Quinine therapy in severe *Plasmodium falciparum* malaria during pregnancy in Sudan

I. Adam,[1] O.A. Mirghani,[2] O.K. Saed,[2] S.M. Ahmed,[2] A.A. Mohamadani,[2] H.M. Ahmed,[2] C.D. Mackenzie,[3] M.M.A. Homeida[4] and M.I. Elbashir[5]

معالجة الملاريا الناجمة عن المتصورات المنجلية بالكينين أثناء الحمل في السودان

اسحق آدم، عمر مرغني، عصمان سعيد، سعيد أحمد، أحمد محمداني، حسان أحمد، سي. دي ماكنزي، مأمون حميدة، مصطفى البشير

الخلاصة: أجريت دراسة استباقية في منطقة تعاني من سراية غير مستقرة للملاريا في وسط السودان للتعرف على نجاعة وسمية الكينين أثناء الحمل. فقد عولجت بالكينين 33 حاملاً مصابة بملاريا وخيمة ناجمة عن المتصورات المنجلية وكان وسطي عمر الحمل لديهن 288 أسبوعاً، واستمرت المعالجة سبعة أيام، وكان وسطي درجة حرارة الجسم أثناء القدوم لدى 3 حوامل ممن ولدن قبل الأوان أعلى بشكل ملحوظ (392 ± 0.7) من درجة حرارة الجسم لدى الحوامل اللواتي ولدن في تمام الحمل (38.7 ± 1.3). ولم يكن هناك فرق بين المجموعتين من حيث المتثابتات السريرية أو البيولوجية والطبية الأخرى. ولم يكن هناك تشوهات خلقية يمكن كشفها ولا عيوب بصرية أو سمعية أو عصبية في المولدان وقت ولادتهم ولا بعد مرور 6 شهور على ولادتهم. وعلى هذا، فقد يكون الكينين دواءً مأموناً لمعالجة الملاريا الوخيمة الناجمة عن المتصورات المنجلية أثناء الحمل.

ABSTRACT A prospective study was carried out in an area of unstable malaria transmission in central Sudan to determine the efficacy and toxicity of quinine in pregnancy. Thirty-three pregnant women with severe *Plasmodium falciparum* malaria at mean 28.8 weeks gestational age were treated with quinine for 7 days. The mean body temperature on presentation for 3 patients who delivered prematurely was significantly higher than for those who delivered at term (39.2 ± 0.7 °C versus 38.7 ± 1.3 °C). There were no significant differences between the 2 groups in other clinical or biochemical parameters. There were no clinically detectable congenital malformations and no auditory, visual or other neurological deficits in the babies at birth or 6 months later. Quinine may be safe in the treatment of severe falciparum malaria during pregnancy.

Traitement par quinine du paludisme sévère à *Plasmodium falciparum* pendant la grossesse au Soudan

RESUME Une étude prospective a été réalisée dans une zone de transmission instable du paludisme au centre du Soudan afin de déterminer l'efficacité et la toxicité de la quinine pendant la grossesse. Trente-trois femmes enceintes atteintes de paludisme sévère à *Plasmodium falciparum* à un âge gestationnel moyen de 28,8 semaines ont été traitées par quinine pendant 7 jours. La température corporelle moyenne au moment de la présentation pour trois patientes ayant eu un accouchement prématuré était significativement plus élevée que pour celles ayant accouché à terme (39,2 ± 0,7 °C versus 38,7 ± 1,3 °C). Il n'y avait aucune différence significative entre les deux groupes pour les autres paramètres cliniques ou biochimiques. Il n'y avait pas de malformations congénitales cliniquement détectables ni de déficits auditifs, visuels ou autres déficiences neurologiques chez les bébés à la naissance ou six mois après. La quinine peut être utilisée en toute sécurité pour le traitement du paludisme sévère à *Plasmodium falciparum* pendant la grossesse.

