Evaluation of pharmacokinetics of single-dose chloroquine in malnourished children with malaria- a comparative study with normally nourished children

Prashant P. Kadam, Nithya Jaideep Gogtay, Sunil Karande¹, V. Shah¹, Urmila M. Thatte

Abstract:
Objectives: Studies on antimalarial kinetics in children or adults who are undernourished or malnourished are both limited and have yielded conflicting results. The present study was carried out with the objectives of evaluating the pharmacokinetics of single dose chloroquine and its metabolite desethylchloroquine in children who were undernourished and compare them with children who were normally nourished.

Methods: Children of either gender between the ages of 5 and 12 years, smear positive for P. vivax malaria and classified either as well nourished or undernourished were included. Undernourishment was adjudged based on the Indian Academy of Pediatrics (IAP) classification of protein energy malnutrition [PEM] which in turn was based on Khadilkar’s growth charts. All participants received 10 mg/kg on the first day followed by 10 mg/kg on Day 2 and 5 mg/kg on Day 3 along with supportive treatment. Blood samples for the levels of chloroquine [CQ] and desethylchloroquine [DECQ] were collected at 0, 0.5, 1, 2, 4, 8, 12, 24, 48, 72 hours and 14 days after the first dose and levels assessed by High Performance Liquid Chromatography.

Results: A total of 12 children who were normally nourished and 13 who were undernourished were studied. Wide inter-individual variability was seen in the levels of both drug and metabolite in both groups of patients. However, the differences in Cmax, AUC 0-inf, Clearance, half life and Vd between the two groups were not significantly different.

Discussion: Our results indicate that dosage requirement is unlikely to be needed for chloroquine in undernourished children with uncomplicated P. vivax malaria.

Key words: Children, chloroquine, nourishment status, pharmacokinetics

Malaria is a major public health problem in India, with 1.1 million cases being reported in 2011 as per the World Malaria Report.[3] The report also estimates the prevalence of Plasmodium falciparum and Plasmodium vivax to be 51% and 49%, respectively, although there is significant within-country variation of the prevalence.[3] The national antimalarial policy of India (2007) recommends the use of chloroquine (CQ) plus primaquine for the treatment of P. vivax malaria which remains the predominant species in Mumbai.[2,3]

Similar to malaria, despite economic advances, malnourishment in India also remains a significant problem. The prevalence of children who are underweight in this country is twice that of Sub-Saharan Africa.[4] A report published by the Government of India in 2012 estimates that 48% of children under the age of 5 years are stunted, indicating that close to half of the country’s children are chronically malnourished.[5] Acute malnutrition as evidenced by wasting is seen in 19.8% of children in the same age group and 43% of children under the age of 5 years are underweight for their age.[5] As malaria and malnourishment coexist geographically, and

How to cite this article: Kadam PP, Gogtay NJ, Karande S, Shah V, Thatte UM. Evaluation of pharmacokinetics of single-dose chloroquine in malnourished children with malaria- a comparative study with normally nourished children. Indian J Pharmacol 2016;48:498-502.
both continue to remain major problems, an assessment of antimalarial kinetics in facing malnourishment would yield useful information that could guide drug dosing in children.

Studies on antimalarial kinetics in children or adults who are undernourished or malnourished are both limited and have yielded conflicting results.\textsuperscript{6‑8} Wharton and McChesney reported that CQ was metabolized or absorbed differently by the malnourished child as compared to what was observed on recovery.\textsuperscript{6} A study by Walker \textit{et al.} (\(n = 5\)) in Nigerian children showed evidence for decreased absorption of CQ in children with kwashiorkor.\textsuperscript{7} Tulpule and Krishnaswamy showed no differences in the kinetics of CQ in adult Indian males (\(n = 15\)) who were undernourished versus those who were normally nourished.\textsuperscript{8} In view of the lack of data from our country on CQ kinetics in children with the presence of malnourishment, the present study was carried out. The objectives were to assess levels of CQ and its metabolite desethylchloroquine (DECQ) in patients with smear-positive uncomplicated \textit{P. \textit{vivax}} malaria and to compare levels obtained in normally nourished and malnourished children.

Methods

Ethics
The study protocol was approved by the Institutional Ethics Committee and written informed consent was obtained from parents or guardians. In addition, children in the age range of 7–12 years gave their assent for the study. The study protocol is registered with the clinical trials registry of India (CTRI/2012/12/003188).

Setting
The study was carried out in a 2250-bedded tertiary referral center in Mumbai, India.

Study Design
It was an open-label study in consecutive patients who were smear positive for \textit{P. \textit{vivax}} malaria and consented to participate.

