10-DAY MELARSOPROL TREATMENT OF *TRYPANOSOMA BRUCEI GAMBIENSE* SLEEPING SICKNESS:

FROM EFFICACY TO EFFECTIVENESS

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Caecilia Schmid

aus Schüpfheim (LU)

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Basel, den 21. September 2004

Prof. Dr. Marcel Tanner

Dekan

to the memory of my father

Willy Franz Schmid

who waited so long for this

TABLE OF CONTENT

PART 3: IMPAMEL II – EFFECTIVENESS UNDER NATURAL CONDITIONS, A MULTINATIONAL EVALUATION

PART 4: DISCUSSION, CONCLUSIONS AND PERSPECTIVES

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SUMMARY

Treatment of human African trypanosomiasis (sleeping sickness) with the currently available drugs is unsatisfactory and new drugs and approaches are urgently needed. Despite being associated with severe adverse reactions and a long, complicated treatment schedule, melarsoprol (Arsobal®) is expected to remain the most used drug for the treatment of late-stage sleeping sickness for the next decade because alternative treatments are too expensive and only at very preliminary stages of development.

In the presented study, the overall effectiveness of an abridged application scheme of melarsoprol for the treatment of late-stage gambiense sleeping sickness was evaluated. In a first part, the long-term efficacy of the 10-day schedule was concluded based on the follow-up of the patients treated in a large-scale controlled clinical trial in Angola in 1998 (IMPAMEL I). In a second part, the overall effectiveness of this abridged treatment schedule was assessed in a multinational drug utilisation study (IMPAMEL II) that was executed under field conditions. Clinical effectiveness was shown by addressing specifically the usefulness in different settings, e.g. in different countries / centres and in children below 15 years of age. An economic appraisal was also done to assess the monetary benefit if switching from the standard treatment schedule to the short course of melarsoprol.

2800 patients from 16 different treatment centres of 7 African countries endemic for *T.b gambiense* trypanosomiasis were treated with 10 daily doses of 2.2 mg melarsoprol/kg bodyweight on consecutive days. The short- and long-term efficacies of the 10-day schedule were good and comparable to the standard schedules found in the randomised, controlled clinical trial in Angola and in previous trials published in literature. However, poor follow-up is an inherent problem of sleeping sickness control and therefore highly variable attendance rates of the follow-up examinations could be anticipated. In our studies, they varied from acceptable in the controlled trial in Angola to rather low rates in many treatment centres of the multinational study.

Highly variable outcomes were also found for the safety of the 10-day treatment schedule reported from the different treatment centres in the multinational evaluation. But nevertheless, the safety under field conditions proved to be well comparable to the findings of the clinical trial previously executed in Angola, the literature and the retrospective data from the participating treatment centres. No unexpected findings were reported.

In addition, the tolerability and effectiveness of the abridged treatment schedule in children were assessed by reviewing all patients treated in the multinational study who were below the age of 15 years. There is evidence that the safety and efficacy profile of the 10-day schedule is similar in children and adults. The abridged treatment schedule was well

tolerated by the children and we found only non-significant differences in the occurrence of adverse events compared to adults. Some of these differences could be explained by higher rates of concomitant parasitic diseases in children and the fact that some adverse events cannot be separated from common signs and symptoms of the disease, especially in younger children (e.g. headache). The cure rates were identical in the subpopulations.

We found the 10-day treatment schedule to be more cost-effective than the standard treatment and a highly cost-effective treatment option for late-stage gambiense sleeping sickness in areas with scarce resources. The costs of treatment (diagnosis, hospitalisation and sleeping sickness specific treatment) were assessed in two rural treatment centres and compared to the benefits of the 10-day treatment and of the standard treatments, measured by the cost of treatment per DALY (disability-adjusted life-year) averted. The net benefit from switching from the standard (26 to 30 days hospitalisation) to the 10-day treatment schedule did reduce the costs per DALY averted by almost half of the costs calculated for the standard schedules and represented a “good value for money” option in the control of sleeping sickness.

In addition, the 10-day schedule bears several advantages over the standard national treatment schedules: It reduces treatment duration, hospitalisation time, and total drug amount per patient, it is easier to implement in basic, rural treatment centres, and it increases the treatment centres’ capacity.

Based on our findings and the experience of the sleeping sickness control programs in the respective countries, the abridged protocol was recommended by the 27th ISCTRC in late 2003 as the standard schedule for melarsoprol treatment of late-stage sleeping sickness due to *T.b. gambiense.* However, because of the different clinical nature and the high parasitaemia, the use of the 10-day schedule against *T.b. rhodesiense* is strongly discouraged until the necessary clinical evaluation will be conducted. Based on its simplified implementation, the 10-day schedule offers straightforward adaptation for combination therapy with other existing drugs, especially for melarsoprol refractory patients.

RÉSUMÉ

Le traitement de la trypanosomiase humaine africaine (maladie du sommeil) à l'aide des médicaments actuellement disponibles est insatisfaisant. Il y a donc un besoin urgent de trouver de nouveaux médicaments et de nouvelles approches thérapeutiques. Malgré de ses effets secondaires sévères et son schéma thérapeutique long et compliqué, le mélarsoprol devrait rester au cours de la prochaine décennie le médicament le plus utilisé pour le traitement de la maladie du sommeil au stade neurologique. Les traitements alternatifs étant trop chers ou à des stades préliminaires de développement.

Dans l'étude présentée, l'efficacité globale d'un schéma d'administration raccourci de mélarsoprol pour le traitement de la maladie du sommeil à *T.b. gambiense* au stade neurologique a été évaluée. Dans la première partie, l'évaluation de l'efficacité à long terme du schéma de dix jours a été effectuée sur la base d'un suivi des malades traités au cours d'un essai clinique en Angola en 1998 (IMPAMEL II). Dans la deuxième partie, l'efficacité globale de ce schéma abrégé a été évaluée dans une étude multinationale d'utilisation du médicament, effectuée dans les conditions naturelles de terrain. L'efficacité clinique a été étudiée dans le cadre des différents contextes existant dans les pays/centres participant à l'étude, ainsi que chez des enfants âgés de moins de 15 ans. Une évaluation économique de l'impact monétaire de la substitution du schéma standard par le schéma court a été effectuée.

Pendant une année, 2800 malades issus de 16 centres de traitement dans 7 pays africains endémiques pour la maladie à *T.b. gambiense* ont été traités avec 10 doses consécutives de 2.2 mg/kg de poids corporel de mélarsoprol par jour. L'efficacité à court et à long terme du schéma de 10 jours fut très bonne. Elle est comparable à celle observée lors d'une étude randomisée et contrôlée avec le schéma standard en Angola et à celle observée dans les essais cliniques décrits dans la littérature. Néanmoins, le suivi des malades étant un problème inhérent au contrôle de la maladie du sommeil, des taux très variables d'examens de suivi étaient prévisibles. Dans nos études, ceux-ci ont varié des taux acceptables observés dans l'étude contrôlée en Angola jusqu'à des taux plutôt bas observés dans de nombreux centres inclus dans l'essai multinational.

Des taux très variables de résultat ont aussi été observés par rapport à la sûreté du schéma de 10 jours, tel que rapporté par les différents centres de traitement inclus dans l'évaluation multinationale. Cependant, la sûreté du schéma dans les conditions de terrain s'est révélée comparable à celle de l'essai clinique réalisé en Angola, à celle décrite dans la littérature et à celle rétrospectivement disponible dans les centres de traitement participant à cette étude. Aucun résultat inattendu n'a été observé.

La tolérabilité et l'efficacité du schéma abrégé chez les enfants ont été évaluées en examinant tous les malades au dessous de 15 ans traités lors de l'étude multinationale. Les

données montrent que le profil de sûreté et d'efficacité chez l'enfant est identique à celui de l'adulte. Le traitement abrégé fut bien toléré chez les enfants; nous avons détecté seulement des différences non significatives par rapport aux effets adverses observés chez les adultes. Certaines de ces différences pourraient être attribuées aux taux d'infection parasitaire supérieurs, observés chez les enfants et au fait que beaucoup d'effets adverses ne soient pas facilement séparables des manifestations cliniques de la maladie pédiatrique (par exemple les céphalées). Le taux de guérison fut identique dans les deux groupes.

Nous avons trouvé que le rapport coût efficacité du schéma de 10 jours est meilleur que celui du schéma standard ; et de ce fait constitue une option favorable pour le traitement de la maladie *T.b. gambiense* en phase neurologique dans des régions à ressources limitées. Le coût du traitement (diagnostic, hospitalisation, et coût du médicament spécifique), en termes de coût par DALY épargné, a été évalué dans deux centres de traitement ruraux. Le bénéfice net est une réduction de presque de la moitié des coûts, lorsqu'on substitue le schéma standard (entre 26 et 30 jours d'hospitalisation) par le schéma de 10 jours, représentant ainsi une option valable pour le contrôle de la maladie du sommeil.

En plus de son efficacité clinique, le schéma court de mélarsoprol représente donc une option ayant un rapport coût efficacité fortement favorable. Il présente aussi des avantages par rapport aux schémas de thérapeutiques nationaux: il réduit la durée du traitement et d'hospitalisation aussi bien que la quantité de médicament utilisé par malade; il est plus facile à adopter par des centres de traitement rudimentaires en zone rurale, et de ce fait augmente leur capacité opérationnelle.

En prenant en considération les données de notre étude et l'expérience obtenue par les programmes de lutte contre la maladie du sommeil dans chaque pays participant, le protocole abrégé a été recommandé en septembre 2003 par le 27^{ième} CISRLT comme le nouveau schéma standard pour le traitement de la maladie du sommeil à *T.b. gambiense* au stade neurologique. Jusqu'à ce que la nécessaire évaluation clinique soit effectuée, l'utilisation du schéma de 10 jours en cas de *T.b. rhodesiense* est cependant fortement découragée, en fonction des caractéristiques cliniques différentes et de la haute parasitémie présenté dans cette forme de la maladie. Étant donné sa plus simple implantation, le schéma de 10 jours est aussi très convenable pour utilisation en traitement combinée avec d'autres médicaments existants, surtout pour les malades réfractaires au mélarsoprol.

PART 1: INTRODUCTION, OBJECTIVES AND STUDY DESIGN

INTRODUCTION

Epidemiology

Case detection and treatment of the cases is the cornerstone to the control of human African trypanosomiasis (HAT) or sleeping sickness, a fatal parasitic disease. Nearly eliminated in the 1960s, HAT showed a dramatic comeback of epidemic proportions due to the collapse of health systems, other health priorities, war, and population movements over the past two decades.

Today, in 36 sub-Saharan African countries, 60 million people are at risk of infection and less than 10% are under surveillance [WHO 1998]. And as only around 40'000 annual cases have been reported in the last years, the real prevalence is estimated at around 350'000 cases [WHO 2001]. Sleeping sickness affects mainly the poor, rural African population and the socio-economic impact is considered very high amongst tropical parasitic diseases. The affected population suffers most from economic loss due to reduced workforce and family disruption. In terms of disease burden expressed in DALYs (disability-adjusted life years), HAT ranks third of all parasitic diseases in sub-Saharan Africa, just behind malaria and helminths [WorldBank 1993; WorldHealthReport 2004]. Untreated, the disease leads inevitably to death.

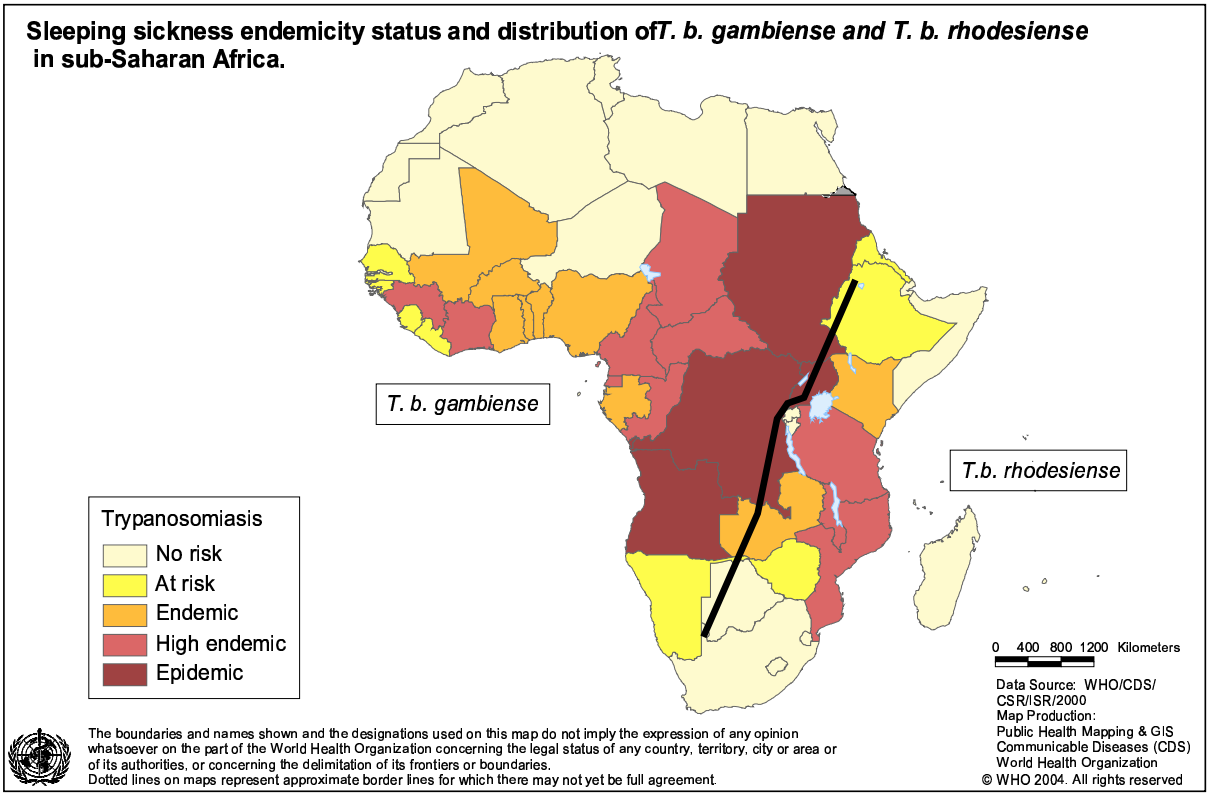
Sleeping sickness is caused by the parasitic protozoa *Trypanosoma brucei gambiense* (*T.b. gambiense*) and *Trypanosoma brucei rhodesiense (T.b. rhodesiense)*, which are transmitted by the bite of the tsetse fly, *Glossina* sp. The disease is distributed in distinct foci throughout the tsetse-infested zone between the latitudes 14°N and 20°S of sub-Saharan Africa and considerable variations in the endemicity levels are reported (Figure 1).

The disease occurs in two distinct forms: the chronic form due to *T.b. gambiense* that is confined to Central and Western Africa and the more acute *T.b. rhodesiense* form that is prevalent in Eastern Africa [WHO 1998]. Currently, most of the cases reported are due the gambiense form that has a long course (up to several years) and only a few hundreds of cases are being diagnosed with the acute rhodesiense form that exhibits a short disease progression (several months).

T.b. rhodesiense has an important zoonotic component, with only occasional transmission to people from both, domestic livestock and game animals [WHO 1998]. Measures within the community to reduce morbidity and mortality in individuals include prevention of exposure and case management (surveillance of population at risk, treatment and follow-up of cases). But more important are control measures that limit the spread and transmission from the animal reservoir to the humans, mainly through controlling animal reservoir and vector

control (trapping flies, aerial spraying, and destroying breeding sites). The gambiense reservoir is almost entirely in the human population. Consequently, the most effective form of control of gambiense sleeping sickness is medical surveillance, relying on case detection and treatment to reduce the human reservoir of the disease so as to lower its incidence [WHO 1998, 2001]. Therefore, appropriate treatment of HAT is a crucial measure for control although it is hampered by major obstacles that are discussed in the following sections and chapters.

Figure 1: Distribution of HAT in sub-Saharan Africa, by endemicity levels of the countries affected (© Map: Source: WHO2004)



Transmission and clinical manifestations

Symptoms and signs of sleeping sickness are classified according to the clinical progression of the disease: the early haemolymphatic stage and the late meningoencephalitic stage and may differ substantially between the rhodesiense and gambiense form (Table 1; [Burri and Brun 2002]).

Table 1 Typical symptoms and signs of sleeping sickness

Early stage
Chancre (*T.b. rhodesiense* mainly)
Unspecific signs: fever, headache, joint pain, general malaise, pruritus, hyperesthesia, (rash)
Adenopathy (*T.b. gambiense*)
Anaemia
Localized oedema
Splenomegaly
Irritability, changes of mood
Weight loss
Cardiac abnormalities (tachycardia - pancarditis)
Late-stage
Headache
Abnormal movements
Sensation problems (hyperesthesia, parestesia, neuralgia)
Impaired motor functions (walking, speech, dyskinesia)
Archaic reflexes
Endocrine disorders (e.g. reduced libido, amenorrhea, bulimia or loss of appetite, facial oedema)
Psychological problems: changes of behaviour, mental deterioration, psychosis (e.g. mania, paranoia)
Reduced vigilance and sleep, later reversal of sleep pattern
Coma

Following an infective bite of the tsetse fly, a swollen chancre may develop at the site (mainly with *T.b. rhodesiense*) with widespread lymph node enlargement. Early in the infection, the trypanosomes become established in the lymph and blood where they multiply and signs of the disease may be rather unspecific, with episodes of fever, headache, arthralgia and generalised weakness. In the blood the trypanosomes survive due to their remarkable

degree of antigenic variation that misdirects the immune response and leads to a gradual exhaustion of the patient's immune system. Accompanying the immune stimulation, lymph node enlargement is a common sign, especially in *T.b. gambiense* infection, and often the patients present with pruritus, general malaise, localised oedema and cardiac involvement.

This is followed by the central nervous system (CNS) invasion of the trypanosomes. As the disease progresses into the late meningoencephalitic stage, symptoms of the early haemolymphatic stage may persist and signs of the nervous system involvement become obvious. Clinically, the patients display disturbances of consciousness and reversal of the normal sleep-wake cycle in which daytime somnolence alternates with nocturnal insomnia ("sleeping sickness"). Characteristic of the disease are mental disturbances that may be subtle and include irritability, lassitude, personality changes and overt psychiatric presentations such as violence, hallucinations and mania. Motor system and sensory involvement are common and may manifest as tremors, speech impairment, abnormal movements and hyperaesthesia, respectively [WHO 1998]. The patient, if left untreated, progresses to the final stage of the disease, which is characterised by seizures, severe somnolence, coma and inevitable death. This progresses much more rapidly in the rhodesiense infection, causing the death of the patient within a couple of months. The gambiense form of the disease is characterised by low parasitaemia and a gradual onset of neurological symptoms and death more than 2 years after initial infection.

Diagnosis

The clinical presentation of the patient is very unspecific and diagnosis is not possible based only on the symptoms and signs. Diagnosis usually follows a sequential approach: a card agglutination test is used to identify patients with potential *T.b. gambiense* infections (CATT; [Magnus *et al.,* 1978]) while the indirect immuno-fluorescent test is used to detect *T.b. rhodesiense* (IFT; [Geigy *et al.,* 1975]); seropositive cases are confirmed by microscopic detection of the parasites in blood, lymph node aspirate and/or cerebrospinal fluid (CSF, [Woo 1969; Lumsden *et al.,* 1979; Bailey and Smith 1994]. Parasite detection is mandatory, as is the determination of the disease stage, for therapeutic decision and to prevent the patient from risks associated with treatment. Accurate staging is crucial because failure to treat a patient with CNS infection will inevitably lead to death from the disease, yet inappropriate CNS treatment in an early-stage patient carries a high risk of unnecessary drug toxicity. Therefore, the CSF is examined for either the presence of trypanosomes by concentration techniques (centrifugation, m-AECT, [Louis *et al.,* 2001] and/or an elevation of the white blood cell (WBC) count in CSF [WHO 1998]. However, the criteria have been challenged by some investigators [Doua *et al.,* 1996; Stanghellini and Josenando 2001; Lejon 2002] and thus, different cut-off values are used today in different countries: more than 5 cells/mm^3 in most countries, except for more or equal 10 WBC/mm^3 in Equatorial Guinea and more or equal 20 WBC/mm^3 in Angola and Côte d'Ivoire.

Recently, a very sensitive marker for CNS involvement –detection of intrathecal IgM synthesis- has been demonstrated and translated into a latex agglutination assay that is of high value for diagnosis in the field [Lejon *et al.,* 2003]. The CSF IgM quantification assay has considerable promise for both, staging sleeping sickness and monitoring relapsing from treatment.

After treatment, a patient is considered cured only when during a 2 year follow-up period no trypanosomes can be detected and/or the WBC counts in CSF were reduced to normal values and/or no reappearance of the clinical symptoms and signs were observed [WHO 1998].

Treatment

Sleeping sickness treatment relies on therapies that are unsatisfactory for several reasons [WHO 1998]. Four drugs are currently approved for the treatment of HAT, namely suramin, pentamidine, melarsoprol, and eflornithine. And nifurtimox, a drug which is registered for Chagas disease, is currently undergoing evaluation in combination therapy with approved drugs for HAT (Table 2). Most of these drugs were developed over 50 years ago and bear the disadvantages of either unacceptable toxicity, undesirable route of administration, limited efficacy, drug resistance, and/or lengthy treatment schedules. Furthermore, the treatment of sleeping sickness is complicated by the different disease stages: the selective permeability of the blood-brain barrier prevents most drugs from reaching levels in the CSF that can kill the parasites. However, a large fraction of infected people only seek treatment when the disease has already advanced to the late meningoencephalitic stage.

Early-stage disease is treated with suramin (Germanin®, Bayer) in rhodesiense infection and with pentamidine (Lomidine®, Aventis) in gambiense disease; both drugs are ineffective in treating the late-stage. Suramin was introduced in the early 1920s, it is administered by intravenous injections and adverse drug reactions include: vomiting, nausea, collapse, shock, and delayed reactions as kidney damage, exfoliative dermatitis, jaundice, severe diarrhoea, all of which can be fatal. Pentamidine, the drug of choice to treat early *T.b. gambiense* infections, was first introduced in the 1940s and the preferred and most effective route of administration is by intramuscular injections. It can cause damage to the liver, kidneys, and the pancreas, but generally only minor adverse reactions are observed. Despite their use over decades, so far no resistance to the two drugs has emerged [WHO 1998].

Melarsoprol (Arsobal®, Aventis) and eflornithine (Ornidyl®, Aventis) are effective for treatment of the late meningoencephalitic stage of the disease; however, melarsoprol is the only effective drug for both, rhodesiense and gambiense. Eflornithine has become increasingly the preferred therapy for gambiense infections, but is largely ineffective for rhodesiense infections [Iten *et al.,* 1995] and less effective in children [Milord *et al.,* 1993]. Although less toxic than melarsoprol, the drug is far from ideal: it is costly and difficult to administer, requiring four daily infusions for 14 days, demanding sophisticated equipment and well-trained staff and therefore of limited use in basic, rural treatment centres [Louis *et al.,* 2003; Burri and Brun 2003]. An oral formulation of eflornithine would be advantageous over the injectable form and greatly facilitate the practical use in resource-poor settings. Such development is currently subject of research and under clinical investigation [WHO 2001].

Nifurtimox (Lampit®, Bayer) is the only other potential alternative treatment for late-stage disease. It has been registered for the treatment of Chagas disease and is administered orally, but well-documented evidence of efficacy and safety for the treatment of HAT is still lacking. Its use is more likely to be in the context of combination therapy for melarsoprol refractory cases or when eflornithine is not available [Pepin *et al.,* 1989; Jennings 1990; Pepin *et al.,* 1992].

Table 2 Drugs for the treatment of human African trypanosomiasis

First Stage	**Introduction**	**Advantage**	**Problem**
Suramin	1920	*T. b. rhodesiense* and *T. b. gambiense*	No penetration into CSF
Pentamidine	1940	Few adverse reactions	Limited penetration into CSF *T. b. gambiense* only
Second stage		**Advantage**	**Problem**
Melarsoprol	1949	*T. b. rhodesiense* and *T. b. gambiense*	Adverse reactions Empirical schedules (Treatment duration)
Eflornithine (DFMO)	1981	Few adverse effects (Oral application possible)	Availability Affordability Logistics *T.b. gambiense* only
(Nifurtimox)	1972	*T. b. rhodesiense* and *T. b. gambiense*	Not registered Alone low efficacy Adverse reactions

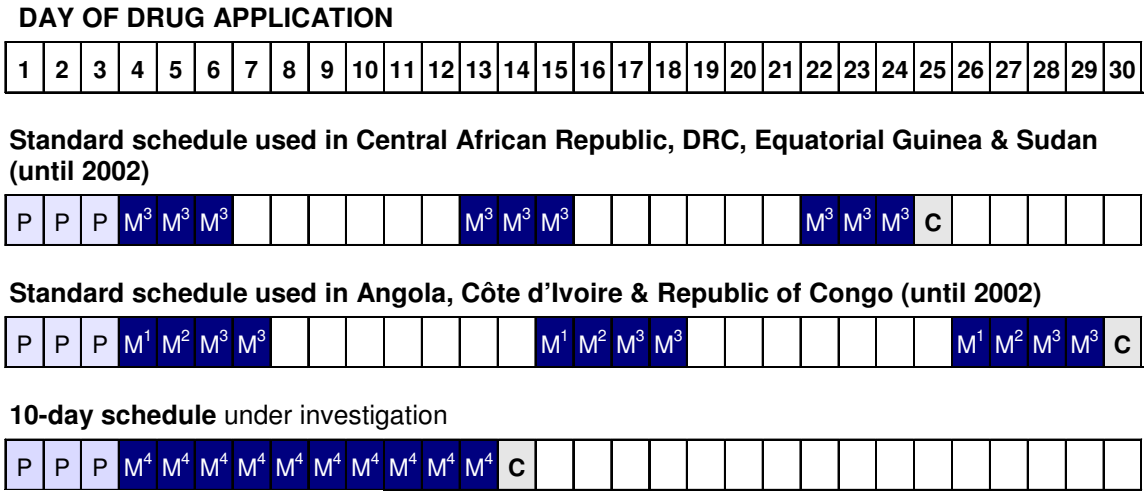
Melarsoprol

Melarsoprol is a trivalent organic arsenical that was introduced in 1949 [Friedheim 1949]. Today, it is still the most used drug to treat late-stage gambiense disease and the only drug for treatment of late-stage rhodesiense sleeping sickness, although it bears severe disadvantages. Although a high proportion of the patients are cured with standard regimens, there is evidence of an increasing failure rate, up to 30% in northern Uganda, northern Angola and southern Sudan [Legros *et al.,* 1999; Stanghellini and Josenando 2001; Moore 2001].

Melarsoprol is insoluble in water and must be given intravenously dissolved in propylene glycol, a solvent that is highly irritant to tissues. Adverse drug reactions of melarsoprol may be severe and life threatening. The most important is the encephalopathic syndrome that occurs in up to 10% of all treated patients, and which is fatal in 50–70% of the cases [Pepin and Milord 1994; WHO 1998]. The cause of this reaction has been discussed extensively in the past, but still remains a controversial issue and detailed mechanisms remain unknown [Haller *et al.,* 1986; Pepin and Milord 1994; WHO 1998]. Generally, an immune reaction is thought to underlie the syndrome [Haller *et al.,* 1986; Pepin *et al.,* 1989; Keiser *et al.,* 2000] and several additional factors are believed to be associated with the syndrome: concomitant infections, other anti-parasitic drugs, presence of trypanosomes in CSF and high white blood cell count in CSF, impaired nutritional status, seasonal variations and alcohol intake [Ancelle *et al.,* 1994; Pepin *et al.,* 1995; Blum *et al.,* 2001]. Other frequent reactions to melarsoprol include exfoliative and maculopapular skin reactions, polyneuropathies, tachycardia, fever, abdominal pain, diarrhoea, vomiting, pruritus, chest pain and headache. A local skin reaction at the injection site, thrombophlebitis and deep vein fibrosis, may occur due to the propylene glycerol solvent [WHO 1998].

Another major drawback of melarsoprol therapy is the specific treatment regimens that vary considerably among different countries and depending on whether the infection is due to *T.b. rhodesiense* or *T.b. gambiense*. The regimens are based on empiric development, and typically a course of 3 to 4 series of 3 to 4 i.v. injections of increasing doses every 24 hours spaced by rest periods of 6 to 10 days were given (Figure 2, [WHO 1998]). This empiric treatment regimen results in a long hospitalisation period of up to 30 days, which poses major social and economic burden to the patients and their accompanying relatives. Recently acquired knowledge about the pharmacokinetics of melarsoprol led to the suggestion of a concise 10-day treatment schedule [Burri *et al.,* 2000] that is currently being evaluated in a multicountry study (IMPAMEL program) and subject of this thesis.

Figure 2: Comparison of melarsoprol treatment schedules for late-stage sleeping sickness



P: anti-parasitic pre-treatment; M^1: 1.2 mg/kg melarsoprol; M^2: 2.4 mg/kg melarsoprol; M^3: 3.6 mg/kg (max 5 ml) melarsoprol; M^4: 2.2 mg/kg (max 5 ml) melarsoprol; C: treatment control examination

Impamel program

A major disadvantage of melarsoprol treatment is its long duration. 55 years after its market introduction [Friedheim 1949], the treatment regimens still vary considerably [WHO 1998] and are based on empiricism. To optimise and standardise the treatment with melarsoprol, a concise treatment regimen has been elaborated based on rational scientific investigations. Table 3 summarises the sequence of scientific investigations done by the Swiss Tropical Institute (group of Prof. Brun and Dr. Burri) prior to the clinical evaluation in patients. As a result, an abridged 10-day treatment protocol for melarsoprol has been proposed based on pharmacological investigations, animal experiments and pilot testing in sleeping sickness patients in the former Zaire. The favourable outcome of the pilot trial in 11 sleeping sickness patients in Vanga, DRC [Burri *et al.,* 1995] led to a large-scale randomised, controlled clinical trial in Angola, which assessed the efficacy and safety of the 10-day schedule in 500 patients (IMPAMEL I).

