Low Efficacy of Vocamine (MMH8®, Pediatric Formulation) in the Treatment of Uncomplicated *Plasmodium falciparum* Malaria

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Abstract: *Background*: This paper reports for the first time, the antimalarial efficacy of a five-day course of paediatric formulation of "vocamine" named MMH8® from Millenia Hope Inc® for the treatment of uncomplicated *Plasmodium falciparum* malaria.

Methods: We used the standard 14-day WHO protocol to assess therapeutic responses in children less than 5 years in Bangui (Central African Republic) between January and March 2005.

Results: We observed high rate of failure treatment: 81 % overall treatment failure with 51 % of Early Treatment Failure and 28.6 % of Late Treatment Failure.

Conclusion: Convinced that this drug has only a limited antimalarial effect, the Ministry of Health of the Central African Republic has decided to stop this clinical trial.

BACKGROUND

Development of resistance of *Plasmodium falciparum* is an increasing problem for antimalarial chemotherapy because resistance against most available drugs, especially chloroquine and pyrimethamine-sulfadoxine (SP), has developed in the majority of world-wide parasite populations [1]. Therefore, several strategies to counteract resistance-development are in place as the use of combined therapies with artemisinin derivatives but identification of new natural compounds remains essential.

Founded in 1997, Millenia Hope Inc®, a small biotech company based in Montreal obtained an Italian patent four years ago for a natural compound called "vocamine", derived from the roots and barks of the Brazilian plant *Peschiera fuchsiaefolia*, a source of traditional remedies against fever. Since several years, this company has developed the extract into a new antimalarial drug named MALAREX®. Though Millenia Hope Inc® may not understand the drug's mechanism of action of this drug, the company does claim to have demonstrated, *in vitro* as well as in animals and humans, the drug's ability to kill the malaria parasite *Plasmodium falciparum*, and to do so safely [2,3]. The most recent study, published by Ramanitrahasimbola *et al*. [4], confirms that the alkaloid has some effect on malarial parasites both in cell cultures and mice. Only one clinical trial of this antimalarial drug conducted in Yaoundé (Cameroon) in 2002 was reported. The results were only published on the website of Millenia Hope Inc® and it was stated that all patients (30 adults treated) were cured of their malarial symptoms within four days of the 5-day treatment regimen [3].

In 2005, Millenia Hope Inc® contacted the Ministry of Health of the Central African Republic (CAR) to carry out a clinical trial of the paediatric formulation of MALAREX® named MMH8®. On the request of the Ministry of Health of Central African Republic (CAR), a scientific committee was created including the National Malaria Control Program (NMCP) of the CAR, the University of Medicine, the CAR offices of WHO and UNICEF and the Malaria Unit of the Institute Pasteur de Bangui, to evaluate the clinical efficacy of MMH8®. This clinical trial based on WHO protocol 2003 [5] was performed in Bangui under the supervision of this scientific committee.

METHODS

Study Area

This study was carried out between January and March 2005 in Gobongo, an urban health centre located in the northern Bangui, the capital of the Central African Republic (CAR).

Bangui is located beside Oubangui river in the heart of the Central Africa, north of Democratic Republic of the Congo (Geographic coordinates 7 00 N, 21 00 E). The climate is tropical and rainfall peaks from April to November. The average temperature varies from 19 to 32°C. Plasmodium transmission occurs all over the year with peaks at the beginning and the end of the rainy season. Malaria is hyper-endemic and the main parasite responsible is *Plasmodium falciparum.* The parasite prevalence in children aged less than 5 years is 31.8 % [6].

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Patient Recruitment

Febrile patients aged 6 to 59 months presenting at health facilities were enrolled in the study only after receiving and uniformed consent by their parent or guardian and if the following inclusion criteria were met: axillary temperature ≥ 37.5 °C; mono-infection with *P. falciparum*, with parasitemia in the range of 2000–200,000 asexual parasites per microliter blood; no other cause for fever than malaria; no general danger signs (unable to sit or stand up, unable to drink or breastfeed, lethargy or unconsciousness, recent history of convulsions, persistent vomiting) or signs of severe and complicated falciparum malaria according to the definition given by WHO [5].

For participation, patients needed to be able to attend the stipulated follow-up visits and to come to the health facility when required. Parents or guardians were interviewed by a study physician about symptoms, duration of the illness, previous antimalarial therapy and other medication. Children were examined for pallor and jaundice or any other danger sign, and their axillary temperature and weight were determined.

