Melarsoprol versus eflornithine for treating late-stage Gambian trypanosomiasis in the Republic of the Congo

Manica Balasegaram,[a] Steve Harris,[b] Francesco Checchi,[c] Sara Ghorashian,[b] Catherine Hamel,[b] & Unni Karunakara[b]

Objective To compare the effectiveness of melarsoprol and eflornithine in treating late-stage Gambian trypanosomiasis in the Republic of the Congo.

Methods We analysed the outcomes of death during treatment and relapse within 1 year of discharge for 288 patients treated with eflornithine, 311 patients treated with the standard melarsoprol regimen and 62 patients treated with a short-course (10-day) melarsoprol regimen between April 2001 and April 2005.

Findings A total of 1.7% (5/288) of patients treated with eflornithine died compared with 4.8% (15/311) of those treated with standard melarsoprol and 6.5% (4/62) of those treated with short-course melarsoprol. Patients treated with eflornithine tended to be younger and were more likely to have trypanosomes or higher white blood cell counts in their cerebrospinal fluid. The cumulated incidence of relapse among patients who attended at least one follow-up visit 1 year after discharge was 8.1% (11/136) for those treated with eflornithine, 14% (36/258) for those treated with standard melarsoprol and 15.5% (9/58) for those treated with short-course melarsoprol. In a multivariate analysis, when compared with eflornithine, standard melarsoprol was found to be a risk factor for both death (odds ratio (OR) = 2.87; 95% confidence interval (CI) = 1.03–8.00) and relapse (hazard ratio (HR) = 2.47; 95% CI = 1.22–5.03); when compared with eflornithine, short-course melarsoprol was also found to be a risk factor for death (OR = 3.90; 95% CI = 1.02–14.98) and relapse (HR = 6.65; 95% CI = 2.61–16.94).

Conclusion The effectiveness of melarsoprol treatment appears to have diminished. Eflornithine seems to be a better first-line therapy for treating late-stage Gambian trypanosomiasis in the Republic of the Congo.

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يمكن الاطلاع على الملخص بالعربية في صفحة 790.

Introduction

African trypanosomiasis is a public health hazard in many countries in sub-Saharan Africa, with an incidence of around 20 000 new cases a year.[1,2] The disease is fatal if untreated. Control programmes have been severely weakened by war and civil instability in many of the countries with the highest prevalence.[3,4] In central and west Africa the disease is predominantly caused by the protozoan *Trypanosoma brucei gambiense* and is transmitted by the tsetse fly (*Glossina* spp.) in a human–fly–human cycle. Pentamidine, first-line treatment for early-stage disease, cannot be used if the parasites have invaded the central nervous system because the drug does not cross the blood–brain barrier. The principal treatment options for late-stage (or stage-2) disease are either melarsoprol (an organoarsenic compound that inhibits parasite glycolysis) or eflornithine (an irreversible inhibitor of ornithine decarboxylase which is necessary for the parasite's synthesis of DNA and RNA). Both drugs must be administered intravenously over a period of 1–4 weeks, which is logistically challenging in health-care systems in the developing world. Melarsoprol is a highly toxic drug that causes encephalopathy in 5–10% of patients and approximately 40% of these patients will die.[1,5] Eflornithine produces a reversible pancytopenia but otherwise appears to be safer than melarsoprol.[6]

Clinical research into new therapeutic options for treating late-stage disease remains limited and is conducted by only a few national programmes, research institutions and nongovernmental organizations. Because it is unlikely that there will be any new molecules available in the next few years to treat late-stage disease, recent research has focused on optimizing the therapeutic regimens of the two registered drugs as well as on developing a combination treatment involving a third drug, nifurtimox, which is unregistered to treat late-stage African trypanosomiasis but is available for compassionate use.[4,7–12] The lack of new therapeutic options makes it crucial to monitor the use and effectiveness of the drug regimens currently being used.

Resistance to melarsoprol has been documented since the 1970s, but the majority of these reports come from east Africa.[13,14] Health departments in countries in central and west Africa, including Angola, Côte d'Ivoire and the Republic of the Congo, still recommend melarsoprol as first-line therapy for late-stage disease, although Angola has documented resistance to the drug.[15]

In the Republic of the Congo, following a period of civil war in the 1990s, Médecins Sans Frontières (MSF) assisted the Ministry of Health in implementing

[a] Médecins Sans Frontières, 67–74 Saffron Hill, London EC1N 8QX, England. Correspondence to this author (email: manica.balasegaram@london.msf.org).

[b] Médecins Sans Frontières, Plantage Middenlaan 14, 1018 DD Amsterdam, the Netherlands.

[c] Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London WC1E 7HT, England.

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its national control programme for trypanosomiasis. We present a retrospective analysis of the outcomes of patients with late-stage disease treated by this programme. Our analysis focuses on patients newly diagnosed with late-stage disease who were treated with one of the three first-line protocols used in the programme (eflornithine or the standard melarsoprol regimen or a 10-day short-course melarsoprol regimen). The outcomes assessed were death during treatment and relapse within the first year after finishing treatment. We also investigated risk factors for both outcomes.

