Peer reviewed article

Treatment of late stage sleeping sickness caused by *T. b. gambiense*: a new approach to the use of an old drug

Johannes Blum, C. Burri

Swiss Tropical Institute, Basel, Switzerland

Summary

Melarsoprol is the standard treatment of late stage trypanosomiasis. The development of treatment schedules was previously purely empirical. Generally melarsoprol is given in 3 series of three to four consecutive injections, given every 24 hours, with an interval of about one week between the series.

Based on pharmacokinetic analysis, computer simulations and extensive literature research covering all schedules previously used and tested, a new schedule, consisting of ten daily consecutive doses of 2.16 mg/kg of the drug was suggested. The pharmacokinetic model was validated in uninfected vervet monkeys. No unexpected drug accumulation and no systemic toxic effects were observed. In a pilot clinical trial in Congo RDC a small group of *T. b. gambiense* patients (n = 11) was treated successfully with the new schedule. In an open randomised clinical trial conducted in 500 patients in Angola the clinical efficacy and safety of this new concise treatment were compared to those of standard protocol treatment. Parasitological cure 24 hours after treatment was 100% in both groups. Statistical analysis yielded no significant differences for adverse events between the two treatment protocols. The new schedule reduces the amount and cost for the drug by about one third, and those for hospitalisation by about half.

Key words: human African trypanosomiasis; sleeping sickness; treatment; melarsoprol

Epidemiology

Current estimates indicate that some 300,000–500,000 people have human African trypanosomiasis (HAT) or sleeping sickness, and that about 60 million people live in areas where the disease is transmitted [1]. Thirty-six sub-Saharan countries of Africa are affected by the problem at different levels of endemicity (figure 1). The areas most affected are parts of the Democratic Republic of Congo (DRC), Angola, Southern Sudan, and Northern Uganda [2]. The epidemiological situation in some countries is totally unknown. Only a fraction of the population at risk is under appropriate surveillance and therefore the reported number of cases in 1999 (45,000) rather reflects poor reporting than the real situation [1].

Sleeping sickness is an ancient disease, which recently has regained epidemic dimensions. Large-scale control campaigns largely reduced the case number and in the mid sixties only sporadic cases occurred throughout the continent. Subsequently, following the attainment of independence from colonial rule, sleeping sickness control has not been given due attention by National Health Authorities because of political and civil unrest, deteriorating economies of the endemic countries, overpopulation, and competing health priorities [3]. Recent data on sleeping sickness surveillance indicate an important increase of the number of detected cases per year [4].

In some regions of the Democratic Republic of Congo trypanosomes were detected in 40–70% of the examined people of rural areas. The mortality caused by HAT and AIDS in this country is now of a comparable magnitude [5]. A prevalence survey conducted in 13 villages in Sudan showed a marked increase of the seroprevalence from 0.3% in 1988 to 20.4% in 1997 [6]. If the DALY figures (i.e. loss of healthy life years by premature mortality and disability) are considered the social and economic impact of trypanosomiasis ranks third of all parasitic diseases behind malaria and schistosomiasis in sub-Saharan Africa [7].

No financial support declared.

