

Therapeutic monitoring of Chloroquine in pregnant women with malaria

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Summary

Therapeutic monitoring of chloroquine was carried out in pregnant women with confirmed laboratory and clinical malaria after administration of 10mg/kg body weight of the drug at 0 and 24th hour and 5mg/kg body weight at the 48th hour. Venous blood was withdrawn at scheduled intervals. Plasma chloroquine level was determined using a highly sensitive and specific liquid chromatographic method. The time of peak plasma concentration, (t_{max}) after the first dose was found to be 3.5 hours while peak plasma concentrations, (Cp_{max}) were obtained at 2, 28, and 52 hours with values of 204.36, 343.51 and 257.04 ng/ml respectively. There was total parasitaemia clearance before the end of 96 hours in all the subjects.

Keywords: Chloroquine, Malaria, Parasitaemia, Pregnancy

Résumé

On avait effectué une surveillance continue thérapeutique chez des enceintes avec une confirmation laboratoire et le paludisme clinique après l'administration de 10mg/kg poids de corps de drogue à 0 et 24 heures et 5mg/kg poids de corps à 48 heures.

Le sang veineux a été retiré à intervalles réguliers. On avait noté le niveau du plasma chloroquine tout en utilisant une méthode d'un liquide chromatographique spécifique fortement sensible. Le temps de concentration maximum du plasma (t_{max}) après la première dose était noté d'être 3,5 heures tandis que trois concentrations maximum de plasma (Cp_{max}) ont été obtenues à 2, 28, et 52 heures avec des valeurs 204.36, 343.51 et 257,04 ng/ml respectivement. Il y avait une clairance totale de parasitisme avant la fin de 96 heures chez tous les patients.

Introduction

Pregnant women are known to be at greater risk of malaria infection than their nonpregnant counterparts living in the same endemic condition. It could result in hyperparasitaemia, anaemia, still birth and low birth weight infants. Falciparum malaria can be a fatal disease in pregnancy for both the pregnant woman and the foetus¹. In highly endemic areas such as tropical Africa, there is usually a high frequency of malaria infestation of the placenta with a consequent reduction in birth weight with neonatal and infant mortality being subsequently higher in such children^{2,3}. The sequestration of erythrocytes within the placental capillaries containing mature form of the parasite, Plasmodium falciparum, causes interferences with transplacental transfer of oxygen and nutrients leading to foetal distress^{4,5}. This has been established to be a major cause of low birth weight. Women in their first pregnancies (primigravids) are more available to malaria than multigravida^{7,8}. It is also not uncommon to find women whose peripheral blood are microscopically negative for malaria but placenta positive.⁹

In view of the danger which malaria poses during pregnancy, WHO recommends that antimalarial therapy be indicated during pregnancy in endemic areas. Chloroquine, in spite of advancing resistance from P. falciparum, remains the most popular and first drug of choice for the management of malaria in Nigeria¹⁰ and this is because of its ready availability, low toxicity and cheap cost.¹¹

Chloroquine is known to bind to tissues and subsequently manifest a large volume of distribution leading to low plasma concentrations, which may eventually expose the malaria parasite to sub-

therapeutic concentrations of the drugs. This study was therefore designed to monitor plasma levels of chloroquine during therapy in malarious pregnant women with the aim of establishing if the plasma level achieved is adequate for the treatment of malaria, and if there is a correlation between parasite clearance level during therapy.

Methods

Pregnant women with packed cell volume (PCV) of not less than 30% and with microscopically confirmed falciparum malaria were recruited into the study. Only four women who gave informed consent and met criteria were recruited into the study. They aged 30±2.25 years and had average weight of 60.25±8.88kg. Each of the women was given Chloroquine (Nivaquine[®]) tablets, May & Baker PLC, Nigeria) at the World Health Organisation (WHO) recommended dose of 10mg/kg body weight at the 0 and 24th hour and 5mg/kg body weight at the 48 hour. Five milliliters of venous blood sample was taken before and at the following intervals after drug administration: 1, 2, 4, 8, 24, 48, 52, 72, 96 and 168 hours. Plasma was separated and stored at -200C until analysed. Blood smears were also prepared to monitor parasite clearance.

Extraction analyses of chloroquine (CQ) and desethylchloroquine (DCQ) in the plasma samples were carried out using an HPLC method developed in our laboratory¹². Briefly, the drug was extracted by basifying 1 ml of the sample with 1ml of 2M NaOH and 4 ml of diethylether. Ten microlitre of 5ug/ml papaverine was used as internal standard. The organic layer was separated by centrifugation and the drug reconstituted into 100ul of 0.1N HCL. Ten microlitre aliquot was injected into the HPLC using mobile phase of 0.2M sodium dehydrogen orthophosphate methanol: acetonitrile (65:20:15) with 0.8ml perchloric acid.