[1]*New Halfa Hospital, New Halfa, Sudan.*
[2]*Faculty of Medicine, University of Gezira, Wad Medani, Sudan.*
[3]*Michigan State University, East Lansing, Michigan, United States of America.*
[4]*Academy of Medical Science and Technology, Khartoum, Sudan.*
[5]*Faculty of Medicine, University of Khartoum, Khartoum, Sudan.*
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Introduction

In Africa, each year some 24 million women become pregnant in malaria endemic areas. Pregnancy increases susceptibility to malaria and pregnant women are more likely to develop clinical attacks of malaria and serious complications than non-pregnant women of the same age. The increased susceptibility of pregnant women to malaria is thought to be in part the result of a certain degree of immune suppression during pregnancy required for fetal allograft retention [*1*]. Malaria in pregnant women is associated with serious adverse effects on pregnancy causing abortion, preterm labour, low birth weight, intrauterine fetal death and maternal death [*2–4*].

The epidemiological profile and clinical pattern of malaria vary according to the endemicity of the disease. In areas where malaria transmission is seasonal and unstable, both the mother and her fetus suffer from severe complications of the disease [*5*].

High-grade resistance of the malaria parasite to chloroquine has been reported in eastern and central Sudan [*6,7*]. This has led to the use of alternative drugs, such as quinine. There are few detailed reports on the effect of quinine in pregnant women and its effect on the outcome of pregnancy, and doubts remain about its safety in pregnancy. Through its oxytocic effect, quinine is capable of inducing abortion and labour [*8*]. Moreover, it can cause maternal hypoglycaemia through the release of insulin [*9*]. However, quinine is still the drug of choice for treatment of severe falciparum malaria in Sudan. The objectives of this work were to study the clinical efficacy and toxicity of quinine on mothers with severe falciparum malaria and their babies and to demonstrate the manifestations of severe falciparum malaria during pregnancy in the study group

Methods

Study area and patients

This study was carried out at Wad Medani teaching hospital, Gezira state, central Sudan, an area of seasonal unstable malaria transmission [*6*]. It is the main hospital where all seriously ill patients are referred from health centres and other single-doctor hospitals in the area.

All patients included in the study were selected from around 850 pregnant women seen and admitted to the hospital during the period September 1997 to January 1998 (the main malaria transmission season). Pregnant women were included in the study if they had a positive blood film for *Plasmodium falciparum* and 1 or more of the following criteria for severe malaria [*10*]: cerebral malaria (unarousable coma for > 30 min), repeated generalized convulsions, hyperpyrexia (rectal temperature > 40 °C), severe anaemia (haematocrit < 15% or haemoglobin < 50g/L), hypotension or shock (systolic blood pressure < 70 mmHg), jaundice (high serum bilirubin), pulmonary oedema, hypoglycaemia (blood glucose < 2.2 mmol/L), renal failure (< 400 mL urine/24h despite rehydration, and serum creatinine > 265 µmol/L), spontaneous bleeding or evidence of disseminated intravascular coagulation and hyperparasitaemia (> 250 000 rings/µL). Patients in labour, and those with twin pregnancy, intrauterine fetal death or vaginal bleeding were excluded from the study.

The patients or their relatives gave oral consent for admission to the study after full explanation of the purpose of the study and its expected risks.

Data collection

A full medical and obstetric history and physical examination were performed on

the participants and recorded using a case report form.

Parasitological diagnosis of malaria was confirmed by thick and thin blood films using Giemsa stain. The parasite was counted against 200 white blood cells and the extent of parasitaemia was calculated using the patients' white blood cells.

The following investigations were performed for all patients included in the study. Urine analysis was carried out (including presence of haemoglobin). Blood was analysed for haemoglobin level, white blood cell count and reticulocyte count. Serum levels of bilirubin, albumin, urea, creatinine, calcium alkaline phosphatase, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were also determined. Blood glucose level was determined on presentation and repeated if hypoglycaemia was suspected clinically.

Ultrasound examination to confirm the gestational age and viability of the fetus was performed on admission and every 4–6 weeks. Chest X-ray was performed using necessary protective precautions if pulmonary oedema was suspected and the pregnancy was more than 28 weeks.

