

Quinine for chloroquine-resistant falciparum malaria in pregnant Sudanese women in the first trimester

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الكينين لمعالجة الملاريا المنجلية المقاومة للكلوروكين في الحوامل السودانيات في الأثلوث الأول من الحمل

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الخلاصة: أجريت دراسة استباقية سريرية في شرق السودان لوصف فعالية وسُمِّية تناول الكينين في بداية الحمل لدى الحوامل المصابات بالملاريا المنجلية المقاومة للكلوروكين. فقد أعطيت 26 من الحوامل السودانيات في الأثلوث الأول من حملهن (العمر الحاملي الوسطي 8.5 أسبوعاً) 10 ميلي غرام/كيلو غرام من الكينين ثلاث مرات يومياً لمدة سبعة أيام، وتلا ذلك تكرار المعالجة كل أسبوعين حتى الولادة. وقد أجهضت إحدى المريضات (3.8%) وعانت مريضتان (7.7%) من التهديد بالإجهاض، إلا إنهما أمتنا حملهما وولدتا طفلين في الأوان. وقد لوحظ النكس أو عودة العدوى في اليوم الحادي والعشرين لدى إحدى المريضات. ومات أحد الولدان في عمر 6 أشهر، ولم يكن هناك أي تشوّه ولادي يمكن كشفه ولا عيوب سمعية أو بصرية أو عصبية لدى الأطفال الآخرين عند ولادتهم، وحتى بعد مرور سنة على ذلك. ويستنتج من ذلك أن الكينين قد يكون مأموناً في الأثلوث الأول من الحمل.

ABSTRACT A prospective clinical study in eastern Sudan described the efficacy and toxicity of quinine in early pregnancy in mothers with chloroquine-resistant falciparum malaria. Twenty-six pregnant Sudanese women in their first trimester (mean gestational age 8.5 weeks) were given quinine 10 mg/kg 3 times per day for 7 days and followed up every 2 weeks until delivery. One patient aborted (3.8%) and 2 patients (7.7%) experienced threatened abortion but delivered term babies. Recrudescence or re-infection was observed on day 21 in 1 patient. One baby died aged 6 months. There were no detectable congenital malformations, no auditory or visual defects or any other neurological deficits in the remaining infants at birth or 1 year later. Quinine may be safe in the first trimester of pregnancy.

La quinine pour le paludisme à falciparum chloroquino-résistant chez des femmes enceintes soudanaises durant le premier trimestre de la grossesse

RÉSUMÉ Une étude clinique prospective au Soudan oriental a décrit l'efficacité et la toxicité de la quinine au début de la grossesse chez des mères atteintes de paludisme à falciparum résistant à la chloroquine. On a administré de la quinine à raison de 10 mg/kg trois fois par jour pendant 7 jours à vingt-six femmes enceintes soudanaises durant le premier trimestre de la grossesse (âge gestationnel moyen de 8,5 semaines) et celles-ci ont été suivies toutes les 2 semaines jusqu'à l'accouchement. Une patiente a avorté (3,8 %) et 2 patientes (7,7 %) ont débuté une menace d'avortement mais ont mis au monde leur bébé à terme. Une recrudescence ou une réinfection a été observée au 21^e jour chez une patiente. Un bébé est décédé à l'âge de six mois. Il n'y avait aucune malformation congénitale décelable, aucun handicap visuel ou auditif ou autre déficit neurologique chez les autres enfants à la naissance ou un an plus tard. La quinine peut être considérée comme sans danger durant le premier trimestre de la grossesse.

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Introduction

Malaria is a major health problem in tropical countries especially sub-Saharan Africa, where about 90% of clinical cases occur. There are nearly 500 million clinical cases of malaria worldwide each year and 1.1 to 2.7 million people die annually [1]. In areas where malaria transmission is seasonal, as in eastern Sudan, there is low transmission and hence low immunity. In Sudan, pregnant women are particularly vulnerable to falciparum malaria; the disease has adverse effects on pregnancy, affecting all parities [2,3], and all manifestations are seen including cerebral malaria and haemoglobinuria [4]. In central Sudan, falciparum malaria was found to be the leading cause of low birth weight, maternal anaemia and maternal and perinatal mortality [5–7].

