Toxicity of a nifurtimox-melarsoprol combination treatment for relapsing trypanosomiasis patients in Northern Uganda and Southern Sudan.

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1 Background

Infection with the protozoan parasite *Trypanosoma brucei gambiense* causes sleeping sickness or Human African Trypanosomiasis (HAT). After the infective tsetse bite, trypanosomes spread into blood and lymphoid tissues, initiating the heamolymphatic disease stage. When trypanosomes invade the central nervous system (CNS), the second, meningoencephalitic stage is initiated. At the second stage of the disease, the first line classic treatment is a series of intravenous injections of melarsoprol, an arsenic derivative[1].

The usual proportion of treatment failures after melarsoprol for cases of late-stage HAT is thought to be between 3% and 9% [2]. However, a higher proportion of relapsing cases has been described in Arua district reaching 28.7 % in 1995-1996 [3] and data from the treatment centre in Ibba, Western Equatoria, indicates a failure rate of 18.4 % at six months of follow-up in 1999 [4] [†]. Eflornithine (DFMO) is the second line drug to be used in case of melarsoprol failure. Although difficult to administer, this drug is better tolerated and much more effective than a second course of melarsoprol (91.3% treatment failure among patients retreated with melarsoprol in Arua[3]). Unfortunately, the production of eflornithine has been stopped, and the remaining stock shall only permit to treat around 1,300 patients. Therefore, as recommended by WHO, and in face of the absence of new medicines for HAT, existing therapies should be optimised and all possible drug combinations explored [1].

In view of the unprecedented relapse rates observed after treatment with melarsoprol in both populations of Arua and Ibba and the lack of DFMO, MSF decided in September 1999 to establish a new treatment protocol combining nifurtimox and melarsoprol for relapsing patients on a compassionate basis.

1.1 Treatment protocol

On the first day of admission, patients received a systematic treatment of Mebendazole 500 mg OD / 2 days, and a course of antimalarials: in Omugo, Sulfadoxine-Pyrimethamine 25 mg/kg stat; in Ibba, a three-day course of Chloroquine.

Prednisolone tablets were given at 1mg/kg/day from day 1 to day 11 in Omugo and from day 2 to 11 in Ibba (IDA, batch N° 01/99, expiry date: 08/2004).
Melarsoprol was given at 2.2 mg/kg/day IV, from day 2 to day 11. (ARSOBAL®, batch N° 709, expiry date: 03/2001).

Nifurtimox was given at 15 mg/kg/day per os, from day 4 to day 17 (LAMPIT®, Bayer Argentina, tablets of 120 mg, batch N° 696606, expiry date: 06/2001) (Figure 1).
The same batches of melarsoprol and nifurtimox were used in both treatment centres.

Figure 1: Treatment protocol used for relapsing HAT cases in Northern Uganda and Southern Sudan, September 1999 – February 2000

[†] Relapse rates are calculated as follows: (relapses + deaths during follow-up) / all patients treated with melarsoprol and discharged alive x 100.

Day of drug administration

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18

Omugo schedule

P	P	P	P	P	P	P	P	P	P	P							
	M	M	M	M	M	M	M	M	M	M							
			N	N	N	N	N	N	N	N	N	N	N	N	N	N	

Ibba schedule

	P	P	P	P	P	P	P	P	P	P							
	M	M	M	M	M	M	M	M	M	M							
			N	N	N	N	N	N	N	N	N	N	N	N	N	N	

P: prednisolone M: melarsoprol N: nifurtimox

1.2 Particulars of Nifurtimox

Nifurtimox, a nitrofurfurylidene derivative, is effective in the treatment of the acute stages of American Trypanosomiasis (Chagas disease) since the late 1960's. The American *trypanosoma* has an intracellular form, which imposes prolonged treatment courses of 1 to 3 months. Taken orally, it reaches peak serum concentrations in 3.5 h and the mean elimination half-life is almost 3 h [5]. This rapid decline of serum concentrations of unchanged nifurtimox is presumably due to an almost complete metabolisation in the liver, which raises the question of the therapeutic activity of its metabolites[16]. Its mechanism of action on the parasite remains unclear.
Nifurtimox in monotherapy has been tested in case series for the treatment of HAT in several places with contradictory results [6, 7, 8]. Its use as a second-line drug cannot be recommended unless extensive investigations are performed [3]. However, preliminary evidence indicates a promising efficacy when used in combination with melarsoprol [9].