Methods

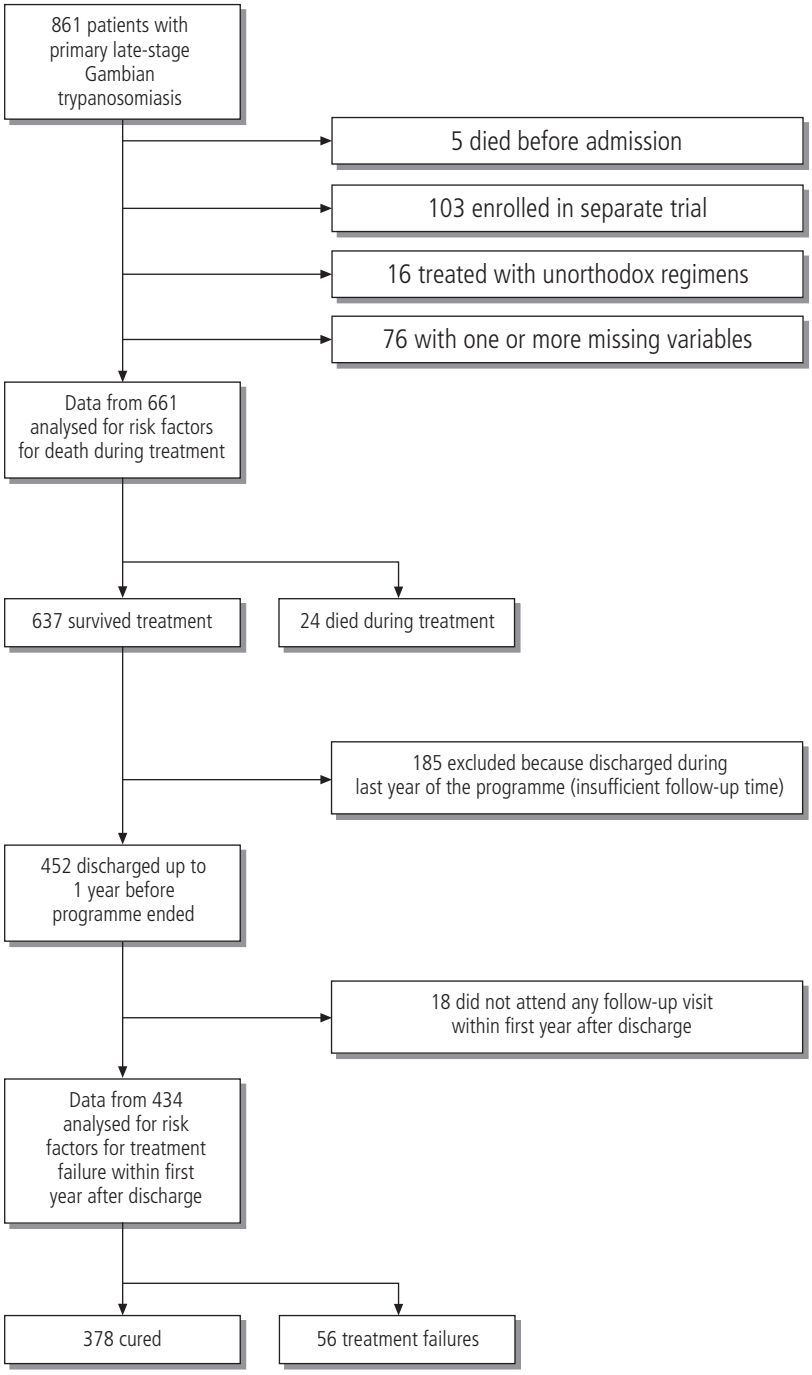
Diagnostic and treatment strategy

Between April 2001 and April 2005, the population of three separate historical foci of Gambian trypanosomiasis in the Republic of the Congo (Bouenza, Gamboma and Mossaka) were systematically screened by MSF in conjunction with the ministry of health's control programme. Screening was performed using the card agglutination test for trypanosomes and physical examination for posterior cervical lymphadenopathy (Winterbottom's sign). For patients who had a positive agglutination test a venous blood sample was examined for trypanosomes using the Woo haematocrit centrifuge technique or quantitative buffy coat technique. Gambian trypanosomiasis was diagnosed if trypanosomes were seen in blood or lymph node samples, or if the agglutination test remained positive at a dilution of 1 in 8 or greater. All patients diagnosed with the disease had a cerebrospinal fluid sample taken by lumbar puncture; the sample was examined for trypanosomes and leukocytosis. The national protocol diagnosed central nervous system involvement (that is, late-stage disease) if trypanosomes were seen in the cerebrospinal fluid or if the white cell count in the cerebrospinal fluid was greater than 5 cells/mm³. From September 2002, following guidance from the ministry of health, MSF raised this threshold to 10 cells/mm³ in order to reduce the number of patients exposed to the risk of melarsoprol toxicity.[16] This was accompanied by a formal change in the programme's protocol in 2003.[16,17]

Both melarsoprol and eflornithine were available throughout the duration of the programme but melarsoprol remained the first-line therapy until August 2003; eflornithine was reserved for patients whom clinicians felt were too ill for melarsoprol. Internal analysis of the MSF programme results at this time led to eflornithine becoming the first-line therapy at all MSF sites as a result of a high case–fatality rate and relapse rate among patients treated with melarsoprol: 3/46 (6.5%) patients treated with eflornithine died or relapsed compared with 46/429 (10.7%) treated with melarsoprol. For the majority of patients melarsoprol was administered according to the standard regimen, although the short-course 10-day regimen was used to treat a minority of patients (Fig. 1). Details of the various treatment regimens are given in Table 1.

