

Safety and effectiveness of first line eflornithine for *Trypanosoma brucei gambiense* sleeping sickness in Sudan: cohort study

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ABSTRACT

Objective To assess the safety and effectiveness of eflornithine as first line treatment for human African trypanosomiasis.

Design Cohort study.

Setting Control programme in Ibba, southern Sudan.

Participants 1055 adults and children newly diagnosed with second stage disease in a 16 month period.

Main outcome measures Deaths, severe drug reactions, and cure at 24 months.

Results 1055 patients received eflornithine for 14 days (400 mg/kg/day in adults and 600 mg/kg/day in a subgroup of 96 children). Overall, 2824 drug reactions (2.7 per patient) occurred during hospital stay, 1219 (43.2%) after the first week. Severe reactions affected 138 (13.1%) patients (mainly seizures, fever, diarrhoea, and bacterial infections), leading to 15 deaths. Risk factors for severe reactions included cerebrospinal fluid leucocyte counts $\geq 100 \times 10^9/l$ (adults: odds ratio 2.6, 95% confidence interval 1.5 to 4.6), seizures (adults: 5.9, 2.0 to 13.3), and stupor (children: 9.3, 2.5 to 34.2). Children receiving higher doses did not experience increased toxicity. Follow-up data were obtained for 924 (87.6%) patients at any follow-up but for only 533 (50.5%) at 24 months. Of 924 cases followed, 16 (1.7%) died during treatment, 70 (7.6%) relapsed, 15 (1.6%) died of disease, 403 (43.6%) were confirmed cured, and 420 (45.5%) were probably cured. The probability of event free survival at 24 months was 0.88 (0.86 to 0.91). Most (65.8%, 52/79) relapses and disease related deaths occurred after 12 months. Risk factors for relapse included being male (incidence rate ratio 2.42, 1.47 to 3.97) and cerebrospinal fluid leucocytosis: $20-99 \times 10^9/l$ (2.35, 1.36 to 4.06); $\geq 100 \times 10^9/l$ (1.87, 1.07 to 3.27). Higher doses did not yield better effectiveness among children (0.87 v 0.85, P=0.981).

Conclusions Eflornithine shows acceptable safety and effectiveness as first line treatment for human African trypanosomiasis. Relapses did occur more than 12 months after treatment. Higher doses in children were well tolerated but showed no advantage in effectiveness.

INTRODUCTION

Most patients with second stage human African trypanosomiasis (meningoencephalitic invasion) are treated with intravenous injections of melarsoprol, but this drug is associated with severe toxic effects^{1,2} and an increase in treatment failures.³⁻⁵

Eflornithine is the only alternative drug registered for the treatment of second stage human African

trypanosomiasis. Adverse effects of eflornithine include seizures, gastrointestinal disorders, and myelosuppression. A major disadvantage of the drug is the labour intense mode of its administration, requiring one intravenous infusion every six hours for 14 days. Before 2001, when a five year donation from the manufacturer (Sanofi-Aventis) made eflornithine available to all African countries, its extensive use was unaffordable. We assessed the safety and effectiveness of first line treatment with eflornithine for second stage human African trypanosomiasis.

METHODS

Our cohort comprised patients with newly diagnosed second stage human African trypanosomiasis (see bmj.com for definition) who were treated with eflornithine in Ibba, southern Sudan between September 2001 and December 2002.

Diagnostic examinations included microscopy of lymph node fluid and blood, cerebrospinal fluid for parasite detection, and leucocyte counts, as well as serology with the card agglutination test for trypanosomiasis.

Adults received eflornithine 400 mg/kg/day for 14 days and children received a higher dose (600 mg/kg/day) on the basis of reports^{6,7} showing lower concentrations of eflornithine in cerebrospinal fluid of under 12s. This higher dose was adopted in January 2002 with an age cut-off point initially set at 15 years, modified later in 2002 to 12 years. Therefore only a subgroup of under 15s received the higher dose.

Patients were admitted to hospital for round the clock medical surveillance. The responsible clinician interrupted or stopped treatment according to the severity of adverse reactions. Treatments were resumed from the point of interruption when the patient's condition improved.

We characterised adverse events using the international common toxicity criteria⁸: 1 to 4 (mild, moderate, severe, very severe), the relation between the drug and event (not related, unlikely, possible, probable, definite, unknown), and outcome (complete recovery, still present at discharge, sequelae, death). We graded adverse events retrospectively from medical records and discussion with patients' clinicians.