Treatments

Participants were treated with MMH8® according to Millenia Hope Inc® recommendations with one bottle of 100 mg of powder for drinkable solution twice a day for five days. Drugs were obtained from Millenia Hope Inc®, Montréal, Canada.

The first administration was done at the time of the consultation and repeated in case of vomiting within 30 min. The following doses were given at home after information of parents. In the case of therapeutic failure or of severe symptoms, quinine was given for seven days. In addition, paracetamol was administered on days 0 and 1.

Patient Follow-Up

Follow-up appointments were scheduled for days 1, 2, 3, 7 and 14, and consisted of physical examination and completion of a standardised form. Parents and guardians were encouraged to return to the clinic at any time if their children felt unwell. Blood was collected by finger prick on days 0, 3, 7 and 14 (used to prepare thick and thin blood smears) and whenever necessary based on clinical examination.

Patients who did not turn up on a scheduled day were visited at home. Patients were excluded from the study if : [1] they reported self-administration of antimalarial drug during the follow-up, [2] they withdrew consent, [3] a concomitant disease occurred that would interfere with the evaluation of treatment efficacy, [4] the patient moved out of the follow-up area. In any other condition, patients who did not turn up on a critical day or were not seen at home were considered lost to follow-up.

Laboratory Tests

Finger prick samples collected on day 0 were used to prepare thick and thin blood films. The smears were stained with 4 % Giemsa for 20 min. Parasite density was calculated by counting the number of asexual parasites per 200 white blood cells (WBC), and adjusting for 8000 WBC per microliter. Thin blood smears were also examined for other *Plasmodium spp*.

Outcome Measures

Clinical outcomes were classified into three categories as it recommended by WHO protocol 2003: Early Treatment Failure (ETF); Late Treatment Failure (LTF), divided into two categories, Late Clinical Failure (LCF) and Late Parasitological Failure (LPF); and Adequate clinical and parasitological response (ACPR).

An adverse event was defined as an unexpected change in the baseline situation, whether or not that change was associated with the study drug.

Statistical Analysis

Efficacy data were assessed on intention to treat (ITT) analysis that included all patients who enrolled in the study. Qualitative variables were compared by using either the χ^2 test or Fisher's exact test, and quantitative variables were compared by analysis of variance or the Kruskal-Wallis test. The 95% confidence intervals of percentages were calculated using the exact binomial test. The level of significance (P) was fixed at 0.05 for all statistical tests. The data were analysed using the Epi lnfo 2000 software©.

Ethical Approval

Because of lack of National Ethical Committee in CAR, this study was approved by the expert committee for the antimalarial drug policy and the Ministry of Health in CAR.

RESULTS

From January through March 2005, 51 children were enrolled, of whom 3 (5.9 %) were excluded, 6 (11.6 %) lost to follow-up, yielding 42 (82.3 %) who completed follow-up.

The baseline characteristics of the 42 patients followed up until day 14 are summarised in Table **1**. The overall treatment failure rate was 81 % with 51 % of ETF and 28.6 % of LTF (Table **2**).

Among patients classified as early treatment failure (ETF), we observed:

a) 8 cases (19 %) with danger signs (prostration, oedema, respiratory distress and jaundice) in the presence of parasitaemia either at day 1 (6 cases, 39.1°C of mean axillary temperature, 37134 parasites par µl of mean parasitaemia density) or at day 3 (2 cases). For children with danger signs at day 1, the average increase of the parasitaemia density was significantly higher with children who did not have a previous chloroquine therapy (2.9-fold vs 1.1-fold higher, $p< 0.05$)..

b) one children (2.4 %) with a parasitaemia at day 2, 1.3-fold higher than on day 0 and 39.3°C axillary temperature;

c) six patients with a parasitaemia at day 3 with axillary temperature ≥ 37.5°C (38.3°C of mean axillary temperature). For 2 children who did not have previously a chloroquine therapy, we observed a average 1.1-fold increase of the parasitaemia density;

Table 1. Baseline Characteristics of Centrafrican Children Under 5 with Acute Uncomplicated Falciparum Malaria Treated with MMH8® between January and March 2005[a]

Patient Characteristic	Value
No. of males/no. of females	22/20
Age (months)	22 (11.8)
Wt (kg)	10.5 (2.4)
Temp (°C)	38.5 (0.8)
Previous antimalarial therapy (%)[b]	28.6
Parasitological density (geometric mean no.of parasites/µl [range])	11,233 (2,001-62,632)

[a]Data are given as the mean (SD) unless indicated otherwise. Forty two patients were treated and evaluated.
[b]Chloroquine was used in all cases.