Treatment and follow-up

The women were treated with quinine (Laboratoires Renaudin, France) at a dose of 30 mg salt/kg per day for 7 days. It was given first by intravenous infusion in 5% dextrose solution over 2–4 hours 3 times a day, and when the patient could tolerate it, therapy was continued orally in the form of tablets. Paracetamol was used to lower the fever. When haemoglobin was less than 70 g/L, packed red cells were infused as necessary. The patients were discharged after completing the full dose of quinine on day 8. They were seen at the antenatal clinic every 2 weeks until delivery.

The obstetrician supervised all hospital deliveries and kept close links with those who decided to deliver at home. Delivery followed the standard management procedure adopted in Wad Medani teaching hospital. A paediatrician examined and followed up all the babies to exclude congenital malformations. Weight and head circumference were recorded for babies delivered in hospital or at home. All the babies, whether hospital or home delivered, were followed up until 6 months of age by the same paediatrician to make an initial assessment of hearing (ability to respond to a rattle in a calm quite room) and vision (ability to respond to a coloured object moving in front of the child). If defects were suspected, more specialized tests would be performed, e.g. brain stem test and fundoscopy.

Definitions

Abortion was defined as expulsion of a dead fetus before 28 weeks of gestation. Premature labour was delivery after 28 weeks of gestation and before the 37 weeks. Perinatal death was death of the baby from 28 weeks *in utero* until the age of 1 week. Anaemia was defined as haemoglobin < 100 g/L.

Statistics

Data was entered into the computer using *SPSS*, version 10.0 batching for data analysis. Simple frequency distributions, descriptive statistics, mean, standard deviation (SD), *t*-test and chi-squared tests were used, with a probability level of < 0.05 for statistical tests.

Ethics

Ethical clearance for the study was obtained from the ethical committee of the Faculty of Medicine University of Khar

toum and national ethical committee at the Sudanese Federal Ministry of Health.

Results

Clinical presentation on admission

Thirty-five pregnant women with severe *P. falciparum* infection were initially admitted to the study: 33 patients completed the study and 2 patients decided to discontinue after the first dose of quinine (initial data collected from these patients is reported here).

The mean ± SD parity was 1.8 ± 2.2. Of the 35 patients, 11 were primigravidae, 9 were in the second pregnancy and 15 were in the third pregnancy or more (1 patient was a grand multipara in her ninth pregnancy). On presentation, the mean gestational age was 28.8 + 8.7 weeks. One patient had received quinine during the first 8 weeks of pregnancy.

The main presenting symptoms among the initial sample were: fever (77.1%), vomiting (68.6%), headache (57.1%), cough (22.9%) and diarrhoea (14.3%). Table 1 summarizes the clinical and laboratory findings obtained on admission. The mean values for all biochemical parameters measured were within normal ranges, except for bilirubin which was slightly raised.

The major manifestations of severe malaria among the 35 patients who started quinine therapy were: cerebral malaria (unarousable coma) (2 patients), severe anaemia (4), jaundice (11), hyperpyrexia (17), haemoglobinuria (11), hypotension (2), hypoglycaemia (1), and pulmonary oedema (1). Some patients presented with more than 1 symptom and 1 patient developed hypoglycaemia on day 7 of quinine treatment. However, no patient presented with renal failure or spontaneous bleeding from the gums or nose, and none were defined with hyperparasitaemia (> 250 000 rings/μL). The spleen was palpable in 8 patients on admission.

Table 1 **Major clinical and laboratory findings on admission in 35 pregnant women with severe malaria**

Parameter	Mean	SD
Age (years)	26.3	4.7
Gravidity (No.)	3.2	2.5
Parity (No.)	1.8	2.2
Weight (kg)	60.5	10.9
Gestational age (weeks)	28.8	8.7
Systolic blood pressure (mmHg)	102.3	11.5
Temperature (°C)	38.8	1.3
Parasite count (rings/μL)	18735	21819
Haemoglobin (g/L)	89	25
White blood cells (cells/mm³)	4400	900
Blood urea (mmol/L)	23.7	5.5
Blood glucose (mmol/L)	5.70	2.50
Creatinine (mg/dL)	0.83	0.11
Bilirubin (mg/dL)	1.90	1.40
Albumin (g/L)	31.4	5.2
Calcium (mg/dL)	10.2	0.4
ALT (IU/L)[a]	5.14	9.70
AST (IU/L)[b]	3.17	6.11
Alkaline phosphatase (IU/L)	23.6	12.1

[a]ALT = alanine aminotransferase; normal values 0–45 IU/L.
[b]AST = aspartate aminotransferase; normal values 0–41 IU/L.
SD = standard deviation.