Result

Table 1 shows the plasma concentration of CQ and DCQ after multiple dosage regimens. Three peak plasma concentration time, t_{max1} , t_{max2} and t_{max3} (2, 28 and 52h) hours, were obtained with corresponding peak plasma concentrations $Cp_{max 1, 2 \text{ and } 3}$ of 204.36 ± 134.74ng/ml, 343.51±135.31ng/ml and 257.04±74.73ng/ml respectively. The highest mean peak plasma concentration, Cp_{max1} was 345.51±135.35ng/ml at 28hour as can be seen in Figure 1

Table 1 Plasma concentration of chloroquine in pregnant women showing rate of parasitaemia clearance

Time (hours)	Plasma Concentration (ng/ml) CQ	DCQ	Asexual Parasitaemia Geometric mean
0	0.00±0.00	0.00 ± 0.00	3.0845
1	107.21 ± 90.17	3.42 ± 4.68	No Done
2	204.36 ± 134.74	19.95 ± 22.95	No Done
4	168.64 ± 39.23	52.59 ± 33.29	2.3470
8	108.08 ± 34.60	99.85 ± 144.90	2.5841
24	94.26 ± 34.94	69.10 ± 45.91	2.3522
28	343.51 ± 135.31	78.73 ± 40.71	2.2104
48	151.96 ± 68.84	83.39 ± 34.98	1.3129
52	257.04 ± 74.73	141.78 ± 9.48	1.0933
72	131.88 ± 29.09	125.26 ± 62.05	0.8094
96	67.53 ± 21.81	98.74 ± 61.20	0.000
168	53.07 ± 0.643	72.91 ± 13.21	0.000

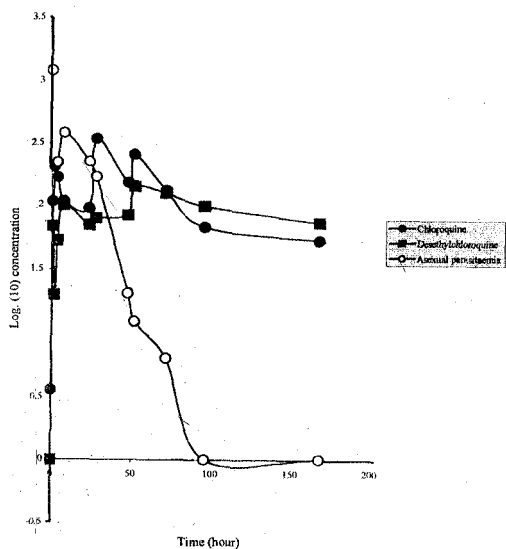


Fig. 1 Plasma level time curve after administration of chloroquine to pregnant women showing asexual parasitaemia count

The rate of parasite clearance for the subjects are shown in Figure 1. There was total parasite clearance before the 48th hour in two subjects. In the third subject, the parasites became cleared before the end of the 96th hour whilst in the fourth subject the parasite got cleared within 24 hours. Overall, between the 4th and 24th hour, there was a general increase in the parasitaemia level but by the end of the 96th hour, there was total clearance in all patients.

Discussion

We report the plasma concentration of CQ and its major metabolite DCQ, with respect to parasite clearance in pregnant women administered with multiple dosage of CQ. Chloroquine is known to exhibit a large apparent volume of distribution, and in a pregnant woman, it is expected that there are tissues available for distribution due to the presence of deeper tissues such as the foetus and amniotic sac, with a resultant low plasma level. The plasma concentration levels obtained in the present study were however not significantly different from those reported for non-pregnant individuals¹¹. It was observed that very high plasma levels were obtained at 28 and 52 hours (four hours each after the 2nd and 3rd doses of CQ) which exceeded the critical value of 250ng/ml above which adverse reactions such as postural hypotension, vomiting and dizziness have been reported to occur¹⁴. However, the only side effects experienced by the subjects in this study were fatigue and pruritus. DCQ appeared in the first sample collected after drug administration (1hr) and was observed throughout the period of sample collection. DCQ has been reported to have considered anti-malarial activities like CQ¹⁵.

The W. H.O. recommended dosage for chloroquine therapy could be said to be adequate since right from hour 0 to the 168th hour, the plasma level of the drug did not fall below 20ng/ml which is the minimum effective concentration against sensitive *P.falciparum*. The high concentration of CQ in plasma will ensure that the drug was effective in those subjects as the parasites were completely cleared in all by 96 hours. There was, however, fluctuation in parasitaemia level between the 4th and 24th hours which must have been due to release of parasites from tissues such as the liver, that invade new erythrocytes in the circulatory system.

This study has confirmed that the multiple dose of chloroquine recommended by W.H.O. is adequate to cause total parasite clearance within hours of initiation of therapy in CQ sensitive parasites infections in pregnant women.

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