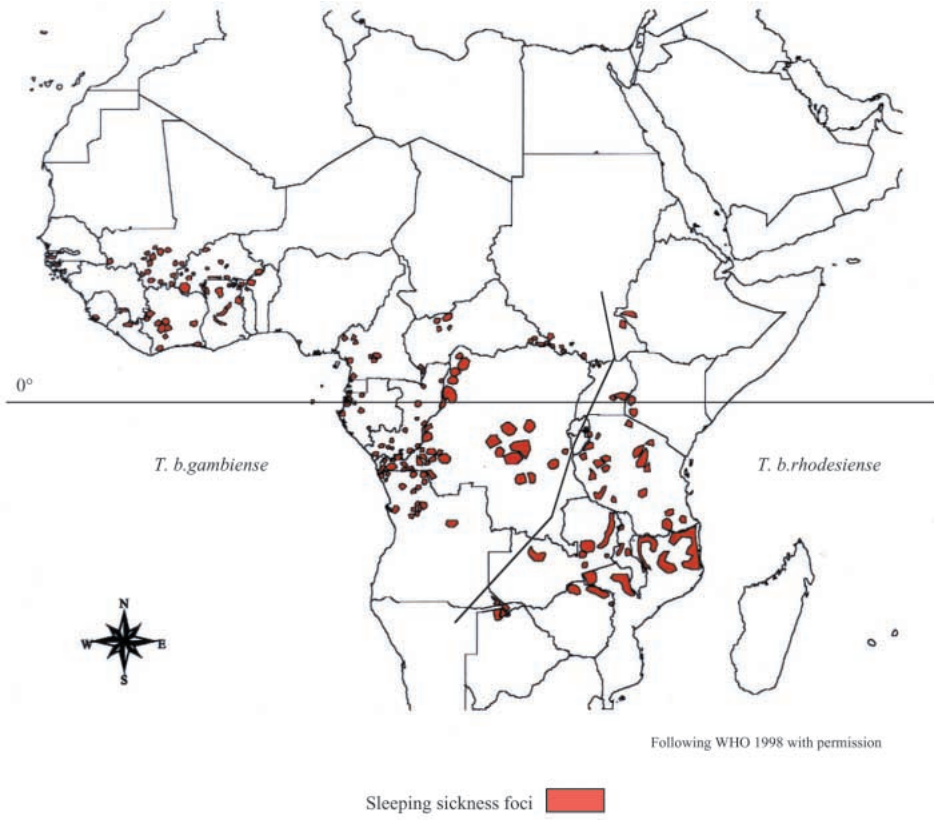


Figure 1
Distribution of human African trypanosomiasis.

Clinical aspects

The disease is caused by the protozoan parasites *Trypanosoma brucei gambiense* (West African form) and *Trypanosoma brucei rhodesiense* (East African form), and is solely transmitted by the Tsetse fly, *Glossina* sp [7].

Table 1
Symptoms and signs in 500 late stage patients from Dondo, Angola.

	n/N[1]	%
Lymphadenopathy	425	85.0
Headache	349	69.8
General motor weakness	256	51.2
Absence of menstruation[3]	66/214	30.8
Diurnal somnolence	143	28.6
Nocturnal insomnia	143	28.6
Aggressiveness	116	23.2
Gave birth in the last 9 months[2]	40/214	19.0
Tremors	95	19.0
Pruritus	87	17.4
Disturbed appetite	51	10.2
Unusual behaviour	48	9.6
Fever (Temp. >37.5 °C)	47	9.4
Hepatomegaly	35	7.0
Abnormal movements[3]	29	5.8
Splenomegaly	25	5.0
Epileptiform attacks[4]	14	2.8
Impaired speech	7.0	1.4
Inability to walk unaided	6	1.2

[1] If not indicated N is 250
[2] Considers only women who have not yet reached menopause
[3] Preventing the patient from performing daily tasks
[4] History reported by patient

The West African form of sleeping sickness is characterised by a chronic progressive course, which may last from months up to several years before death. The East African form is usually acute and death occurs within weeks or months. In this article we focus on the West African form of sleeping sickness.

Early or hemolymphatic stage

In rare instances a chancre may become visible at the site of inoculation of the trypanosomes. Intermittent fever attacks, persistent headache, joint pains, weight loss, and pruritus are common symptoms of the early hemolymphatic stage. Weeks or months after the infection a general lymphadenopathy develops and typically the posterior cervical lymph nodes are often visibly enlarged ("Winterbottoms sign"). Generalised endocrine disorders like reduced libido, amenorrhea, abnormal thirst or appetite, and prominent anaemia are frequent [8]. The liver and the spleen may be slightly enlarged and a localised oedema may be observed.

Late stage

The onset of the clinically different late stage is defined by the invasion of the CNS by trypanosomes [8].