For a patient's data to be included in the study the patient had to have been diagnosed with late-stage disease using the standard national protocol algorithm, had to have had no previous treatment for the disease, and had to have been admitted to an MSF treatment centre between April 2001 and April 2005.

Fig. 1. **Flow of patients through the treatment programmes and data analysis**



Statistical analysis

Death during treatment

We investigated potential risk factors for death due to any cause during the first 30 days after admission among patients with late-stage disease. We excluded from this analysis patients who were enrolled in an ongoing equivalence trial of eflornithine plus nifurtimox, had been treated with regimens other than melarsoprol (standard or short-course) or eflornithine, or for whom key baseline variables, such as age, sex, parasitological findings and treatment outcome, had not been reported.

First, we explored the univariate associations between death and potential risk factors (sex, age, screening mode — those cases identified by mobile teams in villages were denoted as active and those who self-presented at fixed screening posts were denoted as passive, technique on which parasitological confirmation was based, presence of trypanosomes in the cerebrospinal fluid, cerebrospinal fluid white cell count and drug regimen) and potential confounders (site, project period — that is, before or after eflornithine was used as first-line treatment in August 2003) by calculating crude odds ratios (OR). We then fit a multivariate logistic regression model to adjust for the effects of confounding. Variables were entered into the model if they were associated with the outcome at the $P < 0.20$ level in the univariate analysis, and we gradually eliminated variables with nonsignificant multivariate associations ($P > 0.05$); we performed likelihood ratio tests after each elimination, until we reached the final reduced model. We tested the model's assumptions, including the correctness of specification and goodness of fit.

Relapse

To make best use of the data (consisting of observations from patients with varying durations of follow-up), we used survival analysis to investigate risk factors for treatment failure during the first year of follow-up. We computed univariate hazard ratios (HR) for failure as described in the section on "Death during treatment", and then used Cox proportional hazards regression to adjust for confounders in a multivariate model. In addition to the exclusion criteria, we also excluded from this analysis all patients who were admitted less than 1 year before closure of the MSF programme or who did not attend at least one follow-up visit in the first year after discharge. We restricted our analysis to the first year of follow-up, since follow-up rates were unacceptably low for longer periods. We considered any visit after discharge occurring from month 10 (day 304) to month 14 (day 425) as a valid 1-year follow-up visit.

We defined relapse (or failure to have been cured at 1 year) as: death due to any cause after discharge, recurrence of parasites in any body fluid, white cell count in cerebrospinal fluid >50 cells/mm^3 and at least doubled from the previous measurement, or white cell count in cerebrospinal fluid 20–49 cells/mm^3 with a significant increase from the previous measurement and/or symptoms suggestive of disease.

We calculated the person–time under observation as the time between discharge and treatment failure or loss to follow-up if these occurred before day 425 after discharge or the 1-year follow-up date for patients for whom treatment had not failed and who had not left before treatment was completed. The model was constructed as described in the previous section. We also tested for interactions among covariates and between covariates and time (proportional hazards assumption).

Table 1. **Treatments for late-stage Gambian trypanosomiasis used in the Republic of the Congo, April 2001–April 2005**

Treatment	Dose
Pre-treatment	
Anti-malarial drugs[a]	Artemisinin combination therapy
Anthelminthic drugs[b]	Albendazole 400 mg to all patients
Anti-trypanosomal treatment	
Standard melarsoprol regimen	Day 1: 1.2 mg/kg IV[c] Day 2: 2.4 mg/kg IV Day 3–4: 3.6mg/kg IV (Sequence repeats on days 12–15 and days 23–26)
Short-course melarsoprol regimen	2.2 mg/kg IV for 10 days
Eflornithine regimen	100–150mg/kg IV every 6 hours for 14 days
Additional treatment	
Prednisolone[d]	Day 1–4: 1mg/kg Day 12–15: 0.5mg/kg Day 23–26: 0.25mg/kg[e]

[a] Administered to febrile patients with positive thick-film or rapid test (Paracheck, Orchid, India).
[b] Administered to all patients.
[c] IV = intravenous.
[d] Prednisolone administered to patients receiving melarsoprol.
[e] Administered to patients being treated with the standard melarsoprol regimen.

Data collection and analysis

Personal, laboratory, treatment and outcome data from source documents were entered into a Microsoft Excel database (in Gamboma) or YoTryps (in Bouenza and Mossaka), a Microsoft Access-based software program specifically designed for African trypanosomiasis programmes by MSF, at programme locations. Data were analysed using Stata software version 8.0 (Stata Corp, College Station, Texas, USA).