The main side effects of nifurtimox described in the literature are gastro-intestinal : loss of appetite (with weight loss), nausea, vomiting and gastric trouble, often relieved with antacids. Central or peripheral nervous system symptoms are less frequent : forgetfulness, sleep disturbances, nystagmus, agitation, convulsions or psychotic manifestations, tremor, paresthesia, slight polyneuritis, muscular weakness [10, 11, 12]. Other uncommon side effects include : vertigo, status epilepticus, cerebellar syndrome, peripheral polyneuropathy, skin rashes, and exacerbation of pre-existing symptoms (headache, arthralgia, etc.) [6].

Adverse effects of nifurtimox are related more to the cumulative total dose than to the daily dose[13]. Moens *et al*, using doses of 12.5-15 mg/kg/day during 2 months for the treatment of 15 HAT patients, reported one case of convulsions followed by coma, after 6 weeks of nifurtimox and a case of a 6 years old child developing mutism with choreic movements after 5 days of treatment[14]. Pépin *et al.* reported significant toxicity among 30 HAT patients treated with high-dose nifurtimox (30mg/kg/day) during 30 days: confusion followed by coma and death at D13 in one patient, confusion in 13% of patients, tremor in 17%, vertigo in 10%, anorexia and weight loss in 40%. Fever, skin rash, dysarthria and convulsions were observed in one patient each. Usual onset of symptoms was during the second week of

treatment[7]. A previous trial with lower doses (12-17mg/kg/day) for a period of 60 days had produced milder side effects that appeared after 15 to 46 days of treatment[15].

1.3 Melarsoprol toxicity

The use of melarsoprol is associated in 15% of cases with side effects such as diarrhoea, cardiomyopathy and skin necrosis that lead to treatment interruptions. The most severe side effect is the treatment-induced encephalopathy, which occurs in 5-10 % of patients and bears a 10-50 % lethality [1]. Abnormal behaviour and psychotic reactions are sometimes considered as a less severe form of "reactive arsenical encephalopathy". Other neurological manifestations described include peripheral polyneuropathy, subjective sensations of heat, disturbance of smell, headache, tremors and myalgia. Other adverse effects include fever, nausea, chest and abdominal pain, vomiting, diarrhea, cutaneous eruptions, Lyell syndrome, thrombophlebitis, cardiotoxicity, renal dysfunction, hepatic dysfunction and agranulocytosis[16, 17].

1.4 Side effects reported by MSF teams

The medical team in Omugo reported unusual neurological adverse events among cases treated with the melarsoprol + nifurtimox protocol. They consisted mainly of severe mental disturbances and motor symptoms. One patient had died after seizures and coma, several others had prolonged hallucinations and behavioural changes that created concern among the team. It was feared that this kind of manifestations would create alarm in the community and lead to refusal of hospitalisation of sleeping sickness cases.
The team at Ibba, having treated more patients with the same protocol, reported no problems of the same severity, only mild, short lasting symptoms.

At this point, Médecins Sans Frontières requested EPICENTRE to carry out an investigation to describe the phenomenon and research its possible causes.

2 Objectives

The objectives of this study were to:

- Describe the occurrence of severe neurological side effects among late stage HAT patients treated with the combination nifurtimox + melarsoprol in Omugo and Ibba
- Identify risk factors explaining the occurrence of these unusual side effects
- Identify factors explaining the difference reported between Omugo and Ibba in the frequency and intensity of these side effects

3 Methods

For security reasons, it was not possible for the investigator to obtain more detail about the signs and symptoms in Ibba directly from the field medical staff, but two of the expatriate medical professionals were interviewed retrospectively once outside the country. The information was therefore mainly extracted from the medical records of the patients, while in Omugo this was further developed via interviews of the medical staff and the use of a special form to systematically collect data from these patients during the treatment.

Case definition
A case definition for severe neurological side effects was developed: patients with late stage HAT treated with the combination of nifurtimox and melarsoprol that developed one or more of the following symptoms with onset AFTER day 4 : hallucinations, nightmares (loud, unusual), disorientation, tremor, convulsions.