Early signs are changes of the personality and the behaviour, and may be very subtle. Speech may become indistinct and slow, and frequently extrapyramidal signs occur with tremors of the tongue and the fingers. The most impressive sign

is daytime somnolence, often alternating with insomnia at night. Epileptiform seizures, euphoria and manical changes are observed and the patient becomes indifferent to his environment. The final phase is characterised by progressive mental deterioration and general wasting. Death results from the disease itself, concurrent infections like pneumonia, or malnutrition. The symptoms and signs of 500 patients treated for late stage sleeping sickness in Dondo, Angola, are listed in table 1.

The distinction of the stages influences the choice of drugs for treatment and is based on the analysis of the cerebrospinal fluid (CSF). If trypanosomes can be found in the CSF, or if the WBC count is more than 5 WBC/mm^2, or if there is a protein content above 25 mg/100 ml (method of Siccard & Cantaloube) the patient is attributed to the late stage and treated with melarsoprol [2].

Treatment

Pentamidine is currently used for treatment of early stage *T. b. gambiense* sleeping sickness. The organo-arsenical compound melarsoprol (Arsobal®) is the drug mainly used in the late stage. The recently introduced α-difluoromethylornithine (DFMO; eflornithine) [9] is effective in Gambian sleeping sickness in over 95%. However, the use of eflornithine is limited due to its application in four infusions per day for fourteen days. In addition the drug is very expensive due to its very complex synthesis, and had no longer been produced for several years. In the year 2001 an agreement between WHO and Aventis was reached guaranteeing the free availability of the drug over the next five years [10]. This will only allow the use of the drug in selected situations, like the treatment of relapse patients, interventions financed by non-governmental organizations, and treatment of patients in industrialised countries. The complicated and costly application will prevent the replacement of melarsoprol as the first line drug. Therefore WHO TDR has recently initiated a program to investigate the application by oral route.

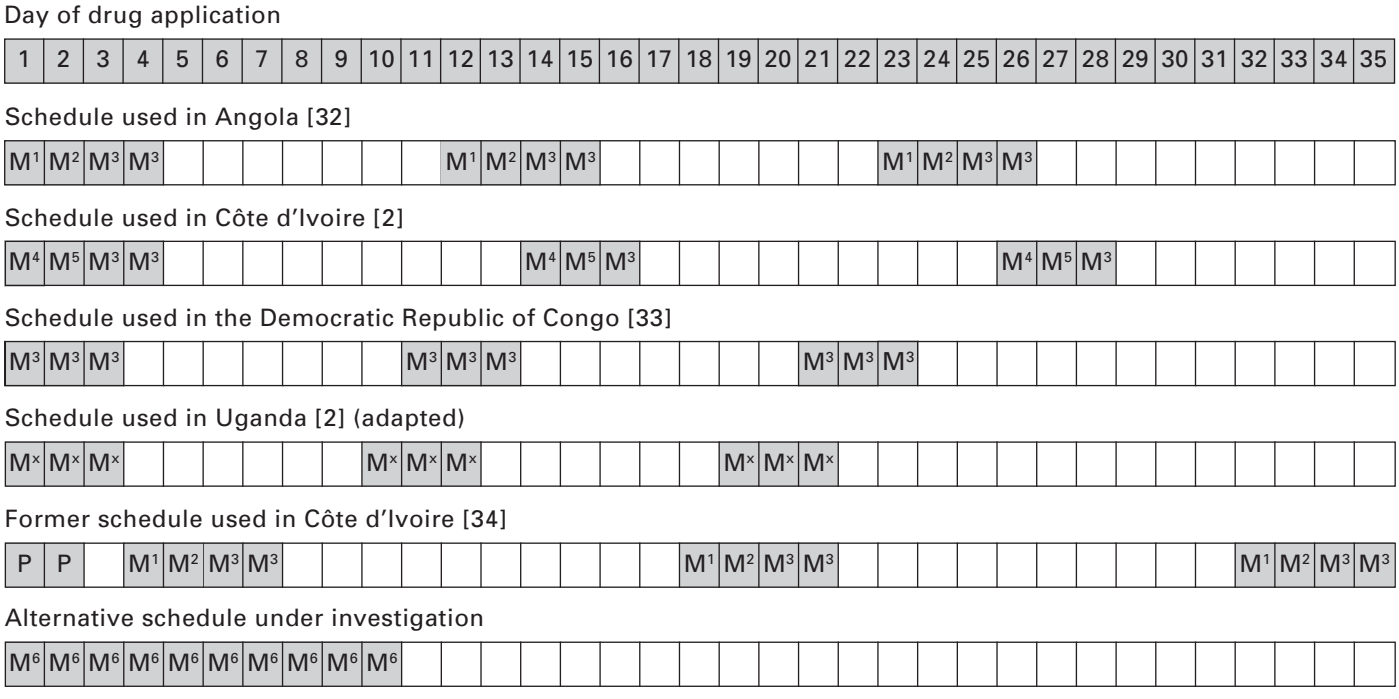
Despite ample basic research on trypanosomes and screening activities to identify new active molecules, no new compounds are currently under development for treatment of second stage sleeping sickness. Therefore melarsoprol is likely to remain the first-line drug for the next decade. For this reason WHO has advocated optimisation of the use of the present drugs [2].

