

Research Article

Efficacy of artemether-lumfantrine (Co-Artesiane[®]) suspension in the treatment of uncomplicated *Plasmodium falciparum* malaria among children under 5 years in eastern Sudan

Muntaisr T. Salah¹, Mohamed Faroug², Mamoum M. Magzoub²,
Ishag Adam³

¹Ribat University, Sudan, ²Kassala University, Sudan, ³Faculty of Medicine, University of Khartoum, Sudan and The Academy of Medical Sciences and Technology

Abstract

Purpose the aim of the present study was to investigate the efficacy of artemether-lumfantrine (Co-Artesiane[®]) suspension for the treatment of uncomplicated *Plasmodium falciparum* malaria in children (aged 6-59 months) in Kassala in eastern Sudan.

Method This was a prospective clinical trial where the artemether-lumfantrine (Co-Artesiane[®]) suspension was given for three days and the patients were followed-up for 28 days

Results: Forty-eight patients were enrolled in the study and 43 of them completed the 28-days follow-up. Treatment rapidly cleared parasitemia and fever. The overall 28-day cure rate was 100% and no clinical or parasitological failures were observed among these patients. Mild side effects were observed in three (7%) children.

Conclusion: Artemether-lumfantrine (coartem) suspension appears to be efficacious and safe for the treatment of uncomplicated malaria.

Keywords: Artemether-lumfantrine, Co-Artesiane, children, falciparum, malaria, Sudan

*Corresponding Author: E-mail: Dr. Ishag Adam P. O. Box 102 Faculty of Medicine, University of Khartoum, Sudan.
Tel+ 249912168988 Fax +249183224799 E.mail : ishagadamm@yahoo.com

INTRODUCTION

There are almost one million childhood deaths in Africa due to *P. falciparum* infections every year¹. Children are at higher risk for developing drug-resistant falciparum malaria than older individuals². Countries with high levels of resistance have witnessed increased childhood morbidity and mortality³.

Malaria causes around 7.5 – 10 million clinical cases and 35,000 deaths every year in Sudan⁴. High levels of chloroquine and sulphadoxine/pyrimethamine resistance were reported among Sudanese children⁵⁻⁶. Due to the spread of multidrug-resistant *Plasmodium falciparum* malaria in Sudan⁷, artesunate plus sulfadoxine–pyrimethamine (AS+SP) is recommended as the first-line drug while artemether-lumefantrine (AT-LU, Coartem[®]) is the second line drug in the treatment of uncomplicated *P. falciparum* malaria. The assessment and monitoring of antimalarial therapeutic efficacy is key to the provision of sound evidence for policy decisions making, regarding which antimalarials can be adopted for malaria case management. The choice of an artemisinin-combinations therapy (ACTs) in specific malaria-endemic areas needs to take into account their efficacy, tolerability, cost and ease of administration. Most therapies with ACTs last for 3 days and in some instances the patient has to swallow up to 24 tablets. However, this mode of administration may be unsuitable for infants and young children. It is, therefore, imperative that a simpler mode of administration is developed. Such a dosage form should be stable under tropical conditions⁸. The preliminary reports on an AT-LU suspension (Co-artesiane[®]) developed by Dafra Pharma NV. The objective of this trial, therefore, was to investigate the efficacy of this drug (Co-Artesiane[®] suspension) in the treatment of uncomplicated *P. falciparum* malaria in under five children in a health centre in Sudan.

MATERIAL AND METHODS

Study area

The study was conducted at the health center in Kassala area in eastern Sudan during the period September-November 2005. Kassala is

an agricultural area, located 500 Km from Khartoum. It is characterized by unstable malaria transmission with the peak during the rainy and post-rainy season⁹. The predominant malaria species is *P. falciparum*, and *Anopheles arabiensis* is the sole malaria vector in the area¹⁰. The study received ethical clearance from the Ethical Board of The Academy of Medical Sciences and Technology.

Patients

Children (6-59 months of age) with documented axillary temperature ≥ 37.5 °C and *P. falciparum* infection were eligible for inclusion if their parents gave informed consent. Children were excluded if they had one or more of manifestations of severe malaria¹¹/ concurrent infection.

All the enrolled children underwent a thorough history and physical examination conducted by a medical officer and thereafter received AT-LU (Co-Artesiane[®]) suspension according to the manufacturers` (Dafra Pharma NV) instructions. The dry powder was advised to be dissolved in water to prepare 60 ml of the drug, containing 180 mg of artemether and 1080 mg of lumefantrine. The dose was calculated according to body weight; 4mg artemether/kg for three days. However, an approximation was used and the following dosage regimens were administered: 7ml for children weighing less than 5kg, 10ml for those weighing >5 – 7.5kg, 14ml for >7.5 – 10kg and 20ml for children weighing 10kg and higher.

