Effect of quinine therapy on plasma glucose and plasma insulin levels in pregnant women infected with *Plasmodium falciparum* malaria in Gezira state

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تأثير المعالجة بالكينين على مستويات الغلوكوز والأنسولين في بلازما الحوامل الـمُنْعَدِيات بالملاريا المنجليّة في ولاية الجزيرة بالسودان

نور الدائم النعمان البدوي، مها إسماعيل محمد، عقيل يوسف داوود، خالد التوم علي، عمر حسن داوود، المهدي محمد علي، البشير قسم البارئ أحمد، أحمد الطاهر محمد

الخلاصة: لتحديد ما إذا كان للكينين أيُّ مفعول استقلابي أثناء علاج الملاريا الوخيمة المصحوبة بمضاعفات، درس الباحثون تأثيراته على مستويات الغلوكوز والأنسولين في البلازما في مئة وخمسين من الحوامل المصابات بالملاريا، تمَّت إحالتهنّ إلى مستشفى «مدني» التعليمي لرعاية الأمومة في ولاية الجزيرة، وفي خمسين امرأة حاملاً سليمة كمجموعة من الشواهد. وحُدِدَت المستويات القاعدية (في اليوم صفر) أي قبل بدء العلاج بالكينين، وبعد يومين من بدء العلاج (بعد الجرعة الرابعة بساعتَيْن)، وبعد سبعة أيام من العلاج (اليوم الثامن). وتبيّن أن هناك زيادة يُعتدُّ بها إحصائياً في تركيزات الأنسولين في البلازما أثناء إعطاء الكينين تسريباً مع انخفاض في تركيز الغلوكوز في البلازما ($P<0.001$). مما يدل على أن إعطاء الكينين حسب الجرعة والمعدّل الموصى بهما، يمكن أن يُخِلَّ باستتباب الغلوكوز في البلازما، مع أن الكينين مازال يمثِّل الخيار الأفضل لعلاج الملاريا الوخيمة المصحوبة بمضاعفات في السودان.

ABSTRACT To determine if quinine has a metabolic effect during treatment of severe or complicated malaria, we studied its effects on plasma glucose and plasma insulin levels in 150 pregnant women with malaria referred to Madani maternity teaching hospital, Gezira state and 50 healthy pregnant controls. Levels were determined at baseline (day 0) before the start of quinine treatment, after 2 days of treatment (2 hours after the 4th dose) and after 7 days of treatment (day 8). There was a statistically significant increase in plasma insulin concentrations during the quinine infusion and fall in plasma glucose concentration ($P < 0.001$). Quinine administered at the recommended dose and rate can disrupt plasma glucose homeostasis although it is still the drug of choice for severe and complicated malaria in Sudan.

Effet du traitement à base de quinine sur le taux de glycémie et d'insuline plasmatique chez les femmes enceintes infectées par le paludisme à *Plasmodium falciparum* dans l'État d'Al-Jazira

RÉSUMÉ Afin de déterminer si la quinine a un effet métabolique pendant le traitement du paludisme grave ou compliqué, nous avons étudié ses effets sur les taux de glycémie et d'insuline plasmatique chez 150 femmes enceintes atteintes de paludisme et ayant été orientées vers la maternité de l'Hôpital universitaire Madani, dans l'État d'Al-Jazira, et chez 50 femmes enceintes témoins en bonne santé. Les taux ont été observés au début de l'étude (jour 0) avant l'administration du traitement à base de quinine, après deux jours de traitement (deux heures après la quatrième dose) et après sept jours de traitement (jour 8). Une élévation statistiquement significative du taux d'insuline plasmatique pendant la perfusion de quinine et une chute du taux de glycémie ont été enregistrées ($P < 0,001$). Le traitement par la quinine administré à la posologie et à la vitesse de perfusion recommandées peut perturber l'homéostasie glycémique. Toutefois, la quinine reste le médicament de choix pour traiter le paludisme grave et compliqué au Soudan.

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Introduction

Malaria is the leading cause of morbidity and mortality in Sudan, with an annual estimated 7.5 million clinical cases and 35 000 deaths. *Plasmodium falciparum* is the dominant parasite and the principal mosquito vectors are *Anopheles arabiensis, An. gambiae* and *An. fenstus* [1]. The adverse impact of malaria in pregnancy is largely caused by *P. falciparum*; approximately 90% of *P. falciparum* clinical cases globally occur in sub-Saharan Africa [2].

Malaria infection during pregnancy poses substantial risks to the mother, her fetus and the neonate. Consequences of malaria in pregnancy include severe anaemia, placental parasitaemia and intrauterine growth retardation, which contribute to low birth weight, a principal cause of infant mortality in the African region. Malaria is more common in pregnancy compared to in the general population. Immunosuppression and loss of acquired immunity to malaria could be reasons for this [3].