Tables 2a and 2b. Treatment Responses to MMH8® in Centrafrican Children with Acute Uncomplicated Falciparum Malaria, Bangui, Central African Republic, January – March 2005

Table 2a.

Therapeutic Responses			Age (Months)	Sex	Weight (kg)	Previous CQ Therapy	Patients follow-up							
							D0		D1		D2		D3	
							AT	P	AT	P	AT	P	AT	P
Overall treatment failure (OTF) **(81%)**	Early treatment failure (ECF) **(52.4%)**	Danger signs or severe malaria on day 1, 2 or 3, in the presence of parasitaemia **(19%)**	25	F	11,0	No	39,3	32800	38,0	64400				
			59	M	19,5	Yes	39,4	23000	39,3	26954				
			36	F	12,0	Yes	39,6	62632	39,3	46340				
			19	M	10,5	Yes	38,8	24800	39,2	27760				
			14	F	9,5	Yes	40,3	32640	39,7	38480				
			36	M	12,0	No	38,0	7547	39,1	28870				
			20	F	11,0	Yes	40,1	26000					37,3	8887
			17	F	8,5	Yes	39,3	27840					36,0	36
		Parasitaemia on day 2 higher than on day 0, irrespective of axillary temperature **(2.4%)**	9	F	11,0	No	37,8	8452			39,3	11517		
		Parasitaemia on day 3 with axillary temperature ≥ 37.5 °C **(14.3%)**	24	M	10,3	No	37,5	4848					38,6	15215
			42	M	10,90	Yes	39,0	18560					37,6	1120
			18	M	12,5	No	39,0	23600					40,0	92
			13	F	8,85	Yes	38,8	6800					38,0	573
			9	M	7,0	Yes	37,5	11680					37,6	3874
			24	F	10,0	No	37,5	27664					37,8	5885
		Parasitaemia on day 3 ≥ 25% of count on day 0 **(16.6%)**	14	M	8,4	No	37,5	2001					36,2	24519
			17	F	8,8	No	39,0	57725					35,9	20352
			36	F	13,0	No	39,1	4075					36,8	1458
			6	M	7,5	No	39,6	5267					36,8	2514
			30	M	8,6	No	39,0	19000					36,8	11440
			48	F	12,6	No	37,6	3949					36,9	1509
			20	M	10,6	No	39,7	11276					36,8	11524

AT: Axillary temperature.
P: Parasitaemia density per µl.
DO: Day 0; D1: Day 1; D2: Day 2; D3: Day 3.

Table 2b. **(Table 2) contd….**

Therapeutic Responses			Age (Months)	Sex	Weight (kg)	Previous CQ Therapy	Patients Follow-Up															
							D0		D1		D2		D3		D7		D8		D12		D14	
							AT	P	AT	P	AT	P	AT	P	AT	P	AT	P	AT	P	AT	P
Overall treatment failure (OTF) **(81%)**	Late treatment failure (LTF) **(28.6%)**	Late Clinical Failure (LCF) Axillary temperature ≥ 37.5 °C in the presence of parasitaemia on any day between day 4 and day 14, without the patient previously meeting any of the criteria of early **(14.3%)**	21	M	8,0	No	37,5	5256					36,8	94	38,0	7207						
			16	M	12,0	No	37,5	7772					36,4	153	37,5	17739						
			24	M	10,0	Yes	39,9	61149					37,0	992	37,7	560						
			14	F	12,0	No	39,2	17160					37,0	4300	37,6	4100						
			18	M	9,0	No	38,0	2340					36,9	61	36,7	436	37,5	480				
			8	F	8,8	No	38,8	2050					36,8	310	37,0	0			39,0	957		
		Late Parasitological Failure (LPF) Presence of parasitaemia between day 4 and day 14 with temperature <37.5 °C, without the patient previously meeting any of the criteria of early treatment failure or late clinical failure **(14.3%)**	36	F	15,0	No	39,8	13307					36,8	574	36,0	40					36,8	4136
			12	F	6,7	No	39,2	5345					36,7	40	36,9	0					35,7	364
			24	M	9,6	No	37,5	2002					36,0	0	37,3	0					36,4	6630
			10	M	13,0	No	39,0	20593					36,9	512	36,0	150					36,8	9057
			6	M	7,6	No	37,5	15250					36,7	40	36,7	0					37,2	553
			34	F	12,0	Yes	39,0	6820					36,8	0	36,2	40					37,0	635
Adequate clinical and parasitological response (ACPR) **(19%)**		Absence of parasitaemia on day 14, irrespective of axillary temperature, without the patient meeting any of the criteria of early treatment failure, late clinical failure or late parasitological failure	36	M	10,5	No	37,5	7699					36,8	118	36,4	80					37,4	0
			10	F	7,2	No	37,5	22532					36,1	0	36,6	0					37,1	0
			24	F	13,0	No	37,5	15520					36,6	235	36,3	0					36,6	0
			14	M	10,4	No	38,9	4033					36,7	40	37,2	0					36,9	0
			24	F	13,0	No	37,5	10168					36,7	0	36,8	0					36,9	0
			11	M	8,1	No	39,6	4899					38,3	0	37,2	0					37,6	0
			23	F	9,5	No	38,3	27857					36,7	40	35,9	0					37,1	0
			24	M	11,50	Yes	38,0	8095					37,3	40	36,3	0					37,1	0