Patients care
In Omugo, patients under treatment at the time of the consultation were examined. In addition, a patient that had been discharged in a state of hallucinations and mental confusion was traced at her address in the village.
The different members of the medical team were interviewed to reconstruct the picture. The "Transmission Book" where nurses on duty report the status of patients was examined for additional information and double-checking.
The actual drugs were examined and their references noted. Finally, the food rations provided were assessed and cross-checked with the person in charge of the food distribution.

Collection and analysis of data
The files of 105 patients were examined and pertinent data was extracted. Information was collected on factors thought to be potential etiological factors for the unusual side effects observed and for the differences between the two treatment centres. This included time, personal characteristics of patients, concomitant treatments, results of biological tests on admission, Karnofsky index (overall function) and Glasgow coma scale (neurological function) on admission (information on factors such as hematocrit, Karnofsky index and Glasgow coma scale were available only from Omugo treatment centre). The association of these variables with the occurrence of severe side effects (as per case definition) was tested using the relative risk (RR) estimates and their 95% confidence interval. EpiInfo version 6.04b (CDC/WHO) was used for data collection and analysis.

4 Results

4.1 Baseline characteristics

At the Omugo and Ibba treatment centres 38 and 67 patients respectively were treated with the nifurtimox-melarsoprol combined schedule between September 1999 and February 2000. All these patients were relapses in stage II of the disease and followed the same treatment protocol. The patients treated in Omugo and Ibba were comparable with regards to their characteristics on admission (Table 1) although in Ibba there was a predominance of male patients. Data was not available for other assessments of interest such as nutritional status and other clinical signs and symptoms.

Table 1 : Baseline characteristics of HAT patients treated with a combination of Nifurtimox and Melarsoprol in Northern Uganda and Southern Sudan, September 1999 – February 2000

	Omugo (n = 38)		Ibba (n = 67)		p
	n	(%)	n	(%)	
Demographics					
Male	19	(50.0)	41	(61.2)	0.27
Age					
0 – 14	8	(21.1)	14	(20.9)	0.98
15 and over	30	(78.9)	53	(79.1)	
Laboratory					
Tryps in lymph nodes	1	(2.6)	1	(1.5)	-
Tryps in blood	5	(13.2)	5	(7.5)	0.54
Tryps in CSF	23	(60.5)	46	(68.7)	0.39
WBC per uL in CSF					.
0 – 100	12	(31.6)	18	(27.3)	0.61
101 and over	26	(68.4)	48	(72.7)	
Mean [SD] hematocrit	38.8 [4.4]		-		-
Clinical parameters					
Karnofsky index					
80% – 100%	28	(73.7)	-	-	-
less than 80%	10	(26.3)	-	-	
Glasgow coma score					
15 (normal value)	35	(92.1)	-	-	-
less than 15	3	(7.9)	-	-	

4.2 Incidence of side effects

Besides the expected weight loss and gastrointestinal symptoms, consisting mainly of epigastric pain, there was a predominance of neurological signs and symptoms that was unexpected both in their variety and intensity (Table 2). It is important to note that the severity and duration of the side effects in Ibba were markedly lesser than those observed in Omugo. The impression of the Ibba medical team (radio contacts and interviews a posteriori) was that the treatment was generally well tolerated, while this was not at all the same experience in Omugo.

Table 2 : Occurrence of side effects among HAT patients treated with a combination of Nifurtimox and Melarsoprol in Northern Uganda and Southern Sudan, September 1999 – February 2000

	Omugo (n = 38)	Ibba (n = 67)	Total (n = 105)

	n	(%)	n	(%)	n	(%)
Severe neurological side effects	18	(47.4)	16	(23.9)	34	(32.4)
Hallucinations	14	(36.8)	1	(1.5)	15	(14.3)
Nightmares	13	(34.2)	0	(0.0)	13	(12.4)
Disorientation	9	(23.7)	16*	(23.9)	25	(23.8)
Tremor	4	(10.5)	4	(6.0)	8	(7.6)
Convulsions	1	(2.6)	8	(11.9)	9	(8.6)
Other neurol. side effects						
Severe neurol. disturbance	0	(0.0)	1	(1.5)	1	(1.0)
Speech disturbance	0	(0.0)	1	(1.5)	1	(1.0)
Behaviour change	5	(13.2)	0	(0.0)	5	(4.8)
Insomnia	0	(0.0)	4	(6.0)	4	(3.8)
Shivering	0	(0.0)	1	(1.5)	1	(1.0)
Headache	1	(2.6)	3	(4.5)	4	(3.8)
Dizziness	1	(2.6)	14	(20.9)	15	(14.3)
Weight loss	23	(60.5)	not recorded		-	-
Anorexia	7	(18.4)	2	(3.0)	9	(8.6)
Gastro intestinal	13	(34.2)	23	(34.3)	36	(34.3)
Fever	11	(29.0)	8	(11.9)	19	(18.1)
Death	1	(2.6)	0	(0.0)	1	(1.0)
Any side effect	24	(63.2)	42	(62.7)	66	(62.9)