Impamel I: Clinical evaluation in patients in Angola

In an open, randomized equivalence trial conducted with 500 patients in Kwanza Norte, Angola from April 1997 to September 1998, the efficacy and safety of the new 10-day treatment schedule for melarsoprol were assessed (IMPAMEL I). The control group followed the 26-day standard national Angolan schedule of 3 series of 4 daily injections of melarsoprol at doses increasing from 1.2 to 3.6 mg/kg bodyweight within each series, with a 7-day rest between series (Figure 2). The new treatment schedule comprised 10 days of one daily injection of 2.2 mg/kg bodyweight. The outcome of this trial has recently been published [Burri *et al.,* 2000]. It could be shown that the new, concise schedule was equivalent to the standard protocol in its short-term efficacy, and that no difference was found for the primary safety outcomes (death in temporal relationship to treatment and rate of encephalopathic syndromes). A non-significant increase of skin reactions was observed under the 10-day schedule, possibly due to hypersensitivity reactions or drug accumulation in the skin. Other known adverse reactions (neuropathies, diarrhoea, fever, and headache) occurred at similar rates in both groups. During the follow-up, the number of patients who relapsed was comparable in both groups, suggesting the new schedule being equivalent to the standard protocol in its long-term efficacy as well. The follow-up has just been completed and was analysed in detail with regard to risk factors for relapsing (chapter 2).

Table 3 Sequence of scientific investigations to the development of the concise 10-day schedule for melarsoprol

Development of analytical methods	
	- Development of bioassay to determine melarsoprol in body fluids - Principle: in vitro killing of trypanosomes by active metabolites of melarsoprol [Burri and Brun 1992]
Drug metabolism and pharmacokinetics	
	- Determination of melarsoprol and metabolites concentrations in body fluids by HPLC method - Determination of pharmacokinetics in 19 patients of Côte d'Ivoire - Confirmation of melarsoprol and metabolite concentration in body fluids by atomic absorption spectrophotometry - Development of pharmacokinetic model [Burri *et al.,* 1993] [Bronner *et al.,* 1998] [Keiser *et al.,* 2000]
Computer modelling	
	- Topfit simulation for alternative treatment protocols based on established pharmacokinetics - Proposition of 10-day schedule [Burri *et al.,* 1993]
Validation in animal model	
	- 6 uninfected vervet monkeys treated with standard or 10-day schedule - Validation of model and confirmation of pharmacokinetics - Establishment of pharmacokinetics in CSF [Burri *et al.,* 1994]
Pilot testing in humans, DRC	
	- 11 late-stage *T.b. gambiense* patients in Vanga, DRC treated with 10-day schedule compared to 23 patients previously treated with standard schedule - Equivalent outcome in treatment and adverse events - Elevated fever, diarrhoea and skin reactions in test group - Comparable long-term efficacy at follow-up [Burri 1994] [Burri *et al.,* 1995]
IMPAMEL I: Clinical evaluation in patients in Angola	
	- Large-scale clinical trial - 500 patients, randomized, controlled - Standard 26-day schedule versus 10-day schedule - Result: proven non-inferiority in efficacy and safety [Burri *et al.,* 2000]

Impamel II: Confirmation under field conditions

The concise 10-day schedule has proved its non-inferiority in terms of safety and efficacy (adverse events, fatality, and parasite-free after therapy) in the large-scale clinical trial in Angola (IMPAMEL I; [Burri *et al.,* 2000]). Not surprisingly, the shorter course was well accepted by the patients and the treating staff through its practical application (no daily dose adjustments and no rest periods). Additionally, the short treatment course bears several socio-economic advantages, like a reduction of total time spent in hospital per patient, a decrease of the total amount of drug per patient, and an increase of the hospital capacity. In the view of changing recommendations and harmonising the treatment for late-stage gambiense sleeping sickness with melarsoprol among the endemic African countries, the promising outcome of the large-scale trial in Angola led to an expansion of the evaluation in several African countries under field conditions (IMPAMEL II program).

Aim and objectives of the IMPAMEL II program

The IMPAMEL II programme aims at the clinical assessment in different populations of the new, concise schedule for melarsoprol (Arsobal®) treatment of late-stage sleeping sickness, developed under IMPAMEL I, by

- Monitoring on the basis of a questionnaire the outcome of treatment in selected centres in different endemic countries after introduction of the new protocol.
- Assessing risk factors for an adverse outcome of late-stage sleeping sickness treatment with melarsoprol ten days schedule.

Further, some additional goals of the IMPAMEL II program were defined aiming at the assessment of the overall effectiveness of the 10-day treatment schedule, these were:

- To compare the cost-effectiveness of the new and the standard treatment schedules.
- To elaborate in collaboration with WHO comprehensive guidelines on the treatment of African sleeping sickness, including the management of adverse events and provide recommendations for the treatment of non-responders.
- To establish in collaboration with national Trypanosomiasis Control Programs and WHO, in the framework of the Programme Against African Trypanosomiasis (PAAT) and the WHO Human African Trypanosomiasis Treatment and Drug Resistance Network, a database for clinical data with spatial reference.

OBJECTIVES

The presented Ph.D. thesis was done in the frame of the IMPAMEL II programme. The aim of the thesis was to appraise the overall effectiveness of the 10-day treatment schedule for melarsoprol under natural conditions, by following the specific objectives:

- To evaluate the long-term efficacy of the 10-day melarsoprol schedule under controlled conditions (IMPAMEL I, chapter 1)
- To assess the safety and efficacy of the10-day melarsoprol schedule under natural field conditions (IMPAMEL II, chapter 2)
- To study the influence of concomitant infections on the disease progression and treatment outcome (chapter 3)
- To assess the safety and efficacy of the 10-day schedule for children below 15 years of age (chapter 4)
- To perform an economic analysis to provide a sound basis for the cost-effectiveness of the 10-day treatment schedule (chapter 5)

STUDY DESIGN (METHODS)

General design

IMPAMEL II was a non-controlled, multinational, multi-centre drug utilisation study to evaluate the abridged treatment schedule of melarsoprol in late-stage *T.b. gambiense* sleeping sickness patients under true field conditions. A very simple study design without randomisation and sample size calculation was decided due to the limited number of centres with good accessibility and security with a sufficiently large number of patients to conduct clinical trials and the generally very basic equipment of rural sleeping sickness treatment centres. Additionally, the staff in such remote treatment centres are normally not trained for clinical trials.

Based on data of previous years provided by the national sleeping sickness programs and NGOs, we could assume more than 2000 patients to be treated in this program (Table 4).

Centre selection

The assessment was performed in centres (facilities) that were suggested by the responsible national sleeping sickness programs, or NGO's where applicable, of different countries with endemic *T.b. gambiense.* The national programs of Angola, Central African Republic, Côte d'Ivoire, Democratic Republic of Congo, Equatorial Guinea and Republic of Congo and NGOs in Republic of Congo and South Sudan agreed to participate with several centres in the IMPAMEL II program (Table 4). The national program of Uganda initially agreed to participate but at the time of the study start the program has shifted first-line treatment of late-stage patients to eflornithine and thus was unable to contribute a centre.

The criteria for the centre selection were: good accessibility of the centre, provision of reliable retrospective data on the standard treatment of melarsoprol for at least one year prior to the study period and the exclusive use of the new treatment schedule for melarsoprol for all late-stage gambiense sleeping sickness patients. The enrolment period for each centre was 12 months to balance seasonal variations [Ancelle *et al.,* 1994].

Patient inclusion

The single inclusion criterion for a patient was confirmed late-stage sleeping sickness due to *T.b. gambiense* according to the criteria of the respective national sleeping sickness control programs or NGOs. These were: diagnosis of late-stage by microscopic examination of the cerebrospinal fluid (CSF) for the presence of trypanosomes and/or an elevated white blood cell (WBC) count. Several cut-off criteria for the WBC in CSF for the different countries

existed: more than 5 WBC/mm^3 in the Central African Republic (CAR), Democratic Republic of Congo (DRC), Republic of Congo (RoC) and Sudan, more or equal 10 WBC/mm^3 in Equatorial Guinea, and more or equal 20 WBC/mm^3 in Angola and Côte d'Ivoire [WHO 1998]. For each patient a case report form was filled, that contained demographic, diagnostic and clinical characteristics before and after treatment, and an assessment of adverse events during melarsoprol treatment on a graded scale from 0 to 2 (none, moderate, severe reaction).

Table 4 Expected number of patients to be treated in the IMPAMEL II program, estimates were provided by the participating countries / organisations and projections are based on retrospective data available from the selected centres

Country **Authority / Organisation**	**Suggested centres**	**Expected number of patients (1 year)**
Angola	Viana	
Instituto de Combate e de Controlo da Tripanossomíase ICCT)	Dondo, N'Dalatando Caxito Uige	500 - 1000
Congo Brazzaville	Brazzaville	
Programme National de Lutte Contre la Trypanosomiase	Mossaka Gamboma	> 30
MSF Holland		
Côte d'Ivoire		
Programme National de Lutte Contre la Trypanosomiase	Daloa	na
Democratic Republic of Congo	CDTC Maluku	
Programme National de Lutte Contre la Trypanosomiase Humaine Africaine	CNPP/CUK Kinshasa CDTC Kionzo	> 500
Equatorial Guinea	Mbini	
Centro de control de Tripanosomiasis (Collaboration with Fundació CIDOB)	Kogo	30
Central African Republic		
Programme National de Lutte contre la Trypanosomiase Humaine Africaine	Batangafo	30
Sudan (Southern)	LiRangu	
International Medical Corps (IMC)	Tambura	> 900
MSF Switzerland	Ibba	
	Kajo Keji	
Uganda	Moyo	
National Sleeping Sickness Control Program	Adjumani	> 200
7 countries	**19 centres**	**2200-2700 patients**

Ethical considerations

The study was approved by the ethics committee of the two cantons of Basel (EKBB) and the relevant ethics committees and authorities in the respective countries. In the selected centres the abridged schedule was introduced as the standard treatment and therefore no consent was obtained from the patients.

Treatment

All patients were treated with 2.2 mg/kg/day melarsoprol for 10 days, as a 3.6% solution in propylene glycol, by slow intravenous injection. Before melarsoprol treatment, all patients received anti-parasitic medication, multivitamins and paracetamol (acetaminophen) after the lumbar puncture. During melarsoprol treatment, prophylactic corticosteroid therapies were given according to the national guidelines.

Adverse events were treated following the national guidelines, and in case of a severe adverse drug reaction, the treatment with melarsoprol was suspended and the patient treated accordingly and if possible, the melarsoprol treatment was resumed after 1 to 3 days, or considered completed if at least 8 doses were given.

Outcome measures of efficacy

Efficacy of the treatment was demonstrated by microscopic examination of the blood and/or lymph and CSF for the absence of trypanosomes and/or a reduction of the white blood cells. Patients were scheduled for clinical examination including lumbar puncture 24 hours after treatment and every 6 months during 2 years after treatment to monitor for treatment failures and relapses. Treatment failures were defined as cases in which trypanosomes could still be found in any body fluid 24 hours after treatment (primary efficacy outcome) and relapses (secondary efficacy outcome) as patients presenting at any time during the follow-up with trypanosomes in any compartment. Suspected relapses were patients who presented at any follow-up examination with an increased WBC count to more than 50 cells/mm^3 and have doubled compared to previous examination or if the WBC count was 6 to 49 cells/mm^3 and clear symptoms attributed to relapse (somnolence, long lasting headache, recurrent fever) were present.

Outcome measures of safety

The safety of the treatment was determined by the frequency of adverse events. The primary safety outcomes were death in temporal relation to treatment and the frequency of

encephalopathic syndromes. The rate of other severe adverse reactions (skin reactions, sensory and motor neuropathies) was defined as secondary outcome. The observation time for adverse events that were temporally related to the treatment was defined as from treatment start to hospital discharge (irrespective of the duration of hospitalisation).

Follow-up

Each patient was scheduled for clinical examination including lumbar puncture every 6 months during 2 years after treatment to monitor for relapses. In addition to the regular case report forms, a follow-up form had to be filled for each patient.

Conduct, responsibilities and monitoring

The Swiss Tropical Institute had the overall responsibility of project execution. This included the design of the study, administrative aspects (coordination, communication, reporting) and the scientific evaluation and documentation of the study.

On national levels, the program was coordinated with the sleeping sickness programs, or the NGO's responsible for treatment where applicable. Locally, the execution of the project was the responsibility of the regular staff of the respective organisations. Apart from the introduction of a different treatment schedule and a case report form to fill per patient, a minimum of changes of existing structures and organisation was attempted. Each treating organisation was responsible for the correct follow-up of the patients according to the rules of the respective national authority.

Ethical clearance in the respective countries for the conduct of the study was the responsibility of the national sleeping sickness control authorities.

A data and safety monitoring board (DSMB) of experts was created to monitor the progress of the program on an annual basis and to evaluate cases of severe adverse events.

Data Management and statistical analysis

Data Management was done using EpiData 2.1 software [Lauritsen and Bruus 2001] and analysis with the statistical software package STATA 7.0 [Stata 2001]. The findings were compared to retrospective data of the participating centres, to literature and to the randomised clinical trial recently executed in Angola [Burri *et al.,* 2000]. For the calculation of the efficacy, all patients treated were used as denominator to allow the comparison to previously reported rates.

PART 2: IMPAMEL I - LONG-TERM EFFICACY UNDER CONTROLLED CONDITIONS

CHAPTER 1

Efficacy of 10-day melarsoprol schedule 2 years after treatment for late-stage gambiense sleeping sickness

Caecilia Schmid[1], Sebastiao Nkunku[2], Ada Merolle[3], Penelope Vounatsou[1], Christian Burri[1]

[1]Swiss Tropical Institute, Basel, Switzerland; [2]WHO EHA/DES/AFRO, Brazzaville, Republic of Congo;

[3]Norwegians Peoples Aid, Luanda, Angola

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In 2000, we reported that a new short treatment schedule of melarsoprol was not worse than the longer and demanding standard treatment for late-stage human African trypanosomiasis. This alternative schedule was assessed in an open, randomised clinical equivalence trial of 500 patients in Angola. 24 h after treatment, all patients were parasite free. Of 442 patients, 12 (3%) had relapsed after one year, of whom 7 (3%) had had standard treatment and 5 (2%) the alternative treatment. After 2 years, 23 (5%) relapsing patients were reported, 11 (5%) in the standard treatment group and 12 (6%) in the new group. The results at the 2 year follow-up support and strengthen our previous findings.

Melarsoprol is still the first-line drug for treatment of late-stage human African trypanosomiasis. After 50 years of this empirical treatment, an alternative short therapy was tested in an open, randomised clinical equivalence trial of 500 patients in two Angolan trypanosomiasis treatment centres (Cassoalala, Dondo) [Burri *et al.,* 2000]. The clinical efficacy and safety of the alternative schedule was compared with that of the national standard treatment. Patients gave informed consent. The study protocol was approved by the review board of the Swiss Tropical Institute, the ethics committee of the University Hospital, Basel, Switzerland, and the ethics committee of the Ministry of Health, Luanda, Angola. The alternative treatment consisted of ten injections (2.2 mg/kg bodyweight) on consecutive days. Standard treatment consisted of three series of four consecutive injections of melarsoprol at doses increasing from 1.2 to 3.6 mg/kg bodyweight within each series; injections were given every 24 h, with a 7-day rest between the series. Parasitological cure 24 h after treatment was 100% in both groups, and frequency and type of adverse events did not differ.

We have now followed the patients for 2 years, as recommended by WHO [WHO 1998]. Patients were examined every 6 months after treatment. At all examinations a lumbar puncture was done and blood samples were taken. Blood and cerebrospinal fluid (CSF) were examined for trypanosomes and CSF for white blood cell count. Patients who did not attend were visited in the village and interviewed about their health status. Those not seen at a treatment centre or not interviewed at least once were regarded as lost to follow-up. Relapses were defined as patients with trypanosomes in CSF (or blood), or patients with a CSF white blood cell count of more than 50 cells per μL, which had at least doubled since the previous examination. Generally, the infection rate for sleeping sickness is low, and we did not have the technology to identify reinfections. Therefore all treatment failures were regarded as relapses.

We compared cure rates at 24 h and at 2 years after melarsoprol treatment, expressed as percentages of all parasite-negative patients who survived, irrespective the last time point of follow-up. Only 46 (9%) of patients treated had a CSF-confirmed infection, and 188 (38%) had a CSF white blood cell count of 6 -19 cells per µL (standard treatment 102 [41%], alternative treatment 86 [34.4%]). This distribution could lead to a general underestimation of the relapse rate in this trial. Cure rates were compared by Blackwelder's [Blackwelder 1982] method to test for equivalency, with the one-sided null hypothesis as follows: H_0: $\theta \geq \delta$ (where θ is the difference of the success measures between the standard and the alternative treatments, and δ the specified difference between the efficacy of the two treatments of no more than 5%). Time to relapse was calculated with a modified formula of Blackwelder (SAS [Atherton Skaff and Sloan]).

Of the 500 patients in the original trial, 483 had been discharged as cured (table). Patient baseline characteristics were similar for the two treatment regimens in both treatment centres. Despite the difficult political situation in Angola, 426 (88%) patients returned for at least one lumbar puncture during follow-up. 413 (86%) patients were seen at least once during the first year (391 [81.%] lumbar puncture, 22 [5%] interview). 301 (63%) patients were seen during the second year of follow-up (295 [61%] lumbar puncture, 6 [1%] interview). The compliance of patients with follow-up was acceptable, although it was lowest in the alternative treatment group towards the end of the 24 months.

The cure rates of the two treatment schedules at discharge and at 2 years after treatment were much the same (table). During the 2 years of follow-up, 14 (3%) deaths were reported, one in each group being due to late complications of trypanosomiasis. Of the survivors, 23 were deemed to have relapsed. In eight relapsing patients (35%; five [45%] on standard treatment; three [25%] on alternative treatment) trypanosomes were identified in CSF or blood. All other cases were diagnosed because of substantially raised CSF white blood cell counts. 12 (3%) of the relapses were diagnosed in the first year of follow-up and 11 (3%) in the second year. The mean time to relapse was 345 days (SD 210) since the end of treatment (standard treatment 314 days [SD 192]; alternative treatment 392 days [SD 203]) and time to relapse differed between the two treatment schedules (θ=-78 days; 95% CI -∞ to 57.5, p=0.128). There was no evidence of increased risk of relapsing in the study population (23/442 [5%]) compared with rates reported earlier in this area (2/56 [3.5%] [Ruiz *et al.,* 2002]), and the rates did not differ between the schedules.

Irrespective of treatment schedule, several factors present on admission were associated with an increased risk of treatment failure: previous treatment for trypanosomiasis; CSF white blood cell count greater than 100 cells per µL; and trypanosomes in CSF. These findings accord with previously described risk factors for treatment failure after melarsoprol [Legros *et*

al., 1999]. Of the enrolled patients, 42 (standard treatment 19, alternative treatment 23) had been treated for HAT during the 24 months (median 15 months) before the trial, half with melarsoprol. Patients who had been treated previously for trypanosomiasis were at increased risk to relapse (risk ratio 5.8 [95% CI 2.5–13.7]; p=0.0003). A CSF white blood cell count of more than 100 cells per µL on admission was an important determinant of relapse (8.2 [2.8–19.7]; p<0.0001). Trypanosomes in CSF were seen in 46 of 500 patients at admission, and nine individuals subsequently relapsed (7.6 [2.8–13.8]; p=0.0002). Other factors associated with a higher risk of relapse in this study were: patients with a reduced level of consciousness at admission (2.6 [1.1–5.8]; p=0.036); body mass index less than 18.5 (2.8 [1.1–6.4]; p=0.025); and treatment at the Dondo centre (3.8 [1.1–11.9]; p=0.041). In both groups, some patients had deviated from the treatment schedules [Burri *et al.,* 2000] (standard treatment 89, alternative treatment 44), but this deviation did not have a significant effect on the later risk of relapse (1.2 [0.5–2.9]; p=0.853).

Our results accord with the conclusion from our previous trial and provide evidence for the long-term effectiveness of the alternative treatment. The alternative schedule has proved as safe and effective as the standard schedule, and even though a lower total dose of melarsoprol was given, it did not increase the risk of treatment failure. The new regimen is a major advance over conventional regimens: it shortens time in hospital and leads to a reduction in melarsoprol dosage and costs. There is evidence that the alternative treatment is equal to the standard treatment in terms of safety and efficacy. A large-scale multinational trial is underway to corroborate these results.

Contributors

C Schmid did the statistical analysis and wrote the manuscript. S Nkunku and A Merolle were responsible for examination of the patients and data collection. P Vounatsou gave specialist advice on statistical aspects and supervised the analysis. C Burri was responsible for the study design and the conduct of the trial. Conflict of interest: None declared.

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Table: Treatment outcome and results of follow-up after melarsoprol treatment, by treatment schedule

	Standard schedule (S)			Alternative schedule (A)			Difference*	95% CI†	p‡
	n	N	%	n	N	%	θ (%)		
Treatment outcome									
Number of patients treated		250			250				
Cure rate at discharge§	239	250	95.6	244	250	97.6	-2.0	-100, 0.7	<0.0001
Follow up (24 months)									
Compliance during follow up¶	224	239	93.7	218	244	89.3	4.4	-100, 8.5	0.403
Number of patients seen for lumbar puncture	219	239	91.6	207	244	84.8	6.8	-100, 11.6	0.731
Compliance ≤12 months¶	208	239	87.0	205	244	84.0	3.0	-100, 8.3	0.267
Compliance 13 - 24 months¶	166	239	69.5	135	244	55.3	14.1	-100, 21.3	0.982
Survival during follow up	216	224	96.4	212	218	97.2	-0.8	-100, 1.9	0.0002
Survival ≤ 12 months	220	224	98.2	214	218	98.2	0.0	-100, 2.1	<0.0001
Survival 13 - 24 months	220	224	98.2	216	218	99.1	-0.9	-100, 0.9	<0.0001
Non-relapse during follow up	213	224	95.1	206	218	94.5	0.6	-100, 4.1	0.019
Non-relapse ≤ 12 months	217	224	96.9	213	218	97.7	-0.8	-100, 1.7	<0.0001
Non-relapse 13 - 24 months	220	224	98.2	211	218	96.8	1.4	-100, 3.9	0.008
Cured 24 months after treatment**	205	224	91.5	200	218	91.7	-0.2	-100, 4.1	0.024

Patient baseline characteristics and demographics are published in reference 1. n=number of affected individuals. N=Treatment group total. *Percentage difference of the outcome of standard and alternative schedules. †According to method of Blackwelder.[3] ‡Left-hand sided p-value, a p-value smaller than 0.05 indicates equivalence between the standard and the alternative schedule. §Percentage of parasite-negative patients. ¶At least one lumbar puncture or oral interview in the respective period. **Number of patients seen at least once during follow up for which no report about a relapse or death was made.

PART 3: IMPAMEL II – EFFECTIVENESS UNDER NATURAL CONDITIONS, A MULTINATIONAL EVALUATION

CHAPTER 2

Effectiveness of the 10-day melarsoprol schedule for the treatment of late-stage human African trypanosomiasis: Confirmation from a multinational study (IMPAMEL II)

Caecilia Schmid[1], Michaleen Richer[2], Constantin Miaka Mia Bilenge[3], Theophile Josenando[4], Francois Chappuis[5], Claude R. Manthelot[6], Auguste Nangouma[7], Félix Doua[8], Pedro N. Asumu[9], Pere P. Simarro[10] and Christian Burri[1]

[1]Swiss Tropical Institute, Basel, Switzerland ; [2]International Medical Corps, Nairobi, Kenya ; [3]Programme Nationale de Lutte contre la Trypanosomiase Humaine Africaine, Kinshasa, Democratic Republic of Congo; [4]Instituto de Combate e de Controlo das Tripanossomíases, Luanda, Angola ; [5]Médécins sans Frontières, Geneva, Switzerland ; [6]Programme National de Lutte contre la Trypanosomiase, Brazzaville, Republic of Congo ; [7]Programme National de Lutte contre la Trypanosomiase Humaine Africaine, Bangui, République Centrafricaine ; [8]Projet de Recherche Clinique sur la Trypanosomiase, Daloa, Côte d'Ivoire ; [9]Programo Nacional de Control de Tripanosomiasis, Bata, Equatorial Guinea ; [10]CIDOB, Barcelona, Spain

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ABSTRACT

Background

Treatment of late-stage human African trypanosomiasis with melarsoprol can be substantially improved by abridging the treatment regimen. A previous large-scale controlled clinical trial had demonstrated non-inferiority of a new 10-day treatment schedule for melarsoprol. We now demonstrated the effectiveness of this abridged treatment in a non-controlled multinational drug utilisation study (IMPAMEL II).

Methods

2020 late-stage gambiense sleeping sickness patients were treated with the 10-day melarsoprol schedule in 16 centres of 7 African countries. The outcome was assessed based on the major adverse events and the cure rate after the treatment and a 2 years follow-up period.

Results

In average, the cure rate 24 hours after treatment was 93.9%. The effectiveness two years after treatment was 86%, but many patients did not attend any follow-up examination (46.3%). The overall fatality rate was 5.9%. Eight percent of the treated patients suffered from an encephalopathic syndrome, with a fatal outcome in 45.5%. The rate of severe bullous or maculopapular eruptions was 7.3%. All results showed the expected inter-centre variation

Conclusions

The treatment outcome of this study is very similar to the previously conducted controlled trial, to the retrospective data available from the centres and to literature. The 10-day treatment with melarsoprol has several advantages over the standard national treatment schedules: It reduces treatment duration, drug amount and hospitalisation costs per patient and it increases the treatment centres' capacity. The abridged protocol was recommended by the 27th ISCTRC as the standard schedule for melarsoprol treatment of late-stage sleeping sickness due to *T.b. gambiense.*

BACKGROUND

Human African Trypanosomiasis (HAT or sleeping sickness) ranks 3rd of all parasitic diseases in sub-Saharan Africa behind malaria and filariasis [WHO 1998] in terms of disease burden expressed in DALYs [2004]. Sixty million people in 36 African countries are at risk of becoming infected and the number of cases is estimated at 350'000 [WHO 1998]. Currently, only a fraction of the population at risk is under surveillance and therefore the 50'000 cases reported and treated per year may be a significant underestimation. Sleeping sickness is caused by the protozoan parasite *Trypanosoma brucei* sp. and is transmitted by the bite of the tsetse fly *Glossina* sp. [Burri and Brun 2002].

HAT occurs in two distinct forms: a chronic form due to *Trypanosoma brucei gambiense* and an acute form due to *Trypanosoma brucei rhodesiense*, whereof *T.b. gambiense* currently represents 99.5 percent of the cases [WHO 1998; Burri and Brun 2002]. In the early haemo-lymphatic disease stage the trypanosomes multiply in blood and lymph glands, followed by central nervous system (CNS) invasion, corresponding to the late or meningo-encephalitic disease stage. Without treatment, the disease is invariably fatal.

Today, two drugs are available for the treatment of the late-stage of HAT, eflornithine and melarsoprol. Eflornithine is difficult to administer, requires good logistics, and is expensive to manufacture. Therefore, it is of very limited use in rural treatment centres. In addition, it is ineffective against the acute form of the disease (*T.b. rhodesiense*). For those reasons and the lack of alternatives, melarsoprol, an organo-arsenic drug which is highly toxic and does not have a 100% cure rate [Legros *et al.,* 1999; Stanghellini 2000], still remains the main drug for the treatment of late-stage HAT. A major problem of melarsoprol treatment is its long duration. 55 years after its market introduction, the treatment regimens vary considerably [WHO 1998]. Generally, 3 to 4 series of 3 to 4 injections of increasing doses spaced by rest periods of 7 to 10 days were given. To optimise and standardise melarsoprol treatment, an abridged 10-day protocol has been elaborated based on pharmacological investigations [Burri and Brun 1992; Burri *et al.,* 1993; Burri 1994], animal experiments [Burri *et al.,* 1994] and pilot testing in sleeping sickness patients in the former Zaire [Burri *et al.,* 1995]. Its non-inferiority in terms of safety and efficacy to standard treatment regimen was shown in a large-scale randomised clinical trial in Angola [Burri *et al.,* 2000; Schmid *et al.,* 2004]. Treatment of sleeping sickness is often done in very basic centres in remote areas. To assess the effectiveness of the 10-day melarsoprol regimen under such conditions we carried out a multinational, multicentre drug utilisation study for the treatment of late-stage *T.b. gambiense* sleeping sickness.

METHODS

Centres and patients

The study was implemented in 16 sleeping sickness treatment centres suggested by the respective national sleeping sickness programs, or NGO's where applicable, of 7 sub-Saharan African countries with endemic *T.b. gambiense*. The minimal conditions for the centre selection were: reasonable accessibility, availability of retrospective data on HAT treatment for at least 12 months and the exclusive use of the new treatment schedule during the enrolment period of 12 months.

Study design and implementation

There are only few centres with good accessibility, security, sufficiently large number of patients to conduct clinical trials, and the equipment of rural sleeping sickness treatment centres is minimal and the staff is not trained for clinical trials. Therefore, a very simple study design without randomisation and sample size calculation was chosen. The enrolment period for each centre was 12 months to balance seasonal variations. The study was approved by the ethics committee of the two cantons of Basel (EKBB) and the relevant ethics committees and authorities in the respective countries. In the selected centres the abridged schedule was introduced as the standard treatment and therefore no consent was obtained from the patients.

Inclusion criterion was confirmed late-stage gambiense sleeping sickness according to the criteria of the respective national sleeping sickness control program. Diagnosis of late-stage was done by microscopic examination of the cerebrospinal fluid (CSF) for the presence of trypanosomes and/or an elevated white blood cell (WBC) count. Different cut-off criteria for the WBC in CSF were used: > 5 WBC/mm^3 in the Democratic Republic of Congo, Republic of Congo and Sudan; ≥ 10 WBC/mm^3 in Equatorial Guinea; ≥ 20 WBC/mm^3 in Angola and Côte d'Ivoire.