AT: Axillary temperature.
P: Parasitaemia density per µl.
DO: Day 0; D1: Day 1; D2: Day 2; D3: Day 3; D7: Day 7;D8: Day 8;D12: Day 12;D14: Day 14.

d) seven patients (16.6 %) with a parasitaemia at day 3 ≥ 25% of count of day 0. All patients did not have a previous chloroquine therapy and showed an axillary temperature < 37.5 °C. The mean increase of parasitaemia density between day 0 and day 3 was estimated to be to 2.2-fold higher.

Among patients classified as late treatment failure (LTF), we observed:

a) in the Late Clinical Failure group, 6 patients (14.3%) with an axillary temperature ≥ 37.5 °C in the presence of parasitaemia either at day 7 (n = 4) or at day 8 (n = 1) or at day 12 (n = 1). Except in one case at day 7, none patients completely cleared their parasites.

b) in the Late Parasitological Failure group, parasites were not cleared at any day in 2 cases, or parasites were cleared at day 3 in 2 cases and reappeared at day 7 (n = 1) or day 14 (n = 1), or parasites were cleared at day 7 and reappeared at day 14 in 3 cases.

Among 8 patients classified as adequate clinical and parasitological response (ACPR), parasite elimination was achieved at day 3 in 3 cases (37.5 %), at day 7 in 4 cases (87.5 %) and at day 14 in one case (100%). Fever was more rapidly cleared in all cases at day 3.

There was no significant relation between therapeutic response groups and age, previous antimalarial therapy, axillary temperature or parasitaemia density at day 0.

DISCUSSION

As far as we now, this study is the first controlled clinical trial for establishing the efficacy of vocamine in the treatment of uncomplicated *Plasmodium falciparum* malaria in children less than five years. It is also the first clinical trial ever to have been published.

Contrarily to the claims by the Millenia Hope Company, our results confirm the doubts concerning the efficacy of this drug and its interest in the therapeutic arsenal of antimalarials available in the uncomplicated malaria treatment, as expressed by Orellana [7] and Martindale [8].

It has been previously said that the WHO protocol 2003 is not adapted to the evaluation of new antimalarial drugs or malaria treatment for over 3 days. However, this protocol remains the best available because [1] it is the only accepted

at an international level and [2] and we have ascertained its value for monitoring 7 day courses of artesunate for the treatment of uncomplicated *P. falciparum* malaria in non-immune patients (European expatriates) living in Bangui (CAR) [9].

Compared to the results of the therapeutic trials conducted in 2002-2004 in Bangui [10], it appears that in children under five years with non-complicated malaria, the efficacy of MMH8® with 81% of overall treatment failure rate is far lower than that of three-day courses of chloroquine (40,9% of treatment failure rates), of amodiaquine (20% of failure rates) or of sulfadoxine-pyrimethamine association treatment (22.8% of treatment failure rates), the best therapeutic option being the association of chloroquine and sulfadoxine-pyrimethamine (7.2% of failure rates) and amodiaquine plus sulfadoxine-pyrimethamine (no failure), the last one being currently recommended by the Ministry of Health of the CAR as the first line antimalarial drug, until best therapeutic option like Artemisinin-based Combination Therapies (ACT) become available at low prices.

Thus, the paediatric formulation of MMH8® was ineffective in the clearance of the parasites since the majority of the treated children showed an increase of their parasitaemia densities in the days following the beginning of the treatment (except for those which had taken chloroquine before). Because of its formulation, MMH8® is not adapted for treatment in young children because of the volume (100 ml of drinkable solution 2 times per day) and of its unpleasant taste. Because of these pitfalls, we cannot ascertain that the administration of the product at home was regularly completed thus minimizing its apparent clinical efficacy. Nonetheless, as such an eventuality would not be the case for the majority of children, one can consider that this drug has only a limited therapeutic effect.

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