Mefloquine in the treatment of falciparum malaria during pregnancy in Eastern Sudan

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ABSTRACT

Objective: To test the efficacy and toxicity of mefloquine therapy both on expectant mothers and the outcome of their pregnancies.

Methods: We performed a prospective non-comparative clinical trial in New Halfa Teaching Hospital, Eastern Sudan, during the period October 1998 to June 2001. Pregnant Sudanese women were given mefloquine 25 mg/kg for treatment of falciparum malaria following chloroquine failure. The women were followed every 2 weeks in the antenatal clinic until delivery. The babies were followed until the age of one year.

Results: Forty pregnant women were enrolled in the second and third trimesters. Itching which occurred in 17.5% and nausea which occurred in 35% were the cardinal side effects of the patients. Recrudescence or re-infection occurred on day 14 in one patient (2.5%). One patient that received mefloquine at 34 weeks gestational age delivered low birth weight (2.1 kg) at 39 weeks gestational age. One child died at the age of 7 months due to unexplained febrile illness. There was no abortion, no stillbirth and no congenital abnormality in the newborn children and no maternal death.

Conclusion: This relatively small study reported that mefloquine could be used safely for the treatment of malaria in the second and third trimester of pregnancy and a larger study is recommended.

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Malaria is the major threat to the pregnant woman in the tropics.[1] In areas where malaria transmission is seasonal (like in our situation), pregnant women suffer most and the disease has an adverse effects on the pregnancy.[2] We have previously observed that, all manifestations of severe falciparum malaria (cerebral malaria, pulmonary edema and anemia) among pregnant Sudanese women where all parities, were infected and not only primigravidae as in areas of high transmission.[3] In Sudan, falciparum malaria was found to be the leading cause of low birth weight.[4] In a community-based study, we reported 17.4% of the women infected with falciparum malaria and the infected group have significantly low hemoglobin level and their babies have significantly low birth weight.[5] Treatment of the malarial infection remains the main available means to limit the impact of malaria on pregnancy.[2] The antimalarial drugs themselves are not free of adverse effects during pregnancy, such as quinine and hypoglycemia; mefloquine and stillbirth.[6,7] *Plasmodium falciparum* (*P. falciparum)* isolates from Eastern Sudan have the highest levels of antimalarial-drug resistance in the country, where chloroquine were found to be 76% and quinine resistance were found to be 9.6%.[8,9] Mefloquine is a relatively new drug and it has been shown to be effective and safe in non-pregnant patients in the eastern Sudan.[10] The objective of this work was to

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test the efficacy and toxicity (if any) of mefloquine therapy both on the mothers and the expectant outcome of their pregnancies.

Methods. We performed a prospective study in New Halfa Hospital, Eastern Sudan, during the period October 1998 to June 2001. Forty pregnant women in the second and third trimesters presenting to the antenatal clinic with symptoms of falciparum malaria after a full course of chloroquine therapy were included in the study. Ethical clearance was obtained from the ethical committee of the Faculty of Medicine at the University of Khartoum, Khartoum, Sudan. After a well-informed consent, full history, physical examination and record keeping were performed. Peripheral blood smears were prepared stained with Giemsa and examined under oil immersion for malaria parasite. Parasites and leucocytes were counted in the same fields until 200 leucocytes were counted. Parasites densities were estimated using an assumed leucocyte count of 6000 cells/mm^3 of blood. Ultrasound was performed initially to confirm the gestational age, viability of the fetus, placental localization and to exclude congenital malformations.

Patients were hospitalized for one day to receive mefloquine (Lariam, Hoffmann-La Roche, Basel, Switzerland) treatment as single dose (25 mg/kg body weight) and observed for the expected side effects of mefloquine (nausea, vomiting, abdominal pain, itching and giddiness) and then discharged to be seen on days 7, 14, 21 and 28. Patients were followed in the antenatal clinic by an obstetrician and a physician, with record keeping of fundal level and fetal heart sound. At each visit the hemoglobin level, urine general and blood film for malaria were carried out.