Treatment

Patients were treated with 2.2 mg/kg/day melarsoprol for 10 days, as a 3.6% solution in propylene glycol (Arsobal® Aventis), by slow intravenous injection. Before melarsoprol treatment, all patients received supplementary medication: antimalarials (3 days chloroquine or Fansidar or 7 days quinine), mebendazole, multivitamins and paracetamol (acetaminophen). During melarsoprol treatment, different prophylactic corticosteroid therapies were given: prednisolone at a dose of 1 mg/kg on days 1-7, 0.75 mg/kg on day 8,

0.5 mg/kg on day 9 and 0.25 mg/kg on day 10 in Democratic Republic of Congo (Maluku and Kionzo), in Equatorial Guinea and in Sudan (Kajo Keji and some patients in LiRangu and Tambura); 1 mg/kg on days 1-9, 0.75 mg/kg on day 10, 0.5 mg/kg on day 11 and 0.25 mg/kg on day 12 in Angola; 1 mg/kg on days 1-9, 0.75 mg/kg on day 10 and 0.5 mg/kg on day 11 in Central African Republic; 0.75 mg/kg on days 1-10 in the Republic of Congo; 1 ml bethamethasone in Côte d'Ivoire; no prednisolone but promethazine (antihistamine) on days 1-10 was given to the patients in one centre of the Democratic Republic of Congo (CNPP/CUK Kinshasa).

In case of a severe adverse event or encephalopathic syndrome, the treatment with melarsoprol was suspended and the patient was treated following the national guidelines, e.g. with adrenaline (epinephrine), corticosteroids (usually hydrocortisone) and/or diazepam. If possible, the melarsoprol treatment was resumed after 1 to 3 days, or considered completed if already 8 or more doses were given.

For each patient a case report form was filled, which contained demographic, diagnostic and clinical characteristics before and after treatment, and an assessment of adverse events on a graded scale from 0 to 2 (none, moderate, severe reaction).

Outcome measures

Efficacy of the treatment was demonstrated by microscopic examination of the blood and/or lymph and CSF for the absence of trypanosomes and/or a reduction of the white blood cells. Patients were scheduled for clinical examination including lumbar puncture 24 hours after treatment and every 6 months during 2 years after treatment to monitor for treatment failures and relapses. Treatment failures were defined as cases in which trypanosomes could still be found in any body fluid 24 hours after treatment, relapses as patients presenting at any time during the follow-up with trypanosomes in any compartment and/or an increase of the WBC in CSF to more than 50 cells/mm^3 or have a duplication of WBC compared to the previous examination with clear symptoms attributed to relapse (somnolence, long lasting headache, recurrent fever). The primary efficacy outcome was parasitological cure 24 hours after treatment (treatment failures) and the secondary relapsing within the follow-up period.

The safety of the treatment was determined by the frequency of adverse events. The primary safety outcomes were death in temporal relation to treatment and the frequency of encephalopathic syndromes. The rate of other severe adverse reactions (skin reactions, sensory and motor neuropathies) was defined as secondary outcome.

Data Management and statistical analysis

All data were double entered and verified using EpiData 2.1 [Lauritsen and Bruus 2001] software and analysis was done with the statistical software package STATA 7.0 [Stata 2001]. The findings were compared to historic data from the participating centres, to literature (Table 4) and to the randomised clinical trial recently executed in Angola [Burri *et al.,* 2000; Schmid *et al.,* 2004]. For calculation of the efficacy the totality of the patients treated were used as denominator to allow the comparison to previously reported rates.

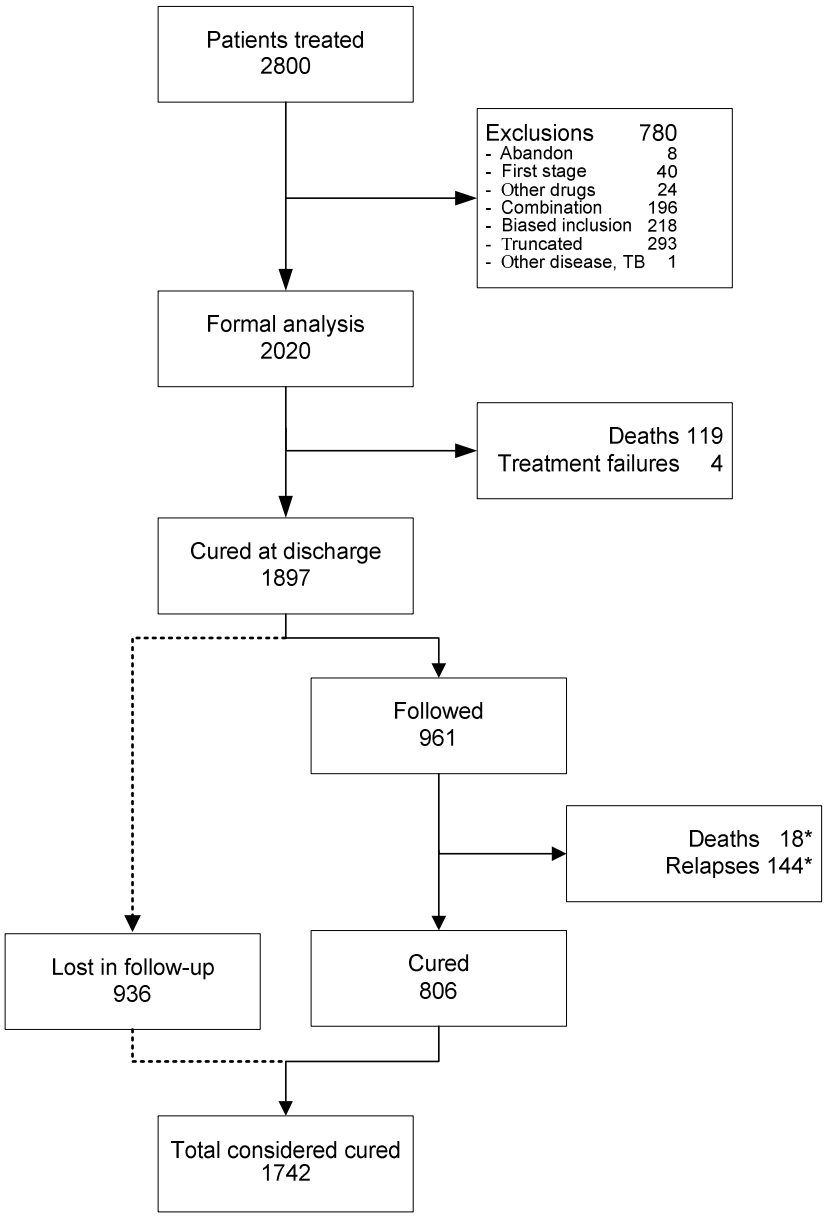
RESULTS

Study population and baseline characteristics

A total of 2800 patients were enrolled between June 1999 and June 2002. 780 patients were not eligible for the analysis (Graph 1) due to erroneous classification (early stage patients, tuberculosis case), abandon during treatment, other treatment than 10-day melarsoprol schedule (eflornithine, nifurtimox or combination therapy), biased inclusion (selected enrolment of patients in good health state or restriction to adults only) or centres enrolling for less or more than 12 months (in the latter centres the data were truncated to the first 12 months). The final cohort analysed consisted of 2020 patients correctly diagnosed and treated according to protocol with or without treatment interruptions from 10 sleeping sickness treatment centres of 5 countries.

The demographic, diagnostic and clinical characteristics of the patients are shown in Table 1. Age, sex and nutritional status distributions at admission were similar in the patients from the different centres. The diagnostic findings varied from centre to centre probably influenced by different methodology and cut-off criteria. The majority of the patients presented with lymphadenopathy, headache, pruritus, general weakness and sleeping disorders but a large variation of clinical manifestations between the centres was evident. Concomitant infections were frequent, in 70% of all patients at least one other parasitic infection apart from sleeping sickness was diagnosed (malaria, schistosomes, filaria, amoeba, giardia, geohelminths or hookworms), but not all patients were systematically screened for those diseases, causing a high grade of missing data (data not presented).

Graph 1: Study profile of IMPAMEL II



*7 of the relapses died during follow-up and are also included in the deaths during follow-up

Table 1: Pre-treatment characteristics of the patients

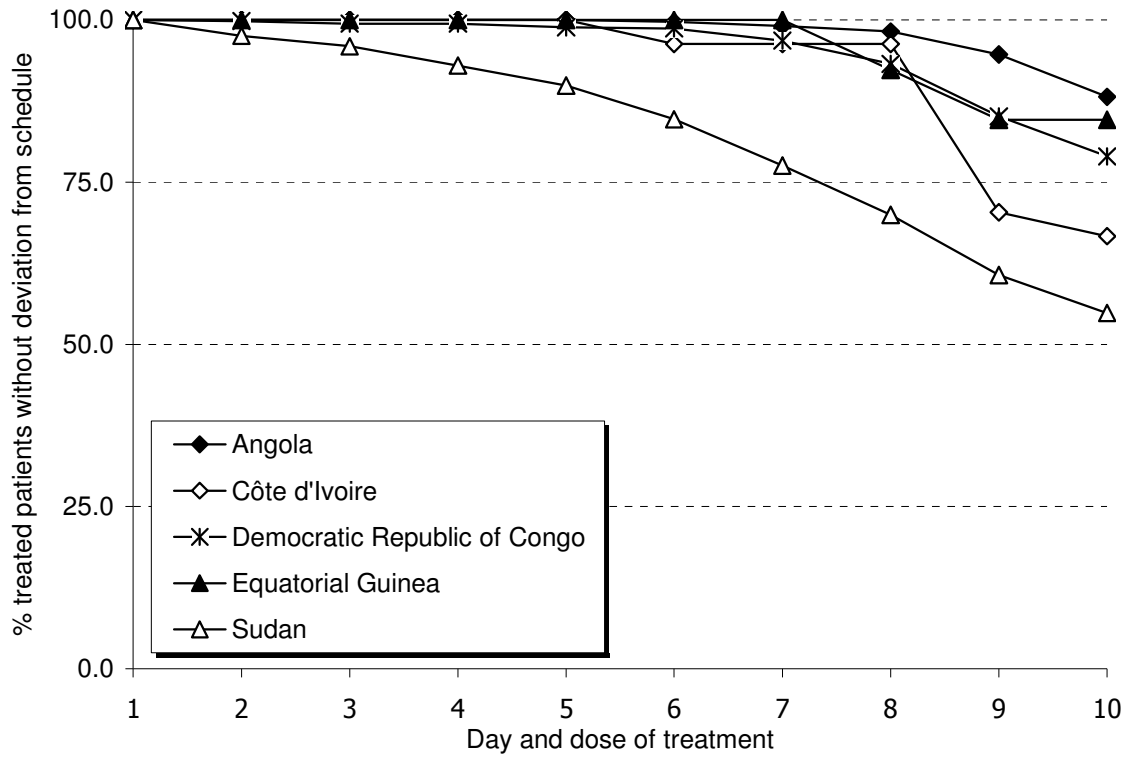
	Total (N = 2020)	Angola (N = 337)	Côte d'Ivoire (N = 27)	Dem Rep Congo (N = 532)	Equatorial Guinea (N = 13)	Sudan (N = 1111)
Age (years)						
Median	27	25	15	30	30	26
Range	1 - 80	1 - 74	2 - 51	1 - 80	11 - 64	1 - 70
Male Sex - no. (%)	988 (49)	177 (53)	13 (48)	261 (49)	9 (69)	528 (48)
Nutritional status						
Body Mass Index (BMI, kg/m^2) - mean ± SD	18.5 ± 3.1	18.2 ± 3.4	17 ± 2.7	18.8 ± 3.6	19 ± 2.9	18.4 ± 2.8
Severe malnutrition (BMI<16.5)* - no. (%)	551 (27)	115 (34)	7 (26)	153 (29)	5 (38)	271 (24)
Previous HAT treatment** - no. (%)	151 (7)	17 (5)	8 (30)	17 (3)	0 (0)	109 (10)
thereof Arsobal - no. (%)	45 (30)	1 (6)	1 (13)	12 (71)	0 (0)	31 (28)
Diagnostic findings						
Lymphadenopathy - no. (%)	1178 (58)	192 (57)	9 (33)	288 (54)	13 (100)	676 (61)
Trypanosomes in any compartment - no. (%)	1755 (87)	278 (82)	27 (100)	508 (95)	12 (92)	930 (84)
Trypanosomes in CSF - no. (%)	816 (40)	227 (67)	25 (93)	229 (43)	6 (46)	329 (30)
Trypanosomes in blood / lymph - no. (%)	1043 (52)	176 (52)	15 (56)	260 (49)	11 (85)	581 (52)
White Blood Cell Count in CSF						
5 - 19 cells/ul - no. (%)	536 (26)	2 (1)	0 (0)	151 (28)	0 (0)	383 (34)
20 - 100 cells/ul - no. (%)	604 (30)	100 (29)	4 (15)	131 (25)	6 (46)	363 (33)
> 100 cells/ul - no. (%)	880 (44)	235 (70)	23 (85)	250 (47)	7 (54)	365 (33)
Median	70	170	278	82	118	37
Mean ± SD	180 ± 240	230 ± 210	320 ± 210	240 ± 310	200 ± 210	130 ± 200
Clinical manifestations						
Drowsy - no. (%)	318 (16)	108 (32)	3 (11)	128 (24)	1 (8)	78 (7)
Headache - no. (%)	1616 (80)	308 (91)	19 (70)	342 (61)	11 (85)	954 (86)
Fever (>37.5°C) - no. (%)	326 (16)	41 (12)	13 (48)	25 (5)	nd	247 (22)
Pruritus - no. (%)	1017 (50)	106 (31)	15 (56)	168 (32)	11 (84)	717 (65)
Weakness - no. (%)	692 (34)	131 (39)	7 (26)	244 (86)	7 (54)	303 (27)
Walking difficulties - no. (%)	419 (21)	113 (34)	5 (19)	89 (17)	5 (38)	207 (19)
Abnormal movements - no. (%)	201 (10)	39 (12)	8 (30)	71 (13)	0 (0)	83 (7)
Speech impairment - no. (%)	266 (13)	77 (23)	6 (22)	79 (15)	2 (15)	102 (9)
Sleeping disorder - no. (%)	1466 (73)	202 (60)	25 (93)	504 (95)	12 (92)	723 (65)
Strange behaviour - no. (%)	520 (26)	54 (16)	18 (67)	81 (15)	2 (15)	365 (33)

*age and sex adjusted in case of children; ** within two years before admission to IMPAMEL II; nd: determination not done

Treatment compliance

The average adherence to the treatment regimen was 67.1% (1355/2020; Graph 2). 78.1% (1578/2020) finished treatment with an interruption of less than 2 days and overall, 88.8% (1793/2020) of the patients received the 10 doses. Non-adherence resulted from treatment interruption due to severe adverse reactions but treatment was resumed in most cases after 2-4 days (median 2; mean 4, standard deviation 4 and range 1–24 days). Most of the interruptions occurred on days 8 to 10 of treatment. The treatment centres in South Sudan reported a much higher deviation from the treatment schedule and compliance as low as 54% compared to 67-88% in the other countries. These were also the centres with the highest rates of reported moderate adverse events (Table 3).

Graph 2: Compliance to treatment schedule, by country



Effectiveness

Parasitological cure 24 hours after treatment was 93.9% (1897/2020, centres' range 85.7–100%; Graph 1, Table 2). 119 (5.9%) patients died during treatment and in 4 (0.2%) patients trypanosomes were detected, they were treated for relapse. Two years after treatment, the observed cure rate was 86.2% (1742/2020) with a considerable inter-centre variation (range from 70.9 to 100%). Follow-up participation was highly variable (15% to 100%, data not shown). Many of the patients cured at discharge did not attend any of the foreseen clinical follow-up examination (936/1897, 49.3%) and were considered cured. 50.7% (961/1897) underwent at least one of the four prescribed follow-up examinations with lumbar puncture (LP) and thereof 144 (7.1%; 144/2020) were diagnosed as relapses. 18 patients (0.9%, 18/2020) died during the follow-up, 7 after relapsing (0.3%, 7/2020). In 53 (36.8%, 53/144) of the relapses, trypanosomes could either be demonstrated in blood (7, 4.9%) or in CSF (46, 31.9%). All other relapses were diagnosed by an elevated WBC CSF count of more than 50 cells/mm^3 (61, 42.4%) or by a WBC CSF count that had at least doubled since hospital discharge and with clear symptoms of the disease (30, 20.8%). Relapses were not further analysed due to the high variation of the follow-up coverage of the different centres.

Safety

The safety results are presented in Table 3, the adverse events are tabulated in numbers and proportions of patients affected, detailed by country and the recorded grades. The results reflect the expected high variation observed in sleeping sickness treatment.

During treatment, 119 patients died, in average after 9 days of treatment (range 1–29 days). The major causes were encephalopathic syndromes, attributing to 67.2% (80/119) of the fatalities. Other causes were: advanced HAT (15, 12.6%), concomitant diseases (10, 8.4%), unknown aetiology (9, 7.6%) and bullous skin reactions (5, 4.2%).

176 (8.7%) patients suffered from an encephalopathic syndrome and they generally received i.v. steroids at different doses. The onset of the encephalopathic syndrome was reported after an average of 9 days of treatment (median 9, mean 9.2, range 1–28 days). In those who survived, treatment was resumed after a suspension of 3 days (median 3, mean 3.2, range 1–12 days). No significant seasonal variation was observed in any of the centres (data not shown). Headache preceded the onset of the encephalopathic syndrome in 34% (60/176) and fever in 54% (95/176) of the cases. In 23% (40/176) of the patients suffering from an encephalopathic syndrome, malaria parasites were detected during the syndrome, probably causing the fever in 20 (11.4%, 20/176) of them. The effect of prophylactic use of

prednisolone could only be evaluated for 2 southern Sudanese centres that provided reliable information for each patient. In those centres, 163 of 607 (26.8%) patients received prednisolone. The risks of those to develop an encephalopathic syndrome or of a fatal outcome were non-significant (RR=1.3, 95% confidence interval 0.8 to 2.2, p=0.286 and RR=1.4, 95% confidence interval 0.5 to 3.9, p=0.598, respectively).

The frequency of skin reactions was high (28.3%, 571/2020) but varied between the centres. The majority of recorded skin reactions were moderate (grade 1) pruritus (20.4%, 412/2020). Only one third of the patients with skin reactions suffered from severe (grade 2) maculopapular eruptions (6.8%, 138/2020), pruritus (3.3%, 66/2020) or bullous eruptions (0.84%, 17/2020), which lead to temporary suspension of treatment. Most of the skin reactions were consistently not considered a significant problem by the treating staff and could be controlled with steroids or promethazine. Patients in south Sudan who received prednisolone as prophylactic treatment were at a lower risk of developing a moderate skin reaction (RR=0.6, 95% confidence interval 0.4 to 0.8, p=0.0004).

Motor and sensitivity neuropathies occurred at a frequency of 6.3% (128/2020). Other adverse drug reactions often reported included fever and headache. However, these are common symptoms and signs of the disease and not easy to discriminate from adverse event during treatment. Less frequently reported reactions included diarrhoea, jaundice and hypotension.

Table 2: Short and long-term efficacy of the 10-day melarsoprol treatment schedule (24 hours after treatment and during follow-up), compared to IMPAMEL I, centres history and literature

	Impamel II	Center History	Impamel I		Literature
	10-day treatment (N = 2020)	Standard treatment (N = 2215)	10-day treatment (N = 250)	Standard treatment (N = 250)	Standard treatment (%)*
Fatalities during treatment - no. (%)	119 (5.9)	117 (5.3)	6 (2.4)	6 (2.4)	9.4
Treatment failures at discharge - no. (%)	4 (0.2)	18 (0.8)	0 (0)	0 (0)	< 1
Cured at discharge - no. (%)	1897 (93.9)	2080 (93.9)	244 (97.6)	239 (95.6)	90.6
Fatalities during follow up - no. (%)	18 (0.9)**	nd	6 (2.8)	8 (3.6)	nd
Relapses during follow up - no. (%)	144 (7.7)**	54 (2.6)	12 (5.5)	11 (4.9)	< 30
Lost during follow up - no. (%)***	936 (49.3)	2026 (97.4)	26 (10.7)	15 (6.3)	nd
Cured 2 years after treatment - no. (%)***	1742 (86.2)	2026 (91.5)	226 (90.4)	230 (92)	70-90

*N highly variable, often only percentages were published; **7 of the relapses died and are included in both, the relapses and the deaths; ***Assumption: All patients lost are considered cured, denominator = all patients treated; nd: no data available

Table 3: Adverse events by country

	Total (N = 2020)	Angola (N = 337)	Côte d'Ivoire (N = 27)	Dem Rep Congo (N = 532)	Equatorial Guinea (N = 13)	Sudan (N = 1111)
Fatalities - no. (%)*	119 (5.9)	24 (7.1)	2 (7.4)	45 (8.5)	1 (7.7)	47 (4.2)
Encephalopathic syndromes (ES)	176 (8.7)	18 (5.3)	0 (0)	49 (9.2)	1 (7.7)	108 (9.7)
Grade 3 (fatal) - no. (%)	80 (4.0)	13 (3.9)	0 (0)	33 (6.2)	1 (7.7)	33 (3)
Case fatality rate (% fatal ES)	45	72	0	67	100	31
Grade 2 (coma, convulsion) - no. (%)	72 (3.6)	5 (1.5)	0 (0)	13 (2.4)	0 (0)	54 (4.9)
Grade 1 (psychotic) - no. (%)	24 (1.2)	0 (0)	0 (0)	3 (0.6)	0 (0)	21 (1.9)
Bulluous eruptions						
Any - no. (%)	30 (1.5)	7 (2.1)	0 (0)	12 (2.3)	1 (7.7)	10 (0.9)
Severe - no. (%)	17 (0.8)	3 (0.9)	0 (0)	8 (1.5)	0 (0)	6 (0.5)
Maculopapular eruptions						
Any - no. (%)	228 (11.3)	31 (9.2)	9 (33.3)	58 (10.9)	1 (7.7)	129 (11.6)
Severe - no. (%)	138 (6.8)	25 (7.4)	7 (26.0)	45 (8.5)	0 (0)	61 (5.5)
Pruritus						
Any - no. (%)	478 (23.7)	41 (12.2)	4 (14.8)	44 (8.3)	2 (15.4)	387 (34.8)
Severe - no. (%)	66 (3.2)	1 (0.3)	0 (0)	26 (4.9)	0 (0)	39 (3.5)
Motor polyneuropathy						
Any - no. (%)	128 (6.3)	13 (3.9)	0 (0)	9 (1.7)	0 (0)	106 (9.5)
Severe - no. (%)	37 (1.4)	6 (1.8)	0 (0)	8 (1.5)	0 (0)	23 (2.1)
Sensitivity polyneuropathy						
Any - no. (%)	64 (3.2)	1 (0.3)	0 (0)	4 (0.7)	0 (0)	59 (5.3)
Severe - no. (%)	24 (1.2)	0 (0)	0 (0)	3 (0.6)	0 (0)	21 (1.9)
Febrile reaction						
Any (37.5 - 39°C)	653 (32.3)	39 (11.6)	24 (88.9)	109 (20.5)	2 (15.4)	479 (43.1)
Severe (>39°C)	233 (11.5)	17 (5.0)	11 (40.7)	53 (10.0)	1 (7.7)	151 (13.6)
Headache						
Any - no. (%)	599 (29.6)	43 (12.8)	4 (14.8)	21 (4)	4 (30.8)	527 (47.6)
Severe - no. (%)	146 (7.2)	16 (4.8)	0 (0)	11 (2.1)	2 (15.4)	117 (10.5)
Diarrhea						
Any - no. (%)	173 (8.6)	5 (1.5)	0 (0)	11 (2.1)	3 (23.1)	154 (13.9)
Severe - no. (%)	45 (2.2)	1 (0.3)	0 (0)	3 (0.6)	1 (7.7)	40 (3.6)
Hypotension						
Any - no. (%)	60 (3.0)	5 (0.5)	0 (0)	23 (4.3)	0 (0)	32 (2.9)
Severe - no. (%)	16 (0.8)	0 (0)	0 (0)	13 (2.4)	0 (0)	3 (0.3)
Jaundice						
Any - no. (%)	9 (0.5)	1 (0.3)	0 (0)	2 (0.4)	0 (0)	6 (0.5)
Severe - no. (%)	5 (0.2)	0 (0)	0 (0)	2 (0.4)	0 (0)	3 (0.2)

The results are comparable to those obtained in the controlled clinical trial conducted by Burri et al., 2000 in Angola; *All fatalities during treatment, including fatal ES

Table 4: Comparison of the occurrence of severe adverse events during the 10-day melarsoprol treatment schedule (IMPAMEL II) with the standard treatment (IMPAMEL I), the centres history and the literature

	Impamel II	Center History	Impamel I		Literature
	10 day treatment (N = 2020)	Standard treatment (N = 2215)	10 day treatment (N = 250)	Standard treatment (N = 250)	Standard treatment mean % (range)*
Fatalities - no. (%)	119 (5.9)	117 (5.3)	6 (2.4)	6 (2.4)	9.4 (2.7 - 34)
Encephalopathic syndromes (ES)† - no. (%)	152 (7.5)	184 (8.3)	14 (5.6)	14 (5.6)	4.7 (1.5 - 23.5)
Grade 3 (fatal) - no. (%)	80 (4.0)	87 (3.9)	6 (2.4)	6 (2.4)	4.1 (3.3 - 34)
Case fatality rate (% fatal ES)	52.6	47.3	42.9	42.9	43.8 (33 - 100)
Skin reactions - no. (%)	166 (8.2)	35 (1.6)	23 (9.2)	13 (5.2)	< 3
Bulluous eruptions - no. (%)	17 (0.8)	4 (0.2)	3 (1.2)	1 (0.4)	< 1
Maculopapular eruptions - no. (%)	138 (6.8)	20 (0.9)	12 (4.8)	6 (2.4)	nd
Pruritus - no. (%)	66 (3.3)	11 (0.5)	8 (3.2)	6 (2.4)	5
Polyneuropathies‡ - no. (%)	54 (2.7)	24 (1.1)	2 (0.8)	1 (0.4)	< 10
Febrile reaction - no. (%)	233 (11.5)	72 (3.2)	15 (6.0)	12 (4.8)	12
Headache - no. (%)	146 (7.2)	43 (1.9)	nd	nd	nd
Diarrhea - no. (%)	45 (2.2)	19 (0.9)	6 (2.4)	4 (1.6)	< 25
Hypotension - no. (%)	16 (0.8)	19 (0.9)	nd	nd	< 1
Jaundice - no. (%)	5 (0.2)	3 (0.1)	nd	nd	< 3

*N highly variable, often only percentages were published; †Grades 2 (convulsion, coma) and Grades 3 (fatal); ‡motor or sensitivity polyneuropathies; nd: not determined or no data available

DISCUSSION

The presented study (IMPAMEL II) was a non-controlled, multinational, multi-centre drug utilisation study to evaluate the abridged treatment schedule of melarsoprol in late-stage *T.b. gambiense* sleeping sickness patients under true field conditions. Due to the very basic equipment of the treating centres, the often low level of staff qualification and the lack of experience in the conduct of clinical trials it was not possible to conduct a randomised study. Cluster randomization was also considered impossible because of the inherent differences in the outcome of the sleeping sickness treatment in different centres and countries and the limited number of centres available for participation. The 12 months enrolment period was selected to make apparent a potential seasonal variation of the outcome [Ancelle *et al.,* 1994]; centres that enrolled patients for less than 12 months were excluded from the formal analysis and those reporting for a longer period were truncated after the first 12 months. Other patients excluded from the formal analysis were those treated in a centre where a patient selection based on self-defined criteria was applied, e.g. adults only or patients admitted in a good health state.

The study population corresponded to the average population of African countries [UNDP 2003] except for the patients treated in Côte d'Ivoire (n=27), which were much younger (median age 15 years) than the overall study population (median age 27 years). The clinical conditions and the diagnostic characteristics of the patients at admission were highly variable between the centres, reflecting the different levels of surveillance activities in the countries, the diverse qualification of staff (nurses versus medical doctors, national control programs versus NGOs), and the different possibilities and perceptions of the staff. However, there was no difference in the outcome of the treatment between the cohorts diagnosed according to the different cut-off criteria in use (data not shown).

The average short term (93.9%; 1897/2020) and long term (86.2%; 1742/2020) effectiveness, based on "all patients treated" as denominator and considering patients not seen during the follow-up as cured, were comparable to the standard treatment [Richet *et al.,* 1959; Dutertre and Labusquiere 1966; Bertrand *et al.,* 1973; Burri *et al.,* 2000; Atouguia and Kennedy 2000; Brun *et al.,* 2001; Pepin *et al.,* 2002] and the centre histories, where available. This approach is somewhat unsatisfactory since it leads to an overestimation of the effectiveness, but allows best the comparison to the literature. The follow-up coverage rates in our study were highly variable between the centres (0% - 100%). In average only 50% of all patients attended at least one follow-up examination, most of them within the first year after treatment, and therefore the true failure rates in this study are difficult to estimate.

The safety and tolerability of the 10-day melarsoprol treatment schedule were similar to those of the standard treatment schedules [Ginoux *et al.,* 1984; Nkanga *et al.,* 1988; Pepin *et al.,* 1989; Doua and Yapo 1993; Pepin *et al.,* 1995; Burri *et al.,* 2000; Blum *et al.,* 2001; Seixas *et al.,* 2004] with the exception of skin reactions, fever and headache (Table 4). The variability of the adverse events between the different study centres was high, but in an expected range and comparable results were found in a separate analysis of the patients excluded from the formal analysis. Mild symptoms and signs like fever (32.3%), headache (29.6%) and pruritus (23.7%), which are also common symptoms and signs of the disease were more frequently reported during the study. This may be an observation bias prompted by soliciting information which usually is not recorded. The notion that more treatment interruptions caused by moderate adverse events were reported in centres run by NGOs supports this reflection.