Melarsoprol treatment

Melarsoprol was introduced in 1949 [11] but its basic pharmaco-chemical and pharmacological properties were only investigated recently. The terminal elimination half life ($t_{1/2}$) is 35 hours, as determined by a biological assay [12]. The corresponding parameter determined by HPLC was 1

Figure 2

Examples of different schedules for treatment of late stage *T. b. gambiense* sleeping sickness.



M^1 = Melarsoprol 1.2 mg/kg bw; M^2 = Melarsoprol 2.4 mg/kg bw; M^3 = Melarsoprol 3.6 mg/kg bw (max. 5 ml)
M^4 = Melarsoprol 1.08 mg/kg bw; M^5 = Melarsoprol 2.52 mg/kg bw; M^3 = Melarsoprol 3.6 mg/kg bw (max. 5 ml)
M^x = 1 series of 1.8, 2.16, 2.52 mg/kg bw, 1 series of 2.52, 2.88, 3.25 mg/kg bw, 1 series of 3.6, 3.6, 3.6 mg/kg bw (max. 5 ml); P = Pentamidine 4 mg/kg; M^6 = Melarsoprol 2.16 mg/kg bw (max. 5 ml)

hour, indicating the existence of active metabolites [13], which currently are under investigation. The total protein binding of melarsoprol is 79% as determined by ultrafiltration [14]. The exact mode of action of melarsoprol remains unclear, but the drug was shown to unspecifically bind to disulphide moieties of proteins [15].

Early studies performed in urine indicated that melarsoprol was only eliminated from the body to a very limited extent. To avoid accumulation of arsenic in the body, treatment interruptions after each 3rd or 4th injection of melarsoprol were introduced [16, 17]. Later studies revealing that melarsoprol is mainly eliminated in the faeces didn't get proper attention and hence treatment schedules have remained unchanged since 50 years. No unusual drug accumulation was found in elimination studies in rats [18], and kinetic investigations in monkeys [19] and humans [12, 18].

The development of treatment schedules is purely empirical and there is no standardised treatment regimen [20]. Generally, melarsoprol treatment consists of several series of three or four consecutive injections, given every 24 hours, with an interval of about one week between each series. In most of the schedules the doses increase progressively either during the course of treatment or within a single series (see fig. 2) [2].

Melarsoprol treatment is frequently accompanied by adverse effects, which may be severe. Common problems with melarsoprol are motor and sensitivity polyneuropathies, skin reactions, fever, diarrhoea, pruritus, and pain in the chest. A local reaction that can be attributed to the propyleneglycol solvent is thrombophlebitis at the site where the drug has been injected.

However, the most feared complications of melarsoprol treatment are encephalopathies. They occur at varying frequencies in 5–10% of all treated cases. The reaction is fatal for about 10–70% of the patients afflicted [2, 21].