After treatment we followed-up patients at 6, 12, and 24 months with clinical and laboratory parasitological assessments. We regarded those who were in good general health at 24 months or later but refused to travel

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for the final laboratory assessment as “probably cured.” We considered a relapse to have occurred when trypanosomes were seen in any body fluid or if the cerebrospinal fluid leucocyte count had significantly increased.

Safety and effectiveness analyses

We focused the analysis of risk factors on major drug reactions (grade 3 or 4). Logistic regression was used for univariable and multivariable analysis of risk factors. We tested one degree interaction effects between variables with plausible biological links.

We carried out survival analysis with the Kaplan-Meier method. The follow-up time was calculated from the date of admission until the date of relapse, death, or last visit. We used Poisson regression analysis to test risk factors for relapse.

To permit comparisons with previous publications and with monitoring data from other treatment centres we calculated proportions (a more customary approach).

RESULTS

From September 2001 to December 2002, 1055 patients with newly diagnosed second stage human African trypanosomiasis received eflornithine. This group comprised the study cohort. Adults (median age 22) predominated (829, 78.6%). Trypanosomes were seen in lymph or blood in 1005 (95.3%) patients but in cerebrospinal fluid in only one third. Cerebrospinal fluid leucocyte counts were greater than $20 \times 10^9/l$ in 605 (57.3%) patients (see *bmj.com*). Nineteen patients (1.8%) were diagnosed on the basis of positive serology at dilutions of 1:4 or higher combined with more than 20 cells in cerebrospinal fluid.

Safety

Overall, 2990 adverse events were recorded during hospital stay. In most cases the distinction between events provoked by the treatment, the disease itself, or concomitant conditions could not be established. Thus the association with eflornithine was classified as unrelated in 5.5% cases, unlikely in 9.0%, possible in 36.8%, probable in 35.5%, definite in 9.2%, and unknown in 4.0%. Excluding the 166 unrelated events, the remaining 2824 were regarded as drug reactions (see *bmj.com*).

Most patients (91.2%, $n=962$) experienced drug reactions, with 2.7 reactions per patient (range 0-9; interquartile range 2-4). The overall death rate was 1.4% ($n=15$), and 0.4% (1/226) occurred among the under 15s.

Owing to incomplete medical records 242 drug reactions could not be graded. Of the graded drug reactions, 6.5% (167/2582) were classified as major, consisting mainly of 67 fever peaks (6% of cohort), 41 seizures (4%), 17 episodes of diarrhoea (2%), and nine bacterial infections (1%).

Minor (grade 1 or 2) reactions were common (2.5 reactions per patient). Mild and moderate abdominal pain and headache predominated, followed by fever and reactions at injection sites. Soft tissue infections and pneumonia were common.

The median time to onset of drug reactions was at day 6 of treatment, and 1219 (43.2%) reactions occurred after day 7. Some of the most clinically significant drug reactions were among those of late onset, such as diarrhoea and bacterial infections. Most neurological and dermatological reactions occurred during the first week. Seizures appeared consistently at the beginning of treatment (median day 3).

Table 1 | Risk factors for developing one or more major drug reactions among 1055 patients with newly diagnosed second stage human African trypanosomiasis included in cohort, by age group

Risk factors	Univariable		Multivariable	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Children <15 years (n=226)				
Trypanosomes in cerebrospinal fluid	2.2 (1.1 to 4.6)	0.028	—	NS
Cerebrospinal fluid leucocytes $\times 10^9/l$:				
21-99 $v \leq 20$	0.5 (0.2 to 1.6)	0.269	0.4 (0.1 to 1.4)	0.167
$\geq 100 v \leq 20$	2.2 (1.0 to 4.7)	0.048	1.6 (0.7 to 3.8)	0.249
Confusion or stupor	8.3 (2.5 to 27.7)	0.001	9.3 (2.5 to 34.2)	0.001
Seizures	5.6 (1.5 to 20.3)	0.009	3.6 (0.9 to 14.6)	0.078
Eflornithine 600 v 400 mg/kg/day	1.1 (0.6 to 2.3)	0.757	—	NS
Adults (n=829)				
Trypanosomes in lymph or blood	0.3 (0.2 to 0.7)	0.005	0.51 (0.2 to 1.2)	0.107
Trypanosomes in cerebrospinal fluid	2.3 (1.5 to 3.5)	<0.001	—	NS
Cerebrospinal fluid leucocytes $\times 10^9/l$:				
21-99 $v \leq 20$	2.1 (1.2 to 3.9)	0.013	2.1 (1.2 to 3.9)	0.017
100 $v \leq 20$	3.4 (2.0 to 5.8)	<0.001	2.6 (1.5 to 4.6)	0.001
Confusion or stupor	2.9 (1.5 to 5.4)	0.001	1.7 (0.8 to 3.4)	0.151
Seizures	7.3 (3.0 to 17.6)	<0.001	5.9 (2.0 to 13.3)	0.001
Musculoskeletal pain	0.5 (0.2 to 0.9)	0.024	0.3 (0.2 to 0.7)	0.003
Dehydration	3.3 (1.0 to 11.0)	0.049	2.6 (0.7 to 9.5)	0.143