The frequency of treatment related death was 5.9% (119/2020) and the most severe reactions were encephalopathic syndromes (8.7%, 176/2020). These rates are comparable to published rates [Kuzoe 1993; Pepin and Milord 1994; Seixas *et al.,* 2004] although at the upper end of the range. In line with previous reports [Ginoux *et al.,* 1984; Doua *et al.,* 1985; Adams *et al.,* 1986; Pepin and Milord 1994; Ancelle *et al.,* 1994; Soignet *et al.,* 1999; Burri *et al.,* 2000; Blum *et al.,* 2001; Seixas *et al.,* 2004] encephalopathic syndromes occurred between days 1 and 28 after the initial injection of melarsoprol with a maximum between days 9 and 11 (mean 9.2, standard deviation 4 days), supporting the view that the event is independent of the treatment schedule and dose applied. Also, the resumption of melarsoprol after interruption and improvement of the patient did never result in a recurring reaction. In our cohort we could not make a clear distinction of the type of the encephalopathic syndrome as described by Blum et al. [Blum *et al.,* 2001] (data not shown). The effect of prednisolone prophylaxis could only be evaluated for 2 treatment centres in Sudan because all other centres used different dosage regimes or for many patients information was not detailed enough. There was no prophylactic effect of prednisolone on the development of an encephalopathic syndrome or a difference in the case fatality rate in this cohort as was suggested by Pepin et al [Pepin *et al.,* 1989]. However, a clear protection of the development of moderate drug related skin reactions could be observed with prednisolone [Pepin and Milord 1994].

This study (IMPAMEL II) corroborates the results of the randomised controlled clinical trial previously conducted in Angola [Burri *et al.,* 2000] (IMPAMEL I) that had demonstrated non-inferiority in terms of efficacy and safety of the 10-day melarsoprol treatment schedule compared to the standard treatment schedule: The overall frequency of adverse events was high, but again there was no increase compared to the standard treatment schedules, except for skin reactions. At hospital discharge, symptoms and signs, like pruritus, fever, headache,

tremor, weakness and unusual behaviour had substantially improved (data not shown). Also, the long-term effectiveness appeared to be equivalent to the standard treatment [Schmid *et al.,* 2004] in our approach where the follow-up activities were purposely not assisted.

The 10-day schedule has several socio-economic and practical advantages over the very lengthy standard schedules: The suggested treatment is comparable in terms of safety and effectiveness, and favourable in socio-economic (less drug, shorter hospitalisation, increased treatment centre capacity), technical (10 consecutive days, no dosage adjustment), pharmacologic (basis of all combinations of melarsoprol in the compassionate treatment of refractory cases) and psychological terms (patients' and doctors' compliance to adhere to treatment). Therefore, the 10-day schedule has already become a useful alternative to the lengthy standard treatment (average duration 25 – 30 days). Its use was continued in several countries (e.g. Central African Republic, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea and Republic of the Congo). Based on the results of IMPAMEL I and IMPAMEL II and the experiences in the countries, the 10-day melarsoprol treatment was recommended on request of WHO to the endemic countries as standard schedule for treatment of late-stage *T.b. gambiense* sleeping sickness with melarsoprol at the occasion of the 27th ISCTRC congress (International Scientific Counsel for Trypanosomiasis Research and Control) in Pretoria in September 2003 [2003]. The 10-day melarsoprol treatment schedule is currently being implemented by the national sleeping sickness programs.

Cleary, the tolerability and safety of melarsoprol are inferior to those of eflornithine [Burri and Brun 2003]. However, eflornithine administration as slow infusions every 6 hours over 14 days is difficult and requires qualified staff and very good logistics. Therefore, eflornithine remains restricted to centres with substantial and consistent support by NGOs and the vast majority of patients still are treated with melarsoprol.

Also, melarsoprol is still is the only treatment for *T.b. rhodesiense* because of inconsistent efficacy of eflornithine against this form of the parasite. However, the use of the melarsoprol 10-day schedule against *T.b. rhodesiense* is strongly discouraged. The clinical nature of this form is very different and high parasitaemia is observed. However the conduct of confirming clinical evaluation is still pending.

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CHAPTER 3

Adverse events during melarsoprol therapy: the role of concomitant infections

Schmid Caecilia

Working paper

SUMMARY

In many areas endemic for sleeping sickness, high incidences of malaria, filaria or intestinal parasites are common and the overlap in the geographic distribution of these parasites implies that co-infections might occur. In the multinational IMPAMEL II study, a high proportion of patients was diagnosed with other parasites than trypanosomes. To determine the effect of concomitant parasitic infections on the reported adverse events during melarsoprol treatment, we analysed the adverse events with special emphasis to their management and the associations between the concomitant parasites and the occurrence of the events.

In average, 41.7% of the patients were diagnosed on admission or during melarsoprol treatment with other parasitic infections than trypanosomiasis and the rates differed highly between the centres from 0 – 66.3%. Of those, 70.4% suffered from an adverse event during treatment with the 10-day schedule of melarsoprol. The general procedures to manage the adverse events are summarised and explore the association with concomitant parasitic infections, based on the diagnostic findings and the outcome assessment of the study obtained through a standardised questionnaire.

We found elevated risks for adverse events linked to concomitant parasites, which were also reflected by the type of medication given during the management of adverse events. It remains unclear whether the events were related or aggravated due to the concomitant parasitic infections or were real melarsoprol related reactions. Nevertheless, concomitant parasitic infections should be considered on hospital admission and throughout the treatment course of sleeping sickness patients and therefore be diagnosed and treated accordingly and systematically.

BACKGROUND

In sub-Saharan Africa, multiple parasitic infections are widespread and pose an enormous toll on the socio-economic development [Buck *et al.,* 1978; WorldHealthReport 2004]. Amongst all parasitic infections, malaria, filaria and gastro-intestinal parasites are the most important, expressed in disease burden (DALY, [WorldHealthReport 2004]). The overlap in the geographic distribution implies that co-infections might occur in many sleeping sickness endemic areas. In addition, as a result of their disease, sleeping sickness patients are believed to be highly immunosuppressed and likely to be more susceptible to concomitant infections [Greenwood *et al.,* 1973; Sternberg 1998]. Therefore, concomitant parasitism should be a fairly common feature but only few authors have documented concomitant parasites in sleeping sickness patients [Sina *et al.,* 1975; Buyst 1975; Balint and Wenninger 1975; Sina *et al.,* 1977; Buyst 1977; Burri *et al.,* 1995; Aroke *et al.,* 1998]. Even less information is available about the influence of concomitant parasitic infections on the clinical progression or on the outcome of sleeping sickness treatment with melarsoprol. Nevertheless, WHO [WHO 1998], NGOs [Balasegaram *et al.,* 2004] and the national sleeping sickness programs recommend a standardised pre-treatment with antimalarial and anthelminthic drugs before starting the sleeping sickness therapy.

The drug most often used to treat late-stage sleeping sickness is melarsoprol, an organo-arsenic drug which is highly toxic and does not have a 100% cure rate [Legros *et al.,* 1999; Stanghellini and Josenando 2001]. For decades, variable treatment regimens [WHO 1998] were applied until the introduction of the concise 10-day treatment schedule (IMPAMEL I, [Burri *et al.,* 2000]. The effectiveness under normal field conditions of this improved treatment schedule was further assessed in a multinational drug utilisation study in late-stage *T.b. gambiense* sleeping sickness patients [Anonymous 2003; Schmid *et al.,* 2004]. Despite the advantages of the 10-day treatment regimen (less drug, shorter hospitalisation, harmonisation of treatment schedule, increase of treatment centres' capacity and decrease of costs for treatment and hospitalisation), adverse events are still frequent and may be severe [WHO 1998].

The most frequent adverse events are fever, skin reactions and CNS complications like encephalopathic syndromes that may arise in up to 10% of the treated patients [Pepin *et al.,* 1989; Doua and Yapo 1993; WHO 1998]. The measures to reduce the frequency and severity of the CNS complications are often erratic and depend much on the available resources that are scarce in rural sleeping sickness treatment centres. Interruption of melarsoprol and high doses of corticosteroids and anticonvulsive drugs are the recommended measures [WHO 1998]. Psychotic reactions are best managed by sedation (chlorpromazine or diazepam). In contrast, the concomitant administration of corticosteroids

(prednisolone) remains controversial: some authors demonstrated a positive prophylactic effect of prednisolone during melarsoprol treatment [Pepin *et al.,* 1989], whereas others warn of the administration of immunosuppressants in areas with high prevalence of certain infectious diseases for fear of an exacerbation (i.e. HIV, strongyloides, amoeba [Balasegaram *et al.,* 2004]). Recommendations for the management of other severe adverse events (polyneuropathies, skin reactions) are often more general, advising to interrupt treatment (both events) or to perform differential diagnosis to exclude possible concomitant infections (skin reactions). Additionally, for those admitted with severe malnutrition, nutritional supplementation with multivitamins, specific vitamins and folic acid, in some cases also iron is recommended. Routine pre-treatment with broad-spectrum antibiotics is not recommended, except if the patient has evidence of a bacterial infection [Balasegaram *et al.,* 2004].

To determine the effect of concomitant parasitic diseases on the reported drug related adverse events and their management, we analysed the patients treated with melarsoprol in the IMPAMEL II study [Schmid *et al.,* 2004].

METHODS

Study design and study population

Data were collected between June 1999 and June 2002 in the frame of the drug utilisation study IMPAMEL II, which evaluated the 10-day melarsoprol treatment protocol under field conditions. Detailed characteristics of the study population and study design are presented in chapters 2 and 4. Briefly, all patients with confirmed late-stage sleeping sickness due to *T.b. gambiense* were enrolled in 16 selected treatment centres of 7 sub-Saharan African countries (Angola, Central African Republic, Côte d'Ivoire, Democratic Republic of Congo, Equatorial Guinea, Republic of Congo and Sudan). For each patient a questionnaire was completed containing demographic, diagnostic and clinical characteristics at admission, tolerability assessment and management of adverse events during treatment, and efficacy assessment on discharge (24 hours after treatment) and during the 2 years follow-up.

The study was approved by the ethics committee of the two cantons of Basel (EKBB) and the relevant ethics committees and authorities in the respective countries. In the participating centres the abridged schedule was introduced as the sole treatment and therefore no consent was obtained from the patients.

Diagnosis and Treatment

Diagnosis of late-stage sleeping sickness was done by microscopic examination of the cerebrospinal fluid (CSF) for the presence of trypanosomes and/or an elevated white blood cell (WBC) count, of which the cut-off differed slightly between the countries (chapter 2). Patients were treated with 2.2 mg/kg/day melarsoprol for 10 days, as a 3.6% solution in propylene glycol (Arsobal®, Aventis), by slow intravenous injection.

Diagnosis of concomitant parasitic diseases was not mandatory in this study, but prior to melarsoprol treatment, all patients were pre-treated with multivitamins, paracetamol and antiparasitic drugs for 3 days according the respective national guidelines for sleeping sickness therapy: *antimalarials* - Fansidar for 3 days in Southern Sudan for patients allergic or refractory to chloroquine, quinine for 7 days in the CNPP centre in DRC and in some patients in Angola, and chloroquine for 3 days (10mg/kg/day) in all other centres; *anthelminthic* – mebendazole for 3 days (4mg/kg/day) in all countries/centres. Prednisolone was given at different doses according to the criteria of the respective national sleeping sickness control programs or NGOs (detailed in chapter 2).

However, in case of an encephalopathic syndrome, examinations of blood-slides for malaria parasites were mandatory and any confirmed infection was treated either with Fansidar or quinine.

Assessment of adverse events (AE) and their management

The safety of the treatment was determined by the frequency of adverse events using a graded scale from 0 to 2 (none, moderate, severe) for most reactions. Encephalopathic syndromes were scaled from 0 to 3: grade 1 indicating psychotic reactions, grade 2 occurrence of convulsions and/or loss of consciousness and grade 3 death of the patient. Events provoking treatment interruption were defined as severe.

The management of severe adverse events was done according to the respective national guidelines and depended much on the instant resources of the treatment centre. Generally, it was recommended to interrupt melarsoprol treatment, manage the adverse event and if possible, resume the melarsoprol treatment or consider it completed if at least 8 doses were given.

Data management and analysis

Data management and analysis were done using EpiData 2.1 [Lauritsen and Bruus 2001] and STATA 7.0 [Stata 2001] software. The statistical analysis included those patients who were treated exclusively with the 10-day melarsoprol protocol and the proportions were compared with the $\chi 2$ test or the Fisher's exact test whenever appropriate. Differences in proportions, the 95% confidence interval for the difference and the Z test were used in variables with a large number of missing data.

All unstructured data ("observation", "justification" and "additional drugs" fields) containing information on concomitant medications and diseases were coded as follows:

Drugs used in the management of adverse events were grouped as follows: *corticosteroids* – hydrocortisone, prednisolone, betamethasone and dexamethasone; *anti-convulsive* – diazepam (chlorpromazine); *anti-allergic* – promethazine and chlorpheniramine; *analgesic/anti-pyretic* – acetaminophen (paracetamol), aspirine, ibuprofen; *antibiotics* – amoxicilline, ampicilline, bactrim, septrim, cloxacilline and penicilline; *antimalarial* – chloroquine, quinine, pyrimethamin/sulfadoxine (Fansidar); *anti-protozoal/anthelminthic* – metronidazole, praziquantel, mebendazole and ivermectin; *nutritional supplementation* – oral rehydration solution (ORS), Ringer solution, vitamins, iron and glucose; *topical anti-infective* – gentian violet, Whitfield's ointment, benzyl benzoate, zinc oxide and TTC ointment.

Concomitant parasitic diseases were grouped as follows: malaria – patients with confirmed malaria (parasite positive on blood smears) before and/or during melarsoprol treatment; gastro-intestinal parasites – patients with diagnosed amoeba, giardia, hookworm, schistosome, or geohelminthic infections; filaria – Loaloa, Mansonella perstans or Onchocerca volvulus; skin infections – scabies or fungal skin infections (mainly ringworms).

Some diseases, symptoms or signs could not be easily grouped or allocated to a specific agent or were due to viral or bacterial infections, and thus were not considered in this analysis, these included: respiratory infections – upper and lower respiratory tract infections as pneumonia, bronchitis, pulmonary infections, cough, flu, common cold; and even more general terms like “urinary tract infection, sexually transmitted disease, skin infection, itch, pain, general pain, abdominal pain, chest pain, ascites, vomiting, dizziness, nausea, conjunctivitis or gastritis”.

RESULTS

Study population and concomitant parasitic infections

Of the 2800 enrolled patients, 2343 case records of 6 countries were analysed. 457 patients could not be considered because they were not eligible for the evaluation for several reasons: erroneous classification (other disease than sleeping sickness), abandon during treatment (incomplete case records), other treatment than 10-day melarsoprol schedule (eflornithine, nifurtimox or a combination therapy of melarsoprol and nifurtimox), or biased inclusion (selection of patients in good health state or adults only).

The study population corresponded to the average rural population and did not differ in demographic characteristics (chapter 2, Table 1). The baseline characteristics of the cohort analysed here are presented in Table 1. The observed concomitant parasitic infections are tabulated versus the demographic and diagnostic characteristics of the patients.

In 41.7% (977/2343) of the patients, any other parasitic disease apart from trypanosomiasis was diagnosed on admission or during melarsoprol treatment. The rates differed highly with the geographic regions as well as with the treatment centres: generally more infectious diseases were diagnosed in centres run by NGOs or with expatriate doctors, likely due to more systematic screening for those diseases, capacity and resources of these centres. The most frequently reported concomitant parasite was malaria (24.5%, 574/2343), followed by gastro-intestinal parasites (9.8%, 229/2343). In children ≤14 years of age, more malaria parasites (risk rate RR=1.4, 95% confidence interval CI: 1.1-1.7, P value p=0.0035) but less filaria (RR=0.4, CI: 0.2–0.9, p=0.0109) were detected than in adults. Fewer concomitant parasites were diagnosed in patients with malnutrition on admission (defined as age and sex adjusted body mass index) or with a bad general health state (defined by the medical staff), in particular malaria parasites (RR=0.8, CI: 0.7–0.9, p=0.0036 and RR=0.8, CI: 0.7–0.9, p=0.0006, respectively).

At hospital admission, fever was associated with malaria parasites (RR=1.3, CI: 1.1–1.6, p=0.0025) and pruritus with gastro-intestinal parasites (RR=3.0, CI: 2.3–4.1, p<0.0001), filaria (RR= 3.7; CI: 2.3-6.0, p<0.0001) or skin infections (RR=6.1, CI: 3.5-10.4, p<0.0001). Most infections of the skin were diagnosed in the first days of the melarsoprol treatment and were more common in male patients with pruritus on admission (RR=6.4, CI 3.2-12.7, p<0.0001).

Table 1: Baseline of the study population: Demographic, diagnostic and clinical characteristics are plotted versus the concomitant parasitic infections (in %) recorded during the 10-day melarsoprol treatment

		Concomitant parasitic infections (%)				
Characteristics	Patients (n)	Any (N=977)	Malaria (N=574)	Gastrointestinal parasites (N=229)	Filaria (N=100)	Skin infections (N=107)
All patients	2343	41.7	24.5	9.8	4.3	4.6
Country						
Angola	547	33.6	32.4	0.2	0.7	0.2
Central African Republic	30	43.3	0.0	0.0	43.3	0.0
Côte d'Ivoire	27	51.9	51.9	0.0	0.0	0.0
Democratic Republic of Congo	561	24.4	21.8	0.0	1.6	0.2
Equatorial Guinea	23	26.1	4.4	0.0	17.4	0.0
Sudan	1155	53.9	22.5	19.7	6.1	9.1
Sex						
Female	1199	42.8	25.6	9.3	3.7	3.3
Male	1144	40.6	23.3	10.3	4.9	*5.9
Age (years)						
≤14	432	44.0	*28.9	10.2	1.8	3.0
15-80	1911	41.2	23.5	9.7	*4.8	4.9
Nutritional status						
Normal	1624	42.4	*25.8	9.1	4.2	5.0
Malnutrition (BMI<17)[1]	632	38.0	19.1	11.7	4.2	4.1
General health state[2]						
Good	1461	44.9	27.4	9.7	3.9	4.9
Bad	852	*37.1	*20.0	10.2	4.9	4.2
Diagnostic and clinical characteristics						
Trypanosomes in CSF	916	38.0	23.4	8.3	4.1	4.4
WBC ≥100 cells/mm^3	1011	39.4	24.6	7.7	4.8	3.9
Adenopathy	1356	42.9	23.2	*11.2	5.0	5.8
Headache	1883	*44.1	25.8	10.8	4.7	4.6
Fever (>37.5°C)	381	*51.7	*33.3	8.4	4.2	5.8
Pruritus	1177	*47.9	22.9	*14.7	*6.7	*7.8
Motor weakness	793	33.1	22.5	6.7	5.8	4.9
Neurological disorders[3]	2072	41.1	24.4	9.6	4.6	4.2

*indicates a significant difference ($p<0.05$); [1]age and sex adjusted; [2]as defined by medical staff at admission;
[3]abnormal movements, speech and sleep disorders, strange behaviour

Occurrence and management of adverse events

During melarsoprol treatment, adverse events were classified by the medical staff according to the severity of the event. In 56% (1311/2343) of all treated patients any adverse reaction was observed (moderate and severe), 24.7% (578/2343) with a severe reaction. A clear association between the intensity and the number of events per patient could be observed in our cohort ($p<0.0001$): patients with moderate reactions normally experienced only 1 or 2 adverse events (maximum 1, median 2, mean 2.2) and those with severe reactions suffered from 3 or more different adverse events (maximum 3, median 3, mean 3.1). The types, grades and frequencies of adverse events are detailed in chapter 2 and not all are further described here.

The most severe complication, the encephalopathic syndrome, occurred in 8.5% (198/2343) of all treated patients and they were at a high risk to die (47%); 75% of the patients with an encephalopathic syndrome had convulsions, 72% a reduced consciousness level (drowsy or comatose) and the syndrome was always associated with other adverse events, mostly with fever (51%) and/or headache (32%) within 2 days before onset of the syndrome. Among the fatalities during treatment (130, 5.6%), 85 (65.4%) patients died as a consequence of the encephalopathic syndrome, 15 (11.5%) of advanced HAT disease, 15 (11.5%) of unknown aetiology, 10 (7.7%) of concomitant diseases, and 4 (3.9%) of mucocutaneous reaction.

In Table 2, the grouped drugs used to manage the different adverse events are presented. The frequencies of the drug classes used in patients with adverse events are tabulated versus the adverse events and are ranked as follows: x=<30%, xx=30-67% and xxx=>67% of the patients with a certain adverse event were treated with the corresponding drug group.

Most patients suffered from more than one event during the course of treatment; therefore, it was difficult to allocate certain groups of drugs solely to a specific type of adverse event. However, general approaches and tendencies could still be observed, e.g. encephalopathic syndromes were mainly managed by the application of high dose corticosteroids (84.9%) and anti-convulsive drugs (64.1%). The additional medication depended on the type of the syndrome: psychotic reactions (grade 1 encephalopathic syndrome) were often associated with fever (68%), headache (68%), and/or skin reactions (50%) and thus, anti-pyretic and/or anti-allergic drugs were given. Encephalopathic patients with convulsions (grade 2 encephalopathic syndrome) often also suffered from fever (72%), headache (60%), and/or polyneuropathies (38%) and received mainly anti-pyretic drugs and nutritional supplementation. In patients who died of an encephalopathic syndrome, a high incidence of concomitant fever (78%), skin reactions (33%) and/or headache (32%) was reported; supplementary medication included mainly anti-pyretic drugs and nutritional supplementation.

Antibiotics and anti–parasitic (antimalarial, anti-protozoal or anthelminthic) drugs were administered to patients suffering from all different kinds of conditions during treatment at similar frequencies. Antibiotics were more frequently administered to patients suffering from diarrhoea and/or motor neuropathy. Anti-protozoal and/or anthelminthic drugs were mainly used in association with diarrhoea and/or pruritus and less often with other conditions. Antimalarials were mainly received by patients with fever and/or encephalopathic syndrome of the convulsion type. Nutritional supplementation was mostly applied to patients with polyneuropathies, fever, diarrhoea and/or encephalopathic syndromes and topical anti-infectives mainly for skin reactions.

Table 2: Management of severe adverse events of melarsoprol by concomitant medication

	Drug groups applied								
Severe adverse event	Cortico-steroids[1]	Anti-convulsive[2]	Anti-histaminic[3]	Analgesic / Anti-pyretic[4]	Anti-biotics[5]	Anti-malarial[6]	Anti-protozoal / Anti-helminthic[7]	Nutritional supplementation[8]	Topical anti-infective[9]
Encephalopathic syndromes									
grade 3 (death)	xxx	xxx	x	xx	(x)	(x)	(x)	xx	
grade 2 (convulsion or coma)	xxx	xx	xx	xx	(x)	(xx)	(x)	xx	
grade 1 (psychotic)	xxx	xx	xxx	xx	(x)	(x)		x	(x)
Skin reactions									
Maculopapular eruptions	xx	(x)	xx	xx	(x)	(x)		(xx)	(x)
Bullous eruptions	xx	(x)	xxx	xx	(x)	(x)		x	x
Pruritus	x	(x)	xx	xx	(x)	(x)	(x)	(x)	x
Neuropathy									
motor neuropathy	(xx)	(x)	(x)	(xx)	(xx)	(x)	(x)	xxx	(x)
sensitivity neuropathy	(xxx)	(x)	(x)	(xx)	(x)	(x)	(x)	xxx	(x)
Fever	xx	x	xx	xx	x	x	(x)	xx	(x)
Headache	xx	x	x	xx	(x)	(x)	(x)	(xx)	(x)
Diarrhea	(xx)	(x)	x	(xx)	xx	(x)	xxx	xx	(x)

xxx: >67% of the cases received this drug group; xx: 30-67%; x: less than 30%; (x) drug was given to control more than one adverse event

[1]hydrocortisone, prednisolone, betamethasone, dexamethasone; [2]diazepam; [3]promethazine, chlorpheniramine; [4]paracetamol, aspirine, ibuprofen; [5]amoxicilline, ampicilline, bactrim, cloxacilline, penicilline, septrim; [6]chloroquine, quinine, Fansidar; [7]metronidazole, praziquantel, mebendazole; [8]Nutritional supplementation: vitamins, aminoacids, ORS (oral rehydration solution), Ringer solution, glucose; [9]Gentian violet, Whitfields ointment, Benzyl benzoate, Zinc oxide, TTC

Concomitant parasitic infections and severe adverse events

41.7% of the sleeping sickness patients were also diagnosed with another parasitic infection (Table 1). 26.9% (630/2343) of them had a single infection, most frequently malaria parasites, 9.4% (220/2343) had 2 concomitant infections and 5.2% (127/2343) were diagnosed with 3 or more different parasitic infections. The frequencies of concomitant parasitic infections in patients with adverse events are displayed in Graph 1. Significantly higher rates of malarial infections were observed in patients who suffered from an encephalopathic syndrome, or fever, or in patients with a fatal outcome. Gastrointestinal parasites were more often diagnosed in patients with severe adverse events, strikingly in those with diarrhoea (all $p<0.0001$, Table 3). No association was found with filaria and any adverse event. The effect of prednisolone could only be evaluated for the Sudanese centres which were the only ones to provide reliable information for each patient. In patients with prednisolone prophylaxis more gastrointestinal parasites were observed (RR= 1.6, CI: 1.2-2.0, $p=0.0007$).

Treatment interruptions increased with the number of adverse events and/or the number of concomitant parasitic infections detected. (32.9% with a single concomitant infection up to 100% with five concomitant parasitic infections interrupted melarsoprol). In average, the treatment was interrupted for 2 days (range 1–24 days) in patients with concomitant parasitic infections and/or adverse events, in the majority after 7 doses of melarsoprol.

Treatment efficacy was indirectly associated with the occurrence of severe adverse events and concomitant parasitic diseases. Patients suffering from a severe adverse event during melarsoprol treatment had a 4-fold higher risk to die (RR=4.0, CI 3.6-4.4, $p<0.0001$), which gradually increased with the number of adverse events. Patients with any concomitant parasitic infection were more likely to display an adverse event (RR=1.9, CI 1.7-2.1, $p<0.0001$) and were at an elevated risk to die (RR=1.9, CI 1.6-2.2, $p<0.0001$).

Graph 1: Proportion of patients suffering from an adverse event with concomitant parasitic infections, grouped by adverse events

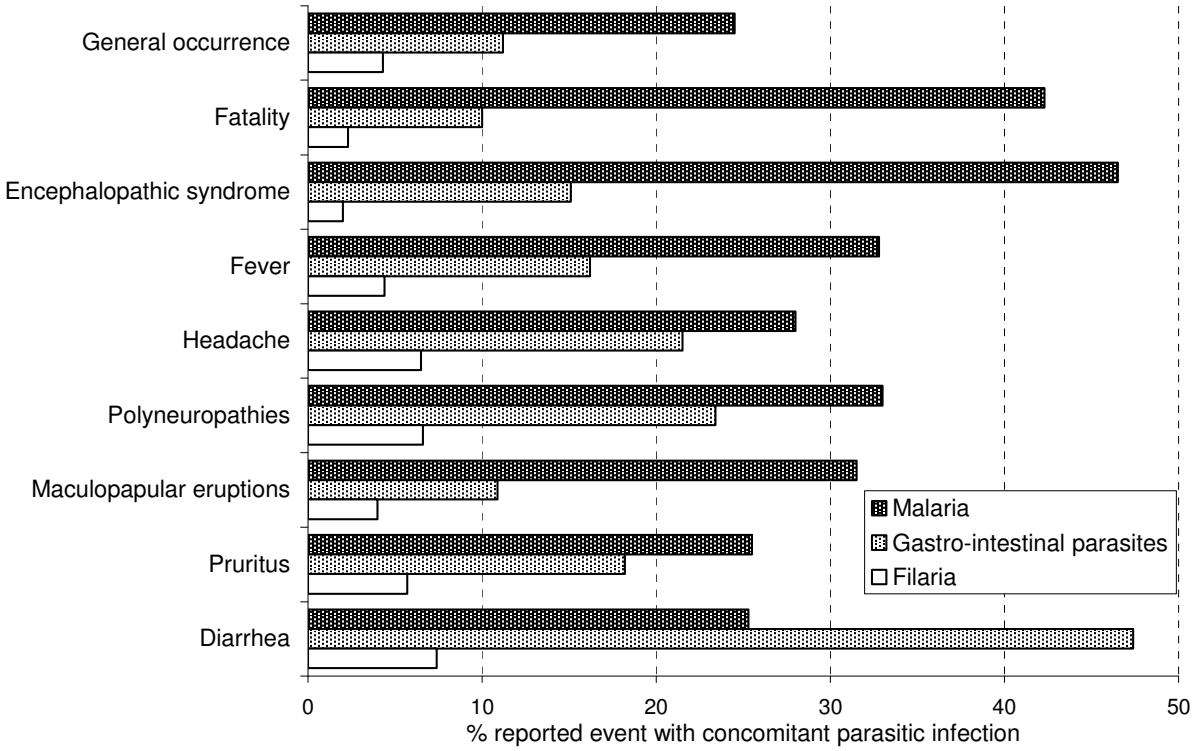

Table 3: Significance of malaria and gastro-intestinal parasites in the assessment of severe adverse events during melarsoprol treatment

Malaria

	Malaria (N=574)	RR	95% CI	P value
Overall prevalence*	35.3			
Fatality	**47.4**	**1.4**	**1.1 to 1.7**	**0.005**
Encephalopathic syndromes	**51.4**	**1.5**	**1.3 to 1.8**	**<0.0001**
Skin reactions (maculopapular eruptions)	**39.3**	**1.2**	**1.0 to 1.3**	**0.043**
Motor and sensitivity polyneuropathy	42.5	1.2	1.0 to 1.5	0.050
Fever	**42.9**	**1.4**	**1.2 to 1.6**	**<0.0001**
Headache	38.8	1.1	1.0 to 1.3	0.063
Diarrhea	32.2	0.9	0.7 to 1.2	0.411
Jaundice	20.0	0.9	0.3 to 2.9	0.920

*denominator=those tested (N=1627)

Gastro-intestinal infections (GI)

	GI (N=229)	RR	95% CI	P value
Overall prevalence**	9.8			
Fatality	6.2	0.6	0.3 to 1.2	0.153
Encephalopathic syndromes	12.6	1.3	0.9 to 2.0	0.158
Skin reactions (Pruritus)	**14.5**	**1.6**	**1.3 to 1.9**	**<0.0001**
Neuropathies (sensitivity, motor)	**20.8**	**2.4**	**1.8 to 3.3**	**<0.0001**
Fever	**14.8**	**1.6**	**1.4 to 1.9**	**<0.0001**
Headache	**20.2**	**2.3**	**2.0 to 2.7**	**<0.0001**
Diarrhea	**41.1**	**6.4**	**5.0 to 8.3**	**<0.0001**
Jaundice	20.0	2.3	0.5 to 10.8	0.225

** denominator=all patients (N=2343)

DISCUSSION

Of the parasitic infections, malaria, filaria and intestinal parasites are highly prevalent in many areas endemic for sleeping sickness and the overlap in the geographic distribution implies that co-infections might occur at substantial rates. However, only few authors have so far described the influence or the occurrence of concomitant parasitism in sleeping sickness patients [Sina *et al.,* 1975; Buyst 1975; Balint and Wenninger 1975; Sina *et al.,* 1977; Buyst 1977; Burri *et al.,* 1995; Aroke *et al.,* 1998]. Yet, probably based on extensive field experience, comprehensive guidelines of WHO and NGOs exist that recommend anti-parasitic pre-treatment of sleeping sickness patients before initiating the specific trypanosomiasis treatment and to perform differential diagnosis to exclude possible concomitant parasitic infections during treatment [WHO 1998; Balasegaram *et al.,* 2004]. The influence of concomitant parasitic infections in sleeping sickness patients on the clinical progression and the treatment outcome needs to be carefully addressed.