Ethical approval

The study was a retrospective analysis of data from Médecins Sans Frontières' operational medical work in the Republic of the Congo. Approval for data exportation, analysis and reporting was obtained from the Ministry of Health's national control programme in the Republic of the Congo. The datasets extracted and used for analysis were anonymized by removing all patients' names, separating the data into a new dataset, and having the data analysed by a statistician unconnected with the programmes.

Findings

Between April 2001 and April 2005, we treated 861 patients with late-stage disease; data on 661 (77%) met the inclusion criteria for analysis. Of these patients, 288 (44%) had been treated with eflornithine, 311 (47%) with the standard melarsoprol regimen and 62 (9%) with short-course melarsoprol. An overall case–fatality rate of 3.6%

Table 2. **Baseline characteristics and outcomes of patients included in the analysis of treatments for late-stage Gambian trypanosomiasis, the Republic of the Congo, April 2001–April 2005**

Patients	Treatment regimen[a]		
	Eflornithine	Melarsoprol (standard)	Melarsoprol (short course)
Baseline characteristics[b]			
No. of patients	288	311	62
Treatment centre (province, town)			
Gamboma (Gamboma town)	16 (5.6)	121 (38.9)	60 (96.8)
Bouenza (Nkayi town)	123 (42.7)	178 (57.2)	0
Mossaka (Mossaka town)	149 (51.7)	12 (3.9)	2 (3.2)
Period of admission			
Before August 2003	53 (18.4)	311 (100.0)	62 (100.0)
On/after August 2003	235 (81.6)	0	0
No. (%) female	143 (49.7)	143 (46.0)	29 (46.8)
Age			
⩾ 15 years	217 (75.4)	259 (83.3)	60 (96.8)
< 15 years	71 (24.6)	52 (16.7)	2 (3.2)
Mode of screening[c]			
Active	169 (58.7)	197 (63.3)	41 (66.1)
Passive	119 (41.3)	114 (36.7)	21 (33.9)
Trypanosomes found in CSF[d]	157 (54.5)	99 (31.8)	7 (11.3)
White blood cell count in CSF (per µL)			
0–19	85 (29.5)	127 (40.8)	34 (54.8)
20–99	74 (25.7)	74 (23.8)	16 (25.8)
⩾ 100	129 (44.8)	110 (35.4)	12 (19.4)
Treatment outcomes			
Died during treatment	5 (1.7)	15 (4.8)	4 (6.5)
Survived treatment	283	296	58
Survived treatment, discharged up to 1 year before project closure (data retained for further analysis)	136	258	58
Attended 6-month follow-up visit	94 (69.1)	206 (79.8)	18 (31.0)
Attended 1-year follow-up visit	70 (51.5)	156 (60.5)	12 (20.7)
Seen at least once during first year post-treatment	132 (97.1)	249 (96.5)	53 (91.4)
Median (interquartile range) person-days under observation	322 (202–366)	325 (184–365)	117 (45–290)
Treatment failed within first year (cumulated incidence assuming all patients lost to follow-up were cured)	11 (8.1)	36 (14.0)	9 (15.5)

[a] See Table 1 for details of treatment regimens.
[b] Values are number (percentage) unless otherwise indicated.
[c] See text for a more detailed description of the mode of screening.
[d] CSF = cerebrospinal fluid.

was found (24/661): 1.7% (5/288) of patients treated with eflornithine died compared with 4.8% (15/311) of those treated with the standard melarsoprol regimen and 6.5% (4/62) of those treated with short-course melarsoprol. Of the 637 patients who survived and could be included in the analysis of relapse rate, 452 (71%) were due for follow-up having been treated more than 1 year before the programme ended. Of these, 434 (96%) attended a follow-up visit within the first year. The cumulated incidence of relapse among those who attended at least one follow-up visit 1 year after discharge was 8.1% (11/136) among those treated with eflornithine, 14% (36/258) among those treated with standard melarsoprol and 15.5% (9/58) among those treated with short-course melarsoprol.

The treatment groups differed significantly ($P < 0.001$) in all baseline characteristics except for sex ratio and screening mode (Table 2). Patients treated with eflornithine were on average younger, were more likely to have trypanosomes in their cerebrospinal fluid and had higher white cell counts in their cerebrospinal fluid.

The case–fatality rate during treatment was lower in the eflornithine group ($P = 0.060$). Follow-up rates and median person–time under observation were comparable between the eflornithine group and the standard melarsoprol group but significantly shorter ($P < 0.001$) in the short-course melarsoprol group, in which only 20.7% (12/58) of patients attended the 1-year follow-up visit (Table 2). Among the 452 patients admitted more than 1 year before the programme ended and discharged alive, those who did not attend the 1-year follow-up visit differed significantly

Table 3. **Risk factors for death (n = 24) within 30 days after admission among patients with late-stage Gambian trypanosomiasis (n = 661) treated with melarsoprol or eflornithine, the Republic of the Congo, April 2001–April 2004**