The 2 comatose patients (with cerebral malaria) also had repeated generalized convulsions, haemoglobinuria, body temperatures of 38.6 °C and 38.9 °C, parasite counts of 7600 rings/μL and 6250 rings/μL, haemoglobin concentrations of 98 g/L

and 91 g/L, and blood glucose levels of 7.8 mmol/L and 3.9 mmol/L, respectively.

The mean ± SD haemoglobin of all the patients was 89 ± 25 g/L. However, 4 patients presented with severe anaemia (haemoglobin < 50 g/L). In these patients the peripheral blood picture showed normocytic normochromic red cells, with anisopoikilocytosis, and the sickling test was negative.

Treatment response

Twenty-one of the patients included in the study had received chloroquine before admission and had not improved. All patients responded well to quinine with dramatic relief of symptoms. The comatose patients recovered consciousness within 24 hours, and the fever subsided within 72 hours. Vomiting was not noticed in any of the patients after 72 hours and treatment was continued with oral quinine. Jaundice disappeared within 5 days in all except 2 patients where it persisted for 7 days. Severe anaemia was corrected by transfusion of packed red cells and the response was satisfactory. Quinine was well tolerated by the patients with limited side-effects (tinnitus and dizziness in about 54% of patients), which were mild and transient.

All patients had negative blood films on day 7. However, 2/33 (6.1%) patients presented on days 17 and 20 with recurrence of malaria symptoms and their blood films were positive. They were admitted and given artemether intramuscularly, 80 mg initially then 80 mg after 12 hours and then daily for 4 days. They were discharged after completing the treatment with full recovery and were followed up closely until delivery.

Pregnancy outcome

Thirty patients delivered at term and 3 patients delivered prematurely (at 32, 33, 34 weeks). One of these 3 patients delivered after the third dose of quinine; the other 2 patients delivered prematurely, but 30 and 50 days after completing quinine therapy which makes it unlikely to be due to quinine.

When we compared the clinical and laboratory findings in the 2 groups of patients (term and pre-term deliveries), there was no significant difference between them regarding mother's age, parity, gestational age when they received quinine therapy, systolic blood pressure, parasitaemia or biochemical findings (blood glucose level, serum bilirubin, blood urea level and haemoglobin concentration). However, the mean ± SD temperature on presentation for the 3 patients who delivered prematurely was 39.2 ± 0.7 °C, whereas it was 38.7 ± 1.3 °C in those who delivered at term, a difference that was significant ($P = 0.05$). On the third day, the temperature was normal in both groups (Table 2).

Fifteen patients delivered in Wad Medani hospital and 18 at home. The mean birth weight of the babies delivered at hospital and at home was 3.0 kg (range 2.2–4.0 kg); the mean head circumference at birth was 35.5 cm. There were no auditory, visual or neurological defects recorded. There were no maternal deaths, abortions, stillbirths or perinatal deaths.

Discussion

The present study was carried out in an area of unstable malaria transmission. More than 50% of the women were parous and different forms of clinical presentation of severe malaria were observed among our study group, including cerebral malaria and hyperpyrexia. This supports the belief that falciparum malaria in areas of low and unstable transmission is usually symptomatic and affects all parities, whereas in areas of

Table 2. **Comparison of the major characteristics of severe malaria in women with term and pre-term deliveries**