Its clinical manifestations are either a fulminant convulsive status, a progressive coma, or psychotic reactions. The fulminant convulsive status seems to be often preceded by minor prodromes such as dizziness or nausea and it is associated with acute cerebral oedema as shown by papilloedema and elevated CSF pressure. The progressive coma develops within hours without signs of cerebral oedema. The pressure of the CSF is normal and the protein levels are just moderately elevated. The psychotic reactions are characterised by aggression, restlessness, and emotional disorders lasting for a few days without other neurological signs [22, 23].

A post mortem study showed no association between the encephalopathy and the severity of the trypanosome-induced meningoencephalitis. The principal abnormalities in patients dying from encephalopathy are hypoxic brain damage, brain swelling, and the features of acute haemorrhagic leukoencephalopathy. The hypoxic brain damage was clinically associated with convulsions or heart failure, the acute haemorrhagic leukoencephalopathy with progressive coma [23, 24].

The cause of the reaction and the influence of the treatment schedule on its frequency, have been extensively discussed during the last decade. Generally an immune reaction is thought to underlie the syndrome [2, 21, 23], but the mechanism remains unknown. In a large-scale study [25] the concomitant application of prednisolone was shown to have a protective effect against encephalopathies. There were also reports of reactive encephalopathy after the application of other trypanocidal drugs like eflornithine and nifurtimox [26]; underlining the idea that this severe adverse event may not be attributed to the inherent toxicity of melarsoprol.

Relapses are another major problem of sleeping sickness treatment with melarsoprol. For many decades the frequency reported remained stable at levels between 1% to 10% [21]. However, significantly higher rates of patients refractory to melarsoprol were recently reported from Northern Uganda (26.9%) [27], Northern Angola (25%) [28], and Southern Sudan. An overview on the epidemiology and research on underlying factors has been done by Brun et al. [29]. No recommendation for the treatment of cases refractory to therapy exists so far. Where feasible eflornithine is used either alone or in combination with melarsoprol. Clinical trials for the evaluation of combination of eflornithine, melarsoprol, and/or nifurtimox are currently ongoing and preliminary results were encouraging. Nifurtimox is the first line drug for treatment of *T. cruzi* (Chagas disease) in South America, but it is not registered for use against human African trypanosomiasis [2].

Finally a severe drawback of melarsoprol therapy is the long period of hospitalisation required due to the complicated treatment schedules (see fig. 2). This is a major social and economic burden for the families affected because all patients must be taken care of at the hospital by family members.

The new concise treatment schedule

Based on pharmacokinetic analysis, computer simulations, and extensive literature research covering all schedules previously used and tested, a new schedule consisting of ten daily consecutive doses of 2.16 mg/kg of the drug was suggested [12] (see fig. 2). The pharmacokinetic model was validated in uninfected vervet monkeys following the new and the standard treatment schedules [19]. No unexpected drug accumulation and no systemic toxic effects were observed in the monkeys used for

the trial. In a pilot clinical trial in Congo RDC a small group of *T. b. gambiense* patients (n = 11) was treated successfully with the new schedule. All patients could leave the hospital in good health after 10 days of melarsoprol treatment or with a distinct improvement of their condition. A non-significant increase of minor adverse reactions (diarrhoea, fever, cutaneous reactions) was observed. No case of reactive encephalopathy occurred and no relapse was reported in this group after 12 months [30].