Atypical manifestations of malaria are more common in pregnancy, particularly in the second half of pregnancy. The most common presenting symptoms are fever, anaemia, and splenomegaly. Complications also tend to be more common and more severe. Hypoglycaemia, anaemia and acute pulmonary oedema are also more common. Jaundice, convulsions, altered sensorium, coma, vomiting/diarrhoea and other complications may be seen. Hypoglycaemia is a recognized complication of malaria in pregnancy, but its pathophysiology is not well understood [4]. It is thought that infected erythrocytes collected in the placenta stimulate pancreatic β-cell production of insulin, leading to hyperinsulinaemia and hypoglycaemia during infection. This contributes to the severity of disease during pregnancy [5,6].

Malaria parasites are now resistant to many of the older antimalarial drugs (for example, quinine). So, since 2006, the World Health Organization (WHO) has recommended that uncomplicated malaria during the second and third trimester of pregnancy is treated with short course (3 d) fixed-dose artemisinin combination therapy (ACT), but quinine is still used in early pregnancy because it is not known whether ACT damages fetal development, which mainly occurs during the first 3 months [7].

Although quinine is the first drug of choice for the treatment of falciparum malaria during pregnancy, its side-effects can be life-threatening. Therefore monitoring of the biochemical profile in general and plasma glucose and plasma insulin is important for the mother and her fetus.

In the present study we assessed the level of plasma glucose and plasma insulin levels in pregnant women in central Sudan infected with *Plasmodium falciparum* under quinine therapy with different presentation patterns on admission. We monitored the level of parasitaemia before, during and after quinine treatment.

Methods

This was a cross-sectional hospital-based study. It was conducted at Madani maternity teaching hospital, Gezira State between September 2004 and January 2006. Gezira State is an area of seasonal mesoendemic malaria transmission [1].

Our sample was pregnant women a positive film of *P. falciparum* confirmed microscopically. Sample size was calculated according to the statistical equation: $n = z^2 \times Pq/d^2$ where: n = sample size, d (precision) = 0.05, z (value of the standard normal distribution at the 5% level) = 1.96, P = success probability, q = failure probability.

We recruited 150 pregnant women who had a positive film of *P. falciparum* confirmed microscopically. Pregnant women with diabetes, those who had used quinine or arthemether in the previous 3 days, and cases where there was intrauterine fetal death or vaginal bleeding were excluded from the study. We selected 50 healthy pregnant women as a control group to compare clinical and biochemical characteristics with the patient group at the start of the study.

Oral consent was taken from the entire study group after full explanation of the aim of the study.

A full medical and obstetrical questionnaire was completed and physical examination was performed by a trained team including obstetrician, physician, biochemist and laboratory technician. Parasitological diagnosis of malaria was confirmed by thick and thin film using Giemsa stain. The parasites were counted against 200 white blood cells and the extent of parasitaemia was calculated using the patients' white blood cells.

Haemoglobin was estimated calorimetrically according to Dacie & Lewis [8]. A 5 mL sample of venous blood was collected from each patient as a baseline on day zero, before the start of intravenous quinine treatment; a second sample was taken after 2 days of treatment (2 hours after the 4th dose of quinine) Treatment lasted 7 days and included 21 doses of quinine. The third blood sample was taken on day 8. Blood samples were centrifuged at 4000 rpm for 10 minutes and the separated sera were kept at –70 °C.

Glucose was estimated colorimetrically (LabTech, India) using the glucose oxidase method (all reagents: SPINREACT SA, Girona, Spain) which involves the oxidation of glucose by glucose oxidase to gluconic acid [9].

Insulin was immunoassayed (all materials: Diagnostic Products Corporation, Los Angeles, California) using an Immulite analyser (catalogue no. LKIN1; 100 tests, test code INS). Immulite insulin is a solid-phase, 2-site chemiluminescent immunometric assay [10].

Statistical methods

Normally distributed continuous variables were compared using analysis of variance and Spearman correlation for non-normally distributed continuous variables were compared by means of the Pearson 2-tailed correlation test. Significance levels of $P < 0.05$ were reported. Statistical programs used were *SPSS* for Windows, version 16.0.

Results

The clinical and laboratory data for the women in the study group and the control group are shown in Table 1. The mean level of haemoglobin and blood glucose were lower than the control group, while the serum insulin level was significantly higher ($P < 0.001$) among the study group. The most common presenting symptoms in the women with malaria were fever (99.3%), body aches (75.0%), vomiting (41.3%), headache (41.3%), chills (31.3%) and diarrhoea (0.7%).

