

Original Article

The Efficacy of Artemether/Lumefantrine for the Treatment of Uncomplicated Falciparum Malaria in Children in an Area of High Transmission in Southern Sudan

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Abstract

Objectives: Sudanese health authority adopted a new antimalarial drug policy in response to the reported high level of chloroquine resistance. "Artesunate+ sulfadoxine/pyrimethamine" (ASP) and "artemether/lumefantrine" (A/L) are recommended as first and second lines for the treatment of uncomplicated falciparum malaria respectively. This study aims to evaluate the clinical and parasitological response to A/L and to report any side effects related to the drug in children living in high transmission areas.

Methods: This evaluation of the clinical and parasitological response to directly observed treatment with 6 doses A/L following WHO protocol for monitoring antimalarial drugs efficacy. Giemsa-stained thick and thin blood smears were examined microscopically on days 0, 2, 3, 7, 14, 21 and 28, or at other times if a patient felt unwell. The primary end point was the 28-day cure rate and the secondary end points were time to parasite clearance.

Results: A total of 75 (40.8%) patients met the inclusion criteria, of them 70 (97.2%) patients showed adequate clinical and parasitological response (radical cure), 2 (2.8%) patients were classified as early treatment failure and 3 (4%) patients were lost to be followed-up by day 3. No progression to severe illness or danger signs occurred for any patient during the study.

Conclusion: The main outcome of study was that A/L was found to be highly effective against *Plasmodium falciparum* uncomplicated malaria, well tolerated by children with no reported serious side effects. Dramatic decrease in parasites density and fever were observed in most of the cases by day 3 of treatment.

Introduction

Malaria is the major public health problem in the Sudan with an estimated 7.5 million cases and 35,000 deaths annually⁽¹⁾. Children and pregnant women are mostly affected. The disease situation is aggravated by many factors; among them is the spread of *P. falciparum* resistant strains to chloroquine⁽²⁾. Studies assessing chloroquine efficacy were performed extensively in Sudan since 1970s; all reflected an ever increasing chloroquine

resistance^(3, 4). Increased *P. falciparum* resistant strains to chloroquine have its negative consequences such as increased morbidity and mortality especially among children below 5 years of age^(5, 6).

The major strategy of the Roll Back Malaria (RBM) initiative, to halve malaria mortality by 2010, is prompt access to effective antimalarial treatment especially among below 5 years children⁽⁶⁾. Sudanese Health Authorities adopted a new

antimalarial drug policy (June 2004), in which artemisinin-based combinations (ACT) are recommended. It identifies artesunate + sulfadoxine/pyrimethamine (ASP) and artemether/lumefantrine (A/L) as first and second lines for the treatment of uncomplicated falciparum malaria respectively. As the ultimate goal of malaria treatment policies is to ensure prompt effective and safe treatment of malaria, the present study aimed to assess the therapeutic efficacy of A/L in an intense transmission area in southern Sudan, more specifically, to evaluate the clinical and parasitological response to the new drug among patients and to trace any side effects related to the drug during the follow-up period.

Materials and Methods

This efficacy study is a simple, one arm, and prospective evaluation of the clinical and parasitological response to directly observed treatment with A/L for the uncomplicated falciparum malaria in children. The study was carried out according to the WHO Protocol for areas with high malaria transmission⁽⁷⁾.

Study Area: The study was conducted during July–August 2004 in Juba, south Sudan. The total population of the state is 450 000 who mainly lived in Juba, the capital of Bahr Elgabal State. The area is characterized by equatorial climate, long rainy season, warm humid weather, forests, rivers and swamps. Malaria transmission is perennial.

Study population, sample size and sampling children below 5 years presented with symptoms and signs suggestive of malaria were subject for the study. According to WHO protocol a minimum sample size of 50 patients is required⁽⁷⁾. This calculation was based on expected clinical failures of 5% (with the confidence level of 95% and the precision of 10%). All patients were eligible to study provided that they were complying with the

inclusion criteria. These include: Axillary temperature $>37.5^{\circ}\text{C}$ or recent history of fever; a microscopically confirmed *P. falciparum* monoinfection with a parasite density of 2 000 – 200 000 asexual parasites/ μl ; an informed consent from patient or guardian and ability to come for the stipulated follow-up visits. Patients with signs of severe malaria, febrile diseases other than malaria, presence of severe malnutrition and history of previous antimalarial drugs use and of hypersensitivity reactions to the drug under the study were excluded. Patients with weight less than 10 Kg were also excluded as the drug at the time of the study is not proved to be safe for this group. Failure to obtain consent is also a reason for exclusion.

