidine 20 mg/kg/day

- One case of gradual onset of ototoxicity, determined by audiogram, definitely drug related (grade 2 mixed deafness at end of treatment, worsened to grade 3 and persisted during follow up)
- One case of gradual onset of ototoxicity, determined by audiogram, thought to be drug related (grade 1 conductive deafness before enrolment, deteriorated to grade 1 sensorineural deafness at end of treatment, reversed to baseline state at day 30 of follow up)

Sodium stibogluconate 20 mg/kg/day

- Two cases of reversible myocarditis, diagnosed by electrocardiography, definitely drug related
- One case of epileptic seizure, not drug related (patient had concealed a history of seizures)

Key messages

- Bihar in north east India accounts for about half the annual worldwide cases of visceral leishmaniasis, and resistance to standard treatment with sodium stibogluconate has been increasing
- We compared the safety and efficacy of three doses of aminosidine with standard regimen of sodium stibogluconate for treating visceral leishmaniasis in Bihar
- Aminosidine given at 16 or 20 mg/kg/day for 21 days was significantly more effective in producing final cure than sodium stibogluconate 20 mg/kg/day for 30 days
- Aminosidine had a low incidence of adverse reactions, including ototoxicity and renal toxicity, and was well tolerated
- Intramuscular injection of aminosidine 16 mg/kg/day for 21 days should be considered as a new first line treatment for visceral leishmaniasis in Bihar

Conclusions

Aminosidine at either 16 or 20 mg/kg/day for 21 days is effective in treating visceral leishmaniasis in Bihar, where the response to standard treatment with antimony for 30 days has become unacceptably low. We propose a 21 day regimen with aminosidine 16 mg/kg/day as the new first line treatment for visceral leishmaniasis in Bihar. An additional advantage of aminosidine over sodium stibogluconate is the lower overall burden to the health system, deriving from the lower cost of the drug and the shorter period of hospitalisation.

We thank Mr F Kuzoe and the Steering Committee on Integrated Chemotherapy (I-Chem), particularly Dr A Bryceson for input and guidance and Dr K Weerasurya for visiting the study centre.

Contributors: TKJ was the principal investigator and participated in data analysis and writing the protocol and paper. PO initiated clinical development of aminosidine for leishmaniasis (following studies by R Neal and L Donno), wrote the protocol (with TKJ, A Bryceson, and R Davidson), analysed the data, and wrote the regulatory report and paper. TPK participated in data analysis and writing the protocol and paper.

Funding: This study was sponsored by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), Geneva, Switzerland.

Conflict of interest: None.

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(Accepted 23 December 1997)

Commentary: Some good news for treatment of visceral leishmaniasis in Bihar

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Bihar is again the centre of an epidemic of visceral leishmaniasis (kala-azar) with an official estimate of 430 000 cases over the past 11 years. Antimony has been the treatment of choice since 1920, but treatment is arduous, requiring daily intravenous injections for 21 days, and up to 83% of patients experience side effects of myalgia or arthralgia.¹ The Bihar epidemic has also been exacerbated by a sharp increase in drug resistance, and in this paper 37% of patients were not cured by antimony.²

New drugs are urgently needed. Amphotericin B was the first alternative assessed, and in an open randomised trial produced significantly better parasite clearance (100% v 70%), resolution of fever, improvements in leucocyte and platelet counts, and regression of spleen size than antimony (sodium stibogluconate).³ The toxicity profile of amphotericin B in this population is poor, and it causes unpredictable drug induced myocarditis as well as anorexia, nausea, and vomiting.⁴ It has been successfully used in a lipid complex preparation but is prohibitively expensive.⁵

The aminoglycoside aminosidine has only recently been used in visceral leishmaniasis.⁶ Jha and colleagues' well designed study shows that in Bihar aminosidine is more effective than sodium stibogluconate.² Patients were appropriately recruited and randomly allocated to either the antimony compound or aminoglycoside, with an impressively high follow up rate in difficult conditions. The study could have been strengthened by blinding of treatments and by detailed auditory testing and HIV testing before treatment. Parasite culture and assessment of in vitro sensitivity to sodium stibogluconate would have produced interesting supplementary data. HIV infection is a risk factor for the development of visceral leishmaniasis⁷ and affects the response to treatment and the occurrence of side effects. The toxicity profile of aminosidine will be a crucial factor determining its usefulness in the field. The aminoglycosides are neuro-ototoxic and have been reported to cause high tone deafness.⁶ The present article does not document the specific side effects that were monitored for.

The epidemic of visceral leishmaniasis has been expensive, costing an estimated \$250m for treatment alone. It is difficult to calculate the full cost of treatment, but the cheapest drug costs per course are sodium stibogluconate (locally produced in India, \$16), aminosi-

dine (\$50), amphotericin (\$60), and AmBisome (\$2000) (A Bryceson, personal communication).

The authors' recommendation of using aminosidine alone may cause future problems. Monotherapy is problematic when used for controlling any intracellular organism; drug resistance developed in both leprosy and tuberculosis during the eras of monotherapy. Other studies suggest that a combination of aminosidine and sodium stibogluconate is more effective than the latter alone.⁸

A final irony is that aminosidine is not currently being marketed. Farmitalia-Carlo Erba originally produced the drug, but during a series of takeovers production slowed and marketing stopped. Once again the needs of patients with a tropical disease have not been able to compete with the high finances of drug companies.

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Endpiece Asherisms

Blind faith in doctors, though convenient, is not always to their benefit.

From *A Sense of Asher*, selected by Ruth Holland
(BMA Publications, 1984)

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