Editorials

African sleeping sickness

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Eflornithine should be the drug of choice for stage 2 disease, but resistance must be monitored

When human African trypanosomiasis (sleeping sickness) killed millions of people during Africa's colonial period 60-100 years ago, interest was similar to that for today's HIV epidemic, but the disease is now largely forgotten. The continuing importance of this disease is highlighted in the accompanying paper by Priotto and colleagues, who report the effectiveness and safety of eflornithine used for its first line treatment.**1**

The most common form of human African trypanosomiasis is caused by the parasite *Trypanosoma brucei gambiense* andis transmitted by the tsetse fly.**2** Because diagnostic tests are too complex to integrate into primary health care, by the time most cases present they have already progressed from the benign easily treatable stage of the disease (haemolymphatic, stage 1) to the late stage (meningoencephalitic, stage 2), where parasites invade the central nervous system. If the disease is untreated, the patient has almost a 100% risk of dying within one to four years, after progressive neurological degeneration.

Only two drugs are available for treatment of late stage disease. The first is a derivative of arsenic, melarsoprol. In areas where resistant parasites may be prevalent—such as Sudan, Uganda, the Democratic Republic of Congo, or Angola—melarsoprol has a cure rate of less than 70%.**3** About 3-5% of patients die from drug induced encephalopathy.

The second treatment is α-difluoromethylornithine (DFMO, eflornithine).**4** This drug, registered in 1990 for human African trypanosomiasis, was abandoned by Aventis in the late 1990s because of its lack of profitability, just as Bristol-Myers-Squibb launched an eflornithine based facial hair removal cream (Vaniqa). Fierce campaigning by the World Health Organization (WHO) and Médecins Sans Frontières (MSF) led Aventis to resume production in 2001. Sanofi-Aventis has made a commitment until 2011 to provide free kits containing the required two week supply of eflornithine plus expensive material for perfusions; this kit is to be distributed by WHO.

This secure availability has encouraged wider adoption of eflornithine over melarsoprol, with the risky

assumption that it would be safer and no less effective. The assumption rested on evidence from about 1000 patients treated with various dosages and formulations who were mostly not followed up beyond 12 months—an insufficient amount of time to detect late relapses.[5] In Priotto and colleagues' study—which follows up 1055 patients with stage 2 disease for cure rates, deaths, and adverse events during treatment—about 64% of people were followed up for at least one year and 50% for two years. The study supports the widespread use of eflornithine by demonstrating its effectiveness and safety, while highlighting the dangers of administration without supportive care.

Priotto and colleagues' study indirectly supports evidence of a lower case fatality rate (1-2%) with eflornithine than with melarsoprol. Surprisingly, no trial has directly compared the two drugs, but some evidence of superiority comes from programmes that used the two drugs sequentially,[6] [7] and fatality rates for melarsoprol are well documented and consistently higher than for eflornithine across various settings.

Severe adverse events (mainly seizures, fever >39.5°C, severe diarrhoea, and severe bacterial infections) were reported in 13% of patients. Although Priotto and colleagues used a retrospective record based assessment of adverse events, which could be hampered by under-reporting, these results are consistent with prospective observations of eflornithine and far lower than those from studies of melarsoprol.Bone marrow toxicity, a known effect of eflornithine not measured in Priotto and colleagues' study, may underlie many of the treatment emergent episodes of infection, and warrants further investigation. Most bacterial infections were successfully managed in this and other studies, but resource poor facilities that lack proper antibiotics, nursing care, and skilled clinicians could experience higher case fatality.

Effectiveness was moderately high (88% by survival analysis), but the occurrence of relapses in at least 7.6% (70/924) of patients is worrisome— patients who relapse have a high risk of death, and anecdotal evidence of treatment failure with eflornithine is accumulating. As with melarsoprol, relapse was associated with severity of illness on admission (eflornithine might not achieve minimum inhibitory concentrations in patients with high parasite density in their cerebrospinal fluid because of poor pharmacokinetic properties[3]) and male sex (reinfection in men with occupational exposure to tsetse bites might confound this association).

Although resistance is not necessarily the reason for treatment failure, resistance is readily induced in vitro andits emergence in the field would be disastrous.[8] Combination treatment might help avert resistance and its transmission. Coadministration of eflornithine and nifurtimox (a drug registered for Chagas' disease and modestly effective as monotherapy for human African trypanosomiasis[3]) is being tested in a multicentric trial, and initial findings show excellent efficacy with equal or better safety than either drug alone, possibly as a result of lower doses.[9] [10] Concerns exist, however, about nifurtimox's possible long term genotoxicity, which has been noted in some animal experiments.[11]

Evidence so far supports the policy of eflornithine replacing melarsoprol as first line treatment of stage 2 disease, but a cautious eye must be kept on resistance. However, eflornithine's cost and cumbersome logistics of administration mean that new and better drugs are urgently needed. The highest level of investment in control since the colonial period has led to a reduction in transmission in most foci of human African trypanosomiasis after two decades of resurgence. This has prompted ambitious calls for elimination, which WHO is committed to spearheading.[12] Research to develop new drugs and diagnostics for this disease is now supported by about $100m (£50m; €67m), mostly from charities. Promising compounds for treatment of stage 2 disease are being explored—for example, by the Bill and

Melinda Gates Foundation funded Consortium for Parasitic Drug Development and the Drugs for Neglected Diseases initiative.[3]

Meanwhile, a combination of eflornithine-nifurtimox could become the therapeutic mainstay by 2010. Advocacy for neglected tropical diseases often focuses on the lack of drugs but should not overlook simple epidemiological realities—earlier case detection through reinforced screening programmes is the best way to avoid the complications of treatment for stage 2 human African trypanosomiasis.

Footnotes

- Research, doi: 10.1136/bmj.39485.592674.BE
- Competing interests: FC was previously employed by MSF and Epicentre, the sponsors of the study that is the subject of this editorial; he also collaborates with some of the study's authors on several research projects on African sleeping sickness, based on data from MSF programmes.
- Provenance and peer review: Commissioned; not externally peer reviewed.

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Back to top