Here we document the prevalence and types of concomitant parasites of late-stage gambiense sleeping sickness patients hospitalised and treated with the 10-day schedule for melarsoprol in the multinational study IMPAMEL II (chapter 2). We also describe the supplementary medication given to the patients and explored the association of concomitant parasitic diseases with the recorded adverse events (that may not necessarily be related to melarsoprol).

The study was not designed to determine concomitant parasitism in sleeping sickness patients and consequently, routine screening for concomitant parasites was not mandatory. Missing data about concomitant parasitic infections in our study are therefore difficult to interpret: either the diagnostic tests were done, but not entered into the questionnaire because it was not mandatory (result positive or negative) or concomitant parasitic infections were not diagnosed at all for whatever reason (result unclear). Therefore, it remains unclear whether the frequencies reported in this study correspond to the true average prevalence in the respective areas.

The study population corresponded to the average rural population of African countries and was comparable for all treatment centres (see chapter 2 for detailed description). The clinical and diagnostic characteristics of the patients on admission and the frequencies of diagnosed concomitant parasitic infections were highly variable between the centres, reflecting the differences in endemicity levels of the disease foci, the different diverse qualification and origin of staff (nurses versus medical doctors, national control programs versus NGOs), and the different capabilities and resources of the treatment centres.

It was suspected that concomitant parasitic infections might influence the clinical progression of the patients and the adverse events during melarsoprol treatment. For example malaria was reported to increase the risk of developing an encephalopathic syndrome [WHO 1998; Blum *et al.,* 2001] and gastro-intestinal parasites (strongyloides and amoeba) a steroid-induced dissemination, respectively [WHO 1998; Balasegaram *et al.,* 2004]. In our study population, a quite large proportion of the patients was diagnosed with a concomitant parasitic infection which seemed to confound the reported rates of symptoms and signs of sleeping sickness or to influence the development of adverse events attributed to melarsoprol. On admission, fever was significantly associated with malaria parasites and pruritus with parasitic gastro-intestinal infections (Table 1). These parasites are supposed to be controlled by the anti-parasitic pre-treatment. Malaria and gastro-intestinal parasites in our study population were clearly correlated with a higher frequency of adverse events during melarsoprol treatment (Graph 1, Table 3): More often malaria parasites were diagnosed in patients who suffered severe adverse events like encephalopathic syndromes, skin reactions (maculopapular eruptions) or who died during the treatment. Patients with gastro-intestinal parasites were also more likely to suffer from neuropathies (sensitivity and/or motor) and/or general symptoms and signs as fever, headache, and pruritus, but were not at higher risk of developing an encephalopathic syndrome. Not surprisingly, we found a strong association between diagnosed protozoan and/or helminthic intestinal infections and reported diarrhoea which has already been shown by Burri *et al.* (1995). These positive associations were also reflected by the types of supplementary drugs given to the patients suffering from adverse events: most anti-parasitic drugs were administered in patients with fever, encephalopathic syndromes or diarrhoea. Except for an increased frequency of pruritus, filaria or parasitic skin infestations showed no significant correlation with other adverse events.

The management of adverse events in this study depended much on the diverse and instant resources the treating organisations had at hand. The questionnaire was not designed for detailed evaluation of the management of adverse events during melarsoprol treatment and in addition, the centres followed the various national or organisational guidelines. Therefore from this study no recommendations for the management of adverse events can be drawn. However, it becomes clear that a thorough screening of the patient for concomitant parasites would ease the management of adverse events during melarsoprol treatment and reduce the risk to develop such.

This analysis has revealed issues that are important in the view of the structure and strategy of the sleeping sickness control. The costs of diagnosis and drugs to treat other conditions than sleeping sickness are not the biggest component for a sleeping sickness control program and normally the staff are already in place; therefore it could be a feasible issue to

systematically screen patients for other diseases, if only these centres had the technical resources and the respectively trained staff. The importance of the correct use of drugs to treat concomitant diseases has been underlined. In particular malaria treatment should be done according the national guidelines. This was often not the case in our study and chloroquine was used in most areas with known resistance. The best approach to concomitant treatment should be the issue of a specifically designed study.

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CHAPTER 4

Melarsoprol short course for the treatment of late stage sleeping sickness in children: a multicentre evaluation of tolerability and effectiveness

Schmid C[1], Chappuis F[2], Richer M[3], Josenando T[4], Miaka Mia Bilenge C[5], Doua F[6], Manthelot CR[7], Nangouma A[8], Asumu Ndongo P[9], Simarro PP[10], and Burri C[1]

[1]Swiss Tropical Institute, Socinstrasse 57, 4002 Basel, Switzerland ; [2]Médécins sans Frontières, Geneva, Switzerland ; [3]International Medical Corps, Nairobi, Kenya; [4]Instituto de Combate e de Controlo das Tripanossomíases, Luanda, Angola ; [5]Programme Nationale de Lutte contre la Trypanosomiase Humaine Africaine, Kinshasa, Democratic Republic of Congo; [6]Projet de Recherche Clinique sur la Trypanosomiase, Daloa, Côte d'Ivoire ; [7]Programme National de Lutte contre la Trypanosomiase, Brazzaville, Republic of Congo; [8]Programme National de Lutte contre la Trypanosomiase Humaine Africaine, Bangui, République Centrafricaine; [9]Programo Nacional de Control de Tripanosomiasis, Bata, Equatorial Guinea ; [10]CIDOB, Barcelona, Spain

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ABSTRACT

To assess the effectiveness of the 10-day melarsoprol treatment schedule in children with late-stage *Trypanosoma brucei gambiense* trypanosomiasis, we reviewed all children treated in the drug utilisation study (IMPAMEL II) executed between June 1999 and June 2002 for demographic, diagnostic and clinical features, tolerability and effectiveness of the treatment, and for reduction of symptoms and signs after therapy. 18.5% of all patients treated were children (n=441) below 15 years of age. There was a non-significant tendency for less encephalopathic syndromes in children (6.6% vs. 8.9% in adults) and an equal treatment related fatality rate as in adults (5.4% vs. 5.6%). In children, we observed significantly fewer polyneuropathies and headache but more maculopapular eruptions and fever, of which the latter can probably be partially explained by the higher rate of concomitant malaria in children. After treatment, the reduction of the symptoms and signs was comparable between children and adults and cure rates were with 94% identical in the subpopulations. There is evidence that the safety and efficacy profile of the 10-day schedule is similar in children and adults.

Keywords: trypanosomiasis, *Trypanosoma brucei gambiense*, melarsoprol, treatment outcome, adverse events, children

INTRODUCTION

Human African trypanosomiasis (sleeping sickness) in children is clearly underreported in the literature given the fact that they may be affected in many ways. First, the proportion of children with sleeping sickness below 15 years of age may be as high as 20-30% [Triolo *et al.,* 1985; Pepin *et al.,* 2002]; second, quite often children of sleeping sickness patients may be at higher risk of infection [Khonde *et al.,* 1997]; and third, an infection in a family reduces the workforce and may impair the nutritional status and health of the children. The few published reports on children are mainly small-scale studies, retrospective case descriptions focussing on clinical symptoms [Debroise *et al.,* 1968; Balint and Wenninger 1975; Le Bras *et al.,* 1977; Buyst 1977; Cramet 1982; Triolo *et al.,* 1985; Lingam *et al.,* 1985; Adams *et al.,* 1986; Buissonniere *et al.,* 1989; Benhamou *et al.,* 1989; Blanchot *et al.,* 1992; Jannin *et al.,* 1993; Kazumba *et al.,* 1993; Koko *et al.,* 1997; Pepin *et al.,* 2002], describing sleeping sickness in children as a fulminant disease, particularly in young children of less than 5 years of age [Aroke *et al.,* 1998], but very rarely dealing with the treatment outcome. Children are also said to suffer more from sequelae than adults [Cramet 1982; Triolo *et al.,* 1985; Kazumba *et al.,* 1993; Koko *et al.,* 1997; Aroke *et al.,* 1998] that may provoke growth retardation, delayed sexual maturity and poorer academic performance [Aroke *et al.,* 1998]. Considering this and the high proportion of children affected, it remains a mystery why so little emphasis has been given to sleeping sickness in children during the past century.

Sleeping sickness is an inevitably fatal disease if the patients are not treated. The drug mainly used to treat second stage *Trypanosoma brucei gambiense* sleeping sickness is melarsoprol, a highly toxic and not 100% effective drug [WHO 1998]. Another drawback are the lengthy, empirically developed treatment schedules used since its introduction more than 50 years ago. Burri et al (2000) developed a new concise treatment schedule and proved its non-inferiority of efficacy and safety in a randomised clinical trial in 500 adult patients. Thereafter, in a multinational drug utilisation study in sleeping sickness endemic countries (IMPAMEL II), the effectiveness under field conditions of the 10-day melarsoprol treatment schedule has been demonstrated [Schmid *et al.,* 2004]. Almost one fifth of the patients in this study were children below 15 years of age.

In this report we describe the clinical features of late-stage gambiense sleeping sickness in children and the treatment outcome after melarsoprol short course therapy.

METHODS

The study was a non-randomised drug utilisation study (IMPAMEL II, [Schmid *et al.,* 2004]) of the 10-day melarsoprol treatment schedule in 16 sleeping sickness treatment centres of 7 sub-Saharan African countries with endemic *T.b. gambiense* (Angola, Central African Republic, Côte d'Ivoire, Democratic Republic of Congo, Equatorial Guinea, Republic of Congo and Sudan). The only inclusion criterion for the patients was confirmed late-stage sleeping sickness due to *T.b. gambiense* according to the criteria of the respective national sleeping sickness control programs. Of the 2800 patients enrolled, 415 patients had to be excluded from this analysis for several reasons: combination treatment, other drug than melarsoprol, other disease than sleeping sickness, run-away during treatment and biased inclusion criteria (selection of adults in a better health state only). 2385 were eventually treated with the 10-day treatment schedule and among those, 441 (18.5%) were children below 15 years of age.

For each patient, a case report form was filled which contained demographic, diagnostic and clinical characteristics before and after treatment, and an assessment of adverse events during treatment on a graded scale from 0 to 2 (none, moderate, severe reaction). Diagnosis of late-stage was done by microscopic examination of the cerebrospinal fluid (CSF) for the presence of trypanosomes and/or an elevated white blood cell (WBC) count. The study was approved by the ethics committee of the two cantons of Basel (EKBB) and the relevant ethical committees and authorities in the respective countries. The 10-day schedule was introduced as the sole treatment in the selected centres and therefore no consent was obtained from the patients.

All patients, adults and children, were treated during 10 days with 2.2 mg/kg/day melarsoprol, as a 3.6% solution in propylene glycol (Arsobal® Aventis), by slow intravenous injection. Before melarsoprol treatment, all patients received supplementary medication: antimalarials (3 days chloroquine or Fansidar or 7 days quinine), mebendazole, multivitamins and paracetamol. During melarsoprol treatment, different prophylactic corticosteroid therapies were given (detailed in [Schmid *et al.,* 2004]). In case of occurrence of a severe (grade 2) adverse event, the treatment was interrupted and the patient was treated following the national guidelines, e.g. with adrenaline (epinephrine), corticosteroids (hydrocortisone or dexamethasone) and/or diazepam.

The safety and efficacy of the treatment were determined by the frequency of adverse events and the parasitological cure after treatment, respectively. Treatment failures were defined as cases in which trypanosomes could still be found in any body fluid 24 hours after treatment,

relapses as patients presenting at any time during follow-up with trypanosomes in any compartment and/or an increase of the white blood cells (WBC) in the cerebro spinal fluid (CSF) to more than 50 cells/mm^3 and have at least doubled compared to the previous examination or with 6 – 49 WBC in CSF and with clear symptoms attributed to relapse (somnolence, long lasting headache, recurrent fever).

Data management and analysis was done using EpiData 2.1 [Lauritsen and Bruus 2001] and STATA 7.0 [Stata 2001] software. Proportions were compared with the X^2 test or Fisher's exact test whenever appropriate and difference in means was demonstrated with the confidence interval for the difference of the means. The findings were compared to the literature, the centres' histories and the randomised clinical trial recently executed in Angola [Burri *et al.,* 2000; Schmid *et al.,* 2004]. For the calculation of the efficacy (i.e. cure rate, treatment failures and relapses) all patients treated were used as denominator to facilitate the comparison to previously reported rates.

RESULTS

Table 1 shows the demographic, diagnostic and clinical characteristics of the study population on admission according to age. Similar to adults, children were diagnosed with a delay of 5 months after onset of symptoms. The diagnostic findings were comparable to adults except for less WBC in the CSF ($p<0.05$). Malnutrition, defined as age- and sex-adjusted body mass index (BMI), was more frequent in children (35.1% vs. 19.1%; $p<0.05$). The mean number of symptoms and signs per patient recorded on admission was 4, equal in both, children and adults. Yet, pre-treatment clinical characteristics differed substantially between the two groups. Children were less frequently admitted with headache, pruritus and motor weakness, but more with fever, abnormal movements and strange behaviour (all $p<0.05$). The rate of concomitant malarial infections found was higher in children than in adults (29.7% vs. 23.8%, $p=0.0023$) that probably may have attributed to the higher fever rate in children.

Adherence to the treatment regimen was high in all patients, 69.7% (1663/2385) were treated without interruptions. At treatment end there was no difference in the proportion of patients that completed the 10 doses of melarsoprol (children 87.5%, adults 89.7%, $p=0.18$). Non-adherence was a result of treatment interruption due to severe (grade 2) adverse reactions but treatment was resumed in most cases after 2-4 days. Treatment was interrupted more often in children than in adults (35.1% vs. 29.2%; $p=0.014$).

Table 2 summarises the adverse events that occurred during the course of treatment according to age. A total of 132 (5.5%) patients died: 24/441 (5.4%) among children compared with 108/1944 (5.6%) among adults ($p=0.93$). No difference was reported in the cause of death between children and adults: 87 (3.6%) cases died of encephalopathic syndrome, 5 (0.3%) of a fatal skin reaction, 15 (0.6%) of advanced disease, 10 (0.4%) of concomitant disease and 15 (0.6%) were not classifiable (data not shown). There was a non-significant tendency in children to develop less encephalopathic syndromes and no difference in the types of syndromes compared to adults was observed. In general, children experienced more severe reactions (31.7% vs. 22.9%, RR 1.43, CI 1.20 to 1.70, $p=0.0001$) that were resolved with treatment interruption and concomitant medication. They developed significantly more fever and maculopapular eruptions, but on the contrary they suffered less from polyneuropathies (motor and sensitivity) and severe headache during treatment. Among all treated patients, there was no significant difference between children and adults with regard to incidence of bullous eruptions, pruritus, hypotension, diarrhoea and jaundice. And disregarding the age of the patient, adverse events occurred in average on day 6 of treatment and lasted 2 to 4 days (median 6, mean 6.1 and standard deviation 3.4 days).

Table 1: Demographic, diagnostic and clinical characteristics of gambiense sleeping sickness patients, according to age

	Children		Adults			
Characteristic	n	%	n	%	RR (95% CI)[a]	P-value
Total patients (N = 2385)	441	18.5	1944	81.5		
Male sex	222	50.3	944	48.6		0.4995
Age categories (years)						
(1) ≤ 2	36	8.2				
(2) 3 - 6	65	14.7				
(3) 7 - 10	127	28.8				
(4) 11 - 14	213	48.3				
(5) ≥ 15			1944	100.0		
Malnutrition[b]	155	35.1	381	19.6	1.87 (1.58 to 2.22)	< 0.0001
Duration of symptoms (months)[c]	5 (7 ± 7)		5 (7.7 ± 7.8)		-0.7 (-1.4 to 0.1)	0.9645
Previous HAT treatment[d]	43	9.8	144	7.4	1.26 (0.96 to 1.67)	0.1086
thereof Arsobal	12	2.7	55	2.8	0.92 (0.68 to 1.24)	0.5852
Diagnostic findings						
Lymphadenopathy	248	56.2	1135	58.4	0.92 (0.78 to 1.10)	0.3481
Trypanosomes in any compartment	375	85.0	1653	85.0	1.00 (0.79 to 1.27)	0.9987
Trypanosomes in CSF	177	40.1	755	38.8	1.04 (0.87 to 1.23)	0.6786
Trypanosomes in blood / lymph	322	73.0	1421	73.1	1.00 (0.94 to 1.06)	0.9724
White Blood Cell Count in CSF[c]	61 (138 ± 192)		76 (178 ± 240)		-40 (-61 to -19)	<0.0001
≤ 19 cells/ul	103	23.4	497	25.6	0.97 (0.80 to 1.67)	0.7248
20 - 100 cells/ul	167	37.8	565	29.1	1.30 (1.13 to 1.49)	0.0003
> 100 cells/ul	171	38.8	882	45.4	0.80 (0.67 to 0.95)	0.0097
Clinical manifestations						
Drowsy	67	15.2	278	14.3	1.06 (0.84 to 1.34)	0.6304
Headache	324	73.5	1580	81.3	0.70 (0.58 to 0.84)	0.0002
Fever (>37.5°C)	116	26.3	278	14.3	1.80 (1.50 to 2.16)	<0.0001
Pruritus	192	43.5	1015	52.2	0.75 (0.64 to 0.89)	0.0012
Tremor	73	16.6	393	20.2	0.82 (0.65 to 1.03)	0.0875
General motor weakness	128	29.0	679	34.9	0.80 (0.66 to 0.96)	0.0188
Walking difficulties	82	18.6	411	21.1	0.89 (0.71 to 1.11)	0.2927
Abnormal movements	58	13.2	188	9.7	1.32 (1.03 to 1.68)	0.0295
Speech impairment[e]	68	15.4	254	13.1	1.23 (0.96 to 1.55)	0.0842
Sleeping disorder	343	77.8	1436	73.9	1.20 (0.98 to 1.48)	0.0758
Appetite problems	111	25.2	426	21.9	1.16 (0.96 to 1.40)	0.1430
Strange behaviour	135	30.6	461	23.7	1.33 (1.11 to 1.59)	0.0023
Inactivity	90	20.4	442	22.7	0.89 (0.72 to 1.10)	0.2985
Aggressivity	39	8.8	132	6.8	1.26 (0.95 to 1.69)	0.1202
Concomitant diseases[f]	190	43.1	767	39.5	1.13 (0.95 to 1.34)	0.1604
Malaria (N=1637)	131	44.0	463	34.6	1.37 (1.12 to 1.69)	0.0023
Intestinal parasites[g]	48	10.9	201	10.3	1.05 (0.80 to 1.37)	0.7355
Filaria[h] (N=1335)	8	3.5	92	8.3	0.44 (0.22 to 0.87)	0.0087

N: total number of patients treated; n: number in each sub-population; RR: risk ratio; CI: 95% confidence interval; a P value smaller than 0.05 is considered significant; CSF: cerebrospinal fluid

[a]X^2 test or 95% CI for the difference of means; [b]age and sex adjusted malnutrition based on body mass index (adults BMI<17); [c]Median (mean ± standard deviation); [d]within 2 years before admission to IMPAMEL II study

[e]only children ≥2 years evaluated; [f]large number of missing data; [g]schistosomes, hookworms, geohelminths, amoeba, giardia; [h]O. volvulus, Loaloa, M. perstans

Table 2: Distribution of adverse events during 10-day melarsoprol treatment, according to age

	Children (N = 441)		Adults (N = 1944)			
Adverse event	n	%	n	%	RR (95% CI)	P-value
Fatalities[a]	24	5.4	108	5.6	0.98 (0.68 to 1.42)	0.9251
Encephalopathic syndromes	29	6.6	173	8.9	0.76 (0.54 to 1.08)	0.1137
Grade 3 (fatal)	13	2.9	74	3.8	0.80 (0.48 to 1.33)	0.3852
Grade 2 (coma, convulsion)	14	3.2	73	3.8	0.87 (0.53 to 1.41)	0.5571
Grade 1 (psychotic)	2	0.5	26	1.3	0.38 (0.10 to 1.46)	0.1447
Bulluous eruptions						
Any	10	2.3	32	1.6	1.29 (0.75 to 2.24)	0.3703
Severe	3	0.7	21	1.1	0.67 (0.23 to 1.95)	0.6011
Maculopapular eruptions						
Any	77	17.5	172	8.8	1.81 (1.47 to 2.23)	<0.0001
Severe	44	10.0	105	5.4	1.66 (1.28 to 2.16)	0.0003
Pruritus						
Any	95	21.5	416	21.4	1.00 (0.82 to 1.24)	0.9474
Severe	16	3.6	53	2.7	1.26 (0.81 to 1.96)	0.3077
Motor polyneuropathy						
Any	16	3.6	135	6.9	0.56 (0.35 to 0.89)	0.0098
Severe	6	1.4	36	1.9	0.77 (0.36 to 1.62)	0.4788
Sensitivity polyneuropathy						
Any	2	0.5	70	3.6	0.15 (0.04 to 0.58)	0.0001
Severe	0	0.0	26	1.3		
Febrile reaction						
Any (37.5 - 39°C)	177	40.1	532	27.4	1.58 (1.34 to 1.88)	<0.0001
Severe (>39°C)	73	16.6	178	9.2	1.68 (1.36 to 2.09)	<0.0001
Headache						
Any	93	21.1	556	28.6	0.71 (0.58 to 0.88)	0.0019
Severe	33	7.5	125	6.4	1.14 (0.83 to 1.56)	0.4222
Diarrhea						
Any	39	8.8	153	7.9	1.11 (0.83 to 1.49)	0.4977
Severe	11	2.5	40	2.1	1.07 (0.69 to 1.99)	0.5671
Hypotension						
Any	15	3.4	75	3.9	0.90 (0.56 to 1.43)	0.6496
Severe	4	0.9	17	0.9	1.03 (0.42 to 2.50)	1.0000
Jaundice						
Any	4	0.9	6	0.3	2.17 (1.01 to 4.66)	0.0954
Severe	3	0.7	3	0.2	2.71 (1.21 to 6.07)	0.0810

N: total number of patients treated in each sub-population; n: number of events; RR: risk ratio; CI: 95 confidence interval; P-value: a value smaller than 0.05 is considered significant; [a]All fatalities during treatment, including fatal ES

After treatment, the clinical symptoms and signs were substantially reduced in children as well as in adults, without significant difference between the groups (Graph 2).

Graph 2: Percent of reduction of the clinical symptoms and signs in children and adults at hospital discharge after 10-day melarsoprol treatment

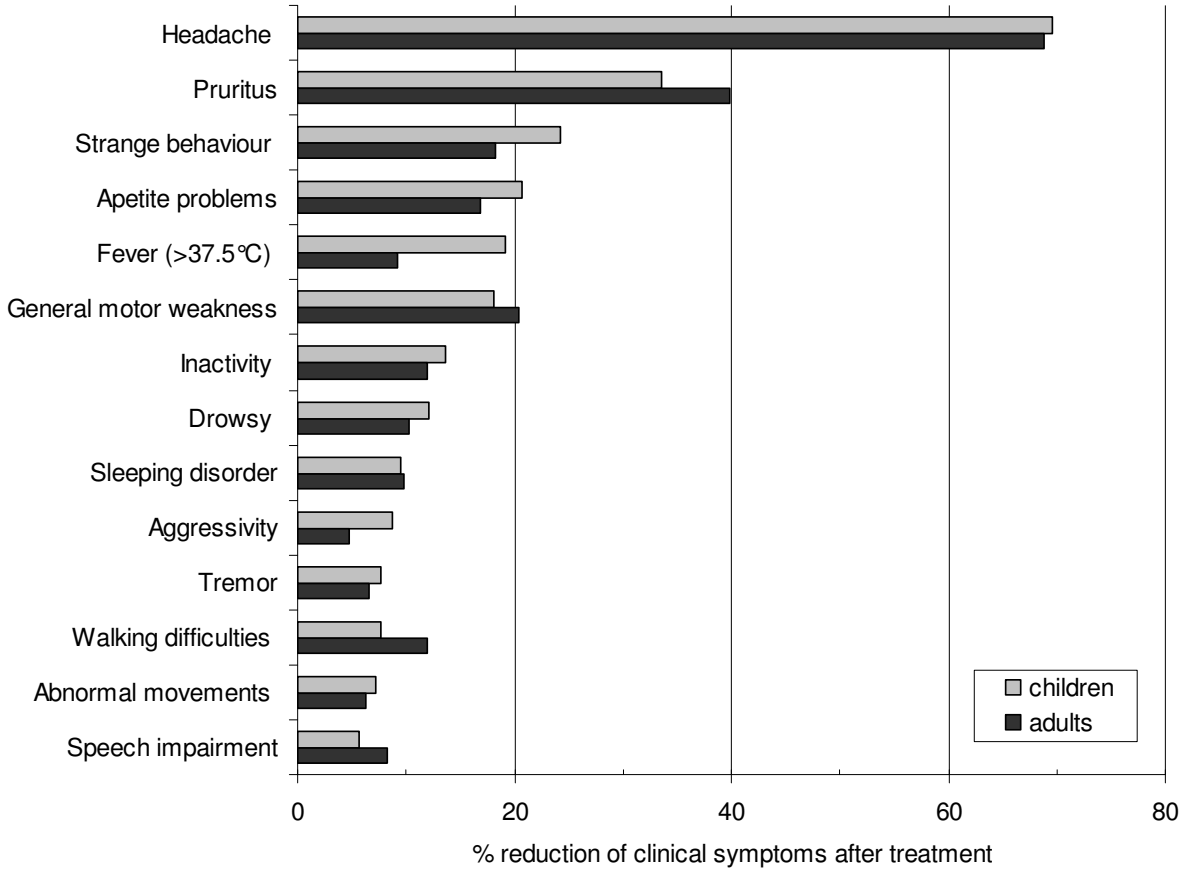

Table 3 shows the treatment efficacy of the 10-day melarsoprol treatment schedule according to age. Twenty four hours after treatment, 5 (0.2%) patients were diagnosed treatment failures, with trypanosomes in CSF in 4 patients (1 child, 3 adults) and in blood in 1 patient (1 child). At discharge, the cure rate was 94.3% for all patients (defined as discharged alive and no parasites detected) without any disparity for the children. During the 2 years' follow-up period, 24 patients died (1%, 24/2385) and 159 (6.7%, 159/2385) were diagnosed as relapses, at comparable rates for children and adults (both not significant). Slightly more children (45%) were seen for at least one follow-up examination as compared to adults (40%; RR 1.2, CI 1.0 to 1.4, p=0.047).

Table 3: Efficacy of the 10-day melarsoprol treatment schedule in children

	Children		Adults			
	n	%	n	%	RR (95% CI)	P value
Treatment						
Patients treated (N = 2385)	441	18.5	1944	81.5		
Fatalities during treatment	24	5.4	108	5.6	0.98 (0.68 to 1.42)	0.9251
Treatment failures at discharge	2	0.5	3	0.2	2.17 (0.74 to 6.36)	0.2324
Cured at discharge	415	94.1	1833	94.3	0.97 (0.68 to 1.39)	0.7897
Follow up*						
Fatalities during follow up[a]	5	1.1	19	1.0	1.13 (0.51 to 2.47)	0.7910
Relapses during follow up[a]	33	7.5	126	6.5	1.13 (0.82 to 1.55)	0.4465
Lost during follow up	242	54.9	1163	59.8	0.84 (0.71 to 1.00)	0.0468
Cured 2 years after treatment	378	85.7	1694	87.1	0.91 (0.71 to 1.15)	0.4234

*Denominator: all patients treated under the assumption that all patients lost were considered cured; [a]1 child and 6 adult relapses died and are included in both, the relapses and the fatalities

DISCUSSION

Sleeping sickness of the child due to *Trypanosoma brucei gambiense* is rarely described in the literature and in particular, studies on the relationship of age to the effects of melarsoprol cannot be found in the paediatric population. Despite of this, some authors and medical authorities recommend a reduced dosage regimen for children [Buyst 1975, 1977; Buck *et al.,* 1978; Pharmacopeia 2003]. Additionally, medical staff treating sleeping sickness inherently believe that melarsoprol harms children more than adults. Therefore, we have specifically analysed the outcome of the 10-day melarsoprol treatment schedule in children with late-stage gambiense sleeping sickness in the frame of a large multicentre drug utilisation study (IMPAMEL II). In this study we could demonstrate that the outcome of treatment with the 10-day melarsoprol protocol in children is not worse than in adults. The findings in terms of safety and efficacy were highly variable between the treatment centres, but in an expected range.