Treatment dosage and schedule All febrile patients were screened and examined microscopically; patients who fulfilled all of the inclusion criteria were enrolled. Artemether- lumefantrine tablets (CoartemTM; Novartis, Beijing, China), each containing 20 mg of artemether and 120 mg of lumefantrine as fixed combination, were administered as six consecutive doses: two doses (body weight 10–14 kg: one tablet; 15–24 kg: two tablets; 25–34 kg: three tablets; >35 kg: three tablets) at 0 and 8 h on day 0, and twice a day on the following 2 days. Tablets for small children were crushed and mixed with sugar to facilitate the intake of the calculated doses. The patients were asked to sit for one hour in the clinic to make sure that the medication was not vomited. If the patient vomited within 30 minutes a full dose was given again.

Follow-up: Patients were asked to participate in the study and to come back for the stipulated follow-up visits on respective days. For the patients who did not show themselves as scheduled, members of the study team went to their homes to administer the drugs and do follow-up examinations. Follow-up

were done as scheduled on days 2, 3, 7, 14, 21 and 28, or at other times if a patient felt unwell. The patients were asked about their condition; both axillary temperature and a blood sample were taken. Patients who had parasitemia were treated with quinine. All information was recorded on standard case-record recommended by WHO protocols. Giemsa-stained thick and thin blood smears were examined microscopically. Parasite density was calculated on the basis of the number of parasitic cells per 200 leukocytes (assuming a peripheral WBC count of 8000 cells/ μ l of blood) detected on a thick film, and was expressed as parasites/ μ l. All slides were rechecked by expert microscopist for quality control at the national malaria control programme referral laboratory.

Classification of the therapeutic outcome and study end points: the therapeutic outcome was classified into 4 groups⁽⁷⁾. 'Early Treatment Failure' (ETF) was the presence of any of the following criteria: development of danger signs or severe malaria on day 1, day 2, or day 3 with parasitemia; parasite count on day 2 higher than on day 0 irrespective of axillary temperature; parasitemia on day 3 with axillary temperature $>37.5^{\circ}$ C; parasitemia on day 3 $>25\%$ of count on day 0. 'Late Treatment Failure' (LTF) was classified as 'Late Parasitological Failure' (LPF) or 'Late Clinical Failure' (LCF) which was defined by presence of any of the following criteria: development of danger signs or severe malaria after day 3 in the presence of parasitemia; presence of parasitemia and axillary temperature $>37.5^{\circ}$ C (or history of fever) on any day from day 4 to day 28. Patients with parasitemia on any day from day 7 to day 28 and axillary temperature $>37.5^{\circ}$ C (and no history of fever) were classified as 'LPF'. 'Adequate Clinical and Parasitological Response' (ACPR) was defined as the absence of parasitemia on day 28 without any of the criteria of 'ETF' or 'LTF'. 'Loss

to Follow-up' (when an enrolled patient could not be found); and 'Withdrawal from Study' (withdrawal of consent to participate in the study; development of a febrile disease that would interfere with the classification of the outcome), were further classifications taken into consideration. The primary end point was the 28-day cure rate and was defined as proportion of patients with ACPR after 28 days of follow-up. Secondary end points were time to parasite clearance.

Data Analysis: Data from case report forms were double-entered in WHO Excel analysis sheet 2004. This provided the answer to the above mentioned classification. Further analysis was done using the SPSS computer-software version 11.

Ethical consideration: Ethical clearance certificate was obtained from the Ethical Committee - Research Directorate - Federal Ministry of Health-Khartoum/Sudan. Informed consents of the parents to allow their children to participate in the study were taken from each separately.

Results

Of 342 febrile patients attending to the clinic during the study period, 184 (53.8%) patients were microscopically confirmed *falciparum* malaria. Among them, 75 (40.8%) patients met the inclusion criteria and were participated in the study. Thirty-six (48%) were female. Their age ranged between 14 to 59 months, with a mean of 39.7 months (SD = 13.9) and their weight ranged between 10 -22 Kg with a mean weight of 13.5 Kg (SD = 2.6). Three (4%) patients were lost to be followed-up by day 3 and hence 72 patients were analyzed for treatment outcome.