Baseline risk factor	Crude odds ratio[a]	Adjusted odds ratio[b]
Treatment centre		
Gamboma	1.00	–
Bouenza	1.15 (0.47–2.80)	
Mossaka	0.29 (0.06–1.40)	
Project period		
Before August 2003	1.00	–
On/after August 2003	0.35 (0.12–1.04)	
Sex		
Male	1.00	–
Female	0.65 (0.28–1.50)	
Age		
⩾ 15 years	1.00	
< 15 years	0.60 (0.18–2.05)	
Mode of screening[c]		
Active	1.00	–
Passive	1.26 (0.56–2.81)	
Technique on which parasitological confirmation was based		
Direct gland puncture	1.00	–
Centrifuge technique (Woo or quantitative buffy coat)	0.40 (0.12–1.38)	
CATT[d] dilution positive	0.45 (0.13–1.56)	
Trypanosomes found in CSF[e]		
No	1.00	–
Yes	0.75 (0.32–1.78)	
White blood cell count in CSF (per µL)		
0–19	1.00	–
20–99	1.73 (0.65–4.57)	
⩾ 100	0.85 (0.30–2.39)	
Drug regimen[f]		
Eflornithine	1.00	1.00
Melarsoprol (standard)	2.87 (1.03–8.00)	2.87 (1.03–8.00)
Melarsoprol (short course)	3.90 (1.02–14.98)	3.90 (1.02–14.98)

[a] Values in parentheses are 95% confidence intervals.
[b] Adjusted odds ratios based on logistic regression model with $P = 0.05$ (for goodness of fit).
[c] See text for a more detailed description of the mode of screening.
[d] CATT = card agglutination test for trypanosomes.
[e] CSF = cerebrospinal fluid.
[f] See Table 1 for details of treatment regimens.

($P < 0.001$) from others in place of origin (47.2% (101/214) of those who did not attend follow-up versus 17.7% (42/238) of those who attended follow-up came from Gamboma), and were more likely to have white cell counts in cerebrospinal fluid ⩾100 cells/mm³ (43.0% (92/214) versus 31.5% (75/238); P = 0.017). Furthermore, among all who did not complete follow-up (214), those in the eflornithine group were more likely to have parasites in their cerebrospinal fluid (51.5% (34/66) versus 29.7% (44/148); P = 0.002).

The cumulated incidence of relapse was nonsignificantly lower in the eflornithine group (P = 0.084 for eflornithine versus standard melarsoprol regimen; P = 0.087 for eflornithine versus short-course melarsoprol). No obvious clustering of relapses in time or by treatment centre was evident.

Multivariate analysis

The treatment centre, project period and diagnostic technique were weakly associated with death among late-stage patients in the univariate analysis, but drug regimen emerged as the only significant risk factor in the final multivariate model (Table 3). Compared with patients receiving eflornithine, patients treated with standard-regimen melarsoprol had an adjusted OR of dying of 2.87 (P = 0.04), while those treated with short-course melarsoprol had an adjusted OR of 3.90 (P = 0.05). Confidence intervals for these associations were wide, ranging from almost no effect to an 8-fold increase in risk for standard melarsoprol and a 15-fold increase for short-course melarsoprol.

Baseline cerebrospinal fluid white cell counts and drug regimen were the only significant risk factors for relapse among patients with late-stage disease within 1 year after discharge in both the univariate and multivariate analyses

(Table 4). Both a high white cell count in cerebrospinal fluid and melarsoprol therapy (compared with eflornithine) increased the risk of relapse. When the project period was retained in the final model, it had a nonsignificant effect (adjusted HR = 0.91; 95% CI = 0.26–3.13), but it appeared to influence marginally the effect of treatment, yielding an adjusted HR for treatment failure of 2.35 (95% CI = 0.85–6.53; P = 0.101) for patients treated with standard melarsoprol and 6.32 (95% CI = 1.90–20.97; P = 0.003) for patients receiving short-course melarsoprol.

Table 4. **Risk factors for treatment failure within the first year after discharge (n = 56) among 434 patients with late-stage Gambian trypanosomiasis treated with melarsoprol or eflornithine, the Republic of the Congo, April 2001–April 2004**

Baseline risk factor	Crude hazard ratio[a]	Adjusted hazard ratio[b]
Treatment centre		
Gamboma	1.00	–
Bouenza	0.89 (0.48–1.68)	
Mossaka	0.56 (0.23–1.35)	
Project period		
Before August 2003	1.00	–
On/after August 2003	0.39 (0.17–0.92)	
Sex		
Male	1.00	–
Female	0.81 (0.48–1.38)	
Age		
⩾ 15 years	1.00	–
> 15 years	0.80 (0.41–1.56)	
Mode of screening[c]		
Active	1.00	–
Passive	1.42 (0.84–2.40)	
Technique on which parasitological confirmation was based		
Direct gland puncture	1.00	–
Centrifuge technique (Woo or quantitative buffy coat)	1.25 (0.67–2.32)	
CATT[d] dilution positive	1.43 (0.72–2.83)	
Trypanosomes found in CSF[e]		
No	1.00	–
Yes	1.21 (0.71–2.06)	
White blood cell count in CSF (per µL)		
0–19	1.00	1.00
20–99	1.57 (0.71–3.55)	1.99 (0.88–4.50)
⩾ 100	3.09 (1.56–6.15)	3.95 (1.96–7.96)
Drug regimen[f]		
Eflornithine	1.00	1.00
Melarsoprol (standard)	2.16 (1.05–4.44)	2.47 (1.22–5.03)
Melarsoprol (short course)	4.66 (1.85–11.77)	6.65 (2.61–16.94)