Some authors raised concern that sleeping sickness was diagnosed in children later after infection than in adults [Balint and Wenninger 1975; Kazumba *et al.,* 1993; Koko *et al.,* 1997] which was assumed to contribute to a worse outcome of treatment in children and to more long-term sequelae from the disease [Cramet 1982; Triolo *et al.,* 1985; Kazumba *et al.,* 1993; Koko *et al.,* 1997; Aroke *et al.,* 1998]. This is not the case in our study, where the self-reported duration of symptoms in the children was in the same range than in adults. The only discrepancy we could note was inter-centre differences in the duration of symptoms, which is rather reflecting the screening activities and mode of admission of the respective treatment centres. The shorter time in hospital allowed by the 10-day treatment schedule may not be translated into a quicker overall time to full recovery, which is certainly the reason for the poor reduction rate of the neurological symptoms shown in graph 2. However, the limited follow-up activities and the design of the study did not allow us to monitor for long-term sequelae in children.

Malnutrition and concomitant diseases in children are known to decrease their resistance for infections and possibly decelerate the cure, or even worse, to increase the risk for a fatal outcome [Balint and Wenninger 1975; Buyst 1977; Aroke *et al.,* 1998]. In our cohort, no effect of malnutrition on the tolerability and effectiveness of the treatment in children could be found although a large proportion of children were seriously undernourished on admission. Patients at any age with concomitant infectious diseases, mainly malaria, were at higher risk to develop an adverse event during treatment (RR 1.9, 95% confidence interval 1.7 to 2.1, $p<0.0001$) and had an elevated risk of a fatal outcome if malaria was diagnosed during the treatment course (RR 1.5, 95% confidence interval 1.3 to 1.8, $p=0.0002$). Hence, in our large

cohort we could demonstrate the suspected detrimental effect of concomitant infections, especially malaria [Buyst 1975; Balint and Wenninger 1975; Blum *et al.,* 2001] not only for the children, but for all patients. Malaria is endemic in the sleeping sickness foci, diagnosis rarely done and drugs in use with known high levels of resistance (e.g. chloroquine). In our series, 90% of the patients received chloroquine as antimalarial pre-treatment and under the assumption that a large proportion of the patients have not been sufficiently cured from malaria, reappearance during the course of melarsoprol might have biased and worsened the outcome. Therefore, there is evidence that diagnosis and complete treatment of concomitant infections with adequate drugs may reduce the risk for the patient. Whereas this holds true for malaria, the approach may be less favourable for diseases with a prolonged treatment course (e.g. filariasis).

Children were diagnosed with fewer white blood cells per mm^3 in CSF than adults without difference in any other diagnostic parameter. Normally, the clinical description is the same as in adults [Ngandu-Kabeya 1976; Kazumba *et al.,* 1993]. In our study, the clinical picture of sleeping sickness in children varied with that of adults, we found that the incidence of fever, altered behaviour and abnormal movements were significantly higher and headache, pruritus and motor weakness much lower in children (all $p<0.05$). Changes in walking ability and speech disorder are difficult to compare between the age groups and findings as headache, fever, pruritus and polyneuropathies are difficult to relate solely to sleeping sickness or to assess in children.

Overall, the fatality rate in this study was 5.5% (5.4% of children, 5.6% of adults) without any difference between the age groups and the distribution of the cause of death. The highest treatment related fatality rate was seen in children aged 1-2 years, however the difference was not significant (8.3%, $p=0.45$). 3 of 36 children in this age group died during treatment, 2 of them from an encephalopathic syndrome and 1 of unknown reason but with malaria parasites detected. Treatment related fatality rates in children were reported by other authors to be associated with a range of factors on admission [Balint and Wenninger 1975; Kazumba *et al.,* 1993; Koko *et al.,* 1997], one of them being the general health state of the child (malnutrition, concomitant infections, number of white blood cells in CSF and grade of neurological involvement). In our cohort, we could only show this relationship for the adult population in which advanced disease (defined as a WBC > 100 cells per mm^3 in CSF) was a risk factor for a fatal outcome of the treatment (RR 1.3, 95% confidence interval 1.1 to 1.6, $p=0.0033$).

Children seemed to develop less encephalopathic syndromes (children 6.6%, adults 8.9%) and in particular less psychotic reactions (termed grade 1 encephalopathic syndrome; children 0.5%, adults 1.3%) but at non-significant levels ($p>0.05$). The latter are not easy to

assess in children and therefore difficult to compare to adults. In addition, there was no difference between the age groups in the risk factors present on admission for the development of an encephalopathic syndrome during melarsoprol treatment, that were identified in previous reports [Ancelle *et al.,* 1994; Pepin *et al.,* 1995; Schmid *et al.,* 2004] like elevated white blood cell count in CSF, headache, malaria, general weakness, polyneuropathies, drowsiness, or a bad general health state.

During melarsoprol treatment, children experienced more severe (grade 2) adverse reactions, mainly fever and maculopapular eruptions, but also more malaria parasites were detected in children than in adults, which may have contributed to the higher fever rate. On the contrary, less polyneuropathies and headache were noted in children. The use of the questionnaire and the fear of treating children with the new treatment schedule, that was felt as more aggressive than the old one, might have introduced an observation bias. Additionally, the doctor's perception may have played an important role in defining the tolerability of the treatment in this non-randomised study approach.

The treatment efficacy of the 10-day melarsoprol schedule was comparable to previous studies [Burri *et al.,* 2000; Pepin *et al.,* 2002; Schmid *et al.,* 2004], with cure rates of 94% at hospital discharge and 87% 2 years after treatment. Treatment efficacy has rarely been described for the children and is therefore difficult to compare to literature. The few reports that deal with the melarsoprol long-term efficacy in children [Le Bras *et al.,* 1977; Triolo *et al.,* 1985; Kazumba *et al.,* 1993] often refer to a high mortality rate in this age group.

Treatment failures and relapses were difficult to assess in this study, since the follow-up was highly variable between centres (0-100%) and only 50% of patients attended at least one follow-up examination. Additionally, for many areas the normal failure rate is unknown.

We showed that the safety and efficacy profile of the 10-day melarsoprol treatment in children is similar to the one in adults. Bearing in mind the current drug situation with limited drugs available, the difficulties in the regular use of eflornithine and little hope for new drugs to come to the market within the next years, melarsoprol remains the most frequently used drug to treat late-stage gambiense sleeping sickness. Thus, an abridged treatment schedule bears the advantages of a shorter treatment duration and hospitalisation of the patients, less drug per patient and reduction of the overall treatment costs.

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CHAPTER 5

An economic appraisal of the melarsoprol 10-day treatment

Schmid C[1], Shaw A[2], Santercole C[3], Kwete J[4], Lutumba P[4] and Burri C[1]

[1]Swiss Tropical Institute, Basel, Switzerland; [2]AP Consultants, Hampshire, UK; [3]Belgian Technical Cooperation, Luanda, Angola ; [4]Programme Nationale de Lutte contre la Trypanosomiase Humaine Africaine, Kinshasa, Democratic Republic of Congo

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A short version of the manuscript will be submitted to the Bulletin WHO

SUMMARY

The most effective form of control of gambiense sleeping sickness is active case detection and treatment of the cases. Until today, the majority of the patients in the advanced stage of the disease are treated with melarsoprol. Only recently, the clinical effectiveness of a new concise treatment schedule has been demonstrated in a large scale multinational study (IMPAMEL II). The focus of this analysis is on the costs of treatment of late-stage sleeping sickness with melarsoprol to identify the costs and benefits that are involved in switching from the lengthy standard treatment schedules to the shorter 10-day schedule.

Data were collected during the multinational study IMPAMEL II in 1999-2004 in 7 sub-Saharan African countries endemic for *T.b. gambiense* sleeping sickness. The costs of treatment (diagnosis, hospitalisation and sleeping sickness specific treatment) were assessed in two rural treatment centres and compared to the benefits of the 10-day treatment and of the standard treatments. The effectiveness was measured by the cost of treatment per DALY (disability-adjusted life-year) averted.

We found the 10-day treatment schedule to be more cost-effective than the standard treatment. The net benefit from switching from the standard to the 10-day treatment schedule did reduce the cost per DALY averted from US$11.5 to US$6.9 in DRC and from US$69.4 to US$33.0 in Angola, a saving of US$4.6 (DRC) or US$36.4 (Angola) per DALY. Added to the clinical effectiveness, the short course melarsoprol schedule also presents as a highly cost-effective treatment option.

Keywords *T.b. gambiense*, melarsoprol, cost-effectiveness, treatment, late-stage, hospitalisation

BACKGROUND

The burden of Human African Trypanosomiasis (HAT) or sleeping sickness ranks third of all parasitic diseases in sub-Saharan Africa, just behind malaria and helminths, in terms of disease burden expressed in DALYs (disability-adjusted life years, [WorldBank 1993; WorldHealthReport 2004]). There are two forms of the disease. The chronic gambiense form, which is found in central and western Africa, has a long course, and its reservoir is almost entirely in the human population. The rhodesiense or eastern African form is a much more acute disease and has an important zoonotic component, with transmission to people from both domestic livestock and game [WHO 1998].

Untreated, the disease is invariably fatal. The chemotherapy of HAT is unsatisfactory, relying on a few drugs which have severe side effects. Melarsoprol, a trivalent organo-arsenical derivative developed in 1949 [Friedheim 1949], is used for the treatment of the late-stage of the disease. The various treatment schedules were developed empirically and all are of long duration. Therefore, a concise treatment regimen has been developed by Burri et al. (2000) and shown that it was possible to reduce the duration of treatment from around 30 to 10 days [Burri *et al.,* 2000; Schmid *et al.,* 2004; Schmid *et al.,* 2004].

The most effective form of control of gambiense sleeping sickness is medical surveillance, involving case detection and treatment to reduce the human reservoir of the disease, so as to lower its incidence [WHO 1998, 2001]. A wide range of options for case detection and treatment do exist [Cattand *et al.,* 2001] and evidence-based information on the relative cost-effectiveness of these is urgently needed both in order to plan resource allocation within the field of HAT control and to demonstrate that controlling this disease is a highly cost-effective use of scarce health resources. However, the economics of different control strategies and their cost-effectiveness have only been studied very sporadically. In their review, [Walker and Fox-Rushby 2000] found only 2 out of 107 papers dealing with HAT, and to date there are still only a handful of papers [Shaw 1989; Politi *et al.,* 1995; Laveissiere *et al.,* 1998; Shaw and Cattand 2001; Ruiz Postigo *et al.,* 2001]. The information that exists is thus often dated, very location specific and large gaps remain. The most important gaps with respect to the costs are treatment and particularly hospitalisation costs. Estimates indicate that the latter may account for 50% or more of the total cost of a control strategy based on active case-finding and detection once the HAT prevalence exceed 1% [Shaw and Cattand 2001].

In the multicountry study IMPAMEL II, we demonstrated the clinical effectiveness of the 10-day melarsoprol treatment schedule under field conditions [Schmid *et al.,* 2004], and we claimed amongst its major advantages over the lengthy standard treatment schedules were reduced

hospitalisation and a lower drug use per patient. To illustrate our assumption we studied the costs of treating a late-stage gambiense sleeping sickness patient. The focus of this analysis was on the identification of the overall costs of treating late-stage gambiense sleeping sickness patients with melarsoprol. This included the costs of diagnostic tests, treatment with melarsoprol 10-day schedule, treatment with the standard schedule, hospitalisation of a patient in a rural sleeping sickness treatment centre and post-treatment follow-up tests. The aim was to calculate net benefit in switching from standard to 10-day melarsoprol treatment schedule.

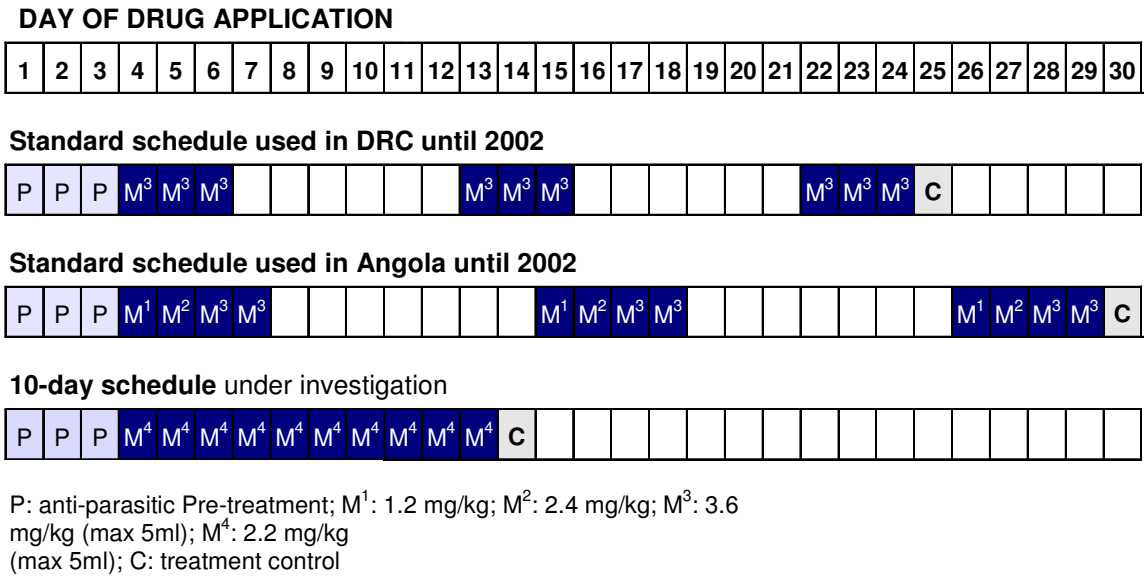
METHODS

Two options of melarsoprol (Arsobal®, Aventis) regimens were considered, the standard treatment as the baseline and the short, 10-day treatment schedule as the alternative. The analysis was done for 2 rural treatment centres in different countries (Maluku in Democratic Republic of Congo (DRC) and Ndalatando in Angola) that participated in the multinational drug utilisation study (IMPAMEL II). Both centres are operated by the national control programs and supported to a high degree by the Belgian Technical Cooperation (CTB). Calculations were performed with reference to 494 gambiense sleeping sickness patients (201 in Maluku and 293 in Ndalatando) treated during 1 year in the respective centres (Maluku in 2001 and Ndalatando in 2003). Current local market prices in each country in US$ for March/April 2004 were used throughout. The use of local market prices reflected the objective of finding out what the range of financial costs in two contrasting situations will be. The resulting analysis is thus, strictly speaking, a financial analysis, but as the value of the drugs which are currently supplied free of charge are included as full cost items, it deals with most of the parameters normally included in a full economic analysis.

Treatment schedules under investigation

Until 2002, the following treatment schedules named “standard” regimens were in use [Cattand 2000] (Graph 1). In the Democratic Republic of Congo (DRC), the duration of hospitalisation for a patient was normally 25 days, comprising of an anti-parasitic pre-treatment lasting 3 days, melarsoprol treatment (3 series of 3*3.6 mg/kg bodyweight (max 5 ml) injections, spaced by 6 days each) and post-treatment examination (1 day). In Angola, the duration of hospitalisation under the standard treatment lasted 30 days: anti-parasitic pre-treatment (3 days), melarsoprol treatment (3 series of 4 injections at increasing doses, 1.2, 2.4, 3.6, 3.6 mg/kg bodyweight (max 5 ml), spaced by 7 days each) and post-treatment examination (1 day). The alternative schedule under investigation consisted of 10*2.2 mg/kg bodyweight (max 5ml) without rest periods [Burri *et al.,* 1995; Burri *et al.,* 2000] and complete hospitalisation lasted 14 days (consisting of 3 days anti-parasitic pre-treatment, 10 days melarsoprol treatment and 1 day post-treatment examination). If treatment was interrupted due to the occurrence of severe adverse events, the total hospitalisation increased on average by another day.

Graph 1: Comparison of the different schedules for late-stage *T.b. gambiense* sleeping sickness treatment with melarsoprol.



P: anti-parasitic Pre-treatment; M^1: 1.2 mg/kg; M^2: 2.4 mg/kg; M^3: 3.6 mg/kg (max 5ml); M^4: 2.2 mg/kg (max 5ml); C: treatment control

Quantifying the costs

Direct costs linked to the treatment options were measured as the total costs of diagnosis (including post-treatment examinations), drug treatment and hospitalisation. Costs involved for diagnosis and follow-up examinations are the same irrespective of the treatment schedule used. Thus, an average value was calculated based on the types and frequencies of tests done during the Impamel II study. The total costs of drug treatment included the cost of melarsoprol, drugs used for pre-treatment and concomitant treatment, and drugs to treat side effects. Hospitalisation costs were calculated based on the consumption of the Maluku treatment centre in DRC in 2001 (at current market prices in US$, March 2004) and the number of patients treated. For comparison, similar calculations were done for the Ndalatando treatment centre in Angola for the year 2003 (at market prices in US$, April 2004).

Quantifying the outcomes

The non-inferiority of the 10-day treatment schedule for melarsoprol has been demonstrated [Burri *et al.,* 2000; Schmid *et al.,* 2004; Schmid *et al.,* 2004], thus, the outcome of both treatment schedules was considered the same.

Effectiveness was quantified using: the net monetary benefit in US$ for the treatment of a late-stage patient with melarsoprol obtained by switching from the lengthy standard treatment to the shorter 10-day treatment schedule and the cost per DALY (disability-adjusted life year) averted, one DALY being defined as the loss of one year of healthy life to disease. The DALY has been calculated based on the method described by Politi *et al*. (1995) using the age-at-death of patients in the IMPAMEL II study and their life expectancies (approximate estimation taken from the World Bank Report 1993, Appendix B, Box 1.3) [WorldBank 1993]. These ages-at-death were taken as giving the best available estimate within the study for the years of life lost (YLL) which late-stage patients who were not treated and cured would have encountered. Although, late-stage patients who were not treated and cured would also have suffered some years of life with disability (YLD), these could not be estimated here. This approach allowed calculation of the cost-effectiveness of the two treatments in this analysis to be compared with previous findings [Politi *et al.,* 1995; WHO 1998, 2001] and also with the preferred drug for late-stage sleeping sickness, eflornithine.

RESULTS

The cost of diagnosis

The prices for the diagnostic tests derived from previous calculations (Dr Pere Simarro, Dr Veerle Lejon, personal communications and [WHO 1998]) and included only material costs; consumables, equipment and salaries of staff were included in the costs of hospitalisation. The average cost for diagnosis of a patient was calculated based on the number of tests done in the two treatment centres during the IMPAMEL II study. Cost of diagnosis also included the examination 24 hours after treatment and the follow-up examinations done during the 2 year follow-up period. The same prices were used for both countries and the total cost calculated for the diagnosis of a patient at the treatment centre was 3.91 US$, comprising the initial serological (CATT) and the subsequent parasitological tests including material for blood, lymph and CSF sampling (Table 1).

Table 1: Cost of diagnosis per patient, based on the frequencies of tests done in DRC and Angola during the Impamel II study, in US$.

		Diagnosis		**Treatment examination**		**Follow up (4 controls)**	
	Price / test US$	Rate of population tested	Cost per test done US$	Rate of population tested	Cost per test done US$	Rate of population tested	Cost per test done US$
CATT	0.33	1.00	0.33	0.00	0.00	0.00	0.00
CATT dilution	0.54	0.50	0.27	0.00	0.00	0.00	0.00
Lymph examination	0.16	0.55	0.09	0.17	0.03	0.17	0.03
Blood examination	0.32	0.38	0.12	0.36	0.12	0.10	0.03
CSF examination (LP)	1.25	1.00	1.25	0.93	1.17	0.37	0.46
Double centrifugation of CSF	0.16	0.05	0.01	0.06	0.01	0.00	0.00
Cost per patient			**2.07**		**1.32**		**0.52**
Total diagnostic costs per patient							**3.91**

The cost of hospitalisation

The hospitalisation costs included the annual hospital costs and the number of patient days spent in the hospital (Table 2). The annual hospital costs were calculated from capital and recurrent costs (detailed in Annex I & II), whereas recurrent consisted of running costs, salaries and consumables and capital costs of equipment depreciation. The patient days per year derived from the number of patients treated during 1 year and were estimated for Angola (based on an average stay of 14 days for the 10-day schedule and 30 days for the standard schedule) and partially calculated for DRC (calculated for the 10-day schedule

based on the IMPAMEL II database and estimated at 25 days for the standard treatment schedule). The items included in these hospitalisation costs were broadly the same for both countries. Both included a relatively high cost for the use of the hospital and laboratory building, a notional rent in DRC and full refurbishment in Angola and in both cases utilities (water and electricity) were supplied free. Rather than include a notional cost for the latter, we estimated that these were adequately covered by the high building cost. Additionally in Angola, some basic food items as sugar, oil and maize were provided to the patients. The resulting estimate of the cost of a patient day would then be US$ 10 in DRC and in US$ 66 in Angola. The reasons for this wide differential are discussed below.

Table 2 Hospitalisation costs calculated as cost per patient day, by centres/countries, in US$.

	DRC Maluku **US $**	Angola Ntalatando **US $**
Recurrent costs		
Running Costs	9'408	39'664
Salaries	23'280	114'696
Consumables[1]	280	946
Total hospital recurrent costs	32'968	155'306
Capital costs		
Equipment (itemised depreciation)[2]	2'771	18'236
Total hospital capital costs	2'771	18'236
Total annual hospital cost	**35'739**	**173'542**
Number of patient days per year[3]		
SS1[4]	612	297
SS2[5]	2'912	2'338
Total patient days	**3'524**	**2'635**
Hospitalisation cost per patient day[6]	**10.14**	**65.86**

[1]includes syringes, gloves, stationaries

[2]furniture, miscroscopes etc

[3]year 2001 for Maluku and 2003 for Ntalatando

[4]SS1: number of days estimated based on theoretic days of hospitalisation

[5]SS2: number of days calculated for Maluku from IMPAMEL II study and for Ntalando estimated on theoretic days of hospitalisation

[6]excluding sleeping sickness specific medication and tests

The cost of treatment

The costs of treatment were calculated based on today's market prices of the two countries (March 2004), the number of patients treated (DRC in 2001, Angola in 2003), and the respective drug consumption in the same year. The results are given in Table 3. The prices of the drugs were highly variable between the two countries.

The anti-parasitic pre-treatment was the same in both countries and consisted of anti-malarial (chloroquine) and anti-helminthic (mebendazole) treatment during 3 days before applying melarsoprol, as described more detailed in the overall IMPAMEL II analysis [Schmid *et al.,* 2004].

Melarsoprol was calculated based on a 50 kg patient as follows:

- 10-day schedule: 10*2.2mg/kg*50 kg = 1100 mg = 6.1 ampoules at the latest price of 8 US$ = 48.9 US$ and if 20% transport costs added = 58.6 US$
- standard schedule in DRC: 3*3*3.6 mg/kg*50 kg = 1620 mg = 9 ampoules at US$ 8 = 72 US$ and if 20% transport costs added = 86.4 US$
- standard schedule in Angola: 3*(1.2+2.4+3.6+3.6) mg/kg*50 kg = 1620 mg = 9 ampoules at US$ 8 = 72 US$ and if 20% transport costs added = 86.4 US$

Concomitant drugs that were given during melarsoprol treatment varied between the centres/countries: in Angola, multivitamins were given to each patient during the whole hospitalisation period and in DRC only to those needing re-nutrition. Corticosteroids (prednisolone) were given to the patients treated with the 10-day treatment schedule in both, Angola and DRC, but at slightly different dosages [Schmid *et al.,* 2004]. However, under the standard treatment for melarsoprol, the use of concomitant corticosteroids was very different: whereas in DRC no prednisolone was given, the patients in Angola received it.

Additional drugs used were mainly for the management of adverse effects of melarsoprol therapy and the costs calculated for these were based on the number of patients with severe adverse events (SAE) and the additional drug consumption in the respective year.

The costs for treatment varied highly between the countries and the different treatment schedules. The large local price differences accounted for the much higher costs in Angola (Appendices I & II).

Table 3 Cost of treatment calculated as cost per patient day. Drugs for pre-treatment, melarsoprol treatment, concomitant medication and management for severe adverse events (SAE) are included, in US$.

	10-day schedule		Standard schedule	
		+ management of SAE		+ management of SAE
Democratic Republic of Congo				
Pre-treatment	0.66	0.66	0.66	0.66
Melarsoprol	58.60	58.60	86.40	86.40
Concomitant drugs	0.58	0.58	0.06	0.06
Drugs for management of SAE[1]	0.00	18.30	0.00	18.30
Total drug costs per patient	**59.84**	**78.14**	**87.12**	**105.42**
Angola				
Pre-treatment	2.70	2.70	2.70	2.70
Melarsoprol	58.60	58.60	86.40	86.40
Concomitant drugs	2.13	2.13	1.58	1.58
Drugs for management of SAE[1]	0.00	80.00	0.00	80.00
Total drug costs per patient	**63.43**	**143.43**	**90.68**	**170.68**

[1]estimate based on total extra costs for SAE divided by # patients with SAE

Total costs per patient treated

The total costs per patient treated are summarised in Table 4 and Graph 2. Depending on the treatment schedule received, the full costs for treating a late-stage sleeping sickness patient varied between 206 and 346 US$ in Maluku, DRC and 990 and 2071 US$ in Ndalatando, Angola. This is illustrated in Graph 2, where the various components have been broken down into 4 categories. The costs of hospitalisation dominate the total costs; this is particularly pronounced in Angola and for the scenarios which illustrate the current financial or budgetary cost with melarsoprol being given for free and only transport costs paid for. The costs for the melarsoprol treatment itself remain fairly stable at 60 – 90 US$ for the different treatment schedules and centres.

Cost effectiveness of the treatments

The clinical effectiveness of the two treatment schedules was considered to be the same, based on the results of the previous large-scale study IMPAMEL I in Angola [Burri *et al.,* 2000; Schmid *et al.,* 2004] and the current multinational evaluation IMPAMEL II [Schmid *et al.,* 2004]. As the overall conclusions do not depend on the specific measures of effectiveness (number of lives saved, DALYs averted), results are presented in terms of DALYs averted (Table 5).

For our study population (IMPAMEL II), 30 DALYs could be saved by treating one patient. For both countries we calculated the costs per DALY averted, selecting several alternatives for a range of DALYs between 20 to 35 years that correspond to previously described estimates [Politi *et al.,* 1995; Moore *et al.,* 1999; Odiit 2003]. In absolute terms, using the 10-day schedule meant that the costs for the treatment of a late-stage sleeping sickness patient could be reduced to about half of the costs incurred under the standard schedule.

Graph 2 Total costs for a full treatment of a late-stage sleeping sickness patient in Maluku, DRC and Ndalatando, Angola, in US$.

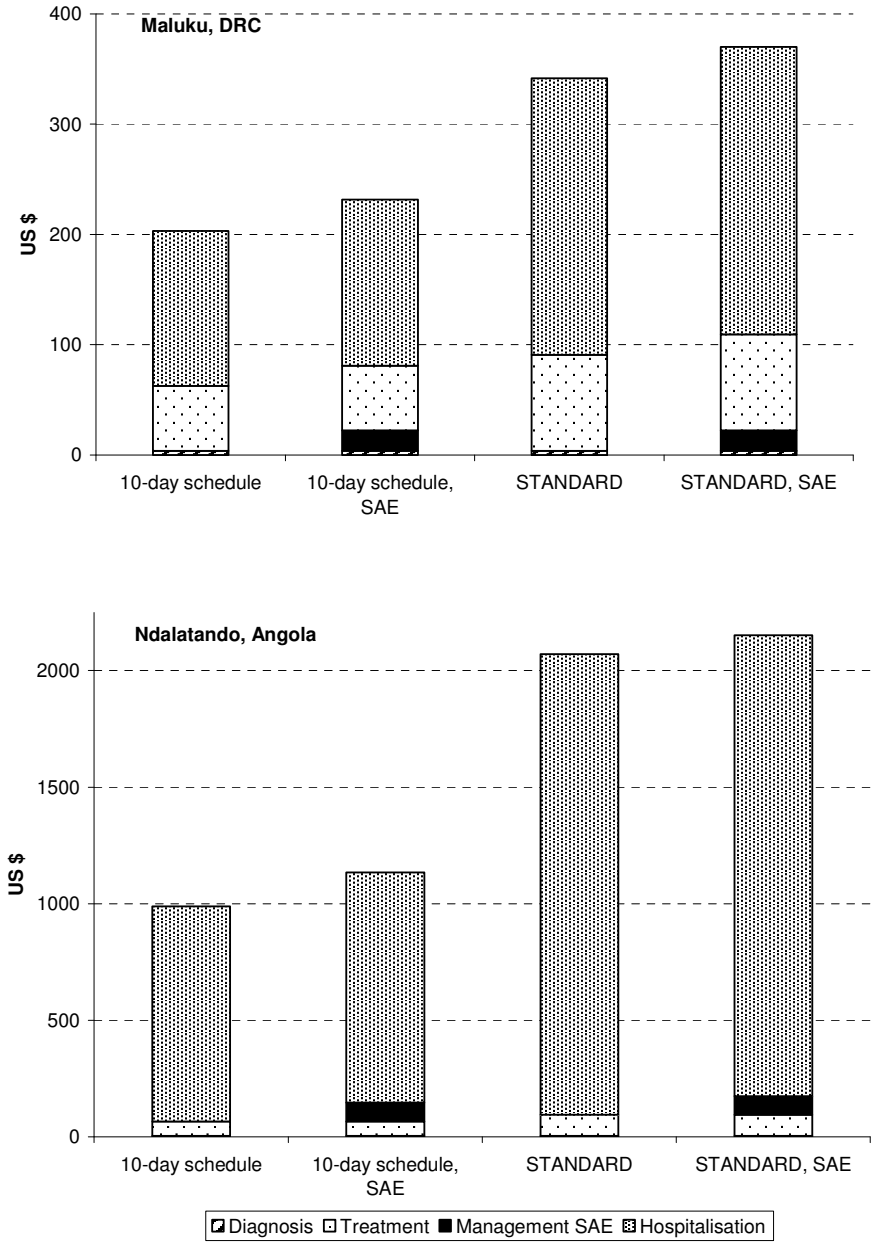


Table 4: Total costs for a full treatment of a late-stage sleeping sickness patient in Maluku, DRc or Ndalatando, Angola, in US$.