The children were given the medication orally under supervision and were monitored for 30 minutes. A second full dose was administered if the child vomited the first dose within this monitoring period. Children who vomited the drug for a second time were excluded from the study and were given parental quinine.

Investigations

Finger prints blood films were prepared, Giemsa-stained and examined by 100x magnification of an oil immersion field. The parasite density was counted against 200 leucocytes, assuming 8000 leucocytes/ μ l. All slides were double-checked blindly and only considered negative if no

parasites were detected in 100 oil immersion fields. If gametocytes were seen, then the count was extended to 500 leucocytes.

Follow-up

Parents were asked to bring their children for follow-up on days 1, 2, 3, 7, 14, 21 and 28 or if they developed febrile symptoms and felt unwell. At each visit, parents were asked about the presence of fever, vomiting and diarrhea. In addition, brief physical examination, including axillary temperature was performed and the blood was taken for thick films.

Outcome measures

Early Treatment Failures (ETF) in case of significant parasitaemia at day 2 or 3 or parasites and fever at day 3, Late Clinical Failures (LCF) for cases with parasites and fever during follow-up after day 3 and Late Parasitological Failures (LPF) for parasite infections with/without fever during the follow-up period. Cases which remained negative during follow-up were considered to be Adequate Clinical and Parasitological Responses (ACPR). These were modified from WHO guidelines¹²⁻¹³.

RESULTS

Forty-three patients (77.5%) out of 48 have completed the 28-day study period. The others were excluded because to loss of follow-up due to change of their addresses.

The presenting mean (SD) of the age was 3.7 (1.2) years and the body weight range was 6 - 23 kg with mean (SD) of 13.9(3.5) kg. The mean (SD) of the temperature and the parasite count were 38.5 (0.6) °C and 7915.4(5869.0) rings / μ l respectively. Fourteen (31.8%) out of the 43 patients were female. On day 1, 15 (34.1%) patients were still febrile and 11(25%) were still parasitaemic. On day 3, fever was not detected in any of the patients and all patients were aparasitaemic. Mild side effects (nausea and diarrhea) were reported among three (7%) children; however, these were mild and resolved spontaneously. Gametocytes were detected in four (9.1%) patients on enrollment and it was detected in one patient (2%) during the follow-up period (day 21).

DISCUSSION

This is probably the first publication on the AT-LU suspension in the treatment of uncomplicated falciparum malaria in children below five years of age. The study was conducted in an area characterized by high (antimalarial) drug resistance¹⁴⁻¹⁵.

The study showed a full efficacy (100%) of the AT-LU suspension for the treatment of uncomplicated falciparum malaria in this area, and no cases of treatment failure detected during the 28-day follow-up period. Recently, a full efficacy of the AT-LU tablets was reported in an area of unstable malaria transmission in central Sudan¹⁶. In an earlier study, AT-LU tablets had shown 93.9% and 97.5% efficacy in African children with uncomplicated falciparum malaria¹⁷⁻¹⁸. In a neighboring country, Ethiopia, 99% efficacy was reported for the AT-LU tablets for the treatment of children with uncomplicated falciparum malaria. Caution should be taken when comparing with the former study, because children weighing less than 10 kg were excluded¹⁹.

Previously AT-LU is available in the form of tablets and the patients had to swallow up to 24 tablets and the idea of this simple form (suspension) was emerged to enhance the compliance. Recently, the bioavailability of chloroquine suspension was comparable with that of chloroquine syrup as standard²⁰. Yet, due to the spread of chloroquine resistance, the chloroquine suspension might not be the preferred choice. The preliminary data on artemisinins suggested artemether as an optimum candidate⁸ and the combination was emerged.

Due to the age factor, it was difficult to monitor or detect the adverse effects in the studied children. However, nausea and mild diarrhea were reported in three patients. One of the limitations of this study was the lack of electrocardiographic monitoring. It had been reported that, AT-LU in the treatment of uncomplicated falciparum malaria was free from any electrocardiographic evidence of cardiotoxicity¹⁷⁻¹⁸.

There was one case of gametocytaemia during the follow-up period. The ability of artesunate to

reduce the post-treatment gametocytaemia is important, as it may reduce transmission ²¹.

CONCLUSION

Artemether-lumfantrine suspension (Co-artesiane[®]) appears to be efficacious and safe for the treatment of uncomplicated malaria.

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