Inclusions
Children of either gender between the ages of 5 and 12 years, smear positive for \textit{P. \textit{vivax}} malaria, and classified either as well-nourished or undernourished were included in the study. For the latter, the Indian Academy of Pediatrics classification of protein-energy malnutrition (PEM) based on Khadilkar’s growth charts was used.\textsuperscript{9}

Exclusions
Those with a history of hypersensitivity to CQ, any clinically significant renal, hepatic, or cardiac disease, history of having received antimalarials in the past 1 month, and with severe or complicated malaria or history of HIV infection were excluded from the study.

Dose of Chloroquine (Ciron Drugs, India)
All participants received 10 mg/kg on the 1st day, followed by 10 mg/kg on day 2 and 5 mg/kg on day 3. They also received supportive management in the form of intravenous fluids, antipyretics and antiemetics.

Blood Collections for Pharmacokinetics
Blood samples for the levels of CQ and DECQ were collected at 0, 0.5, 1, 2, 4, 8, 12, 24, 48, 72 h and 14 days after the first dose. Plasma was immediately separated and stored at −20°C pending analysis.

Estimation of Levels of Chloroquine and Desethylchloroquine
The levels were estimated by reverse phase high-performance liquid chromatography for quantification of CQ and DECQ and were based on the method of Na-Bangchang \textit{et al.}\textsuperscript{[10]}

Pharmacokinetic Analysis
All analyses were done using Winnonlin software version 1.1 (Pharsight Corporation, USA). \(C_{\text{max}}\) and \(T_{\text{max}}\) were obtained directly from the data while area under the curve (AUC)\(_{\text{0-24}}\), AUC\(_{\text{0-48}}\), and Kel were calculated using the linear trapezoidal rule.

Statistical Analysis
Quantitative data were assessed for normality using the Kolmogorov–Smirnov test. Categorical data were expressed as percentages. Between-group comparisons for \(C_{\text{max}}\) and AUC were made using the Mann–Whitney U-test. All analyses were done using GraphPad Instat version 3.06 at 5% significance.

Results

Demographics Details
A total of forty consecutive children were screened from February 2012 to October 2013. Of these, 25 had satisfied the selection criteria and were recruited. The reasons for exclusions of 15 patients were as follows - eight patients were excluded based on a history of antimalarial intake, two for complicated malaria at diagnosis, two with low hemoglobin levels (state level), one with clinically systemic disease, one after analysis for having high-pretreatment CQ levels and one patient’s parent withdrew consent. A total of 12 children were normally nourished and 13 undernourished. Among the latter, 5 had Grade 1, 6 Grade 2, and 2 Grade 3 PEM. There was no child with Grade 4 PEM. There were 12 males and 13 females in all and there was no significant between-group difference [Table 1]. All participants responded to the treatment and were disease-free at day 28 follow-up and had no major adverse events to the antimalarials or concomitant medications.

Blood Levels of the Drug and Metabolite in the Two Groups

Chloroquine

\textbf{Normally nourished children}

The mean peak plasma concentration of CQ (\(C_{\text{max}}\)) was \(331.13 \pm 165.21\) ng/ml which was attained at (\(T_{\text{max}}\)) 4.92 h. The AUC\(_{\text{0-24}}\) was 3266.17 ng.h/ml and clearance (Cl) was 46.8 L/h. Half-life (\(t_{\frac{1}{2}}\)) and volume of distribution (\(V_d\)) were 29.4 h and 1045.7 L, respectively.

\textbf{Undernourished children}

The mean peak plasma concentration of CQ (\(C_{\text{max}}\)) was \(325.7 \pm 127.3\) ng/ml which was attained at (\(T_{\text{max}}\)) 9.1 h. The AUC\(_{\text{0-24}}\) was 4997.1 ng.h/ml. Cl was 25.1 L/h, half-life (\(t_{\frac{1}{2}}\)) was 30.6, and \(V_d\) was 701.8 L. The differences were not statistically significant (\(P > 0.05\)).

Desethylchloroquine

\textbf{Normally nourished children}

The peak plasma concentration of DECQ (\(C_{\text{max}}\)) was \(105.65 \pm 73.33\) ng/ml which was attained at (\(T_{\text{max}}\)) 7.58 h.
The AUC_{max} was 1225.64 ng.h/ml. Cl was 238.5 L/h and half-life (t_{1/2}) was 15.58 h. V_d was 2961 L.

Undernourished children
The peak plasma concentration of DECQ (C_{max}) was 107.7 ng/ml ± 61.1 which was attained at (T_{max}) 11.7 h. The AUC_{max} was 1598.9 ng.h/ml. Cl was 122.62 L/h and half-life (t_{1/2}) was 27.9 h. V_d was 1909 L. The difference was not significantly different (P > 0.05). Details of pharmacokinetic values are given in Table 2 and depicted graphically in Figures 1 and 2.