	10-day schedule		Standard schedule	
		+ management of SAE		+ management of SAE
Maluku, DRC				
Days of hospitalisation	14	15	25	26
Cost per day hopsitalised	10.14	10.14	10.14	10.14
Total hospitalisation cost per patient	141.96	152.10	253.50	263.64
Diagnosis	3.91	3.91	3.91	3.91
Drugs	59.84	78.14	87.12	105.42
Total cost per patient in Maluku	**205.71**	**234.15**	**344.53**	**372.97**
Ndalatando, Angola				
Days of hospitalisation	14	15	30	30
Cost per day hopsitalised	65.89	65.89	65.89	65.89
Total hospitalisation cost per patient	922.46	988.35	1976.70	1976.70
Diagnosis	3.91	3.91	3.91	3.91
Drugs	63.43	143.40	90.68	170.68
Total cost per patient in Ndalatando	**989.80**	**1135.66**	**2071.29**	**2151.29**

Table 5 Cost effectiveness of the two treatment schedules for DRC (A, B) and Angola (C, D), per DALY averted

A: Cost per patient treated (US$), DRC

Item	10-day schedule	Standard
Diagnosis & Control	4	4
Hospitalisation	142	254
Drugs[2]	60	87
Total	**206**	**345**

B: Cost per DALY averted (US$), DRC

DALYs averted[1]	10-day schedule	Standard
20	**10.3**	**17.2**
25	**8.2**	**13.8**
30	**6.9**	**11.5**
35	**5.9**	**9.8**

C: Cost per patient treated (US$), Angola

Item	10-day schedule	Standard
Diagnosis & Control	4	4
Hospitalisation	922	1977
Drugs[2]	63	91
Total	**990**	**2071**

D: Cost per DALY averted (US$), Angola

DALYs averted[1]	10-day schedule	Standard
20	**49.5**	**104.1**
25	**39.6**	**83.3**
30	**33.0**	**69.4**
35	**28.3**	**59.5**

[1]per 2nd stage patient successfully cured; values from literature and IMPAMEL II study
[2]excluding drugs for management for SAE

DISCUSSION

The multinational IMPAMEL II study [Schmid *et al.,* 2004] has demonstrated overall effectiveness of the 10-day melarsoprol schedule in the treatment of late-stage sleeping sickness due to *T.b. gambiense* and depicted the numerous advantages over the lengthy standard treatment regimens: psychological (patients' and doctors' compliance to adhere to treatment), technical (10 consecutive days, no dosage adjustment), pharmacologic (due to its simple application it forms the basis of all potential combinations of melarsoprol in the compassionate treatment of refractory cases) and economic (lower drug requirement, shorter hospitalisation leading to increased treatment centre capacity). In this paper we estimated the economic advantages of the 10-day schedule by analysing the costs involved for the treatment of late-stage sleeping sickness patients with melarsoprol in the two rural treatment centres Maluku and Ndalatando that participated in the IMPAMEL II study. The centres were chosen based on accessibility to comprehensive data and are believed to represent basic (mostly rural) treatment centres operated by the national control programs.

The treatment effectiveness (i.e. cure rates at discharge and 2 years after treatment) were similar for both treatment schedules [Burri *et al.,* 2000; Schmid *et al.,* 2004; Schmid *et al.,* 2004] and comparable to previous reports [Pepin *et al.,* 1989; Van Nieuwenhove 1992; Politi *et al.,* 1995; WHO 1998; Van Nieuwenhove 1999]. Thus, the indicator of effectiveness used in this analysis was DALYs gained by treating patients, enabling the comparison to previous cost-effectiveness calculations [Politi *et al.,* 1995; WHO 2001]. Although work on this subject is ongoing, there is little published information on the burden of the disease in terms of DALYs lost due to either form of sleeping sickness. Odiit et al. (2000) have produced calculations of DALYs for the rhodesiense sleeping sickness based on the age distribution of patients in Uganda and estimated the number of DALYs lost for unreported, therefore untreated, patients to be just over 20 years [Odiit 2000]. First estimations for gambiense patients were based on the age-at-death distribution for rhodesiense patients in Uganda and yielded a DALY of around 25 years [Politi *et al.,* 1995]. Similar results were found in a control program in southern Sudan for gambiense patients which estimated just over 30 years [Trowbridge *et al.,* 2001]. Currently a study is performed to address the burden of the disease in several countries endemic for gambiense sleeping sickness (personal communication Dr Anne Moore, CDC Atlanta). We have calculated a similar value for the DALY for gambiense sleeping sickness (30 years) based on the age-at-death distribution in the IMPAMEL II study which included patients from 7 sub-Saharan African countries. Thus, in Table 5, the results are presented for a range of 20 to 35 DALYs averted per person successfully treated.

The total costs for the treatment of late-stage gambiense sleeping sickness with melarsoprol derived from the costs of diagnosis, treatment and hospitalisation. However, some expenses could not been taken into account which possibly led to an underestimation of the real costs. The screening mode was not considered as in both centres analysed, the patients were admitted mostly passively and diagnosis was done at the respective centres. Were patients found by active screening, the cost of active surveillance would be very high but the same whatever treatment schedule was used; however by detecting second stage patients earlier it could mean that more DALYs were gained per patient found. Additionally, the prevalence, sensitivity and specificity of the diagnostic tests were not explicitly considered, although this could have contributed to slight differences in the overall costs. The figures used represent the actual consumption of the test materials and if GCP and GLP rules were followed, some expenses in our analysis are then clearly underestimated (consumption of gloves, needles, syringes, and disinfectant). Also, the costs borne by patients (including value lost during their illness and accompanying relative) were not evaluated; such an analysis is currently being performed in DRC [Lutumba *et al.,* 2004]. This is certainly a limitation of our analysis as the costs borne by patients due to a long period of illness (months to years) would substantially add to the total costs and therefore, the values given here are actually an underestimation of the benefit.

Generally, treatment of late-stage sleeping sickness was six times more expensive in Angola than in DRC. Price levels in Angola are amongst the highest in Africa and this is clearly reflected in all the cost categories of our analysis. However, differences in staffing levels and in the type of equipment used also contributed significantly to the differential in costs. For example, the cost of beds accounted for almost $2 of the hospitalisation cost in Angola versus $0.04 in DRC.

Salaries were the largest single component of the cost differential. In addition to the about 50% higher salaries, the centre in Angola employed more than three times as many people. However outcomes and recovery rates between the two centres were similar. But the situation in Angola seems to be an exceptional and temporary situation, because the staffs from the peripheral units have been concentrated in the safer provincial capital during the war. Recalculating the hospitalisation costs (assuming same staffing levels and salaries for both countries, taking the average of the two salary levels and a staffing level 50% higher than that currently in use in DRC) increased the hospitalisation cost per patient day in DRC from US$10 to US$16 and reduced it from US$66 to US$39 in Angola. It is felt that these levels probably represent a valid range for this cost in Africa, with the average cost tending to be closer to the lower DRC level.

The drugs for sleeping sickness are donated free of charge by Aventis until 2006, and only the costs of transport and administration are being paid by the national control programs today. But nevertheless, from a budgetary viewpoint, the full cost of the drugs was considered in this analysis for the case that they have again to be paid for in future. More importantly, in an economic analysis this cost must of course be included as it represents a use of real resources. In our study, most of the costs are due to the hospitalisation (around 70% in DRC and approximately 90% in Angola) and melarsoprol contributed 30–34% to the total cost in DRC and 5-7% in Angola.

The costs in DRC for treating a late-stage patient with melarsoprol were US$206 with the 10-day schedule and US$345 with the standard schedule (including costs for management of severe adverse events) and thus, on the basis of 30 DALYs averted per patient successfully treated, the costs per DALY averted (US$ 6.9 and US$11.5) was for both treatments below the 'good value for money' threshold of US$25 [WorldBank 1993]. In Angola, the cost per DALY averted approaches this margin only very closely when using the 10-day treatment schedule. As discussed above, Angola for a variety of reasons represents a very high cost scenario, the type of adjustments to these costs proposed above would bring these costs well within the good value for money threshold.

With the 10-day treatment schedule, the total costs for treatment could almost be halved in both countries. The net benefit from switching from the standard to the 10-day treatment schedule did reduce the cost per DALY averted from US$11.5 to US$6.9 in DRC and from US$69.4 to US$33.0 in Angola, a saving of US$4.6 (DRC) or US$36.4 (Angola) per DALY averted. And as already concluded by Politi *et al*. (1995) "treating late-stage with melarsoprol is an extremely good buy in terms of possible alternative uses of scarce health resources…" we can only confirm these findings.

Treatment of early-stage patients is even more cost-effective [WHO 1998], 110US$ or US$3.9 per DALY averted and can be even less if these patients are not hospitalised. Finding and treating patients in the early stage of the disease would, in terms of disease control, be the most effective form in reducing the human reservoir and the disease transmission. But one has to clearly bear in mind, that finding patients in the early stage of the disease implies periodic and active screening activities that are determined by the local prevalence levels and consequently cost more than passive screening. Thus, all cost components from screening to treatment, including the costs borne by patients should be integrated in the planning of control strategies and funds allocation.

The preferred treatment for late-stage gambiense sleeping sickness these days is eflornithine. Although the drug is being supplied free of charge until 2006, treatment with

eflornithine remains expensive; it has to be given as slow infusions every 6 hours over 14 days, requires expensive administration kits and can only be administered by qualified staff in centres with good logistics. The costs of treatment with eflornithine, including the administration kits, was calculated by Politi *et al.* to be at 481US$ in Uganda in 1995 [Politi *et al.,* 1995]. However, his finding of US$18.4 per DALY averted seems somewhat an underestimation of the real cost today and eflornithine remains restricted to centres with substantial and consistent support by NGOs. From the public health perspective however, melarsoprol saves a substantial number of lives, at very low costs, despite resulting in deaths from its side effects. It can be used as the baseline and decisions about the use of alternative treatments (i.e. eflornithine) cannot ignore the effectiveness of melarsoprol.

Finally, we conclude that the 10-day melarsoprol schedule is a highly cost-effective treatment option for late-stage gambiense sleeping sickness in areas with scarce resources by halving the total costs in switching from the lengthy standard treatment schedules to the 10-day schedule.

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Annex I - Hospitalisation costs Maluku, DRC

Hospitalisation costs are calculated from recurrent (made up of running costs, salaries and consumables, table 1.1) and capital costs (depreciation of general hospital equipment, table 1.2).

Table 1.1 Recurrent costs Maluku, DRC

	Number	Amount / month (US$)	Frequency	Annual cost (US$)
Running costs				
Building, examination room and hospital (notional rent)	1	500	12	6'000
Laboratory building (notional rent)	1	200	12	2'400
Power, water[1]	na			0
Transport, fuel	1	64	12	768
Stationery (lab books, records, pens)	na			0
Communication (mobile)	1	10	12	120
Communication (phonie)	1	10	12	120
Sub-total building and running costs				9'408
Salaries				
MD	1	541	12	6'492
Nurses	4	212	12	10'188
Lab technicians	1	226	12	2'712
Other (Maintenance)	1	120	12	1'440
Other (Guardian)	1	204	12	2'448
Sub-total salaries				23'280
	Number	Price / unit (US$)	Frequency	Annual cost (US$)
Consumables				
Syringes, Needles, Lancettes	800	0.11	1	88
Sondes, catheters	20	0.60	1	12
Gloves	200	0.10	1	20
Slides, cover slips	300	0.04	1	12
Alcohol, Giemsa, immersion oil	1	147.75	1	147.75
Sub-total consumables				280
TOTAL RECURRENT COSTS				**32'968**

[1]not paid since government institution

Table 1.2 Capital costs Maluku, DRC

	Number	Unit cost (US$)	Total cost (US$)	Years used	Total / year (US$)
Beds	20	30	600	10	60
Matresses	20	20	400	5	80
Examinationbed	1	50	50	4	13
Bicycle	1	100	100	4	25
Tables (examination, laboratory and hospital)	3	50	150	2	75
Chairs (examination, laboratory)	8	15	120	2	60
Banks (waiting area patients)	2	25	50	2	25
Cupboards (drugs, files)	3	167	501	2	251
Sideboards	2	28	56	2	28
Curtain	10	30	300	2	150
Paravent	2	20	40	5	8
Microscope (Olympus CH 20)	1	1500	1500	4	375
Centrifuge (benchtop)	1	3394	3394	5	679
Centrifuge (hematocrit)	1	920	920	5	184
Refridgerator	1	830	830	5	166
Freezer	1	450	450	5	90
CATT Rotator	1	150	150	5	30
Weighing balance	1	20	20	3	7
Pipettes	2	300	600	3	200
Counting chambers	2	50	100	1	100
Pots and glasses (staining, storage, waste)	1	200	200	3	67
Thermometers, Stethoscope	2	50	100	3	33
Other lab equipment	1	200	200	3	67
TOTAL CAPITAL COSTS (US$)					**2'771**

Annex II - Hospitalisation costs Ndalatando, Angola

Hospitalisation costs are calculated from recurrent (made up of running costs, salaries and consumables, table 2.1) and capital costs (depreciation of general hospital equipment, table 2.2).

Table 2.1 Recurrent costs Ndalatando, Angola

	Number	Amount / month (US$)	Frequency	Annual cost (US$)
Running costs				
Building (examination, laboratory, hospital) - rehabilitation in 2003	1	11000	1	11'000
Power, water[1]	1	0	12	0
Food (maize, sugar, oil)	1	2186	12	26'232
Transport, fuel	1	40	12	480
Stationery (lab books, records, pens)	1	167	3	500
Communication	1	121	12	1'452
Sub-total building and running costs				39'664
Salaries				
MD	2	1055	12	25'320
Nurses	18	218	12	47'088
Lab technicians	12	273	12	39'312
Other (Maintenance)	2	62	12	1'488
Other (Administration)	2	62	12	1'488
Sub-total salaries				114'696
	Number	Price / unit (US$)	Frequency	Annual cost (US$)
Consumables				
Syringes, Needles, Lancettes	2500	0.11	1	275
Sondes, catheters	10	0.65	1	7
Gloves	1300	0.15	1	192
Slides, cover slips	700	0.05	1	34
Alcohol, Giemsa, immersion oil	1	438.00	1	438
Sub-total consumables				946
TOTAL RECURRENT COSTS				**155'306**

[1]not paid since government institution

Table 2.2 Capital costs Ndalatando, Angola

	Number	Unit cost (US$)	Total cost (US$)	Years used	Total / year (US$)
Beds	40	470	18800	5	3'760
Matresses	40	108	4312	3	1'437
Examinationbed	1	400	400	5	80
Bedsheets, blankets, pillows	70	32	2233	2	1'117
Tables (examination, laboratory and hospital)	5	261	1305	3	435
Chairs (examination, laboratory)	16	65	1040	3	347
Cupboard (drugs)	2	480	960	3	320
Cupboard (files, folders)	7	165	1155	3	385
Curtain, Paravent	5	290	1450	1	1'450
Microscope	3	2420	7260	3	2'420
Centrifuge (benchtop)	1	5741	5741	2	2'871
Centrifuge (hematocrit)	1	3840	3840	2	1'920
Refridgerator	1	874	874	3	291
CATT Rotator	1	150	150	3	50
Weighing balance	3	109	326.7	3	109
Pipettes	2	700	1400	2	700
Counting chambers	4	105	420	2	210
Pots and glasses (staining, storage, waste)	1	200	200	1	200
Thermometers, Stethoscope	2	45	90	2	45
Cooking equipment	10	45	450	5	90
TOTAL CAPITAL COSTS (US$)					**18'236**

PART 4: DISCUSSION, CONCLUSIONS AND PERSPECTIVES

FROM EFFICACY TO EFFECTIVENESS – A DISCUSSION

The approach for drug development by investing in research of an old and toxic drug as melarsoprol, that wouldn't pass a single drug-safety test today, appears to contrast nowadays common agreed policy which aims at the development of safe and effective drugs for sleeping sickness treatment. However, in the absence of valid alternatives (detailed in introduction), melarsoprol remains the most used drug to treat late-stage sleeping sickness in basic rural treatment facilities with scarce resources that are not supported or operated by NGOs. The underlying study aimed at an improved approach of the treatment with melarsoprol of late-stage gambiense sleeping sickness and provided evidence of its overall effectiveness.

Efficacy and effectiveness, the need for definition

Efficacy in clinical trials answers the question "does a treatment work under ideal conditions?" and is optimally achieved by a well-designed, controlled study, in which the intervention is carefully supervised (Table 1). The most common clinical trial which satisfies these rules is the double-blind, randomised controlled trial, where neither patient nor the person issuing the treatment knows who is receiving the treatment studied. Normally, efficacy studies are referred to as Phase I - III clinical trials and the outcome analysed is whether a treatment is effective and safe in a restricted (and therefore a very much controlled) patient population. However, such trials have limitations and the controlled clinical setting used in experiments is a poor model of the complex and dynamic real world.

Effectiveness in contrast, is more ambiguously described and definitions vary largely, generally effectiveness studies do respond to "does the treatment work in the real world?" with emphasis on the applicability of the treatment and therefore try to duplicate the situations that medical personnel will encounter in the practice. Additional questions about outcomes are being answered, patient acceptance, economics of use, long-term safety and efficacy, and practice and use patterns. Effectiveness is strongly affected by compliance, which is influenced by behavioural factors that are in turn affected by access to the intervention, supply, cost, and other factors as differences between population groups and settings. Effectiveness may be monitored and a cost-benefit analysis conducted during the implementation of an effective intervention, and is normally referred to as post-registration study or Phase IV clinical trial.

For the ease of the reading, in the present work we distinguished between two forms of effectiveness, the clinical effectiveness which stands for the clinical outcome and the

economic effectiveness that refers to the costs and effects of the treatment from a public health perspective (also termed efficiency).

Table 1 Comparison of criteria of efficacy and effectiveness trials

EFFICACY				**EFFECTIVENESS**
"does a treatment work under ideal conditions?"		Question		"does the treatment work in the real world?"
Ideal		Condition		Real world
mostly RCT* Phase I - III Pre-registration		Trial design Phase of trial Stage of registration		few RCT*, Historical data design Phase IV Post-registration, Post-marketing
Few	→	Eligibility	→	All
Few	→	Inclusion criteria	→	Not restricted
Many	⇦	Exclusion criteria	⇦	None
High	⇦	Degree of control	⇦	Low

*RCT: randomised controlled trial

Proof of effectiveness

The efficacy of the 10-day treatment schedule of melarsoprol has been shown in a large-scale randomised controlled clinical trial executed in a restricted population in Angola (IMPAMEL I) [Burri *et al.,* 2000]. The authors clearly demonstrated non-inferiority of the 10-day schedule in terms of efficacy and safety compared to the standard treatment schedule used at that time in Angola.

Further, two years after treatment, the follow-up of the patients has been evaluated for its long-term efficacy. The follow-up coverage of the patients was very high (>80%) and the fatality and relapse rates during the follow-up were equal for both treatment groups (2.9% fatalities and 4.8% relapses) and comparable to previous findings in the same area [Ruiz *et al.,* 2002]. The results are in agreement with the conclusions anticipated from the IMPAMEL I trial and provide evidence for the long-term efficacy of the 10-day treatment schedule (chapter 1, [Schmid *et al.,* 2004]). The favourable outcome of the IMPAMEL I trial was received with great interest by representatives of national sleeping sickness control programs, WHO and NGO's, however, a conclusive evaluation and systematic introduction of the 10-day schedule in the affected countries was demanded. The clinical trial in Angola was conducted under controlled conditions in a defined population that may not necessarily reflect the normal sleeping sickness patient and situation. The rate of concomitant infectious diseases (e.g. filaria, HIV) is rather low in that area and generally the patients' conditions on admission were quite good. In addition, prior to the trial, the infrastructure in the two conducting treatment centres was improved, the staff specifically trained, and during the trial, the correct conduct assured by expatriate experts. Therefore, a thorough evaluation under various field conditions of the 10-day schedule was indispensable which consequently led to the multinational evaluation (IMPAMEL II).

IMPAMEL II was a non-controlled, multinational, multi-centre drug utilisation study to evaluate the abridged treatment schedule of melarsoprol in late-stage *T.b. gambiense* sleeping sickness patients under true field conditions. The clinical effectiveness of the 10-day treatment schedule was assessed in more than 2000 patients of 16 sleeping sickness treatment centres in 7 African countries and was to the best of our knowledge the largest clinical study ever conducted in sleeping sickness. The outcome of the IMPAMEL II study confirms the results of the IMPAMEL I study and provides strong evidence for the overall effectiveness of the 10-day schedule:

- The compliance of the patients and the medical staff to the treatment schedule was high; more than two thirds of the patients received the ten doses without treatment interruptions, 89% completed the ten doses, and only 0.3% of the treated patients left the

hospital before treatment completion for unknown reasons (chapter 2). Normally, the compliance of to the lengthy standard treatment schedules of melarsoprol was poor, a large proportion of the patients was reported not to stick to the foreseen treatment regimen or even escaped from the treatment facility before treatment completion [Weir *et al.,* 1985; Burri *et al.,* 2000].

- Many patients presented themselves to those treatment facilities where the 10-day schedule was offered already during the implementation phase of the study. This observation can be interpreted as favouring the 10-day schedule over the old and lengthy standard schedule in the respective countries.
- No unexpected outcome was found in the wider population of this multicentre evaluation. Overall, the results were highly variable between the diverse study centres, but this could be expected due to the inherent differences of the treatment facilities. Similar large differences were already reported by the participating centres for the outcome of melarsoprol treatment with the standard schedules prior to the study (chapter 2).
- Nevertheless, the safety and tolerability of the 10-day schedule were comparable to the standard treatment (chapter 2). The average rates of encephalopathic syndromes and treatment related fatalities in this study were similar to previously reported rates for the standard treatment schedules of melarsoprol (reviewed in [Seixas *et al.,* 2004]. No risk factors for an unfavourable outcome could be identified in this study.
- Also in line with previous reports [Doua *et al.,* 1985; Adams *et al.,* 1986; Blum *et al.,* 2001] was the timing of the occurrence of the encephalopathic syndromes, strongly supporting the view that the event is independent of the treatment schedule and dose applied (chapter 2).
- Elevated rates of skin reactions, fever and headache during treatment with the 10-day schedule were already observed in the IMPAMEL I study [Burri *et al.,* 2000] but could be managed by adequate concomitant medication and treatment interruption where necessary (chapters 2 and 3).
- Despite the fear of many medical staff of treating children with the 10-day treatment schedule, that was felt as more aggressive than the old one, we could confirm a similar safety and efficacy profile in children compared to adults (chapter 4). Children seemed to experience more severe (grade 2) adverse reactions, these were mainly fever and maculopapular eruptions, but the former may have been associated with the higher rate of detected malaria parasites in children. However, the most severe adverse events, encephalopathic syndromes and treatment related fatalities, occurred at equal rates in children as in adults.

- Not surprisingly, patients with concomitant parasites detected during the treatment course experienced more often adverse events, which put them at a higher risk to die and finally led to a reduced clinical effectiveness of the treatment with melarsoprol (chapter 3). Earlier reports have already pointed at the possible risk of concomitant parasitism during melarsoprol treatment by aggravating the treatment outcome regardless of the schedule used [Van Nieuwenhove 1999; Blum *et al.,* 2001].
- The short- as well as the long-term clinical effectiveness appeared to be equivalent to the standard treatment and without differences between adults and children. 94% of the patients were discharged alive without trypanosomes detected in any body fluid. Two years after treatment, 86% of all treated patients were termed cured. These rates are superior to previously reported outcomes of the standard melarsoprol treatment schedules with efficacy as low as 70% [WHO 1998] (chapter 2).
- The follow-up coverage between the centres was highly variable (15%-100% of the treated patients have been followed up in the respective centres), but this discrepancy has already been recognised as an inherent problem of the sleeping sickness control independent of the treatment [WHO 2001].
- The follow-up activities were purposely not assisted in this study with the intention not to interfere with the “normal situation” in the field. Roughly only half of the treated patients have been examined during the follow-up period of two years, and therefore, the average relapse rate of 7.1% may be an underestimation (range by centres: 0–26% versus a relapse rate between 0–30% in literature). However, the relapse rates reported in this study match the rates found in the centre histories of the respective treatment centres (chapter 2).
- Even though a lower total dose of melarsoprol was given, the 10-day schedule did not increase the risk of treatment failures (and relapses), which was a highly debated issue prior to the implementation of the study. Elevated rates of treatment failures (and relapses) were anticipated by introducing a new treatment schedule of melarsoprol monotherapy, especially in areas with known melarsoprol resistance. Most of these areas did not participate in the study, as they switched to eflornithine treatment as first-line treatment for late-stage gambiense sleeping sickness or combination treatment for melarsoprol refractory cases. However, in South Sudan, an area with an elevated relapse rate (15%), the 10-day schedule was successfully applied without increasing the relapse rates.
- The economic effectiveness was assessed and revealed the 10-day schedule to be a highly cost-effective alternative treatment for late-stage gambiense sleeping sickness (chapter 5). In switching to the 10-day schedule, the overall treatment and hospitalisation

costs could be nearly halved compared to the standard treatment schedules. For example, in the Democratic Republic of Congo in 2001, the total costs for treatment and hospitalisation of a patient were reduced from US$345 for the standard to US$205 for the 10-day schedule.

- With the 10-day schedule, the cost per DALY averted could be reduced from US$11.5 to US$6.9 in DRC, which represents an extremely good buy in terms of possible alternative uses of scarce health resources for a sleeping sickness control program (chapter 5).
- The hospitalisation costs were the largest component of the cost differential (US$10 per patient day in DRC) which could be substantially reduced when the total hospitalisation stay of a patient was reduced by applying the 10-day treatment schedule (from 26 days with the standard to 15 days with the 10-day treatment schedule; chapter 5).
- Even if today the drugs for sleeping sickness treatment are free of charge, donated by Aventis until 2006, one should still bear in mind the costs for the drugs in case it has again to be paid for in future. Calculating for an average 50 kg bodyweight, the total drug amount used per patient could be reduced with the 10-day schedule from 1620 mg (9 ampoules at US$8 each) by one third to 1100 mg total melarsoprol (6 ampoules). Thus, the costs for melarsoprol could be reduced by one third, from US$72 to US$48 for a patient with 50 kg bodyweight, which constitutes roughly 20% of the total costs spent for the treatment of a patient (chapter 5).

Validity of the findings

Although the present study was the largest clinical study ever performed in sleeping sickness with its particular strengths of implementation in multiple populations, settings and under absolute real conditions in the field, some limitations became apparent when attempting to apply the results of the randomised clinical trial (IMPAMEL I) to the routine practice (IMPAMEL II):

A randomised design was considered not feasible and above all not ethical. Due to the very basic equipment of the sleeping sickness treatment facilities, the often low level of staff qualification and the lack of experience in the conduct of clinical trials it was not possible to conduct a randomised study. Cluster randomisation was also considered impossible because of the inherent differences in the outcome of the sleeping sickness treatment in different centres and countries and the limited number of centres available for participation. The abridged schedule has been demonstrated to be non-inferior, in terms of safety and efficacy, and in addition, it depicted numerous advantages over the lengthy standard treatment regimens such as psychological (patients' and doctors' compliance to adhere to treatment), technical (10 consecutive days, no dosage adjustment), pharmacologic (basis of all potential combinations of melarsoprol in the compassionate treatment of refractory cases) and economic (lower drug requirement, shorter hospitalisation, increased treatment centre capacity). Therefore it was considered unethical to deprive a fraction of the patients through randomisation from a treatment that was already considered preferable.

As the present study was non-randomised, the population treated was non-controlled and therefore most likely different to the population in the IMPAMEL I trial on which the conclusions are based. Additional to the population differences, the disease prevalence and co-morbidities of the various disease foci did certainly also vary which could have conveyed a different outcome than in the randomised controlled clinical trial. In our study, we have observed an association of concomitant parasitic diseases on the treatment outcome (adverse events, effectiveness) but as the study was not designed to determine concomitant parasitism in sleeping sickness patients, routine screening for concomitant parasites was not mandatory and therefore, the observed influence could not be anticipated and compared to the randomised controlled trial IMPAMEL I.

Another limitation for analysis of temporal as well as causal associations was the simple questionnaire design. It was left as simple as possible in order not to pose too much additional work to the local staff in the field and to avoid asking for assessments and examinations the staff is not trained for, therefore many items were left out. For example in the case of the occurrence of severe adverse events, the investigators were asked to act

according to their national or organisational guidelines, which differed between the countries and centres. And sometimes even, such guidelines could not be followed due to the lack of resources (appropriate staff not in place, no drugs available, inadequate equipment) and the deviations from these guidelines were often not documented, which as a result led to difficulties in the analysis and interpretation of the management of adverse events.

Due to the non-randomised approach and low degree of control, potential bias might have been introduced. a) The most obvious form, selection bias, was indeed encountered in one country of our study: despite the protocol guidance and respective training, the 10-day schedule was not solely used and patients were selected according to their health status and age due to the fear that the abridged schedule is more harmful to children and the sicker adults. All patients from this country treated in the study could not be included in the official analysis. b) An observation bias might have been prompted by the solicited information which usually is not recorded in the general practice. For example, we have noted elevated rates of mild symptoms like fever, headache or pruritus. They are very likely rarely noticed and recorded in a sleeping sickness treatment centre, but are also common symptoms and signs of the disease and as a consequence, these rates were difficult to compare to previously published studies or the centres' histories. Additionally, the doctor's perception may have played an important role in defining the tolerability of the treatment. The notion that more treatment interruptions caused by moderate adverse events were reported in centres operated by NGOs or expatriate doctors supports this reflection.