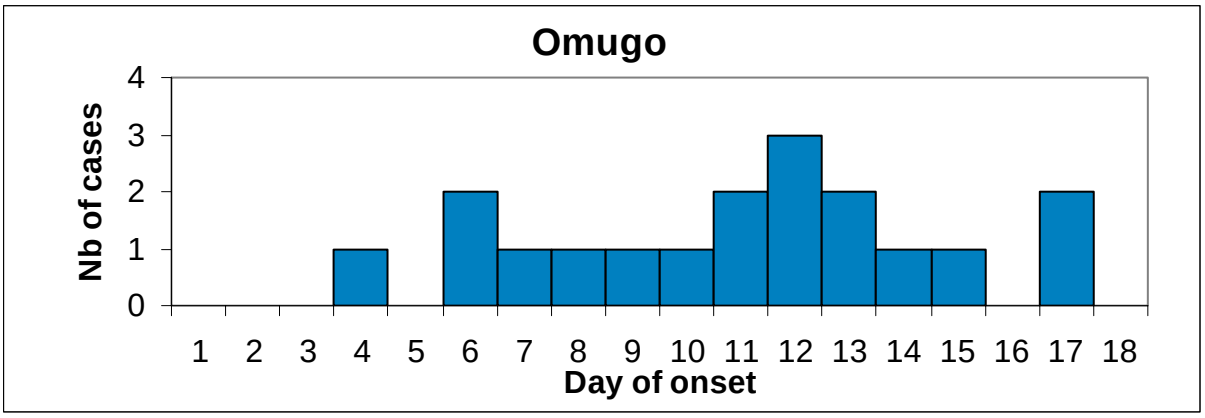
*: In Ibba, several cases had notes of “mental confusion” without further detail (here grouped under “disorientation”).

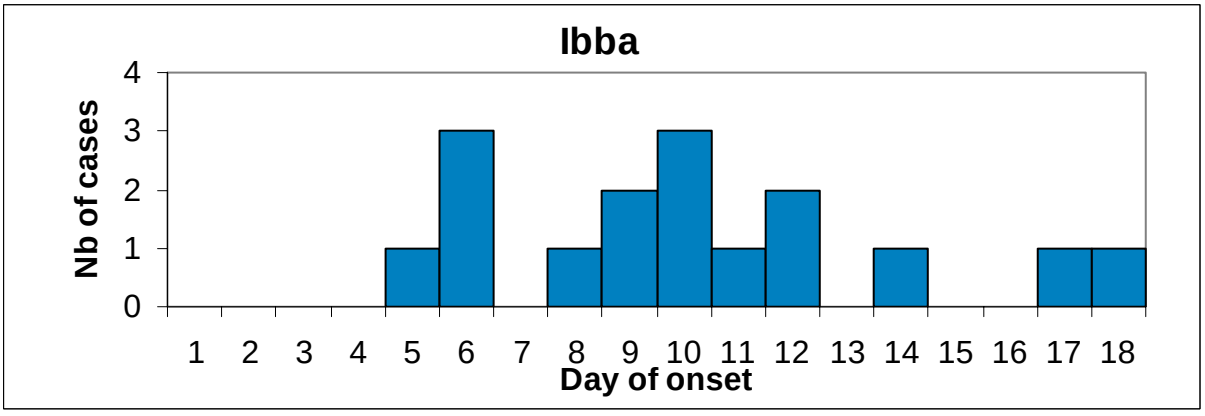
A majority (60.5%) of patients in Omugo experienced weight loss during the treatment (not recorded in Ibba), the mean weight loss being 2,54 kg. However, 7 patients gained weight, one of whom gained 6 kg . The patient that died was a 25 years old man who had hallucinations on D13, convulsions on D14 and finally convulsions, fever, coma and death on D15.