[a] Values in parentheses are 95% confidence intervals.
[b] Adjusted hazard ratios based on Cox regression model with $P < 0.001$ (for goodness of fit).
[c] See text for a more detailed description of the mode of screening.
[d] CATT = card agglutination test for trypanosomes.
[e] CSF = cerebrospinal fluid.
[f] See Table 1 for details of treatment regimens.

Discussion

When compared with eflornithine both regimens of melarsoprol were associated with higher mortality and a higher cumulated incidence of relapse among patients treated for late-stage Gambian trypanosomiasis. Our data confirm the general consensus that eflornithine is safer than melarsoprol, even when used in routine practice. The cumulated incidences of relapse, though likely to be underestimated, were unacceptably high for both melarsoprol regimens. In particular the short-course regimen performed particularly poorly. Given a treatment failure rate of around 14%, we believe that resistance to melarsoprol therapy is a considerable obstacle to the control of sleeping sickness in the Republic of the Congo.

Our data have certain limitations. The non-randomized nature of our study makes it difficult to truly compare treatments, even when differences, such as age, presence of parasites and cerebrospinal fluid white cell counts, are adjusted for. Moreover, data were retrospective and collected from an operational programme not a research programme. However, there are significant challenges involved in implementing and conducting randomized controlled trials of treatment for this disease. Thus there is a scarcity of published data on the use of melarsoprol and eflornithine outside routine care, and there has been only one study published that directly compares the two drugs (melarsoprol and eflornithine).[12] We therefore believe this makes our study relevant and worthwhile.

Another limitation of our study is the generally low rate of follow-up. Our rates are similar to those of other studies, reflecting the real difficulty of tracing patients in resource-poor environments.[9–12] However, follow-up rates for patients treated with the standard melarsoprol regimen and with eflornithine were similar, allowing us to compare the two. It is difficult to predict the implications of loss to follow-up, but it seems problematic to assume that all those who were lost were actually cured. This would imply that all patients who relapsed were followed-up, so it inevitably leads to an underestimate of the true rate of relapse. It is possible that many patients who relapsed may not have wished to return for follow-up. Additionally, deaths that resulted from relapses may also have been included in the category of those who were lost to follow-up. Also, our follow-up was limited to the first year after treatment.

The deliberate decision to change the treatment protocol in our programme is a potential source of bias. However, the baseline characteristics of the two groups would tend to favour a better outcome

for those patients treated with melarsoprol. Patients treated with eflornithine tended to have more risk factors for a poor prognosis such as higher white cell count and/or parasitaemia in cerebrospinal fluid. This bears out anecdotal reports from the field that when the choice is available, clinicians are reluctant to use melarsoprol for those patients who are the most unwell. Despite a better baseline profile, the risk of death and relapse was greater in the melarsoprol group.

Even with these limitations our data still provide useful information on the only drugs available for treating late-stage disease. A literature search identified several prospective studies of each treatment that reported 2-year cure rates of 97% for eflornithine and 86–95% for melarsoprol.[8–12,18] However, there is only one large published retrospective non-randomized comparison of these two drugs. Chappuis et al. showed that eflornithine was safer and caused fewer deaths and adverse events during treatment.[12] However, no statistical difference was seen at 1-year post-treatment, and the follow-up rate at 1 year was 46%.

Apart from melarsoprol's higher toxicity, the higher cumulated incidence of relapse found in our study would in itself justify reconsidering its use as first-line therapy for late-stage Gambian trypanosomiasis in the Republic of the Congo. However, this analysis is important for two other reasons. First, little data has been published in support of the new short-course melarsoprol regimen.[9–11] This new regimen has been justified on the basis of its superiority in terms of clinical implementation rather than of efficacy. The risk of relapse due to drug resistance is therefore likely to be no better with short-course melarsoprol. Indeed, in our small cohort, relapse levels were similar when the short-course was compared with the standard regimen. Short-course melarsoprol is therefore unlikely to solve the problem of the high relapse rate in the Republic of the Congo.

Second, Pepin and Mpia have reported in a longitudinal study that they found no evidence of a change in melarsoprol resistance over 20 years.[18] This would seem to offer some reassurance to those who continue to use melarsoprol. However, the authors made no direct comparison between melarsoprol and eflornithine, and hence this result must be viewed with some caution.