The clinical efficacy and safety of this new concise treatment were compared to those of standard protocol treatment in an open randomised clinical equivalence trial conducted in 500 patients in Angola. Application of melarsoprol was either following the standard National Angolan protocol (S) of 3 series of 4 injections (1.2; 2.4; 3.6; 3.6 mg/kg bw /day) interrupted by rest periods of 7 days, total duration 26 days, or according to the new treatment protocol of 10 consecutive injections (2.2 mg/kg bw /day) of melarsoprol (N) (see fig. 2). The primary outcomes defined were mortality related to treatment, encephalopathy rate, and elimination of parasites at the end of treatment. Parasitological cure 24 hours after treatment was 100% in both groups. Statistical analysis yielded no significant difference for adverse events between the two treatment protocols. A total of 28 patients (S: 14, N: 14; 5.6%) suffered from an encephalopathic syndrome during the treatment, of whom 12 died (S: 6; N: 6; 2.4%). Severe motor (S: 1, N: 2) and sensitivity polyneuropathy (S: 1; N: 0) were extremely rare in both groups. An increase of skin reactions was observed with the new treatment: Severe bullous dermatitis leading to treatment interruption occurred in 4 cases (S: 1; N: 3; 1.2%), severe maculopapular rash in 18 cases (S: 6, 2.4%; N: 8, 3.2%), and severe pruritus in 14 cases (S: 6, 2.4%; N: 8, 3.2%). All reactions could be controlled by treatment interruption and application of corticosteroids, and remitted completely. All moderate adverse effects like fever, diarrhoea, headache were observed at comparable rates in both groups. One year after the end of enrolment (individual observation time 15–32 months) 16 patients had relapsed (S: 7, N: 9) [31].

Currently a large-scale, multinational clinical trial is ongoing to further assess the frequency of adverse events like encephalopathic and skin reactions, and the efficacy of the new treatment schedule in different populations and settings.

We underline that all investigations described here were done in *T. b. gambiense* patients and can not be extrapolated to *T. b. rhodesiense* sleeping sickness due to the differing clinical pattern of the disease and the markedly higher parasitemia. Until credible data are available we recommend the use of the new melarsoprol schedule in such patients, only in defined trial settings and with exceptional caution.

The new schedule reduces the amount and cost for the drug by about one third, and those for hospitalisation by about half. The socio-economic value is even increased by the fact that all patients have to be taken care of by relatives at the hospital. Therefore the duration of treatment has a direct impact on the economic situation of the affected family, and in case of an endemic situation on entire villages. In addition, the capacity of the medical facilities can be more than doubled by the use of the new treatment schedule. This may crucially improve the situation for patients in areas of high endemicity, where the demand largely surpasses the capacities of the centres. These circumstances particularly prevail in war affected countries like Sudan, Angola, and the Democratic Republic of Congo.

Given the economical and practicallity of the concise treatment protocol, it might be a useful alternative to the common lengthy treatment, especially in endemic situations.

We thank Dr. C. Hatz for his critical analysis of the manuscript.

Correspondence:
Dr. Johannes Blum
Swiss Tropical Institute
Socinstrasse 57
P.O. Box
CH-4002 Basel
E-Mail: Johannes.Blum@unibas.ch

References

1 WHO. African Trypanosomiasis. 2001; http://www.who.int/emc/diseases/tryp/index.html
2 WHO. Control and surveillance of African trypanosomiasis. WHO Tech Rep Ser 1998;881:1-114.
3 Kuzoe FAS. Current situation of African trypanosomiasis. Acta Trop 1993;54:153-62.
4 Van Nieuwenhove S. Sleeping sickness resurgence in the DRC: the past decade. Trop Med Int Health 2001;6:335-41.
5 Ekwanzala M, Pepin J, Khonde N, Molisho S, Bruneel H, De Wals P. In the heart of darkness: sleeping sickness in Zaire. Lancet 1996;348:1427-30.
6 Moore A, Richer M, Enrile M, Losio E, Roberts J, Levy D. Resurgence of sleeping sickness in Tambura County, Sudan. Am J Trop Med Hyg 1999;61:315-8.
7 Molyneux DH, Pentreath V, Doua F. African trypanosomiasis in man. in Cook, GCBook. African trypanosomiasis in man. 20 London: W.B. Saunders Company Ltd., 1996:1171-96.
8 Greenwood BM, Whittle HC. The pathogenesis of sleeping sickness. Trans R Soc Trop Med Hyg 1980;74:716-24.
9 Nightingale S. Drug for sleeping sickness approved. JAMA 1991;265:1229.
10 WHO. World Health Organization and Aventis announce a major initiative to step up efforts against sleeping sickness. WHO Press Release 2001;23.
11 Friedheim EAH. Mel B in the treatment of human trypanosomiasis. Am J Trop Med Hyg 1949;29:173-80.