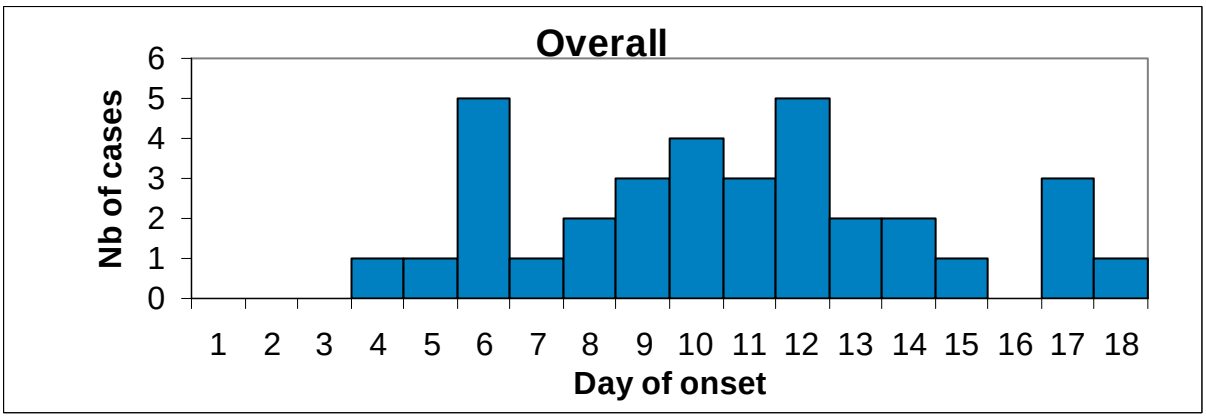
It was observed in Omugo that the majority of hallucination cases occurred by night. The hallucinations were generally described as visions of soldiers, dead people or wild animals attempting to kill the victim. One woman disappeared and was later found inside the pit of the patients’ latrine, where she had entered after taking off her clothes, passing through the very narrow opening and hiding there in complete silence, sitting in the faecal matter. Another woman remained 14 days in a state of hallucination and agitation in the ward, and was discharged in that state. At home the symptoms continued for two more days, and spontaneously disappeared, 10 days after the last dose of nifurtimox.

Overall, 18 (47.4%) and 16 (23.9%) HAT patients treated with the combined therapy were reported with severe neurological side effects in Omugo and Ibba respectively. The median onset time of occurrence of severe neurological side effects ranged from 4 to 18 days after initiation of the protocol (i.e. 0 to 14 days after initiation of nifurtimox) with a median at 10.5 days (i.e. 7.5 days after initiation of nifurtimox). Ranges and medians after initiation of protocol were 4 to 17 days and 11.5 days in Omugo, and 5 to 18 days and 10 days in Ibba (Figure 1).

Figure 1: Occurrence of severe neurological side effects by day of onset among HAT patients treated with a combination of Nifurtimox and Melarsoprol in Northern Uganda and Southern Sudan, September 1999 – February 2000







4.3 Management of side effects

The protocol was interrupted due to side effects in 17 cases (16.2% of the patients treated with the combination therapy): 6 (15.8%) in Omugo and 11 (16.4%) in Ibba. All but 3 of the 17 interruptions fit the description given here of severe neurological side effects. The reasons for the interruption in these three cases, all of them in Ibba, were respectively “arsobal

reaction", severe dizziness and neurological syndrome starting on day 2 (before the administration of nifurtimox). In all cases the treatment was resumed later, as soon as the symptoms cleared.

Depending on the treatment centre, a range of neuroleptics, hypnotics, anxiolytics and analgesics was used in attempting to control the neurological side effects (Table 3). The response to these drugs was not consistently reported in the medical records, while, in addition, many of them were used in association, all of which makes it difficult to assess and quantify their efficacy.