Additionally, although clearly defined in the study protocol, the definition for the encephalopathic syndromes used by the investigators was not consistent and differed between the centres/investigators and thus, comparison of the patients with encephalopathic syndromes was complicated. Particularly the psychotic reactions were left at a wide range for definition. This certainly may have contributed to the large inter-centre differences in the analysis of the encephalopathic syndrome and its types.

However, no similar study exist for melarsoprol, all studies so far documented were of small scale or retrospective analysis of treatment centres' records, with patient cohorts treated with various treatment schedules or under different conditions. And despite the limitations of which we were fully aware prior to the implementation of the study, a simple study design was chosen to duplicate as closely as possible the conditions in the target practice and to ensure the applicability to the wider settings in which the results will be applied. Above all, we strongly believe that for practical and particularly ethical reasons there was no other option.

CONCLUSIONS

Despite resulting in deaths from its side effects, melarsoprol will remain the most used drug for the treatment of late-stage gambiense sleeping sickness. The treatment with melarsoprol can be enhanced by abridging its application scheme. The 10-day treatment schedule showed to be advantageous in many ways over the lengthy standard schedules hospitalising the patients up to 30 days. It is easier to implement even by less qualified staff in resource poor treatment facilities in remote areas, as it does not need daily dose adjustments and complex coordination of the treatment series and rest periods. Patients and their accompanying relatives prefer the shorter course as it renders them an earlier return to their home, and most likely increasing their potential productive time at home. The compliance of the patients and the medical staff to the treatment schedule is likely to be better than with the standard treatment schedules; patients do not run away before treatment completion, which may increase their chances of cure. The short and long-term efficacies are equal to the standard schedules, the patients can be cured by the abridged schedule and it does not cause an increase in the relapse rate. Overall, the safety and efficacy in children are comparable to adults. Concomitant parasitic diseases influence the disease progression and treatment outcome and therefore should be carefully screened and treated regardless the sleeping sickness specific treatment applied.

A substantial reduction of the overall treatment costs can be achieved by applying the 10-day treatment schedule, the total amount of drug used per patient is less (depending on the bodyweight, but may be reduced by one third), the hospitalisation time of a patient is reduced to almost half of the time and therefore, it is cheaper than the standard schedules. The treatment centres' capacities can be largely improved as the patients free the hospital beds earlier and more patients can be treated in the same time as before.

PUBLIC HEALTH IMPACT OF THE 10-DAY SCHEDULE AND PERSPECTIVES

We concluded that the 10-day melarsoprol schedule is a highly cost-effective treatment option for late-stage gambiense sleeping sickness in areas with scarce resources by halving the total costs in switching from the lengthy standard treatment schedules to the 10-day schedule even though the patients are submitted to the risk of a potential terminal outcome of the treatment. However, from the public health perspective, melarsoprol saves a substantial number of lives, at very low costs, and can be used as the baseline for the planning and funds allocation of control strategies and for decisions about the use of alternative treatments (i.e. eflornithine).

Treatment is the cornerstone of human African trypanosomiasis control, the main reservoir of *T.b. gambiense* is in humans and a reduction is achieved by finding and treating those who harbour the parasites. It can be assumed that the shorter treatment course of melarsoprol may more likely attract the patients much earlier to seek diagnosis and treatment due to its various advantages and thus may have an effect in the reduction in the disease reservoir and transmission, leading to lower disease prevalence.

In addition, there is a high gain to the patients and their families. The age distribution of trypanosomiasis patients very closely follows that of the active adult population (80% adults [Odiit 2003]) and the disease tends to hit the most economically productive group of society hardest, affecting family livelihoods and community prosperity very much. Typically, sleeping sickness patients have suffered from symptoms for a prolonged time, and the costs borne to the patients should not be underestimated, they are presumed to be at around US$25 to US$50 [Politi *et al.,* 1995]. These costs include several trips to their rural health centre, or a visit to a local healer, being treated for malaria or other diseases before being diagnosed as having sleeping sickness, and the time taken by relatives to accompany and care for the person [Lutumba *et al.,* 2004]. By treating the patients with the 10-day schedule, the patients return to their home much earlier and most probably feeling more comfortable in their own environment and thus may have a better and quicker recovery and an earlier return to their income generating activities. The accompanying relatives or their families will therefore also be able to generate much earlier their household income.

However, as melarsoprol toxicity is unacceptable new alternatives should arise: There is a clear need for new drugs and easier treatments to better address sleeping sickness. The ideal trypanocidal drug should be safe and effective, active for both forms, gambiense and rhodesiense, cross the blood-brain-barrier to treat the late-stage of the disease, have a simple mode of administration to allow its use under basic rural conditions, and above all should be affordable.

This challenge can only be met by more funding for basic research to find new tools to attack the trypanosomes selectively, such as rationally developed agents inhibiting parasite metabolic pathways, and to increase funding for clinical trials to investigate the new agents. However, the market for sleeping sickness is negligible in comparison with the tremendous cost of developing a new drug for human use and within the next years no new drugs are likely to appear on the market. Consequently, the currently available drugs will be around for at least another decade, and therefore some efforts should be made in improving their use and reducing their toxicity. Therefore, future research should also focus on the better use of existing drugs that will be around for the next decade for sure.

Due to the simple application, the 10-day melarsoprol treatment schedule has already been adapted for combination therapy with other existing drugs and melarsoprol refractory patients are currently treated with those. The combination therapy approach may offer several advantages such as: maximum efficacy, minimum toxicity, shortest possible duration, simplicity, and minimal costs. Combinations currently under investigation are low-dose consecutive melarsoprol combined with short-duration nifurtimox or eflornithine, and nifurtimox and eflornithine. Synergism of some of these combinations was suggested, based on animal experiments [Jennings 1988] or experience in humans [Simarro and Asumu 1996] and has demonstrated superiority to monotherapy with either drug [Mpia and Pepin 2002].

Approaches to reduce toxicity of individual drugs without affecting efficacy would include reduced treatment schedules, lower doses or changes in the administration route (oral application). The latter had been tried in a few instances but never been further followed and may be difficult due to its insolubility in water, but a reduced treatment schedule or lower doses would be worth considering. Based on our observations, the efficacy of melarsoprol was not affected by treatment interruptions that occurred at days 8 or later, thus one would like to suggest an even reduced treatment schedule of 7 or 8 consecutive doses only. In the presented study, the onset of severe adverse events (events that required treatment suspension) was generally reported to happen after 7 or 8 doses of melarsoprol and very often the treatment was not resumed in these patients after the management of the events. Despite the treatment interruption, these patients were not at higher risk to fail the melarsoprol therapy or to relapse during the follow-up period. But of course, even if this is probably already done in certain treatment centres, especially in the cases of severe adverse events, such a further reduced treatment schedule would need careful investigations. A study performed in DRC [Bisser 2001] indicated a decreased efficacy with a reduced melarsoprol treatment schedule of 0.6, 1.2 and 8 x 1.8 mg/kg bodyweight (max 2.5ml) on 10 consecutive days, a treatment regimen that is already very similar to what we tested. Considering the fact that the melarsoprol levels achieved in CSF are only a small fraction (1 – 2%) of those measured in serum and that these levels are at the lower limit to kill the trypanosomes and

that no accumulation in the CSF of the drug has been observed [Burri *et al.,* 1993], we can assume that the 10-day schedule (at 2.2 mg/kg body weight) may already be at the lower limit of effective dosage to clear the parasites from all body compartments. Therefore, without adequate investigations, it is currently not advisable to further reduce the treatment schedule from 10 x 2.2 mg/kg body weight.

As the melarsoprol treatment in *T.b. gambiense* patients has been successfully improved by developing a concise treatment schedule and harmonising the schedule in use in all countries affected by the disease, similar attempts for the use in *T.b. rhodesiense* patients however should be carefully addressed. It is currently not advised to adapt the model to treatment of late-stage *T.b. rhodesiense* infection because of potential dissimilar pharmacokinetics, given that this disease form is much more severe than the gambiense form (different pathology and higher parasitaemia). The blood-brain barrier may be more affected in rhodesiense patients, allowing for higher levels of melarsoprol in the central nervous system and possible neurological side effects. A study of the pharmacokinetics of melarsoprol in late-stage *T.b. rhodesiense* infections is therefore necessary and a new schedule would need to be very cautiously evaluated.

The lack of alternative or new drugs for their efficacy against both, disease form and stages, indicates that an immense amount of work remains to be done for the discovery of an acceptable treatment of sleeping sickness. The situation will become particularly dramatic if less and less donors are willed to finance in one or another way the fight against sleeping sickness. The Aventis Pharma as an example has committed a substantial support to WHO to the control of trypanosomiasis, but this agreement will expire in 2006 and after that, the funding nor the production of the existing drugs are secured.

APPENDIX

APPENDIX I – PICTURES

Angola

Viana treatment centre (Photo Christian Burri, 2001)

Viana, patient ward (Photo Christian Burri, 2001)

Central African Republic

Dr. Nangouma at Nola trypanosomiasis facility (Photo Pierre Lucas, 2001)

Batangafo trypanosomiasis facility (Photo Pierre Lucas, 2001)

Côte d'Ivoire

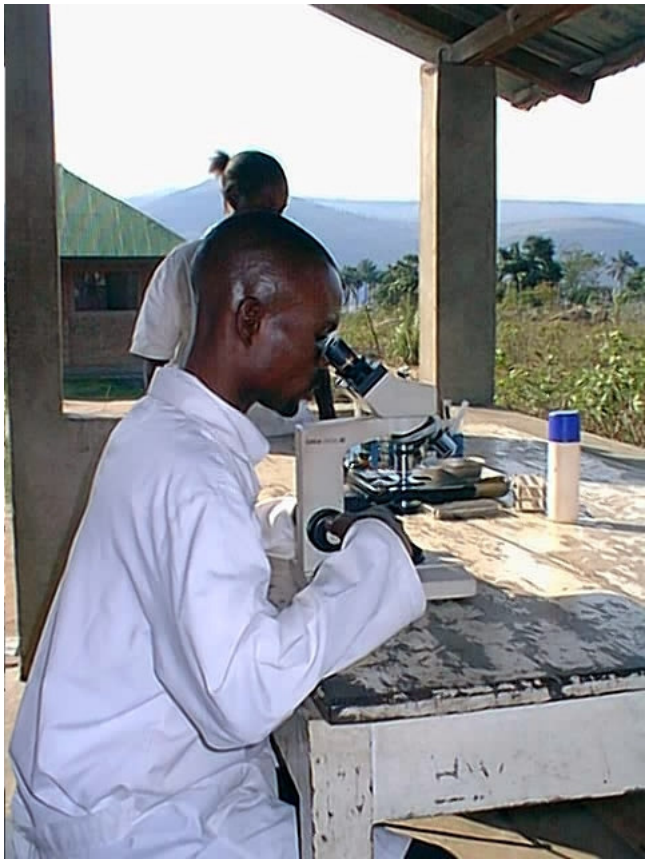
PRCT Daloa (Photo Christian Burri 1995)

Democratic Republic of Congo

Patients at Kionzo treatment centre, Bas-Congo (Photo Caecilia Schmid, 2002)

Kionzo, Central patient registry (Photo Caecilia Schmid, 2002)

Kionzo treatment centre, Bas-Congo (Photo Caecilia Schmid, 2002)



Maluku outdoor laboratory (Photo Caecilia Schmid, 2001)

CNPP / CUK Kinshasa, sleeping sickness treatment centre (Photo Caecilia Schmid, 2002)

Equatorial Guinea

Bata, HAT and TB Pavillon (Photo Pere Simarro, 2001)

Mbini trypanosomiasis centre (Photo Pere Simarro, 2001)

Republic of Congo


Gamboma, patients waiting for treatment (Photo Caecilia Schmid, 2001)


Brazzaville, young late-stage patient during melarsoprol treatment and weighing of an old patient (Photo Caecilia Schmid, 2001)

Sudan

Kajo Keji sleeping sickness treatment centre (MSF Switzerland, Photo Christian Burri, 2003)

Dr. Michey Richer (IMC) and her patients in Western Equatoria (Photo Chicago Tribune, 1999)

Grave of Ibba village head, died of melarsoprol adverse event (Photo Chicaco Tribune, 1999)

CASE REPORT FORM (CRF) IMPAMEL II

(Fill in the information asked ⌊_⌊_⌊_⌋, tick appropriate box ☒, or fill in the grade ⌊_⌋)

Country Code ⌊_⌊_⌋	Center Code ⌊_⌊_⌊_⌋
Name of responsible for treatment ⌊_⌋	

Patient No. ⌊_⌋	
Patient full name ⌊_⌋	
Date of admission ⌊_⌊_⌋ ⌊_⌊_⌋ ⌊_⌊_⌋ (d d m m y y)	Date of discharge ⌊_⌊_⌋ ⌊_⌊_⌋ ⌊_⌊_⌋ (d d m m y y)
Present village of residence ⌊_⌋	
Municipality / District ⌊_⌋	
Probable place of infection (village) ⌊_⌋	
Municipality / District ⌊_⌋	
Age ⌊_⌊_⌋ (Years)	Sex Male ☐ (m) Female ☐ (f)
Weight ⌊_⌊_⌋ (kg)	Height ⌊_⌊_⌊_⌋ (cm)
How long ago were first signs observed ⌊_⌊_⌋ (Months)	
Previous treatment for trypanosomiasis	yes ☐ (y) no ☐ (n)
What medication (Check boxes): Arsobal® ☐ (a); Pentamidine ☐ (p); Other (➥ observ.) ☐ (o); Not known ☐ (n)	Where: Private center ☐ (p); Public center ☐ (u). Was the treatment complete: yes ☐ (y); no ☐ (n)
How long ago (Best match): 1 month ago ☐ (m); 1 year ago ☐ (y); 6 months ago ☐ (s); 2 years or more ago ☐ (y)	

PRESENT TREATMENT WITH MELARSOPROL (NIFURTIMOX / DFMO), DAYS OF DRUG APPLICATION

(Tick box ☒ for each day when melarsoprol was applied, mark box with ❍ for each day when Nifurtimox / DFMO was applied)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50

If treatment deviates from normal schedule give justification in observations section (keywords only)

LABORATORY EXAMINATIONS AT ADMISSION / DISCHARGE

	Before treatment	After treatment
Date of examination	⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋	⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋
Consciousness	Fully conscious ☐ (p) Drowsy ☐ (d) Comatose ☐ (c)	Fully conscious ☐ (p) Drowsy ☐ (d) Comatose ☐ (c)
Lymphadenopathy (Swollen neck lymph nodes)	Absent ☐ (a) Palpable ☐ (p)	(indicate only if > 1 cm)
Serology (If other than CATT used specify in field)	CATT pos ☐ (p) neg ☐ (n) other ☐ (o) n.d. ☐ (b)	(If other test specify) ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋
Trypanosomes in lymph nodes	Microscopy pos ☐ (p) neg ☐ (n) n.d. ☐ (b)	Microscopy pos ☐ (p) neg ☐ (n) n.d. ☐ (b)
Trypanosomes in blood	Microscopy (Blood smear) pos ☐ (p) neg ☐ (n) n.d. ☐ (b)	Microscopy (Blood smear) pos ☐ (p) neg ☐ (n) n.d. ☐ (b)
Trypanosomes in CSF Double centrifugation of CSF used	Microscopy pos ☐ (p) neg ☐ (n) n.d. ☐ (b) yes ☐ (y) no ☐ (n)	Microscopy pos ☐ (p) neg ☐ (n) n.d. ☐ (b) yes ☐ (y) no ☐ (n)
White blood cells in CSF (no / mm^3) (Counting chamber)	Microscopy ⌊_⌋⌊_⌋⌊_⌋	Microscopy ⌊_⌋⌊_⌋⌊_⌋
Malaria	Microscopy pos ☐ (p) neg ☐ (n) n.d. ☐ (b)	
Filariae (incl. *Mansonella perstans*)	Microscopy pos ☐ (p) neg ☐ (n) n.d. ☐ (b)	(Specify species if possible) ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

CLINICAL EXAMINATIONS AT ADMISSION / DISCHARGE

	Before Treatment	After Treatment
Nutritional status (Circumference of upper arm, cm)	⌊_⌋⌊_⌋.⌊_⌋	⌊_⌋⌊_⌋.⌊_⌋
Fever (°C)	⌊_⌋⌊_⌋.⌊_⌋	⌊_⌋⌊_⌋.⌊_⌋
Headache	yes ☐ (y) no ☐ (n)	yes ☐ (y) no ☐ (n)
Pruritus	yes ☐ (y) no ☐ (n)	yes ☐ (y) no ☐ (n)
Daytime sleep	normal ☐ (y) not ☐ (n)	normal ☐ (y) not ☐ (n)
Nighttime sleep	normal ☐ (y) not ☐ (n)	normal ☐ (y) not ☐ (n)
Tremor	yes ☐ (y) no ☐ (n)	yes ☐ (y) no ☐ (n)
Speech impairment	yes ☐ (y) no ☐ (n)	yes ☐ (y) no ☐ (n)

	Before Treatment	After Treatment
Abnormal movements	yes ☐ (y) no ☐ (n)	yes ☐ (y) no ☐ (n)
Walking disability	yes ☐ (y) no ☐ (n)	yes ☐ (y) no ☐ (n)
General motor weakness	yes ☐ (y) no ☐ (n)	yes ☐ (y) no ☐ (n)
Unusual behavior	yes ☐ (y) no ☐ (n)	yes ☐ (y) no ☐ (n)
Inactivity	yes ☐ (y) no ☐ (n)	yes ☐ (y) no ☐ (n)
Aggressivity	yes ☐ (y) no ☐ (n)	yes ☐ (y) no ☐ (n)
Disturbed appetite (bulimia / anorexia)	yes ☐ (y) no ☐ (n)	yes ☐ (y) no ☐ (n)

Check yes if any deviation from normal pattern are observed

SAFETY AND TOLERABILITY

(Complete at day of discharge based on original patient files; indicate maximum degree)

Adverse effects	Grade 0	Grade 1	Grade 2	Maximum grade	Date of onset	Duration of max [days]
Motor trouble (Polyneuropathy)	Absent	Motor weakness, able to walk	Motor weakness, unable to walk	⌊__⌋	⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋	⌊__⌋⌊__⌋
Sensibility trouble (Polyneuropathy)	Absent	Parestesia: "stockings and gloves distribution"	Pain, leading to interruption of melarsoprol treatment	⌊__⌋	⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋	⌊__⌋⌊__⌋
Bullous eruptions (Exfoliative dermatitis)	Absent	Exfoliative skin eruptions not leading to interruption of melarsoprol treatment	Exfoliative skin eruptions leading to interruption of melarsoprol treatment	⌊__⌋	⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋	⌊__⌋⌊__⌋
Maculopapular eruptions (Urticaria)	Absent	Maculopapular or urticarial eruptions not leading to interruption of melarsoprol treatment	Maculopapular or urticarial eruptions leading to interruption of melarsoprol treatment	⌊__⌋	⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋	⌊__⌋⌊__⌋
Pruritus	Absent	Pruritus not leading to interruption of melarsoprol treatment	Pruritus leading to interruption of melarsoprol treatment	⌊__⌋	⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋	⌊__⌋⌊__⌋
Febrile reaction	Absent	37.5 - 38.9°C	≥ 39.0°C	⌊__⌋	⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋	⌊__⌋⌊__⌋
Headache	Absent	Not leading to interruption of melarsoprol treatment	Leading to interruption of melarsoprol treatment	⌊__⌋	⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋	⌊__⌋⌊__⌋
Diarrhea	Absent	Watery diarrhea without dehydration	Bloody diarrhea or watery diarrhea with dehydration	⌊__⌋	⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋	⌊__⌋⌊__⌋
Hypotension	Absent	Systolic blood pressure ≤ 80 mm/Hg	Shock	⌊__⌋	⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋	⌊__⌋⌊__⌋
Jaundice	Absent	Jaundice not leading to interruption of melarsoprol treatment	Jaundice leading to interruption of melarsoprol treatment	⌊__⌋	⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋	⌊__⌋⌊__⌋

Enter “b” for signs / symptoms which can not be assessed for this patient or in this center

Adverse effects	Grade 0	Grade 1	Grade 2	Grade 3	Maximum grade	Date occurred	Duration (if grade 1 / 2)
Encephalopathy	Absent	Psychiatric reactions	Convulsions and / or loss of consciousness	Death	⌊__⌋	⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋	⌊__⌋⌊__⌋

If Grade more than zero only: use Table “EXAMINATIONS AND LABORATORY TESTS IN CASE OF ENCEPHALOPATHY”

OBSERVATIONS AND OTHER DIAGNOSIS

(For additional information and comments only; all entries must be written clearly readable)

Date	Remark	Responsible for remark

For remarks use codes where possible (see Investigators manual)

OTHER DRUGS USED

(Indicate only drugs additional to regular treatment in this center)

Additional drugs used	yes ☐ (y) no ☐ (n)
1.	
2.	
3.	
4.	
5.	

EXAMINATIONS AND LABORATORY TESTS IN CASE OF ENCEPHALOPATHY

Adverse effects	Grade 0	Grade 1	Grade 2	Maximum grade	Date occurred / done	Duration of max [days]
Headache (< 24 hours before onset)	Absent	Sporadic	Continuous	⌊___⌋	⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋	⌊_⌋⌊_⌋
Fever (< 24 hours before onset)	Absent	37.5 - 38.9°C	≥ 39.0°C	⌊___⌋	⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋	⌊_⌋⌊_⌋
Aggressivity	Absent or comatose	Verbal attack	Physical attack	⌊___⌋	⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋	⌊_⌋⌊_⌋
Confusion	Absent or comatose	Correct response on current place	Incorrect response	⌊___⌋	⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋	⌊_⌋⌊_⌋
Convulsions	Absent	Single	Repeated	⌊___⌋	⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋	⌊_⌋⌊_⌋
Consciousness	Fully conscious	Drowsy	Comatose	⌊___⌋	⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋	⌊_⌋⌊_⌋
Malaria	(Thick smear mandatory in all cases of encephalopathy!)			pos ☐ (p) neg ☐ (n)	⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋	
Hemoglobin	Method: _____ ([g/dl] if not done enter "b")			⌊_⌋⌊_⌋.⌊_⌋	⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋	n.d. ☐ (b)
Glucose in blood	Method: _____ ([mg/dl] if not done enter "b")			⌊_⌋⌊_⌋⌊_⌋	⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋	n.d. ☐ (b)
HIV - Test	(Only if testing is routinely done at hospital and if counseling to positive patients is regularly provided)			pos ☐ (p) neg ☐ (n) n.d. ☐ (b)	⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋	

Swiss Tropical Institute
Institut Tropical Suisse
Schweizerisches Tropeninstitut

Swiss Centre for
International Health

FOLLOW UP INFORMATION (IMPAMEL II)

(Return this form at latest 2 months after examination to the STI)

Country Code ⌊_⌊_⌋	**Center Code** ⌊_⌊_⌊_⌋

Patient No. ⌊_⌋	
Patient full name ⌊_⌋	
Date of follow up assessment ⌊_⌊_⌋ ⌊_⌊_⌋ ⌊_⌊_⌋ (d d m m y y)	Date of discharge from hospital ⌊_⌊_⌋ ⌊_⌊_⌋ ⌊_⌊_⌋ (d d m m y y)
Number of follow up assessment 1☐(1) 2 ☐(2) 3 ☐(3) 4 ☐(4) 5 ☐(5) 6 ☐(6)	

Patient examined in hospital	☐(h)					
White blood cells in CSF (number / mm^3)	⌊_⌊_⌊_⌋					
Trypanosomes in CSF	pos	☐(p)	neg	☐(n)	n.d.	☐(b)
Centrifugation of CSF done	yes	☐(y)	no	☐(n)		
CATT Test	pos	☐(p)	neg	☐(n)	n.d.	☐(b)
Trypanosomes in blood	pos	☐(p)	neg	☐(n)	n.d.	☐(b)
Trypanosomes in lymph nodes	pos	☐(p)	neg	☐(n)	n.d.	☐(b)
Condition of patient	good	☐(g)	fair	☐(r)	bad	☐(b)
	died	☐(g)	Date	⌊_⌊_⌋ ⌊_⌊_⌋ ⌊_⌊_⌋ (d d m m y y)		

Patient visited in village	☐ (v)		(If visited in village and laboratory examinations done: use fields above)			
Information from patient	☐ (p)					
Information from relatives / friends	☐ (r)					
Condition of patient	good	☐(g)	fair	☐(r)	bad	☐(b)
	died	☐(g)	Date	⌊_⌊_⌋ ⌊_⌊_⌋ ⌊_⌊_⌋ (d d m m y y)		

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WorldHealthReport (2004). World Health Report.

CURRICULUM VITAE

Name	Schmid, Caecilia
Address (work)	Swiss Tropical Institute, Socinstrasse 57, P.O. Box, CH - 4002 Basel / Switzerland;
	email: Cecile.Schmid@unibas.ch,
	Phone 0041-61-225-2667, fax 0041-61-225-2678
Address (home)	Hauptstrasse 8, 4414 Fuellinsdorf / Switzerland
Born	March 15, 1965
Sex	Female
Citizen of	Schüpfheim / LU, Switzerland
Languages	German, English, French and basic understanding of Italian

Education and Employment:

2001 - 2004 **Research Assistant and PhD student**, thesis: “10-day melarsoprol treatment of *Trypanosoma brucei gambiense* sleeping sickness: from efficacy to effectiveness”, Swiss Centre for International Health, Swiss Tropical Institute (STI), Basel, Switzerland.

Supervisor: Dr C. Burri; Faculty representative: Prof. M. Tanner (Dean Faculty of Science University of Basel and Director Swiss Tropical Institute, Basel, Switzerland), External Expert: Prof. P. Buscher (Institute of Tropical Medicine, Antwerp, Belgium)

1998 - 2001 **MSc** in Control of Infectious Diseases at London School of Hygiene and Tropical Medicine (LSHTM) / University of London (epidemiology, public health, immunology, parasitology, nutrition and infection, health management and research design)

MSc thesis: “Pharmacological and biological study on unusual sleeping sickness cases refractory to treatment with melarsoprol in northern Uganda”, supervisors Dr. D. Legros, Epicentre, Médécins sans Frontières (MSF) France; PD Dr. R. Kaminsky, Novartis, St. Aubin, Switzerland and Dr. Simon Croft, London School of Hygiene and Tropical Medicine (LSHTM), London, UK.

1992 - 2000 Research assistant and Head technician of the protozoology laboratories at the Swiss Tropical Institute. (Head PD Dr. R. Brun, Project leader: PD Dr. R. Kaminsky). Competences and responsibilities see Appendix to CV.

1989 - 1991 Education to **ATA** (Academic technical assistant) at the Swiss Tropical Institute in Basel /Switzerland (University of Basel), Practical training in biochemistry, electron microscopy, immunology and cell biology laboratories

ATA Diploma thesis "Study on the detection of antimalarials in body fluids with high performance thin layer chromatography", biochemistry laboratory, Supervisor: PD Dr. B. Betschart and final examination in Medical Parasitology

Vordiplom in Biology I at the University of Basel (botany, zoology, physics, chemistry and statistics)

1986 - 1991 Studies in Biology at the University of Basel / Switzerland

Postgraduate courses and further training

2003	ICAT 3: International course on African Trypanosomoses by WHO, IAEA, MSF; Lisbon Portugal (12. – 30.05.2003)
2002	Introduction to HealthMapper software, GIS application by WHO in Kinshasa, Democratic Republic of Congo (01. – 08.07.2002)
2001	Postgraduate Diploma of the LSHTM in Infectious Diseases
2000 – 2003	Lectures of the following professors were attended during the postgraduate education at the University of Basel: H.P. Beck, R. Brun, C. Burri, I. Felger, C. Lengeler, G. Pluschke, T. Smith, M. Tanner, P. Vounatsou, M. Weiss, N. Weiss, J. Zinstag

Working Experience in African countries

2004	Democratic Republic of Congo (DRC) and Republic of Congo (RoC): IMPAMEL II program supervision mission; Economic analysis on the cost of treatment with melarsoprol.
2002	Democratic Republic of Congo (DRC): IMPAMEL II program supervision mission; EpiData 2.1 data management software training and introduction to BCT, Kinshasa.
2002	Cameroon: Introduction and training of *in vitro* cultivation techniques to isolate trypanosomes from patients. Consultancy in initiation of a WHO reference cryobank of trypanosome strains in Western Africa at OCEAC, Yaoundé, Cameroon.
2001	Democratic Republic of Congo (DRC) and Republic of Congo (RoC): IMPAMEL II program supervision mission.
1998	Uganda: Research collaboration and field mission with Medecins sans Frontières (MSF France and Epicentre, Paris) in Omugo, North Western Uganda
1997	Uganda: Research collaboration for 2 months at tissue cultivation laboratory at UTRO (Ugandan trypanosomiasis research organization) in Tororo, Uganda.
1996	Uganda: Assistance at the first course of tissue cultivation and establishment of the tissue cultivation unit at the veterinary faculty at the Makerere University in Kampala, Uganda. Research collaboration for 3 months at the tissue cultivation laboratory at UTRO.
1994	Uganda: Leading assistance at the second course of tissue cultivation of trypanosomatids at UTRO.
1993	Uganda: Establishment of a tissue cultivation laboratory at UTRO and leading assistance at the first course of tissue cultivation at UTRO.

Presentations at Meetings, Congresses

2004	Brazzaville, Republic of Congo, First international Congress of Trypanosomiasis: “Protocole de traitement court au mélarsoprol : Résultats d’un essai multicentrique”
2003	Leysin, Switzerland, Swiss Trypanosomatid Meeting: “IMPAMEL I- Safety and long-term efficacy of a new 10 day melarsoprol treatment schedule”
1999	Mombasa, Kenya, 25th ISCTRC: “Melarsoprol and DFMO levels in plasma and cerebrospinal fluids of late-stage sleeping sickness patients in Omugo, NW Uganda

Publication list Caecilia Schmid

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