Because melarsoprol has low cure rates at 1 year, it appears that eflornithine is the better treatment option for new cases of late-stage disease. It has often been argued that eflornithine is difficult to administer in resource-poor settings because patients require a higher level of nursing care. Additional costs related to eflornithine administration (for drip sets, saline infusions, intravenous catheters) are also seen as another hurdle to its widespread use. While it is true that infusions have to be prepared every 6 hours, it is our experience that the technical level of nursing care required has been overestimated. The main priorities in administering eflornithine are to ensure that all infusions are prepared and given regularly in a sterile manner.[12] However, patients on eflornithine experience far fewer adverse events than those on melarsoprol; thus the level of nursing care required beyond the preparation and administration of infusions is considerably less than with melarsoprol treatment, during which patients who experience encephalopathy reactions require intensive nursing care. Hence, the presence of 24-hour nursing care to provide night infusions is probably the more important factor that keeps eflornithine from being used more widely. We therefore recommend eflornithine for first-line treatment of the disease in the Republic of the Congo. We also recommend that the additional materials (including saline infusions, drip sets and intravenous catheters) required for the administration of eflornithine should be provided free as part of the current eflornithine donation project under which the drugs are provided free by manufacturers to WHO to be distributed to affected countries.

Future research into the treatment of African trypanosomiasis should look at combination treatments to improve the efficacy of treatment and delay the development of resistance to eflornithine. A trial of nifurtimox plus eflornithine combination therapy has been undertaken in our centres in the Republic of the Congo (comparing eflornithine 100mg/kg administered intravenously 4 times a day for 14 days versus eflornithine 200mg/kg administered intravenously 2 times a day for 7 days plus nifurtimox 15mg/kg a day divided in 3 doses for 10 days). Data from the study will be published in the future (U Karunakara and G Priotto, personal communication, 2005). Further trials examining this combination treatment are being undertaken at other study sites. This combination offers the advantage of limiting eflornithine infusions to twice a day. We believe this would be an excellent regimen if safety and efficacy can be demonstrated. It will be a useful interim regimen until new molecules are developed and available for use.

Conclusion

In the Republic of the Congo, the effectiveness of melarsoprol is insufficient to justify its continued use as first-line treatment. We recommend administering a 14-day course of eflornithine as first-line treatment until better treatment regimens are available. ■

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Competing interests: none declared.

Résumé

Évaluation comparative du mélarsoprol et de l'éflornithine dans le traitement de la trypanosomiase à *Tr. brucei Gambiense* à un stade avancé en République du Congo

Objectif Comparer l'efficacité du mélarsoprol et de l'éflornithine dans le traitement de la trypanosomiase à *Tr. brucei Gambiense* à un stade avancé en République du Congo.

Méthodes Nous avons analysé les cas de décès pendant le traitement ou à l'occasion d'une rechute dans l'année suivant la sortie du traitement parmi 288 individus traités par l'éflornithine, 311 individus soumis à un traitement standard par le mélarsoprol et 62 autres recevant ou ayant reçu une cure brève de mélarsoprol (10 jours), sur la période allant d'avril 2001 à avril 2005.

Résultats Au total, 1,7 % (5/288) des sujets traités par

l'éflornithine sont morts contre 4,8 % (15/311) de ceux soumis à traitement standard par le mélarsoprol et 6,5 % (4/62) de ceux traités par une cure brève de mélarsoprol. Les sujets traités par l'éflornithine tendaient statistiquement à être plus jeunes et présentaient une plus grande probabilité d'avoir des trypanosomes ou une numération leucocytaire plus élevée dans le liquide céphalorachidien. L'incidence cumulée des rechutes parmi les sujets s'étant présentés à une visite de suivi au moins après leur sortie du traitement était de 8,1 % (11/136) pour les sujets traités par l'éflornithine, de 14 % (36/258) pour ceux ayant reçu un traitement standard par le mélarsoprol et de 15,5 % (9/58) pour ceux soumis à une cure brève de ce médicament. Une analyse multivariée a fait apparaître le traitement standard par le mélarsoprol comme facteur de risque par rapport au traitement par l'éflornithine à la fois pour le décès [odds ratio (OR) = 2,87; IC à 95 % = 1,03 - 8,00 et la rechute (ratio de danger = 2,47; IC à 95 % = 1,22 - 5,03). La cure brève par le mélarsoprol s'est également révélée un facteur de risque par rapport au traitement par l'éflornithine pour le décès (OR = 3,90; IC à 95 % = 1,02 - 14,98) et la rechute (ratio de danger = 6,65; IC à 95 % = 2,61 - 16,94).

Conclusion Il semble que l'efficacité du traitement par le mélarsoprol ait diminué. L'éflornithine semble mieux convenir comme traitement de première intention face à la trypanosomiase «gambienne» à un stade avancé en République du Congo.

Resumen

Comparación del melarsoprol y la eflornitina como tratamiento de la fase tardía de la tripanosomiasis gambiense en la República del Congo

Objetivo Comparar la eficacia del melarsoprol y de la eflornitina como tratamiento de la fase tardía de la tripanosomiasis gambiense en la República del Congo.

Métodos Analizamos los casos de defunción durante el tratamiento y de recaída durante el primer año tras el alta en 288 pacientes tratados con eflornitina, 311 sometidos al régimen estándar de melarsoprol y 62 sometidos al tratamiento de corta duración (10 días) con melarsoprol entre abril de 2001 y abril de 2005.

