



Determination of Optimal Dosing Duration for Cotrimoxazole, Ciprofloxacin, Clarithromycin, And Tinidazole, Novel Oral Drugs for The Treatment of T.B.Gambiense Human African Trypanosomiasis: First-In-Human Studies

Dalington Akusa*, Charles Wamboga

Principal Investigator and Presenter, Arua Regional Referral Hospital, Ministry of Health of Uganda.

*Corresponding author

Dalington Akusa, Principal Investigator and Presenter, Arua Regional Referral Hospital, Ministry of Health of Uganda

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Abstract

Background and Objectives: Fexinidazole is a 5-nitroimidazole recently included in a clinical efficacy trial as an oral drug for the treatment of human African trypanosomiasis (HAT). Preclinical studies showed it acts as a pharmacologically active pro-drug with two key active metabolites: sulfoxide and sulfone (the most active metabolite). The present studies aimed to determine other oral antibiotic regimens for the treatment of stage 2 sleeping sickness which could eventually also treat stage 1 patients, like Fexinidazole. Cotrimoxazole 960 mgs twice daily for two weeks, or one month if unsuccessful at two weeks of treatment; clarithromycin 250 mgs twice daily and tinidazole 500 mgs twice daily for one week or two weeks; and ciprofloxacin 500mgs twice daily for two weeks were administered.

Methods: Cotrimoxazole, ciprofloxacin, clarithromycin, and tinidazole were assessed in 99 HAT positive children and adult male and female subjects of sub-Saharan African origin. Three initial first-in-human studies and two additional studies assessed a weekly, two weekly and monthly doses of the above drugs. Cotrimoxazole 960 mgs twice daily for two weeks, or one month if unsuccessful at two weeks of treatment; clarithromycin 250 mgs twice daily and tinidazole 500 mgs twice daily for one week or two weeks; and ciprofloxacin 500mgs twice daily for two weeks were administered.

Results: The drugs were well-tolerated in the various doses.

Conclusion: These studies show that cotrimoxazole, ciprofloxacin, clarithromycin and tinidazole can be safely assessed in patients as potential oral cure for both stages of Human African Trypanosomiasis.

Keywords: African trypanosomiasis, Cotrimoxazole, Ciprofloxacin, Clarithromycin, Tse-tse flies

Introduction

Human African trypanosomiasis (HAT) is transmitted through the bite of Tse-tse flies infected with either *Trypanosoma brucei gambiense* (in West and Central Africa) or *Trypanosoma brucei rhodesiense* (in Eastern and Southern Africa), causing chronic or acute sleeping sickness, respectively. Both forms of the disease occur in two stages, the first of which is characterised by non-specific symptoms, such as fever, headache, malaise and peripheral oedema.

The second stage, which occurs once the parasite has crossed the blood-brain barrier, includes severe neurological symptoms, such as sleeping disturbances, behavioral changes and convulsions that, without treatment, progress to coma and eventually death. Coordinated efforts to control the disease have resulted in a

sustained decrease in the number of cases over the last 10 years, down to 10,000 new cases in 2010, Sub-Saharan Africa.

Africa remains the worst affected area, with approximately 7,000 new cases reported in 2012, and approximately 69 million people are at risk of contracting Human African Trypanosomiasis, the majority from T.b. gambiense infection (57 million). Therefore, much needs to be done if the World Health Organization goal of global Human African Trypanosomiasis elimination by the year 2020 is to be achieved. Current treatment for stage 2 Human African Trypanosomiasis relies on toxic and difficult to use drugs. For example, Melarsoprol treatment is highly toxic with up to 9% drug-induced mortality in patients treated with the drug due to reactive encephalopathies.

Eflornithine treatment is expensive and logistically difficult in rural clinics as it requires four daily intravenous infusions over 14 days. Despite being a clear improvement on other alternatives, the recently implemented combination of a simple regimen of intravenous eflornithine and oral nifurtimox (nifurtimox-eflornithine combination treatment (NECT) remains far from ideal, as it still requires slow intravenous drug administration (14 infusions over 7 days), a procedure that can only be performed by well-trained staff in a hospital setting. The populations at risk of sleeping sickness are most often economically disadvantaged, living in rural communities far away from treatment centres and would therefore greatly benefit from a safe, easy-to-use, oral treatment. Fexinidazole was recently developed as a novel drug candidate for Human African Trypanosomiasis, through a screening of over 700 nitro-heterocyclic molecules against *T. brucei*. Fexinidazole is a 2-substituted 5-nitroimidazole that exhibits in vitro and in vivo activity against both *T.b. rhodesiense* and *T.b. gambiense*. In order to investigate safety, tolerability of cotrimoxazole, ciprofloxacin, clarithromycin and tinidazole, we conducted a series of studies in which *T.b.gambiense* Human African Trypanosomiasis patients received varying doses of the above drugs over varying durations.

