

Therapy of Human African Trypanosomiasis: Current Situation

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This paper is a review of the current situation of the treatment of human African trypanosomiasis. The existing approved drugs are old, toxic and/or expensive. Therapeutic failures are common. Several factors may contribute to the problems of chemotherapy, including differences in the epidemiology of the disease, difficulties in the diagnosis and staging of the infection, availability, distribution and pharmacologic properties of drugs, standardization of treatment regimens, response to therapy, follow-up period, and relapses and clinical trials. The new therapeutic approaches include the development and approval of new drugs, the use of new therapeutic regimens, the study of drug combinations, and the development of new formulations.

Key words: human African trypanosomiasis - treatment - drugs - review

Current therapy of human African trypanosomiasis is not satisfactory. Most of the drugs still in use have been developed in the first half of the century (suramin, pentamidine, nitrofuranes and arsenicals) (Van Nieuwenhove 1992) and some of them would not pass today's standards for drug safety (Fairlamb 1990). Even diminazene aceturate (Berenil®), developed in the mid-1950s as a cattle trypanocide, although successfully used in the treatment of human trypanosomiasis in several countries, and included as a trypanocidal drug in World Health Organization (WHO) technical reports (WHO 1986), has never been registered for human treatment. Drug development in recent times has been slow and poor. The introduction of DL-a-difluoromethylornithine (DFMO, eflornithine) for the treatment of late-stage Gambian sleeping sickness (Van Nieuwenhove et al. 1985) was not the result of a specific trypanosomiasis drug research. Eflornithine was primarily developed as an anti-tumour proliferation (Sunkara et al. 1987), and modulation of cell differentiation drug (Heby et al. 1987) but the clinical trials showed poor results (Schechter et al. 1987). On the other hand, nifurtimox, largely used in the treatment of *Trypanosoma cruzi* infections, was tried in human African trypanosomiasis with some success (Janssens & De Muyck 1977, Moens et al. 1984, Van

Nieuwenhove 1992). Thus, therapy of human African trypanosomiasis, in early-stage, relies on pentamidine (exclusively for *T. gambiense* infections), suramin or diminazene aceturate, and, in late-stage, on melarsoprol, eflornithine, and, as second choice drugs, usually for melarsoprol relapses (arsenic-resistant trypanosomes) the nitrofuranes nitrofurazone and nifurtimox.

FACTORS WHICH CONTRIBUTE TO THE PROBLEMS OF CHEMOTHERAPY

The epidemiology of the disease - The disease is exclusively African, and only exists in rural areas, increasing the difficulty of mobile teams to reach remote regions (in *T. gambiense* infections) or the access of patients to their local health unit (in *T. rhodesiense* infections). Epidemics, which are occurring now in Angola, Zaire and Sudan, raise the need for technical skilled personnel, diagnostic tools, drugs and other resources which are scarce in those African countries.

Diagnosis and staging of the infection - Some health centres don't have the diagnostic tools to make a correct diagnosis and staging of the disease. Current cerebro-spinal fluid (CSF) parameters, used to make the distinction between disease stages, obligatory for the choice of drug, are unsatisfactory. A person is considered to be in the early-stage when trypanosomes cannot be detected in the CSF, CSF leukocyte count is less than 5/ml and when the CSF protein content is not higher than 37mg/100ml (dye binding method) or 25mg/100ml (Sicard-Cantaloube method). Those criteria are arbitrary. Double centrifugation techniques and cultural methods allow to demonstrate trypanosomes in some otherwise normal CSF samples,

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although these patients may still get cured with early-stage drugs.

The drugs - (1) Risks in the availability of drugs: DFMO is only produced through WHO request; the production of melarsoprol has raised ecological problems; pentamidine is expensive, but WHO is supporting its acquisition and distribution; (2) Difficulties in the distribution of drugs: some health centres can make the diagnosis and the staging of the disease, but don't have the drugs to treat it; (3) There is little information about pharmacokinetics, mode of action and toxicity of some of the existing trypanocides; the available information about pharmacokinetics and pharmacodynamics of some of the drugs, namely melarsoprol and pentamidine, suggests the use of different therapeutic regimens.

Treatment and prevention of concurrent diseases - (1) Patients with human African trypanosomiasis in the late stage of the disease are usually severely ill. Malnutrition, malaria, intestinal helminths and protozoa, and filariasis are the most important concurrent diseases that may be found in the trypanosomiasis patient. The management of these concurrent diseases is of major importance; (2) The use of antibiotics, vitamins, and corticosteroids is not standardized.