As presented in the table 1, 70 (97.2%) patients showed adequate clinical and parasitological response (radical cure) and 2 (2.8%) patients were classified as early treatment failure; one is a 31

months old male and the other is a 48 months old female. the two patients were classified as ETF because the parasite count on day 2 was higher than

on day 0 (40000 and 80000 respectively). No progression to severe illness or danger signs occurred for any patient during the study.

Table 1: Response to treatment among patients receiving the Artemether/Lumefantrine

Summary of classification	Frequency (%)
Early treatment failure (ETF)	2 (2.8)
Late parasitological failure (LPF)	0 (0.0)
Late clinical failure (LCF)	0 (0.0)
Adequate clinical and parasitological response (ACPR)	70 (97.3)
Total number of patient analyse	72
Withdrawal from the study	0 (0.0)
Lost to follow-up	3 (4.0)
Total number of patients enrolled	75

On day 0 the mean (SD) parasite count/ μ l was 15964 (33258). The mean parasite count in females was significantly higher than in male ($P=0.023$). On day 3, 65 (90.3%) patients had either cleared or showed very low parasitaemia and only 7 patients showed parasite count equal or more than 1000 parasite/ μ l. Gametocytes were not detected throughout the study except in one patient on day 21.

Discussion

Drug resistance increases the burden of disease as standard treatments become less effective⁽⁸⁾. The World Health Organization recommends that antimalarial regimens should include an artemisinin derivative to improve the clinical response and cure rate, and also with the aim of slowing the development of parasite resistance⁽⁹⁾.

Artemisinin (Gingahaosu) is a potent antimalarial isolated from the leafy portion of *Artemisia annua*; a plant used in China as herbal medicine for treatment of fevers for many centuries. A/L is a fixed dose combination of artemether (20 mg) and lumefantrine (120 mg). The artemether component of the drug will rapidly reduce parasitaemia, giving symptomatic relief, and the lumefantrine will eliminate residual parasites. It is known that effective drug levels, during 3-4 life cycles of the

parasite, are required for elimination of parasite; this can be achieved by combining the artemisinin with an antimalarial drug having a longer elimination half-life⁽¹⁰⁾. A/L is coming at the top of the list of artemisinin-based combination therapies recommended by WHO^(9, 11).

(A/L) was found to be highly effective against *P. falciparum* uncomplicated malaria. The drug was well tolerated by children; they swallow it without difficulty as it is not bitter in taste and no reported side effects. These were consistent with many other studies⁽¹²⁻¹⁴⁾. The applied regimen in the study was the 6-doses regimen because it provides superior action compared to 4-doses regimen of the same drug for drug resistant *P. falciparum* malaria⁽¹⁵⁾. No signs of toxicity or severe side effect were reported which is complying with other reported evidences⁽¹⁶⁻¹⁸⁾.

In this study, parasite clearance was achieved within 72 hours in more than 90% of the cases which agreed with findings from other countries⁽¹⁰⁾. Fever clearance time in the study was not interpretative for efficacy because paracetamol was given for the febrile cases during the conduction of the study. Another advantage of artemisinin-based combination such as A/L, it has been found not to kill only asexual blood stage but also the early

stages of blood gametocytes and this effect may play a role in interruption of malaria transmission⁽¹⁹⁻²¹⁾.

The unique characteristics of A/L are expected to increase the adherence to and trust of the health care providers in the new launched treatment policy for malaria in Sudan with ASP and A/L as first and second line treatment respectively for falciparum malaria in Sudan.