Patients were encouraged to deliver in the hospital; otherwise, they were traced at home if they did not come for the follow-up. The babies were followed until the age of one year and they were assessed by pediatricians for milestones, and to exclude congenital malformations. Simple frequency distributions, descriptive statistics, mean and standard deviation were carried out.

Results. Among the 40 pregnant Sudanese women enrolled in the study, headache (75%), backache (75%), fever (62.5%), fatigue (50%), dizziness (50%) and diarrhea (12.5%) were the major presenting symptoms. Itching which occurred in 17.5% and nausea which occurred in 35% were the cardinal side effects of the patients. **Table 1** shows the patients' different variables at the time of admission. Two patients (5%) vomited the drug immediately after the ingestion and the full dose was repeated successfully after promethazine injections. One patient (2.5%) presented to the hospital with symptoms of falciparum malaria on day 14. Blood film for malaria was positive, and she was re-admitted to the hospital. She was treated with quinine salt, 30 mg/day for 7 days, and then followed up with the other patients. Twelve patients delivered in hospital; the mean ± SD birth weight of their babies was 3.45 ± 0.76 kg and the rest delivered at home. One patient (2.5%) received mefloquine treatment at 34 weeks gestational age, delivered at 39th weeks by cesarean section due to repeated scars; the baby's birth weight was 2.1 kg, (low birth weight). One baby died at the age of 7th month due to unexplained febrile illness. There were no abortion, stillbirth and no congenital malformations observed. There is no maternal death.

Discussion. Malaria has serious impacts on pregnancy leading to maternal and fetal morbidity especially in areas where the transmission is seasonal.[2] The patients in this study presented with different symptoms (fever, headache and backache), their mean temperature was 37.8^{0}C. This is the characteristic of malaria in areas of unstable transmission, where all parities are infected and the disease presents had different manifestations. Previously, we have shown that pregnant women in the Central Sudan are susceptible to various manifestations of severe falciparum malaria such as cerebral malaria, anemia, jaundice and hyperpyrexia.[3]

The study showed that mefloquine was well tolerated with minimum side effects, which were mild and resolved spontaneously. However, nausea

Table 1 - Different admission variables for pregnant women treated with mefloquine.

Variable	Mean ± SD
Age (years)	28.27 ± 5.12
Weight (kg)	69.9 ± 11.2
Gravidity	3.36 ± 2.12
Parity	2.54 ± 2.26
Gestational age (weeks)	28.8 ± 6.3
Temperature (degree Celsius)	37.86 ± 0.42
Hemoglobin (g/dl)	9.7 ± 1.17
Parasite count (rings/µl)	19186.5 ± 14197.7

was found in 35% of the patients and 2 patients vomited the drug immediately, in the absence of parental preparation of mefloquine, nausea and vomiting may limit its use. One patient (2.5%) presented on day 14 with symptoms of malaria, which was confirmed by positive blood film. This failure of treatment may be due to recrudescence or re-infection. Nevertheless, in a neighboring area, it had been observed that 13.4% of *P. falciparum* isolates were resistant to mefloquine by in-vitro tests[10] and in another study involving pregnant ladies, mefloquine failure was found to be around 28%.[11] Yet, comparison with these 2 studies should be interpreted cautiously; the former one was in-vitro test and the body immune system was known to enhance the drug efficacy. The other one was conducted in Thailand, where mefloquine therapy was used for a long time, either by itself or in combination with the other anti-malarials. This drug pressure could explain the relative high resistance to mefloquine there. One patient who received mefloquine at 34 weeks gestational age, delivered at 39th weeks, and the baby's birth weight was 2.1 kg. This low birth weight cannot be attributed to mefloquine since it was received 5 weeks before the delivery. Malaria itself has been found to be the cause of low birth weight in our community[4] and it has been reported earlier that the infected women have significantly lower birth weight in spite of effective treatment of malaria (quinine).[2,5] There was no abortion or stillbirth among the study group. This could later be explained by the relative presentation of the patients (gestational age was 28.8 ± 6.3 weeks). However, it has been recently found that mefloquine usage in pregnant women is associated with stillbirth in western border of Thailand, an area characterized by unstable transmission and multi-drug resistant *P. falciparum* malaria.[7,12] Steketee et al[13] reported the outcome of 932 pregnancies of women exposed to mefloquine as weekly prophylaxis. Second trimester abortion and perinatal mortality were stated as unrelated to the drug.[13] Earlier, Harinasuta et al[14] compared the outcome of mefloquine to quinine but they did not find any difference in stillbirth.