NS=Not significant.

Drug reactions led to treatment interruptions in 109 (10.3%) patients, but most were brief (<24 hours). Treatment was stopped for 10 patients. At the end of hospital stay 88.0% of the drug reactions had fully subsided. Overall, 15 patients died of causes possibly associated with treatment. In 10 cases the cause was unclear. Eight deaths were attributed to complications of bacterial infections. Two deaths were associated with severe diarrhoea and dehydration, two were of suspected cardiogenic cause, and three were linked to complications of oedema, acute renal failure, and tuberculosis. One child (age 2 years) in the higher dose subgroup died as a result of severe diarrhoea that started on day 11 of treatment.

In the multivariable analysis of risk factors for major drug reactions an interaction effect was observed between age and cerebrospinal fluid leucocyte count, showing a differing association of leucocytes with drug reactions according to age group. Children and adults were therefore analysed separately and different risk factors were identified for the groups (table 1).

Among the 226 under 15s, 38 (16.8%) experienced major drug reactions. Multivariable analysis showed an increased risk for those presenting with confusion or stupor before treatment. All other factors were not significantly associated, including dose: 600 mg/kg/day (96 children) *v* 400 mg/kg/day (130 children).

Of the 829 adults, 100 (12.1%) had major drug reactions. Risk factors among this group after multivariable analysis included cerebrospinal fluid leucocyte counts greater than $20 \times 10^9/l$ and seizures. Musculoskeletal pain was protective.

Effectiveness

Overall, 533 (50.5% of cohort) patients had a known outcome or at least 24 months of follow-up, 672 (63.7%) had at least 12 months of follow-up, and 924 (87.6%) had any follow-up.

Relapses were established in 27 patients without detection of parasites in body fluids. Among them the median increase in leucocyte counts since the previous assessment was 65 cells (range 27-523).

The probability of event free survival for the whole cohort at 24 months was 0.88 (95% confidence interval 0.86 to 0.91; see *bmj.com*), at 12 months 0.95 (0.93 to

0.96), and at 36 months 0.84 (0.81 to 0.87). Among the 226 under 15s the probability of event free survival at 24 months per dose group (600 *v* 400 mg/kg/day) was similar (0.87 *v* 0.85, log rank $P=0.981$).

To permit comparisons with other reports and with programme monitoring data, the effectiveness data are also presented in a more customary analysis (table 2). Of the 924 patients with a known final outcome or who were seen at least once during follow-up, 16 (1.7%) died during treatment, 70 (7.6%) relapsed, 15 (1.6%) died of disease, 403 (43.6%) were cured, and 420 (45.5%) were probably cured. The cure rate among these patients was 89.1% ($n=823$). A more optimistic approach, taking into consideration those lost to follow-up as cured (12.4% of cohort), gave a cure rate of 90.4% ($n=954$).

Of the 70 relapses plus the nine deaths with a known date regarded as relapses, 27 (34%) were detected within 12 months, 46 (58%) within 18 months, 63 (80%) within 24 months, and the remaining 16 (20%) afterwards (see *bmj.com*).

A multivariable Poisson regression analysis (1039 patients discharged) revealed a higher risk of relapse for men than for women and for patients with high cerebrospinal fluid leucocytosis (see *bmj.com*).

DISCUSSION

The use of eflornithine 400 mg/kg/day for 14 days as routine first line treatment for second stage human African trypanosomiasis in isolated foci was feasible and showed satisfactory safety and effectiveness. Relapses occurred more than 12 months after treatment and therefore long term follow-up of patients is important. A higher dose in children (600 mg/kg/day) was well tolerated, but it was no more effective than the standard dose.