12 Burri CTB, Giroud C, Doua F, Welker HA, Brun R. Pharmacokinetic properties of the trypanocidal drug melarsoprol. Chemotherapy 1993;39:225-34.
13 Bronner U, Brun R, Doua F, Ericsson O, Burri C, Keiser J, et al. Discrepancy in plasma melarsoprol concentrations between HPLC and bioassay methods in patients with *T. gambiense* sleeping sickness indicates that melarsoprol is metabolized. Trop Med Int Health 1998;3:913-7.
14 Keiser J, Burri C. Physico-chemical properties of the trypanocidal drug melarsoprol. Acta Trop 2000;74:101-4.
15 Wang CC. Molecular mechanisms and therapeutic approaches to the treatment of African trypanosomiasis. Annu Rev Pharmacol Toxicol 1995;35:93-127.
16 Monnet A, Baylet R. Contribution a l'étude du métabolisme du mélaminyl 4-phenyl-arsenodithioglycerine en solution dans le propylenglycol son passage dans le liquide céphalo-rachidien. Bull Soc Path Exot 1951;44:754-8.
17 Apted FIC. Four years' experience of melarsen oxide/BAL in the treatment of late-stage Rhodesian sleeping sickness. Trans R Soc Trop Med Hyg 1957;51:75-86.
18 Cristeau B, Placidi M, Legait JP. Etude de l'excretion de l'arsenic chez le trypanosomé traité au melarsoprol. Med Trop 1975;35:389-401.
19 Burri C, Onyango JD, Auma JE, Burudi EM, Brun R. Pharmacokinetics of melarsoprol in uninfected vervet monkeys. Acta Trop 1994;58:35-49.
20 Berman J, Fleckenstein L. Pharmacokinetic justification of antiprotozoal therapy. A US perspective. Clin Pharmacokinet 1991; 21:479-93.
21 Pepin J, Milord F. The treatment of human African trypanosomiasis. Adv Parasitol 1994;33:1-47.
22 Blum J, Nkunku S, Burri C. Clinical description of encephalopathic syndromes and risk factors for their occurrence and outcome during melarsoprol treatment of human African trypanosomiasis. Trop Med Int Health 2001;6:390-400.
23 Haller L, Adams H, Merouze F, Dago A. Clinical and pathological aspects of human African trypanosomiasis (*T. b. gambiense*) with particular reference to reactive arsenical encephalopathy. Am J Trop Med Hyg 1986;35:94-9.
24 Adams JH, Haller L, Boa FY, Doua F, Dago A, et al. Human African trypanosomiasis (T. b. gambiense): A study of 16 fatal cases of sleeping sickness with some observations on acute reactive arsenical encephalopathy. Neuropathol Appl Neurobiol 1986;12:81-94.
25 Pepin J, Milord F, Guerin C, Mpia B, Ethier L, Mansinsa D. Trial of prednisolone for prevention of melarsoprol-induced encephalopathy in gambiense sleeping sickness. Lancet 1989; 1:1246-50.
26 Van Nieuwenhove S. Advances in sleeping sickness therapy. Ann Soc Belge Med Trop 1992;72:39-51.
27 Legros D, Fournier C, Etchegorry MG, Maiso F, Szumilin E. Therapeutic failure of melarsoprol among patients treated for late stage of *T. b. gambiense* human African trypanosomiasis in Uganda. Bull Soc Path Exot 1999;92:171-2.
28 Burri C, Keiser J. Pharmacokinetic investigations on patients from Northern Angola refractory to melarsoprol treatment. Trop Med Int Health 2001;6:412-20.
29 Brun R, Schumacher R, Schmid C, Kunz C, Burri C. The phenomenon of treatment failures in Human African Trypanosomiasis. Trop Med Int Health 2001;6:906-14.
30 Burri C, Blum J, Brun R. Alternative application of melarsoprol for treatment of *T. b. gambiense* sleeping sickness. Preliminary results. Ann Soc Belge Med Trop 1995;75:65-71.
31 Burri C, Nkunku S, Merolle A, Smith T, Blum JRB. Efficacy of a new, concise treatment schedule for melarsoprol in treatment of sleeping sickness caused by *Trypanosoma brucei gambiense:* a randomised trial. Lancet 2000;355:1419-25.
32 Josenando T. Manual de regras para o controlo da tripanossomíase humana africana. Luanda 1994; WHO for Republica de Angola, Ministério de Saúde, Direcção National de Controlo de Endemias, Programa National para a Vigilância e Controlo da Tripanossomiase Humana Africana.
33 Ekwanzala MF, Mandiangu P, Molisho SD, Bruneel H, Landua N, Kaninda K. Lutte contre la trypanosomiase humaine africaine au Zaïre: Guide technique a l'usage des Médecins Chefs de zone de santé, des infirmiers de hôpitaux et des infirmiers des centres de santé. Ministère de Santé, Bureau Central de la Trypanosomiase. 1995;26.
34 WHO. Epidemiology and control of African trypanosomiasis. WHO Tech Rep Ser 1986;739.

