DEVOVED TO REDUCING MALARIA DEATHS & SUFFERING IN HUMANITARIAN CRISIS
African trypanosomiasis: Diagnosis, Treatment, and Prevention

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9 March 2012, Version 1
Learning Goals

- Diagnosis
- Treatment
- Prevention
- Linkage between conflict and contagion
Diagnosis

1. Screening
2. Diagnostic Confirmation
3. Staging

Screening

Brun et al., see references
Screening

- CATT
- LATEX
- Immunofluorescence assays
- ELISA
Screening: CATT

Viewing of Wellcome Trust Video:
Screening, continued

- LATEX
- Immunofluorescence assays
- ELISA
Diagnostic Confirmation

- Chancre aspirate
- Lymph node aspirate
- Wet and thick blood films
- Microhematocrit centrifugation technique
- Quantitative buffy coat
- Mini-anion exchange centrifugation technique (mAECT)
Diagnostic Confirmation

Diagnostic Confirmation

Engman-Epting Laboratory, Northwestern University, http://www.engmanlab.northwestern.edu/img/extras/TBrucei.jpg

Diagnostic Confirmation


Kroun M. http://kroun.ulmarweb.dk/test-beh.htm
Staging:

- Hemolymphatic or Meningoencephalitic?
- CSF examination following lumbar puncture

Staging:

Examination of CSF:

– High white blood cell count
– Visualize trypanosomes
– High protein content


### Table 1. Medications Recommended for Treatment of African Trypanosomiasis

<table>
<thead>
<tr>
<th>Type of Trypanosomiasis</th>
<th>Medications</th>
<th>Medications</th>
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</thead>
<tbody>
<tr>
<td>(Hemolymphatic Stage)</td>
<td></td>
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</tr>
<tr>
<td>East African trypanosomiasis (caused by <em>T. brucei rhodesiense</em>)</td>
<td>Suramin 100-200 mg IV test dose, then 1 g IV on days 1, 3, 7, 14, 21</td>
<td>Melarsoprol 2-3.6 mg/kg/d IV for 3 d; after 1 wk, 3.6 mg/kg/d for 3 d; after 10-21 d, repeat the cycle</td>
</tr>
<tr>
<td>West African trypanosomiasis (caused by <em>T. brucei gambiense</em>)</td>
<td>Pentamidine isethionate 4 mg/kg/d IM for 10 d</td>
<td>Melarsoprol 2-3.6 mg/kg/d IV for 3 d; after 1 wk, 3.6 mg/kg/d for 3 days; after 10-21 d, repeat the cycle</td>
</tr>
<tr>
<td>or</td>
<td>Suramin 100-200 mg IV test dose, then 1 g IV on days 1, 3, 7, 14, 21</td>
<td>Eflornithine 400 mg/kg/d IV in 4 divided doses for 14 d</td>
</tr>
</tbody>
</table>

Odero RO et al. See resources.
Melarsoprol


Suramin and Pentamidine

Arsenicals (melarsoprol), pentamidine and suramin in the treatment of human African trypanosomiasis

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Andrew Jonathan Nok

Abstract Human African trypanosomiasis (HAT), otherwise known as sleeping sickness, has remained a disease with no effective treatment. Recent progress in HAT research suggests that a vaccine against the disease is far from being successful. Also the emergence of drug-resistant trypanosomes makes further work in this area imperative. So far the treatment for the early stage of HAT involves the drugs pentamidine and suramin which have been very successful. In the second stage of the disease, during which the trypanosomes reside in the cerebrospinal fluid (CSF), treatment is dependent exclusively on the arsenical compound melarsoprol. This is largely due to the inability to find compounds that can cross the blood brain barrier and kill the CSF-residing trypanosomes. This review summarises our current understanding on the treatment of HAT.

ability to cross the BBB and kill the CSF residing Trypanosoma brucei gambiense and Trypanosoma brucei rhodesiense parasites. Melarsoprol was first introduced in 1949 for the treatment of late stage trypanosomiasis, and has remained the main drug of choice to this day (Friedheim 1949).