Table 3: Drugs used in concomitance during the management of 105 patients treated with a combination of Nifurtimox and Melarsoprol in Northern Uganda and Southern Sudan, September 1999 – February 2000

	Omugo (n = 38)		**Ibba (n = 67)**		**Total (n = 105)**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Paracetamol	15	(39.5)	41	(61.2)	56	(53.3)
Chlorpromazine	13	(34.2)	19	(28.4)	32	(30.5)
Aluminium hydroxide	12	(31.6)	9	(13.4)	21	(20.0)
Ibuprofen	10	(26.3)	0	(0.0)	10	(9.5)
Multivitamins	7	(18.4)	4	(6.0)	11	(10.5)
Promethazine	4	(10.5)	0	(0.0)	4	(3.8)
Diazepam	2	(5.3)	17	(25.4)	19	(18.1)
Metoclopramide	2	(5.3)	3	(4.5)	5	(4.8)
Phenobarbital	1	(2.6)	0	(0.0)	1	(1.0)
Aspirin	1	(2.6)	0	(0.0)	1	(1.0)
Ketamine	1	(2.6)	0	(0.0)	1	(1.0)
Dexamethasone	0	(0.0)	7	(10.4)	7	(6.7)
Furosemide	0	(0.0)	1	(1.5)	1	(1.0)
Any concomitant treatment	32	(84.2)	53	(79.1)	85	(81.0)

4.4 Risk factors for the occurrence of severe neurological side effects

Patients treated in Omugo had a two-fold higher incidence of severe neurological side effects as compared to those treated in Ibba (Table 4). The presence of parasites in the CSF, as well as a WBC count in CSF higher than 100 were found to be protective factors (borderline significance). On the other hand, the presence of parasites in periphery, demonstrated through

gland puncture, QBC or Woo test almost doubled the risk of occurrence of severe neurological side effects.

Table 4: Incidence of side effects among relapsing trypanosomiasis patients treated with a combination of nifurtimox and melarsoprol in Northern Uganda and Southern Sudan. September 1999 – February 2000

	Incidence rate (%)		RR	95% CI
Treatment centre				
Omugo	47.4	(18/38)	2.0	1.2 – 3.4 ‡
Ibba	23.9	(16/67)		
Sex				
Female	37.8	(17/45)	1.3	0.8 – 2.3
Male	28.3	(17/60)		
Age				
0 -14	18.2	(4 / 22)	0.5	0.2 – 1.3
15 and over	36.1	(30/83)		
Tryps in CSF				
Positive	26.1	(18/69)	0.6	0.4 – 1.1 †
Negative	42.9	(15/35)		
WBC in CSF				
0 -100	45.2	(14/31)	1.7	1.0 – 2.7 †
101 and over	27.0	(20/74)		
Tryps in periphery				
Positive	50.0	(6/12)	1.9	0.9 – 3.9 †
Negative	26.5	(13/49)		
Hematocrit*				
Up to 36	44.4	(4/9)	1,0	0.4 – 2.3
37 and over	46.2	(12/26)		
Karnofsky index*				
Less than 80	30.0	(3/10)	0,5	0.2 – 1.5
80 or more	55.6	(15/27)		
Glasgow coma score*				
Less than 15	33.3	(1/3)	0.7	0.1 – 3.4
15 (normal value)	50.0	(17/34)		

*Data available for Uganda only. †Borderline significance. ‡ Significant.

4.5 Food given to patients

In Omugo treatment centre, a ration of 1 300 Kcal/patient/day was given at once for a 12 day period (Table 5). The attendant(s), who is(are) required to accompany the patient during the treatment, were not allocated any food from the program, though they were the ones receiving and cooking it. The health centre staff consistently observed that this ration was shared between the patient and the attendant(s).

In Ibba, the ration distributed weekly was over 4 700 Kcal/patient/day, also to be shared by patient and attendant(s). Patients put on the nifurtimox-melarsoprol combination treatment received extra food in the form of high energy biscuits (BP5) and Unimix (quantities not specified).