Swiss
Medical Weekly

Official journal of
the Swiss Society of Infectious disease
the Swiss Society of Internal Medicine
the Swiss Respiratory Society

The many reasons why you should choose SMW to publish your research

What Swiss Medical Weekly has to offer:

- SMW's impact factor has been steadily rising, to the current 1.537
- Open access to the publication via the Internet, therefore wide audience and impact
- Rapid listing in Medline
- LinkOut-button from PubMed with link to the full text website http://www.smw.ch (direct link from each SMW record in PubMed)

- No-nonsense submission – you submit a single copy of your manuscript by e-mail attachment
- Peer review based on a broad spectrum of international academic referees
- Assistance of our professional statistician for every article with statistical analyses

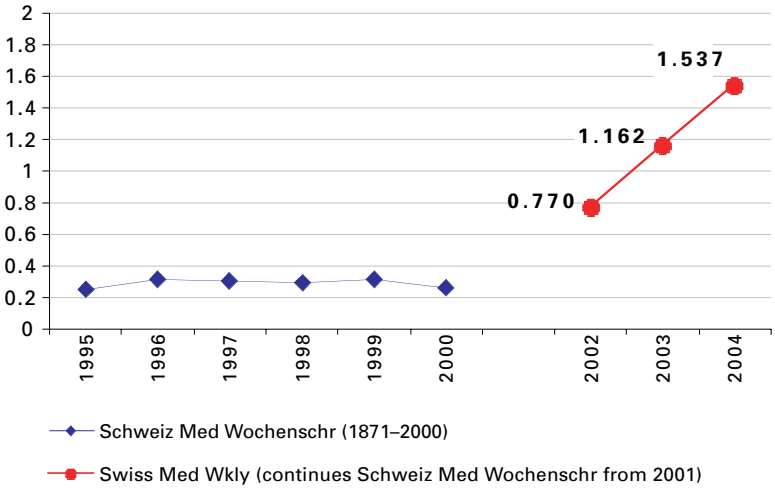
- Fast peer review, by e-mail exchange with the referees
- Prompt decisions based on weekly conferences of the Editorial Board
- Prompt notification on the status of your manuscript by e-mail
- Professional English copy editing
- No page charges and attractive colour offprints at no extra cost

We evaluate manuscripts of broad clinical interest from all specialities, including experimental medicine and clinical investigation.

We look forward to receiving your paper!

Guidelines for authors:
http://www.smw.ch/set_authors.html

Impact factor Swiss Medical Weekly



EMH FMH Schwabe
Editores Medicorum Helveticorum

All manuscripts should be sent in electronic form, to:

EMH Swiss Medical Publishers Ltd.
SMW Editorial Secretariat
Farnsburgerstrasse 8
CH-4132 Muttenz

Manuscripts: submission@smw.ch
Letters to the editor: letters@smw.ch
Editorial Board: red@smw.ch
Internet: http://www.smw.ch