Strengths and weaknesses

Previously published clinical data on eflornithine concerned smaller cohorts (<300 participants), with a mix of naive and re-treated patients and different regimens, whereas our larger cohort comprised naive patients receiving the same treatment. Our sample size and acceptable follow-up provide a more robust measure of safety and effectiveness.

The safety data were collected retrospectively from medical records. Severe events seemed to be consistently reported but inconsequential events tended to be under-reported. The high turnover of the team (doctors were committed to six months) leads to variability in the quality of reporting.

Some caution is needed when interpreting the findings on effectiveness because of the incomplete follow-up after treatment, a challenge in settings affected by war.

A few patients (1.8%) were diagnosed without directly seeing trypanosomes, on the basis of serology combined with more than 20 cells in the cerebrospinal fluid, which are not universally accepted criteria. These criteria were used in this site because of the low sensitivity of laboratory examinations to directly detect the parasites, coupled with the high level of disease transmission in the area at the time, plus the high probability of losing contact with patients.

Table 2 | Outcome after follow-up of 1055 patients with newly diagnosed second stage human African trypanosomiasis treated with eflornithine. Values are percentages unless stated otherwise

Outcome	No of patients	Evaluable group (n=924)	Whole cohort (n=1055)
Cured at 24 months	403	43.6	38.2
Probably cured at 24 months*	29	3.1	2.7
Probably cured (partial follow-up)†	391	42.3	37.1
No follow-up	131	—	12.4
Died during treatment	16‡	1.7	1.5
Relapsed (all in second stage)	70	7.6	6.6
Probably relapsed (died of disease)	15	1.6	1.4

*In good general health but refusing to travel for final laboratory assessment.

†11 patients died of non-disease causes (for example war, accidents) during follow-up.

‡One death was unrelated to treatment.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The relatively good safety and effectiveness profiles of eflornithine have been poorly documented in the field

The difficult mode of its administration is a barrier for extensive access to patients

WHAT THIS STUDY ADDS

Eflornithine shows satisfactory safety and effectiveness as routine first line treatment for second stage human African trypanosomiasis

Children tolerated considerably higher doses but no advantage on effectiveness was seen

Safety

Our overall findings on safety are consistent with those reported in similar settings⁹ and reaffirm the advantage of eflornithine over melarsoprol. The case fatality rate of 1.4% is much lower than that with melarsoprol.

Although drug reactions occurred with eflornithine, major reactions were uncommon (13%). In most patients these conditions resolved favourably with routine management or temporary treatment suspensions.

That nearly half of the drug reactions emerged after day 7 of treatment is consistent with results of another trial,¹⁰ which compared eflornithine for 14 days with seven days.

We found that high leucocyte counts in cerebrospinal fluid increased the risk of severe drug reactions in adults but not in under 15s. Children but not adults presenting with confusion or stupor developed more severe reactions. A history of seizures only in adults was an important risk factor for severe reactions.

Adults presenting with arthralgia or myalgia had a lower risk of major toxicity. It is possible that these symptoms are indicative of an earlier stage of the disease progression.

The Ibba programme was the first to administer a considerably (50%) higher dose to children, which had been empirically suggested to improve eflornithine effectiveness in children. This cohort included 96 under 15s who received this higher dose. Because we also had a group of 130 children who received the standard dose, we examined the association of the higher dose with major drug reactions but found no significant increase in toxicity with the higher dose (600 mg/kg/day). Our data did not show a difference in effectiveness between the two doses, contrary to previous reports.^{6,7,10}

Effectiveness

The level of follow-up for this cohort was good. Our observations indicate that patients who are relapsing tend to come for assessment because of symptoms whereas asymptomatic patients tend to miss assessments for several reasons, and a small proportion may have died without this information reaching the programme.

From our experience of active tracing in this and other cohorts most patients not attending for assessment are cured or in good health. Assuming that relapses are less common among the lost to follow-up group than among

the followed-up group, excluding them from the analysis leads to overestimation of failure rates.

Survival analysis is affected by the same dilemma because patients who are partially or totally lost to follow-up contribute less to the analysis than those who complete the schedule, among whom are all the treatment failures.

Two years is considered an adequate time to assess "cure" and hence it is possible to refer to the 0.88 probability of event free survival at 24 months as the cure rate in this study. This value is in line with the 89.1% (823/924) cure rate by customary analysis (see table 2) in which patients who were lost to follow-up were excluded.

Our data underlines the importance of following patients for more than one year, since only a third of all relapses and deaths with a known date were detected within 12 months.

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