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References

1. Malik EM and Saeed Ok: Malaria in Sudan: past, present and the future. *Gazeera Journal of Health Sciences* 2004, 1
2. Abdel-Hameed AA: Antimalarial drug resistance in the Eastern Mediterranean Region. *East Mediterr Health J* 2003, 9:492-508. Review.
3. Abdel-Hameed AA, El-Jak IE, Faragalla IA: Sentinel posts for monitoring therapeutic efficacy of antimalarial drugs against *Plasmodium falciparum* infections in the Sudan. *Afr J Med Med Sci* 2001, 30:1-5.
4. Adam I, Osman ME, Elghzali G, Ahmed GI, Gustafssons LL, Elbashir MI: Efficacies of chloroquine, sulfadoxine-pyrimethamine and quinine in the treatment of uncomplicated, *Plasmodium falciparum* malaria in eastern Sudan. *Ann Trop Med Parasitol* 2004, 98:661-6.
5. Greenwood BM, Bradley AK, Greenwood AM, Byass P, Jammeh K, Marsh K et al. Mortality and morbidity from malaria among children in a rural area of The Gambia, West Africa. *Trans R Soc Trop Med Hyg.* 1987;81(3):478-86.
6. WHO. Roll Back Malaria Strategic Framework for Scaling up Effective Malaria Case Management. March 2004. available from http://www.rbm.who.int/partnership/wg/wg_management/docs/framework.pdf
7. WHO. Assessment and Monitoring of Antimalarial Drug Efficacy for the treatment of uncomplicated *Falciparum* malaria. WHO/HTM/RBM/2003.50 2003.
8. WHO. Antimalarial drug combination therapy. Report of a WHO Technical Consultation, 4-5 April 2001. WHO/CDS/RBM/2001.35. 2001
9. WHO. Position of WHO's Roll Back Malaria Department on malaria treatment policy. 2003 (<http://www.emro.who.int/rbm/WHOPositionStatement.pdf>).
10. van Agtmael MA, Eggelte TA, van Boxtel CJ. Artemisinin drugs in the treatment of malaria: from medicinal herb to registered medication. *Trends Pharmacol Sci.* 1999 May;20(5):199-205. Review.
11. WHO. Malaria control today: Current WHO Recommendations. RBM Department; WHO. Geneva. 2005.
12. Adam I, A-Elbasit IE, Idris SM, Malik EM, Elbashir MI. A comparison of the efficacy of artesunate plus sulfadoxine-pyrimethamine with that of sulfadoxine-pyrimethamine alone, in the treatment of uncomplicated, *Plasmodium falciparum* malaria in eastern

- Sudan. *Ann Trop Med Parasitol*. 2005 Jul;99(5):449-55.
13. van den Broek I, Amsalu R, Balasegaram M, Hepple P, Alemu E, Hussein el B et al. Montgomery J, Checchi F. Efficacy of two artemisinin combination therapies for uncomplicated falciparum malaria in children under 5 years, Malakal, Upper Nile, Sudan. *Malar J*. 2005 Feb 24;4(1):14.
 14. Stohrer JM, Dittrich S, Thongpaseuth V, Vanisaveth V, Phetsouvanh R, Phompida S et al. Therapeutic efficacy of artemether-lumefantrine and artesunate-mefloquine for treatment of uncomplicated Plasmodium falciparum malaria in Luang Namtha Province, Lao People's Democratic Republic. *Trop Med Int Health*. 2004 Nov;9(11):1175-83.
 15. Vugt MV, Wilairatana P, Gemperli B, Gathmann I, Phaipun L, Brockman A et al. Efficacy of six doses of artemether-lumefantrine (benflumetol) in multidrug-resistant Plasmodium falciparum malaria. *Am J Trop Med Hyg*. 1999 Jun;60(6):936-42.
 16. Olliaro PL, Taylor WR. Developing artemisinin based drug combinations for the treatment of drug resistant falciparum malaria: A review. *J Postgrad Med*. 2004 Jan-Mar;50(1):40-4. Review.
 17. Falade C, Makanga M, Premji Z, Ortmann CE, Stockmeyer M, de Palacios PI. Efficacy and safety of artemether-lumefantrine (Coartem) tablets (six-dose regimen) in African infants and children with acute, uncomplicated falciparum malaria. *Trans R Soc Trop Med Hyg*. 2005 Jun;99(6):459-67.
 18. Lefevre G, Looareesuwan S, Treeprasertsuk S, Krudsood S, Silachamroon U, Gathmann I et al. A clinical and pharmacokinetic trial of six doses of artemether-lumefantrine for multidrug-resistant Plasmodium falciparum malaria in Thailand. *Am J Trop Med Hyg*. 2001 May-Jun;64(5-6):247-56.
 19. Kumar N, Zheng H. Stage-specific gametocytocidal effect in vitro of the antimalaria drug qinghaosu on Plasmodium falciparum. *Parasitol Res*. 1990;76(3):214-8.
 20. Omari AA, Gamble C, Garner P. Artemether-lumefantrine for uncomplicated malaria: a systematic review. *Trop Med Int Health*. 2004 Feb;9(2):192-9. Review.
 21. van den Broek IV, Maung UA, Peters A, Liem L, Kamal M, Rahman M et al. Efficacy of chloroquine + sulfadoxine--pyrimethamine, mefloquine + artesunate and artemether + lumefantrine combination therapies to treat Plasmodium falciparum malaria in the Chittagong Hill Tracts, Bangladesh. *Trans R Soc Trop Med Hyg*. 2005 Oct; 99(10):727-35.