Table 5. Food rations allocated per patient/day at Omugo (Northern Uganda) and Ibba (Southern Sudan) treatment centres. September 1999 – February 2000

		Ibba ration		Omugo ration	
Food item	**Value in Kcal/100g**	**g**	**Kcal**	**g**	**Kcal**
Maize	350	857	3 000	250	875
Beans	335	429	1 437	50	168
Oil	885	27	239	20	177
Sugar	400	0	0	20	80
Fruits	CNP	variable	CNP	0	0
BP5	452	all children	CNP	0	0
Unimix	CNP	all adults	CNP	0	0
Salt	CNP	0	0	20	0
Total			**4 676**		**1 300**

CNP: calculation not possible

5 Discussion

The intensity and frequency of neurological side effects observed in Ibba and in Omugo among the cohort of late stage HAT patients treated with the nifurtimox-melarsoprol combination is without precedent, and was twice as high in Omugo than in Ibba, with a statistically significant difference.

Because the study was retrospective, and the occurrence of the described side effects unexpected, we could not rely on a specific data collection system that would have been designed ad hoc. As a result, some data were not available, and the quality of the reporting could not be checked. The reporting of signs and symptoms was also not entirely comparable between Omugo and Ibba treatment centres. The quality of the medical records from Ibba tended to be lower than in Omugo, regarding consistency, level of detail and clarity. However, because of the overall quality of the 2 programs (laboratory facilities, patients care and follow up, data collection system…), reporting biases seem unlikely to explain our findings.

We believe that the discrepancy observed in the incidence of the severe neurological side effects between Ibba and Omugo is probably related to the difference between the 2 centres in food ration consumed by patients and in the food distribution modality. In Omugo treatment centre, the ration given to patients is considered to be a complement to the food that the patient and the attendant are supposed to bring with them when they come for treatment. Prior to the use of nifurtimox, no major inconvenience had been noticed in relation with the nutritional status of the patients, and the rationale of facilitating the take over by the Ugandan health system in the near future has led to a minimisation of the dependant aspects of the program, hence the sharing of the feeding burden with the patients' families. In Ibba MSF was paying special attention to the nutritional status of patients and providing a much more

substantial diet because of the bad general nutritional status in the population and in particular among the sleeping sickness patients. The daily ration was about 4 times richer than the one in Omugo.

Considering that the attendants are always accompanying the patients and they are the ones cooking, it is reasonable to assume that they also eat from that ration. Therefore the real ration for the patient is half of what is shown in Figure 5, and has to be compared with the recommendations of the MSF nutrition guidelines (minimum ration to meet the nutritional needs of an adult = 2100 Kcal/person/day, of which at least 10% of energy should be from protein and 10% from fat) and of the World Food Program (1900 Kcal/person/day). Furthermore, patients in Omugo received the food for 12 days at treatment initiation. By the time the patient was getting the 2nd dose of nifurtimox (day 5), the food was probably finished and the next food distribution was in 7 days. It is precisely during those 7 days that the majority of the neurological manifestations were observed.

It was observed that among patients coming from Ludara, a current focus of Sleeping Sickness located at 45 km from the Omugo treatment centre (the furthest distance from which patients were coming), the majority (6/7) experienced the severe side effects. A possible explanation could be that the long distance was preventing the attendants to get help with food or money from their family or village, which put these patients at a greater disadvantage, ensuring their nutritional deficiency during the treatment, leading in turn to the appearance of the side effects.

Finally, the hypothesis of food ration related side effects is best supported by the fact that, among 15 relapsing patients treated in Omugo after this investigation, receiving this time a food ration of at least 2100 Kcal/person/day, none has shown the same type of side effects, according to reports of the local team.

The difference noted in the systematic treatment for malaria upon admission is not likely to be related, in our opinion, to the observed difference in side effects between the two sites. This view is further supported by the absence of side effects in the new 15 patients mentioned above, who received Sulfadoxine-Pyrimethamine as well.

Our findings emphasize once again the importance of supportive care for patients suffering of severe diseases such as HAT, and receiving very toxic treatments. Unfortunately, given the scarcity of effective drugs to treat HAT cases and the absence of research in that domain, we are likely to rely on the same therapeutic resources for several years. Hence the need to understand and prevent the occurrence of the side effects of these drugs, knowing that our capacity to take in charge patients with severe adverse reactions in the field is very limited.

6 Recommendations

- ☞ To increase the food ration to at least 2100 Kcal per person (counting the patient and the attendant(s)) for all patients treated with the nifurtimox-melarsoprol combination therapy, and if possible to all late-stage HAT patients.
- ☞ To continue the attentive monitoring of all patients treated with this special regimen.
- ☞ To improve the quality of the recording of medical facts in the patient files.

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