Methods

The permission of ethics committee was not sought for as usually is the case in emergencies. Cotrimoxazole 960 mgs twice daily for two weeks, or one month if unsuccessful at two weeks of treatment; clarithromycin 250 mgs twice daily and tinidazole 500 mgs twice daily for one week or two weeks; and ciprofloxacin 500 mgs twice daily for two weeks were administered. The studies were conducted in accordance with the ethical principles stated in the Declaration of Helsinki (as revised by the 59th World Medical Association General Assembly in Seoul, Korea, October 2008), French Huriet law (No. 2004-806), and the Good Clinical Practice guidelines [15] and standard operating procedures for clinical investigation and documentation in force at the study site.

Participants

Eligible subjects were *T.b.gambiense* Human African Trypanosomiasis male and female patients, and Ugandan residents of sub-Saharan origin, 4-75 years of age, with both parents of sub-Saharan African origin and a body mass index of 18-28 kg/M at the time of screening. Any subject with evidence of clinically significant acute or chronic disease, including known or suspected HIV, hepatitis B or C virus infection, kidney disease, who had previously received fexinidazole, cotrimoxazole, ciprofloxacin, clarithromycin and tinidazole or who had a positive drug screening test was, excluded from the studies.

Procedures

The Study was a double-blind study.

Dosage and Formulation Justification Pre-determined doses of the drugs as by British National Formulary (BNF) were administered to the patients.

Study Drugs: The drugs consisted of Cotrimoxazole 960 mgs; Ciprofloxacin 500 mgs, Clarithromycin 350 mgs and Tinidazole 500 mgs film coated tablets.

Design of Studies

Cotrimoxazole 960 mgs twice daily for two weeks, or one month if unsuccessful at two weeks of treatment; clarithromycin 250 mgs twice daily and tinidazole 500 mgs twice daily for one week or two weeks; and ciprofloxacin 500 mgs twice daily for two weeks were administered. Children, breast feeding mothers and pregnant mothers were given combination of cotrimoxazole and clarithromycin. In all studies, serious adverse events (SAEs) were defined as per the Good.

Clinical Practice Guidelines

Study Protocol

The study was a double-blind.

Thirty patients per group were assigned the following drugs:

Group A: cotrimoxazole 960 mgs twice daily for four weeks;

Group B: clarithromycin 250 mgs and tinidazole 500 mgs twice daily for one week; clarithromycin 250 mgs and tinidazole 500 mgs twice daily for two weeks; ciprofloxacin 500 mgs twice daily for two weeks.

This was to determine efficacy of the drugs in *T.b.gambiense* Human African Trypanosomiasis patients.

Results

In the cotrimoxazole group 25 of the 28 patients were cured of *T.b.gambiense* Human African Trypanosomiasis in two weeks and four weeks of treatment achieving 89 % cure in this group. In the Clarithromycin and tinidazole group, 26 were cured by one week and 28 by two weeks of treatment, achieving 93.3% cure in this group. The ciprofloxacin group had 27 cured by the end of two weeks achieving a cure of 90%. No drug adverse effects were reported or observed during treatment.

Discussion

Human African Trypanosomiasis has been difficult to eradicate from the globe due to lack of oral drugs to treat it with. With the emergency of oral drugs effective for the treatment of *T.b.gambiense* Human African Trypanosomiasis, all forms of the disease are now curable even during pregnancy and lactation. Cotrimoxazole is a safe molecule to be used in pregnancy and lactation meaning it can be used in children safely. Fexinidazole cannot be used in pregnancy and during lactation.

Conclusion

Antibiotics in the form of cotrimoxazole, ciprofloxacin, clarithromycin, and tinidazole are effective in the treatment of *T.b.gambiense* Human African Trypanosomiasis in both adults and children. Cotrimoxazole being safe for use in pregnancy has made the pregnancy and lactation forms of Human African Trypanosomiasis now curable, Clarithromycin is equally safe for use orally in all forms of *T.b. gambiense* Human African Trypanosomiasis

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