Structure and activity

Melarsoprol

As shown in the Fig. 1, melarsoprol contains the trivalent arsenic element with a markedly reactive arsenoxyde group. The presence of the arsenoxyde confers the physicochemical ability of lipid solubility that allows passage across the BBB (Peppin and Milord 1994). Apart from its transport function, the arsenoxyde group mediates in the killing of the parasites in the CSF.
Eflornithine for the treatment of human African trypanosomiasis

Abstract Eflornithine is the only new molecule registered for the treatment of human African trypanosomiasis over the last 50 years. It is the drug used mainly as a back-up for melarsoprol refractory Trypanosoma brucei gambiense cases. The most commonly used dosage regimen for the treatment of T. b. gambiense sleeping sickness consists of 100 mg kg$^{-1}$ body weight at intervals of 6 h for 14 days (150 mg kg$^{-1}$ body weight in children) of eflornithine given as short infusions. Its efficacy against Trypanosoma brucei rhodesiense is limited due to the innate lack of susceptibility of this parasite based on a higher ornithine decarboxylase turnover. Adverse drug reactions during eflornithine therapy are frequent and the characteristics are similar to other cytotoxic drugs for the treatment of cancer. Their occurrence and intensity increase with the duration of treatment and the severity of the general condition of the patient. Generally, adverse reactions to eflornithine are reversible after the end of treatment. They include convulsions (7%), gastrointestinal symptoms like nausea, vomiting and diarrhea (10–30%), bone marrow toxicity leading to pancytopenia, which is the major limiting factor for the application of this drug.

Overview Eflornithine is a white to off-white, odorless, crystalline powder with a formula weight of the base of 182 g mol$^{-1}$ and of the hydrochloride of 237 g mol$^{-1}$ (Fig. 1). The compound is freely soluble in water and sparingly soluble in ethanol (Anonymous 1991). Based on its physico-chemical properties, the drug may be given orally or intravenously. Eflornithine shows antitumor effects in animal models and humans (Griffin et al. 1987), is active against Pneumocystis carinii (Gilman et al. 1987), and has demonstrated antiprotozoal activity in vitro, particularly against Trypanosoma brucei gambiense (Bacchi et al. 1980). The efficacy of the drug against human trypanosomiasis has been confirmed both in animal and...
Combination Therapy

- Nifurtimox and melarsoprol
- Nifurtimox Eflornithine Combination Therapy (NECT)

Nifurtimox-eflornithine combination therapy for second-stage African Trypanosoma brucei gambiense trypanosomiasis: a multicentre, randomised, phase III, non-inferiority trial

Summary

Background Human African trypanosomiasis (HAT; sleeping sickness) caused by Trypanosoma brucei gambiense is a fatal disease. Current treatment options for patients with second-stage disease are toxic, ineffective, or impractical. We assessed the efficacy and safety of nifurtimox-eflornithine combination therapy (NECT) for second-stage disease compared with the standard eflornithine regimen.

Methods A multicentre, randomised, open-label, active control, phase III, non-inferiority trial was done at four HAT treatment centres in the Republic of the Congo and the Democratic Republic of the Congo. Patients aged 15 years or older with confirmed second-stage T. brucei gambiense infection were randomly assigned by computer-generated randomisation sequence to receive intravenous eflornithine (400 mg/kg per day, every 6 h; n=144) for 14 days or intravenous eflornithine (400 mg/kg per day, every 12 h) for 7 days with oral nifurtimox (15 mg/kg per day, every 8 h) for 10 days (NECT; n=145). The primary endpoint was cure (defined as absence of trypanosomes in body fluids and a leucocyte count ≥10 cells per μL) 18 months after treatment. Efficacy analyses were done in the intention-to-treat (ITT), modified ITT, and per-protocol (PP) populations. The non-inferiority margin for the difference in cure rates was defined as 10%. This study is registered with ClinicalTrials.gov, number NCT00146627.