Plasmodium falciparum isolates from eastern Sudan show the highest levels of antimalarial drug resistance in the country with a rate of chloroquine resistance among isolates of 76% [8,9]. This situation necessitates the use of alternative antimalarial drugs for the treatment of falciparum malaria. Quinine the drug of choice for severe falciparum malaria in Sudan.

Worldwide, very few studies have been made on the safety of quinine therapy during early pregnancy [10,11]. Quinine has long been believed to induce abortion and labour [12]; however, malaria itself can also lead to abortion, while quinine, by lowering fever, may in fact be helpful [13]. This is important as the treatment of chloroquine-resistant falciparum malaria in pregnancy is complicated by the poor safety of other drugs, as both artemether and sulphadoxine-pyrimethamine are reported to cause fetal resorption when given in early pregnancy [14,15].

In the light of the emerging multi-drug resistance in malaria-endemic areas, we describe here the efficacy and toxic effects of

quinine on a small group of women with chloroquine-resistant malaria in early pregnancy and its outcome on the infants at 1-year follow-up.

Methods

Patients

The study was carried in New Halfa Hospital, eastern Sudan, between October 2000 and November 2002. The study group were all pregnant women in their first trimester of pregnancy with symptoms of falciparum malaria and failure to respond to chloroquine. Patients presenting with vaginal bleeding were excluded. The women were asked specifically about symptoms suggestive of malaria (fever, headache, sweating, joint pain and vomiting). Physical examination was performed and all information was kept in case report format.

Investigations

Peripheral capillary blood smears were prepared, stained with Giemsa and examined under oil immersion for parasites. Parasites and leukocytes were counted in the same fields until 200 leukocytes were counted; parasites densities were estimated using an assumed leukocyte count of 6000 leukocytes/ μ L blood. Baseline investigations (haemoglobin, urea, creatinine, albumin and bilirubin levels) were also performed.

Ultrasound was performed initially to confirm the pregnancy, gestational age and viability of the fetus, and repeated every 4–6 weeks for placental localization and to exclude congenital malformations.

Treatment and follow-up

The women were treated with quinine (Laboratoires Renaudin, France) at a dose of 30 mg salt/kg/day for 7 days. It was given at first by intravenous infusion in 5% dextrose solution over 2–4 hours, and

when the patient could tolerate it, therapy was continued orally in the form of tablets.

The patients were discharged after completing the full dose of quinine on day 8, then seen on days 14, 21, 28, and every 2 weeks in the antenatal clinic until delivery. In the clinic they were examined by the obstetrician for weight, pallor, temperature, pulse, blood pressure, fundal level, fetal heart sounds and oedema. At every visit the patient's haemoglobin was estimated and blood films for malaria were taken. The obstetrician supervised all hospital deliveries and kept close links with those who decided to deliver at home.

A paediatrician examined all the infants at birth for congenital malformations and made all necessary anthropometric measurements. Infants, both hospital- and home-delivered, were followed up to 1 year of age by the same paediatrician.

Definitions

Chloroquine-resistance was defined as the detection of *P. falciparum* malaria parasites in peripheral blood after a complete course of chloroquine. Abortion was defined as expulsion of a dead fetus before 28 weeks of gestation. Premature labour was delivery after 28 weeks and before 37 weeks of gestation. Perinatal death was death of the baby from 28 weeks *in utero* until the age of 1 week post-delivery.

Analysis

Data were analysed using *SPSS/PC*. Simple frequency distributions, percentages, means and standard deviations were calculated.

Ethics

The study received ethical clearance from the Faculty Research Board at the Faculty of Medicine, University of Khartoum and the Federal Ministry of Health. Written con-

sent for participation in the study was obtained from the patients and their husbands.

Results

Out of 28 patients, 26 pregnant Sudanese women in their first trimester were given quinine to treat falciparum malaria after failure of chloroquine treatment. Two patients were excluded because they presented with vaginal bleeding. Fever, nausea, vomiting, headache, giddiness and insomnia were the major presenting symptoms. Table 1 shows the main clinical and biochemical data at the time of presentation.