Resultados En total murieron el 1,7% (5/288) de los pacientes tratados con eflornitina, frente al 4,8% (15/311) de los sometidos al tratamiento estándar de melarsoprol y el 6,5% (4/62) de los tratados con el régimen de corta duración de melarsoprol. Los pacientes tratados con eflornitina solían ser más jóvenes y tenían más probabilidades de albergar tripanosomas o un mayor número de leucocitos en el líquido cefalorraquídeo. La incidencia acumulada de recaídas entre los pacientes que acudieron al menos a una visita de seguimiento al cabo de un año del alta fue del 8,1% (11/136) para los tratados con eflornitina, 14% (36/258) para los tratados con el régimen estándar de melarsoprol, y 15,5% (9/58) para los sometidos al tratamiento de corta duración con melarsoprol. En el análisis multifactorial realizado, al compararlo con la eflornitina, el régimen estándar de melarsoprol resultó ser un factor de riesgo tanto de defunción (razón de posibilidades (OR) = 2,87; intervalo de confianza (IC) del 95% = 1,03-8,00) como de recaída (razón instantánea de riesgos (RIR) = 2,47; IC95% = 1,22–5,03); en comparación con la eflornitina, el tratamiento de corta duración con melarsoprol también fue un factor de riesgo de defunción (OR = 3,90; IC95% = 1,02–14,98) y de recaídas (RIR = 6,65; IC95% = 2,61–16,94).

Conclusiones La eficacia del melarsoprol ha disminuido. La eflornitina parece una terapia de primera línea preferible para tratar la fase tardía de la tripanosomiasis gambiense en la República del Congo.

ملخص

الميلارسوبرول مقابل الإيفلورنيثين في معالجة داء المثقبيات الغامبية في مرحلته المتأخرة في جمهورية الكونغو

الهدف: مقارنة بين فعّالية الميلارسوبرول وفعّالية الإيفلورنيثين في معالجة المراحل المتقدمة من داء المثقبيات في جمهورية الكونغو.

الطريقة: حلّلنا حصائل الوفيات أثناء المعالجة والنكس خلال فترة سنة من تخرج 288 مريضاً عولجوا بالإيفلورنيثين، و311 مريضاً عولجوا معالجة معيارية بالميلارسوبرول، إلى جانب 62 مريضاً عولجوا بنظام علاجي قصير الأمد (10 أيام) بالميلارسوبرول، في الفترة بين نيسان/إبريل 2001 ونيسان/إبريل 2005.

الموجودات: مات 1.7% (5 من بين 288 مريضاً) ممّن عولجوا بالإيفلورنيثين مقارنةً بـ 4.8% (15 من بين 311 مريضاً) ممّن عولجوا بنظام المعالجة المعيارية بالميلارسوبرول، و6.5% (4 من بين 62 مريضاً) ممّن عولجوا بنظام المعالجة القصيرة الأمد بالميلارسوبرول. ويميل المعالَجين بالإيفلورنيثين لأن يكونوا أصغر عمراً مع تزايد احتمال وجود المثقبيات لديهم أو ارتفاع تعداد الكريات البيض في السائل النخاعي لديهم. وقد بلغ معدل الوقوع التراكمي للنكس لدى المرضى الذين راجعوا لمرة واحدة على الأقل للمتابعة بعد مرور سنة على تخريجهم 8.1% (11 من أصل 136 مريضاً) من بين المعالَجين بالإيفلورنيثين، و14% (36 من بين 258 مريضاً) من المعالَجين بنظام معالجة معيارية بالميلارسوبرول، و15.5% (9 من بين 58 مريضاً) ممّن عولجوا بنظام علاجي قصير الأمد بالميلارسوبرول. وفي التحليل المتعدِّد المتغيرات وجدنا لدى مقارنة النظام العلاجي المعياري بالميلارسوبرول مع المعالجة بالإيفلورنيثين أن النظام العلاجي المعياري بالميلارسوبرول يشكل أحد عوامل الخطر للموت (بنسبة أرجحية 2.87، وبفاصلة ثقة 95%، إذ تراوحت نسب الأرجحية بين 1.03 و8.00) وللنكس (بنسبة أرجحية 2.47 وبفاصلة ثقة 95% إذ تراوحت نسب الأرجحية بين 1.22 و5.03). كما كان نظام المعالجة القصيرة الأمد بالميلارسوبرول لدى مقارنته بالإيفلورنيثين من عوامل الخطر للموت (بنسبة أرجحية 3.90 وبفاصلة ثقة 95% إذ تراوحت نسب الأرجحية بين 1.02 و14.98) وللنكس (بنسبة أرجحية 6.65 وبفاصلة ثقة 95% إذ تراوحت نسب الأرجحية بين 2.61 و16.94).

الاستنتاج: يبدو أن فعّالية المعالجة بالميلارسوبرول قد تناقصت، ويبدو أن الإيفلورنيثين أفضل منه في الخط الأول لمعالجة المراحل المتقدِّمة من داء المثقبيات الغامبية في جمهورية الكونغو الديمقراطية.

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