Response to therapy - (1) The responses to therapy are different in the Gambiense and Rhodesiense forms of sleeping sickness. This differences are not only species-related, but also occur in species in the same geographic area; (2) Many reported adverse effects to treatment are the exacerbation of pre-existing symptoms or may occur during the natural course of trypanosomiasis; (3) Mortality could sometimes be reduced by simple measures like better nutrition and nursing care. In the majority of cases the cause of death is unknown.

Follow-up - (1) The post-treatment follow-up period is extremely long, and requires at least four lumbar punctures. A patient is considered cured if, 24 months after the end of therapy, there are no trypanosomes in any body fluid and CSF-parameters are normal. If a patient has no symptoms, he usually refuses the lumbar puncture, thus only a small proportion of treated patients have a complete follow-up; (2) The use of new diagnostic tools like PCR and antigen detection techniques in the follow-up should be investigated.

Relapses - (1) The distinction between a relapse and a reinfection is sometimes difficult; (2) Increases in CSF leukocyte count and/or protein content without reappearance of trypanosomes until six months after the treatment are not indications of a relapse, at least in *T. gambiense* late-stage infections treated with melarsoprol. They are usually interpreted as such.

Clinical trials - (1) Most clinical trials are compassionate studies using multi-relapsed incurable patients, treated with drugs or drug combinations not included in standard protocols; (2) There is no standardization in patient selection for clinical trials from one health centre to another, in the same or in different countries.

Reporting - Physicians and other technical personnel working in the field do not have time to write papers or to attend trypanosomiasis conferences. Communication is needed.

NEW THERAPEUTICAL APPROACHES

New drugs approach - The development of a new drug is a very expensive process. If a pharmaceutical company develops a compound for the treatment of human African trypanosomiasis, a disease which only exists in Africa, no financial profit will happen. The only possibility of having new trypanocidal drugs available in the near future is the development of new compounds active against diseases of the rich countries, which may be also active against human African trypanosomiasis.

Nevertheless, many compounds have been studied, some with trypanocidal effect *in vitro* and in animal models, but most of them are not investigated anymore. The arsenical IMOL 881, effective on *T. rhodesiense* and *T. gambiense* as well as on the animal trypanosomes, *T. evansi* and *T. equiperdum* (Maes et al. 1993, Doua & Boa Yapo 1994), and the nitroimidazole megazole (Enanga et al. 1997) are two of the new compounds with trypanocidal action under active investigation.

New regimens approach - Studies on pharmacokinetics and pharmacodynamics of melarsoprol suggested the use of a different melarsoprol regimen (Burri & Brun 1992, Burri et al. 1993). An alternative therapy protocol has been proposed for *T. gambiense* infection consisting in ten consecutive injections of 2.2 mg/kg melarsoprol given at intervals of 24 hr (Burri et al. 1995). A clinical trial in Angola is currently under evaluation and the preliminary results are promising (Burri, pers. commun.).

A new regimen using eflornithine in a seven days course is still under evaluation (WHO 1995). When used in patients which have relapsed from a first treatment the results were very good, with a rate of failure of only 6.5% in 47 patients (Khonde et al. 1997).

New drug combinations approach - Some drug combinations have been used in humans, mainly as compassionate studies: metronidazole with suramin (Arroz & Djedje 1988, Foulkes 1996), eflornithine with suramin (Taelman et al. 1996) and eflornithine combined with melarsoprol (Simarro

& Asumu 1996). Controlled clinical trials are urgently needed to clarify the efficacy of these drug combinations.

New formulations approach - The serious venous damage provoked by melarsoprol treatment (Ginoux et al. 1984) added to the problems of using intravenous injections in rural areas, was the reason for the development of the topical melarsoprol formulation. Experimental work in the mouse model showed good results with the topical melarsoprol gel therapy, alone (Atouguia et al. 1995) or in combination with the nitrofurans and the nitroimidazoles (Jennings et al. 1996). Further studies are required, including the development of a transdermal delivery system, and pharmacokinetic and pharmacodynamic investigations before any clinical trials.

CONCLUSIONS

The current situation is very difficult in many areas. Local teams have no drugs, no skilled personnel, no diagnostic tools, and thousands of suspected cases to diagnose and treat. The resolution of these problems is urgent.

Communication is important. Exchange of information between teams facilitates the standardization of procedures, protocol design and supervision.

Development of new drugs and new formulations must continue. If the pharmacokinetic and pharmacodynamic studies of topical melarsoprol are successful, a clinical trial should be designed and executed. Meanwhile, there is an urgent need for clinical trials and comparative studies with drug combinations and new regimens. All these studies must be controlled and performed under the supervision of WHO.

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