During quinine treatment, 1 patient (2.8%) developed vaginal bleeding and abdominal pain. After the third dose of quinine, the cervix was found to be open, implying inevitable abortion, and evacuation was carried out. Two more patients (7.7%) developed slight vaginal bleeding, i.e. threatened abortion, during quinine

Table 1 Major clinical and laboratory findings on admission in 26 pregnant women with chloroquine-resistant malaria

Parameter	Mean	SD
Age (years)	26.2	3.5
Parity (No.)	2.8	2.6
Gestational age (weeks)	8.5	0.9
Weight (kg)	65.8	4.6
Temperature (°C)	38.2	0.6
Haemoglobin (g/dL)	9.2	1.3
Parasite count (rings/ μ L) ^a	5856	1652
Blood glucose (mg/dL)	123.6	12.9
Blood urea (mg/dL)	27.3	3.6
Serum bilirubin (mg/dL)	1.09	0.12

^aGeometric mean.

SD = standard deviation.

therapy on day 2 and 3 respectively, but their pregnancies continued until the delivery of term babies.

All patients had negative blood films on day 7. However, 1 patient presented on day 21 with recurrence of malaria symptoms and the blood film was positive for falciparum malaria parasites. She was readmitted at the 10th week of gestation and given artemether intramuscularly, 80 mg initially followed by 80 mg after 12 hours and then daily for 4 days. She was discharged after completing the treatment with full recovery and was followed up closely until delivery.

Just under half the patients (12/26, 46.2%) delivered in the hospital, the rest (14/26, 53.8%) delivered at home. The mean (SD) birth weight of babies whose mothers delivered at hospital was 2.9 (0.4) kg.

One of the babies died at home at the age of 6 months due to unexplained febrile illness. There were no detectable congenital malformations and no auditory, visual or other neurological deficits in the remaining infants at birth or 1 year later.

Discussion

Pregnant women are more susceptible to malaria infection which can lead to many adverse effects on the pregnancy such as abortion, premature labour and maternal anaemia [3]. The World Health Organization recommends that pregnant women with demonstrable malaria illness should receive prompt treatment with effective and safe antimalarial drugs [16]. This situation is limited by the safety profile of antimalarial drugs themselves [14,15] and the spread of chloroquine-resistant strains of *P. falciparum*.

In this study, 1 patient showed reappearance of the parasite on day 21, which might be due to re-infection or parasite resis-

tance to quinine therapy. In Sudan, resistance to chloroquine has been recorded in almost every region of the country and even quinine resistance has been shown by *in vivo* and *in vitro* tests in the area of the study and in a nearby area [8,17]. We have previously observed that quinine failed to treat 2/33 (6%) of pregnant women in central Sudan [4]. This phenomenon warrants more investigations since quinine is still the first line of treatment for severe falciparum malaria in Africa.

One patient aborted and 2 patients threatened to abort but their pregnancies continued until term. This agrees with McGready and colleagues' report of quinine in early pregnancy [11], where the rate of abortion was not different from the population in our community. In a recent community-based study of risk factors for anaemia in our area, around 50% of women gave a history of previous abortion [18]. We have previously observed that no patient aborted among 33 patients treated with quinine for severe falciparum malaria in central Sudan [4]. However, in that study 3 patients delivered prematurely, 1 of them during the quinine therapy. In another 2 studies there was no effect of quinine on the rate of abortion or preterm labour [19,20]. In the latter studies the patients presented later in pregnancy (the gestational age was > 20 weeks) and this might explain the rate of abortion (1/26, 3.8%) in the present study where quinine was used in early pregnancy. There are difficulties in interpreting the findings of abortion, because malaria itself is a known cause of abortion especially during epidemics [21]. Certainly in our study, 2 out of 28 malaria patients presented with vaginal bleeding and their pregnancies aborted before quinine was started (these women were excluded from the study). Quinine has long ago been reported to induce abortion and

labour [12] and we believe that this has been influential in limiting the use of quinine during pregnancy. The situation remained so until in 1985 it was declared that malaria and its fever were responsible for abortion, while quinine, by lowering temperature, may in fact decrease the amplitude of uterine contractions as confirmed by fetal monitoring [13].

In our study, we found no hearing or visual defects and no congenital or developmental abnormalities in the infants after 1 year. This confirms another recent study [11]. However, deafness and hypoplasia of the optic nerve have been described in children born after unsuccessful attempts to induce abortion in women taking quinine

overdoses [22]. These were retrospective reports and the exact numbers of patients were not known.

In conclusion, our study and that of McGready and colleagues [11] suggests that quinine could be used safely as a cost-effective therapy during the first trimester of pregnancy.

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