Findings One patient from the eflornithine group aborted after receiving the first dose, without any type of assessment done, and was excluded from all analyses. In the ITT population, 131 (91.6%) of 143 patients assigned to eflornithine and 136 (96.5%) of 143 patients assigned to NECT were cured at 18 months (difference -4.9%, one-sided 99% CI -10.3% to 0.6%). In the PP population, 132 (91.7%) of 143 patients in the eflornithine group and 137 (96.6%)...
Prevention

Tsetse fly Stages

1. Tsetse fly takes a blood meal (injects metacyclic trypanosomes)
2. Injected metacyclic trypanosomes transform into bloodstream trypanosomes, which are carried to other sites.
3. Trypanosomes multiply by binary fission in various body fluids, e.g., blood, lymph, and spinal fluid.
4. Trypanosomes in blood
5. Tsetse fly takes a blood meal (bloodstream trypanosomes are ingested)
7. Procyclic trypanosomes leave the midgut and transform into epimastigotes.
8. Epimastigotes multiply in salivary gland. They transform into metacyclic trypanosomes.

Human Stages

1. Infective Stage
2. Diagnostic Stage


DEVOTED TO REDUCING MALARIA DEATHS & SUFFERING IN HUMANITARIAN CRISSES
Prevention

- No vaccine
- Chemoprophylaxis avoided
- Case-finding and treatment
- Control and surveillance
- Vector control of the tsetse flies
Vector Control of Tsetse Flies

- Fly traps
- Sequential aerosol spraying
- Spraying animals
- Sterile insect technique (SIT)
Fly traps

Sequential aerosol spraying

Reservoir Control

A sample of collaborations

- Programme to Eliminate Sleeping Sickness
- Initiative for Central Africa
- Programme Against African Trypanosomiasis (PAAT)
- Pan-African Tsetse and Trypanosomiasis Eradication Campaign (PATTEC)
- Drugs for Neglected Diseases Initiative (DNDi)

NEGLECTED DISEASES: HAVE OUR GOVERNMENTS GOTTEN SLEEPING SICKNESS?

SIGN UP TO URGE YOUR GOVERNMENT TO SUPPORT RESEARCH IN DISEASES OF THE POOR.

DNDi, Drugs for Neglected Diseases initiative

DEVOTED TO REDUCING MALARIA DEATHS & SUFFERING IN HUMANITARIAN CRISSES
Conflict & Contagion: DRC

<table>
<thead>
<tr>
<th>Country</th>
<th>Years</th>
<th>Relative risk&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Estimated lag (yrs)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Expected N. cases</th>
<th>Observed N. cases</th>
</tr>
</thead>
</table>

<sup>a</sup> All clusters listed in table are significant at the 0.001 significance level. Relative risk reflect the risk within the cluster area and period compared to outside of the cluster area and period. Risks are based on national case counts and national population estimates.

<sup>b</sup> From the approximate start of conflict until disease resurgence is first detected (bottom of range) and epidemic peak (top of range). These numbers are approximations as identification of exact dates for disease curves and conflict progression are not feasible. In the case of the DRC, resurgence is not associated with formally recorded conflicts, but is anecdotally associated with ongoing instability. It is therefore not possible to estimate a lag for the DRC.

Berrang-Ford L, et al. See references.
VOICE FROM THE FIELD

DRC: "There is indescribable fear in everyone’s eyes"

AUGUST 21, 2009

A group of women and children stand in front of a shelter at a camp near Faradje in the northeastern Haut-Uélé province.
The next steps forward...

- Consistent, aggressive screening and treatment for *T.b. gambiense*
- Interrupting the cycle of transmission with cattle for *T.b. rhodesiense*
- Continuing to work in even remote and difficult areas of post-conflict zones
- Further research into the promise of combination drugs