Discussion
The present study is one of the few studies worldwide that has evaluated the pharmacokinetics of CQ and its metabolite in both normally nourished and undernourished children with P. vivax malaria. A wide inter-individual variability was seen in the levels of both drug and metabolite in both groups of patients. The difference in pharmacokinetic values between normally nourished and undernourished children was not significantly different.

Optimizing drug dosing requires characterization of pharmacokinetic and pharmacokinetic properties in the intended target population. There are four main determinants of therapeutic response – antimalarial pharmacokinetics, parasite susceptibility, host defense, and parasite burden. Of these, antimalarial pharmacokinetics is affected by age and nourishment status as is host defense. Table 3 compares the results seen by us with similar studies in adults and children in literature. The findings of CQ and metabolite levels in this study show an overlap with values obtained by Adelusi et al. The findings are also similar to the study by Tulipule and Krishnaswamy in eight adult male patients who showed that barring Cl, undernourished male adults do not appear to handle CQ differently relative to normally nourished male adults [Table 3].

Walker et al., however, reported extremely low values of CQ and its metabolite in children with kwashiorkor [Table 3]. One reason for the difference between the present study and the study done by Walker et al. could be that the latter evaluated kinetics in children with P. falciparum infection and the children studied also had a more severe grade of PEM than children in the present study. Conflicting results in studies can be put in perspective given that PEM is not a single disease entity, but rather a disease spectrum with a wide range of pathophysiological changes. The presence of edema in kwashiorkor is likely to explain the changes in pharmacokinetic parameters as seen by Walker et al. In the present study, 11/13
Table 3: Comparison of present study with literature

| Data presentation | Median (Range) | Mean (SD) | Median (Range) | Median (Range) | Mean (SD) | Mean (SD) |
|-------------------|----------------|-----------|----------------|----------------|-----------|-----------|
| Cmax (ng/ml)      | 342.84 (92.73-565.55) | 81.12 (28.60-233.74) | 101 (69-331) | 24 (9-48) | 4 (3-13) | ND ND |
| Tmax (h)          | 4 (1-24) | 12 (1-24) | 2.01±0.31 | 1-8 * | 2-12* | 5 (0.5-8) | 8 (0.5-24) | 3 (2-9) | 8 (1-9) | ND ND |
| t½ (h)            | 17.06 (6.31-181.03) | 11.97 (4.03-133.83) | 135±9 | ND ND | ND ND | 202 | ND ND | 168 (108-285) | 47.3±7.03 | 45.4±8.4 |
| AUC (ng.h/ml)     | 3777.85 (860.015-7365.64) | 1325.115 (222.153-3594.565) | 9250 | ND ND | ND ND | 2320 | ND ND | 23660± | 19010± | ND ND |
| Cl (L/h)          | 20.2 (5.8-171.47) | 94.3 (7.39-730) | ND ND | ND ND | ND ND | ND ND | ND ND | ND ND | ND ND |
| Vd (L/kg)         | 640 (162-2239) | 2290 (607-8169) | ND ND | ND ND | ND ND | ND ND | ND ND | ND ND | ND ND |

Cmax- Concentration maximum, Tmax- Time to concentration maximum, t½- Elimination half life, AUC- Area under the curve, Cl- Clearance, Vd- Volume of distribution, CQ- Chloroquine, D-CQ- Desethyl chloroquine, *- value expressed in range, ND- data not given
children with PEM had relatively milder grades of PEM which could potentially explain the lack of difference compared to the normally nourished children seen by us.

A recent systematic review has looked at pharmacokinetic studies in children with PEM.\textsuperscript{14} Only two antimalarials quinine (oral and intramuscular) and CQ (oral) have been studied in children with PEM, with quinine being the subject of more studies. The review noted that the vast majority of these studies were conducted in the 1970s and 1980s, and despite the problem of PEM continuing in Asia and Africa, there has been significant drop in the number of pharmacokinetic studies in the 2000s in children with PEM. The present study thus adds to the limited body of evidence in this area. Our study does have its limitations. Only single dose kinetics was studied and no children under the age of 5 years were studied. In addition, the number of undernourished children in each PEM category was few. The kinetics of the drug in severe \textit{P. vivax} malaria was also not looked at. Despite these limitations, our results indicate that dosage requirement is unlikely to be required for chloroquine in undernourished children with uncomplicated vivax malaria.

**Financial Support and Sponsorship**

Nil.

**Conflicts of Interest**

There are no conflicts of interest.