Quinine infusions were associated with a rise in plasma insulin concentrations and a decrease in plasma glucose concentrations (Table 2). No subject developed hypoglycaemia (plasma glucose concentration < 2.2 mmol/L). Random plasma glucose concentrations at presentation (range 60–112 mg/dL) were significantly higher than after quinine treatment. Duration of pregnancy also had a non-significant impact on the insulin and glucose levels in women with malaria (Table 3).

The mean level of parasitaemia was 32235.8/200 WBC (SD 40434.96/200 WBC). There was a significant negative correlation ($P < 0.01$) between the level of parasitaemia and haemoglobin ($r = -0.25$) and blood glucose level ($r = -0.66$), while a significant positive correlation ($P = 0.001$) was found between mean insulin levels, fever, chills and headache.

Discussion

The baseline plasma glucose and plasma insulin levels were slightly low in the pregnant women with malaria, but within the normal range and this may be ascribed to the increased host/parasite demand for glucose. This result agrees with that obtained by Binh et al. Following the commencement of quinine therapy, only plasma insulin increased significantly above the normal range compared to the baseline and post-treatment values. The rise in plasma insulin was accompanied by a concomitant decrease in the plasma glucose level, but this did not reach a hypoglycaemic concentration, indicating a hyperinsulinaemic–hypoglycaemic effect of quinine. This result agrees with the results obtained in previous studies [11–13].

Since the plasma glucose concentration falls after the first trimester [14,15], and high density of parasites

Table 1 Clinical and biochemical characteristics of patients and controls

Characteristic	Patients ($n = 150$)	Controls ($n = 50$)	*P*-value
	Mean (SD)	Mean (SD)	
Age (years)	31 (4.3)	29 (4.6)	0.970
Gestational age (weeks)	24.6 (7.2)	21.8 (5.7)	0.034
Gravidity	2.1 (1.4)	1.7 (1.0)	0.003
Parity	1.0 (1.3)	0.7 (1.0)	0.034
Haemoglobin (g/dL)	8.7 (2.0)	11.1 (1.3)	0.026
Range	4.0–12.0	9.0–14.0	
Random plasma glucose (mmol/L)	4.5 (0.6)	5.1 (0.4)	< 0.001
Range	4.6–5.8	5.1–6.2	
Serum insulin (μIU/mL)	16.3 (6.0)	11.3 (2.1)	< 0.001
Range	6.0–27.0	8.0–17.0	
Parasitaemia (/200 white blood cells)	32235.8 (40434.96)	–	

SD = Standard deviation.

Table 2 Mean random blood glucose level and mean insulin concentration before, during and after intravenous quinine treatment

Test	Before treatment (day 0)	During treatment (day 2)	After treatment (day 8)	*P*-value
Mean (SD) random plasma glucose (mg/dL)	83.3 (11.7)	77.9 (10.4)	85.3 (11.0)	< 0.001
Mean (SD) plasma insulin concentration (μIU/mL)	16.3 (6.0)	32.5 (11.6)	18.4 (3.8)	< 0.001

SD = Standard deviation.

Table 3 Mean of random plasma glucose and mean plasma insulin concentrations in different stages of pregnancy

Test	Duration of pregnancy (trimester)			*P*-value
	1st (*n* = 29)	2nd (*n* = 71)	3rd (*n*= 50)	
Mean (SD) random plasma glucose (mg/dL)	80.8 (11.6)	75.4 (9.8)	82.8 (10.8)	0.510
Mean (SD) plasma insulin concentration (μIU/mL)	13.8 (5.8)	30 (11.6)	15.9 (4.0)	0.20

SD = Standard deviation.

and chronic parasite infection in the placental blood and the associated cellular immune response may result in consumption of glucose and oxygen that would have gone to the fetus [16]. In our study we found that the women in the second trimester who suffer greatly from parasitaemia burden had significantly lower levels of plasma glucose and conversely higher plasma insulin levels compared to those in the first and third trimester which compares with Brabin's results[17]. Increased plasma insulin concentrations may play a role in lowering plasma glucose level, but there is also reduced tissue insulin sensitivity. Acute malaria should contribute to insulin resistance in pregnancy but, in severe cases with associated hepatic dysfunction, hypoglycaemia may ensue with serious consequences for mother and fetus [18].

In our patients, there was a significant negative correlation between the parasite count at admission and level of plasma glucose and haemoglobin; this may be due to the fact that the placenta is a favoured site for parasite sequestration and intra-erythrocytic development [18].

Monitoring of plasma glucose level is crucial in pregnant women with falciparum malaria on quinine therapy. There is a need to find an effective alternative medication that will reduce the incidence of hypoglycaemia among this high risk group.

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