Parameter	Women with term delivery ($n = 30$) Mean	SD	Women with pre-term delivery ($n = 3$) Mean	SD	*P*-value[a]
Age (years)	26.6	4.6	22.3	6.8	0.42
Gravidity (No.)	3.2	2.5	3.3	3.2	0.70
Parity (No.)	1.8	2.2	2.3	3.2	0.34
Gestational age at treatment (weeks)	29.3	9.0	29.3	6.0	0.50
Temperature on admission (°C)	38.7	1.3	39.2	0.7	0.05
Temperature on day 3 (°C)	37.2	0.8	37.2	0.9	0.90
Systolic blood pressure (mmHg)	102.3	12.1	103.3	16.7	0.12
Parasite count (rings/μL)	18855	23472	15200	8265	0.32
Haemoglobin (g/L)	87	26	104	12	0.24
Random blood glucose (mg/dL)	106.6	44.7	80.6	13.6	0.33
Blood urea (mg/dL)	24.1	5.3	23.3	5.8	0.90
Serum bilirubin (mg/dL)	1.90	1.50	2.50	0.63	0.38

[a] *Using* t-*test.*
SD = standard deviation

high endemicity, falciparum malaria is more common among primigravidae and patients are usually asymptomatic or present with severe anaemia [*11–13*].

It is of interest to note that, although the patients presented with severe illness, the mean parasite count was relatively low at 18 735 rings/μL, and the highest count was 100 380 rings/μL. The explanation of this phenomenon is not clear. It is possible that the threshold for complications is low in this epidemiological setting. Hypoglycaemia was found in 1 patient on presentation, and only 1 patient developed hypoglycaemia after quinine therapy. However, hypoglycaemia has been reported in around 50% of pregnant women at one stage or another of severe falciparum malaria [*9*].

In this study, the patients responded readily to quinine and all symptoms cleared rapidly as described in the results. Only 2 patients (6%) developed symptoms of malaria with detectable parasitaemia in the third week. We are not sure if this was due to some degree of declining efficacy or even resistance to quinine or due to re-infection. Quinine resistance or failure has been reported in the eastern parts of Sudan among non-pregnant patients [*7,14*], and quinine resistance during pregnancy of around 30% has been documented in Thailand [*15,16*].

Quinine was well tolerated by the mothers and had no adverse effect on the children up to the age of 6 months. There were no maternal deaths, abortions, stillbirths or perinatal deaths. The mean gestational age of the patients at the time of enrolment was 28.8 weeks, which might explain why there was no abortion. This was also reported in 2 recent studies [*15,16*].

In the present report, we showed that 3 patients (9%) had pre-term labour; 1 of them delivered during quinine therapy and the other 2 patients delivered prematurely, 30 and 50 days after completion of quinine therapy. This makes it difficult to relate premature labour to quinine. However, no pre-term labour was reported by Mc Gready et al. in 1998 and 2000 [*15,16*]. This might be explained by the difference in morbidity of the patients included in those studies. In our study, all patients presented to hospital with manifestations of severe falciparum malaria, whereas in the above-mentioned studies, which were community based, the patients presented with uncomplicated malaria. Only 16% and 18% of the patients presented with fever, whereas the mean temperature of our patients on presentation was 38.8 °C. Furthermore, in our study 17 patients presented with hyperpyrexia and the difference in temperature on presentation between patients who delivered prematurely and those who delivered at term was significantly higher. High temperature was the main reason for uterine contraction [*9*]. Malaria can cause abortion and pre-term labour as well [*2*] and in central Sudan it was found to be the leading cause of low birth weight by causing pre-term labour [*17*]. However, the oxytocic effect of quinine on the pregnant uterus cannot be excluded totally, at least in the patient who delivered during quinine treatment. Quinine has been used as an abortifacient and labour inducing agent [*8*].

In this study, the paediatrician did not note any hearing or visual defects, and no congenital or developmental abnormalities in the babies. This agrees with other recent studies [*15,16*]. 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 [*18*]. In humans, organogenesis is in the first 12 weeks of intrauterine life, and during this time only 1 patient in this study received quinine. Very few studies have been made on the safety of quinine during early pregnancy. We think it is necessary to carry out such studies in view of the emerging multidrug-resistant strains of *P. falciparum* and the limited choice of alternative safe and effective drugs for malaria treatment.

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