Generally, few reports on the use of mefloquine in pregnancy are available. Larger controlled comparative elaborate community-based studies are needed in the light of the growing multidrug resistant falciparum malaria in Africa, and the limited number of available effective and affordable drugs.

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References

1. Brabin BJ, Maxwell S, Chimsuku L, Verhoeff F, van der Kaay HJ, Broadhead R et al. Study of the consequences of malaria infection in pregnant women and their infants. ***Parassitologia*** 1993; 35 (Suppl): 9-11.
2. Nosten F, Ter Kuile FO, Maelankirri L, Decludt B, White NJ. Malaria during pregnancy in an area of unstable endemicity. ***Trans R Soc Trop Med Hyg*** 1991; 85: 424-429.
3. Adam I, Mirghani OM, Saed OK, Ahmed SM, Mohamadani AA, Ahmed HM et al. Quinine therapy in severe Plasmodium falciparum malaria during pregnancy in Sudan. ***East Mediterr Health J*** (in press).
4. Taha ET, Ronald HG, Abdalla AM. Malaria and low birth weight in central Sudan. ***Am J Epidemiol*** 1993; 138: 315-325.
5. Adam I, Karar AA, El-Ghazali G, Trape JF, Elbashir MI. Malaria and pregnancy in an area of unstable transmission in eastern Sudan. ***Trop Med Int Health*** (in press).
6. Looarseesuwan S, Phillips RE, White NJ, Kietinum S, Karbwang J, Rackow C et al. Quinine and severe falciparum malaria in late pregnancy. ***Lancet*** 1985; (ii): 4-5.
7. Nosten F, Vincenti M, Simpson J, Yei P, Thwai KL, de Vries A et al. The effect of mefloquine treatment in pregnancy. ***Clin Infect Dis*** 1999; 28: 808-815.
8. Adam I, Elhadi M, Ahmed G, Elbashir MI. In Sudan: Chloroquine resistance is worsening and quinine resistance is emerging. ***Sudan Med J*** 2001; 39; 5-11.
9. Adam I, Ibrahim MH, Elbasit I, Elbashir MI. Efficacy of sulfadoxine-pyrimethamine in the treatment of uncomplicated Plasmodium falciparum malaria in a small sample of Sudanese children. ***East Mediterr Health J*** (In Press).
10. Khalil IF. Sensitivity of chloroquine resistant Plasmodium falciparum to Fansimef, mefloquine and halofantrine in Gadaref, Eastern Sudan [dissertation]. Khartoum (Sudan): University of Khartoum; 1995.
11. McGready R, Cho T, Hkirijaroen L, Simpson J, Chongsuphajaisiddhi T, White NJ et al. Quinine and mefloquine in the treatment of multidrug-resistant Plasmodium falciparum malaria in pregnancy. ***Ann Trop Med Parasitol*** 1998; 92: 643-653.
12. McGready R, Brockman A, Cho T, Cho D, Vagt VM, Lumexemourger C et al. Randomized comparison of mefloquine-arsenate versus quinine in the treatment of multidrug-resistant falciparum malaria in pregnancy. ***Trans R Soc Trop Med Hyg*** 2000; 94: 689-693.
13. Steketee RW, Wirima JJ, Slutsker L, Khormana CO, Heymann DL, Breman JG. Malaria treatment and prevention in pregnancy: indication for use and adverse events associated with the use of chloroquine or mefloquine. ***Am J Trop Med Hyg*** 1996; 55: 50-56.
14. Harinasuta T, Keitinum S, Somlaw SB, Bunnag D, Sheth UK, Wernsdorfer WH. A clinical trial of mefloquine on multidrug-resistant falciparum malaria in pregnant women in Thailand. Bulletin de la Societe Francaise de Parasitologie; 1990. p. 429.