

BRIEF COMMUNICATION

RELATIONSHIP BETWEEN PLASMA AND RED BLOOD CELL CONCENTRATIONS OF QUININE IN BRAZILIAN CHILDREN WITH UNCOMPLICATED *Plasmodium falciparum* MALARIA ON ORAL THERAPY

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SUMMARY

We determined the relationship between plasma and red blood cell concentrations of quinine in children with uncomplicated falciparum malaria from an endemic area of Amazonian region. Quinine was determined by high performance liquid chromatography with ultraviolet detection. In the steady state the ratio between plasma and red blood cell quinine concentration was 1.89 ± 1.25 ranging from 1.05 to 2.34. This result demonstrated that quinine do not concentrate in red blood cell of Brazilian children and characterize the absence of interracial difference in this relationship.

KEYWORDS: Quinine; Quinine levels; Malaria, Chromatography.

In the last decade there has been an effort at monitoring the blood levels of antimalarials in patients with falciparum malaria, an important tool in the evaluation of efficacy and effectiveness of antimalarial drugs^{4,5}. The response of the developing malaria parasite to antimalarials is largely determined by the concentration of drug accessible to the parasite within the red cell and its sensitivity to that drug⁴. The level of antimalarial drug in the plasma is proportional to the concentration within the parasitized red cell and it is determined by several independent variables as the drug formulation, age, race, immunity, the fraction of drug absorbed, the apparent volume of distribution and the clearance^{5,6,7}.

There is a lack of knowledge about the relationship between plasma and red blood cell concentrations of quinine in Brazilian children with uncomplicated falciparum malaria in which the standard treatment with oral quinine was used¹. This is essential for the success of the treatment once a marked interpersonal and interracial difference in quinine disposition have been demonstrated^{3,4,5}. Therefore, this work was done to elucidate this relationship in an endemic area of Amazon region, in a prospective clinical treatment trial.

This study was conducted from January 2006 to January 2007, with 10 male children with signs and symptoms of uncomplicated *P. falciparum* malaria. Their characteristics were as follows (means \pm SDs): age, 9.2 ± 3.1 years (age range; five to 13 years); body weight, 21.2 ± 4.1 Kg, erythrocyte count, $3.21 \pm 0.52 \times 10^6/\mu\text{L}$; white blood count, $11,300 \pm 4700/\mu\text{L}$. The median initial parasitemia was $2100/\mu\text{L}$ (range;

900 to $4500/\mu\text{L}$). The patients were admitted to the public Hospital of Cachoeira do Piriá, Brazil. Informed consent was obtained from their parents. Children with severe or mixed malaria were excluded. Patients who had taken any antimalarial drugs within the previous 48 hours were also excluded. This study was approved by the ethics committee of the Tropical Medicine Center of Para Federal University.

After clinical assessment and confirmation by microscopic examination of blood smears, all patients were treated with 3-day oral treatment regimen of quinine base (487.5 mg), followed by doxycycline hydrochloride for five days and primaquine phosphate in the last day. Reappearance of infection was assessed for at least 28 days, by clinical evaluation and microscopic examination of blood smears^{1,8}.

Venous blood samples were taken for quinine level determination before and on the third day of treatment. All blood samples were taken immediately before the next dose, i.e were measured in different levels. The samples (3 mL) were collected in heparinized tubes and immediately centrifuged at 1500g for 15 minutes. The plasma and red blood cell samples were stored at -20°C until analysis².

Quinine was analyzed by high performance liquid chromatography as described previously². The analytical procedure validated in our laboratory demonstrated that within-day and day-to-day coefficients of variation were 6.7 and 8.1%, respectively. Mean extraction recovery of quinine was 95%. The stability of blank plasma spiked with quinine was

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60 days in the conditions described above. Primaquine, doxycycline, mefloquine, amodiaquine, acetaminophen and chloroquine do not interfere in the detection of quinine².

All patients had been cured following the treatment and no recrudescence was observed after 28 days. The mean time for parasite clearance was 50.4 hours, with interval of 24 to 92 hours.

All samples collected before starting the treatment were negative for quinine. The mean quinine concentration in children plasma samples in the steady state was 0.723 ± 0.6 µg/mL ranging from 0.219 to 1.59 µg/mL. In red blood cell was 0.53 ± 0.88 µg/mL, ranging from 0.19 to 0.948 µg/mL.

The ratio between plasma and red blood cell quinine concentrations in steady state was 1.89 ± 1.25 ranging from 1.05 to 2.34. This result demonstrated that quinine do not concentrate in red blood cell of Brazilian children and demonstrates an absence of interracial differences in agreement with previous studies that show the ratio between the plasma and red blood cell quinine concentrations varied from 0.2 to 2.3. The variability in this relation could be of therapeutic relevance, once the concentration of quinine in plasma and red blood cell must remain above levels which inhibit parasite multiplication throughout the course of treatment to eradicate the infection because there is a higher probability that a resistant strain will emerge if the drug is present at a sub therapeutic concentration^{3,4,7,8}.

RESUMO

Relação entre as concentrações plasmáticas e eritrocitárias de quinina em crianças com malária por *Plasmodium falciparum* não complicada em terapia via oral

Neste estudo foi determinada a relação entre as concentrações plasmáticas e eritrocitárias de quinina em crianças com malária falciparum não complicada, oriundas de área endêmica da Região Amazônica. A quinina foi determinada por cromatografia líquida de alta eficiência. No estado de equilíbrio, a relação foi $1,89 \pm 1,25$ variando de 1,05 a 2,34. Estes resultados demonstraram que a quinina não se concentra nos eritrócitos das crianças e caracterizaram a ausência de diferença racial nesta relação.

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