Quinine disposition in globally malnourished children with cerebral malaria

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Quinine disposition in globally malnourished children with cerebral malaria

Background: **Both malnutrition and malaria affect drug disposition and are frequent among children in the tropics. We assessed their respective influence on quinine distribution.**

Methods: **Forty children were divided into 4 groups: children with normal nutritional status without (group 1) or with (group 2) cerebral malaria, and malnourished children without (group 3) or with (group 4) cerebral malaria. All children received an infusion of 8 mg/kg of a combination solution of cinchona alkaloids that contained 96.1% quinine, 2.5% quinidine, 0.68% cinchonine, and 0.67% cinchonidine (corresponding to 4.7 mg/kg quinine base). The children with malaria then received repeated infusions every 8 hours for 3 days. Pharmacokinetic profiles of plasma and erythrocyte quinine were determined during the first 8 hours, together with quinine protein binding. Additional measurements of plasma quinine concentrations were used to simulate quinine concentrations profiles in children with malaria with and without malnutrition. Clinical recovery and parasitemia clearance times were determined in the children with malaria.**

Results: **Compared with control children, malaria and malnutrition increased plasma concentrations of quinine and reduced both the volume of distribution and the total plasma clearance. Simultaneously, α_1-glycoprotein plasma concentrations and protein-bound fraction of the drug were increased. Erythrocyte quinine concentrations correlated strongly with free plasma quinine but not with the extent of parasitemia. Similar effective and nontoxic quinine concentration profiles were obtained in malaria with and without malnutrition.**

Conclusions: **Severe global malnutrition and cerebral malaria have a similar effect on quinine pharmacokinetics in children. Moderate malnutrition does not potentiate cerebral malaria-mediated modifications of quinine disposition. These results suggest that current parenteral quinine regimens can be used, unmodified, to treat children with both malaria and malnutrition. (Clin Pharmacol Ther 1999;65:500-10.)**

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Falciparum malaria remains a major cause of morbidity and mortality in Africa. More than 90% of malaria-related mortality worldwide involves young children. Malnutrition is the other main cause of health impairment and growth retardation in children. Malaria and malnutrition are sometimes associated in African children, but the impact of this combination on antimalarial treatment is unknown. Because of the global spread of chloroquine resistance, quinine has become the drug of choice for the treatment of *falciparum* malaria. Quinine is given orally for uncomplicated malaria and by intravenous infusion for severe complicated malaria. Quinine has a narrow therapeutic window between effective concentrations and those with cardiovascular, ocular, or auditory toxicities. Quinine is highly bound to plasma proteins, especially the acute-phase protein α_1-acid glycoprotein. Systemic clearance occurs predominantly by hepatic biotransformation into more polar metabolites, and the remaining drug is eliminated unchanged by the kidney. During malaria, there is a gradual contraction in the volume of distribution

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and a reduction in systemic clearance that are proportional to the severity of the disease. The resulting increase in total plasma quinine levels is not associated with toxic side effects because the free fraction of quinine is reduced by an increase in plasma concentrations of α_1-acid glycoprotein, itself proportional to the severity of malaria.[1]

In Africa, children younger than 5 years are most severely affected by protein-energy malnutrition. Several clinical forms of malnutrition have been described, ranging from frank cases of kwashiorkor caused by protein deficiency and marasmus caused by energy deficiency to mild and moderate forms that translate into various degrees of growth retardation. Nutritional status has been shown to influence susceptibility to severe *falciparum* malaria and to alter drug metabolism, pharmacokinetics, pharmacology, and toxicity.[2] In Africa, parenteral quinine is frequently administered to children with both malarial and various states of malnutrition. The relation between nutritional status and quinine disposition was first investigated by Salako et al,[3] who observed a lower rate of absorption and lower clearance of oral quinine in uninfected children with Kwashiorkor than in healthy children. In contrast, after intramuscular injection of the cinchona alkaloid association, Quinimax to children with global malnutrition, an increase in quinine metabolism has been described, together with faster clearance and a shorter half-life than in children with normal nutritional status. The resulting low plasma concentrations in such malnourished children led the authors to recommend a reduction in the interval between Quinimax injections, but parasitologic status could not be assessed in that study.[4]

The possible interactions of malaria and malnutrition with quinine pharmacokinetics led us to evaluate the effects of global malnutrition on quinine disposition in children with cerebral *falciparum* malaria.

METHODS

Patient characteristics. This open study was performed in the Pediatric unit of Niamey hospital, Niger, between July and December 1996, a permanent malaria transmission period. After the reasons for giving quinine to nonparasitemic children were explained, full informed consent was obtained from the parents or the guardians. The protocol was approved by the ethics committee of the Niger Health Ministry. Forty children between the ages of 24 and 72 months were recruited for the study on the basis of their nutritional status and infection caused by *Plasmodium falciparum*. Nutritional status was assessed with 3 anthropometric indicators: weight-for-age (W//A), height-for-age (H//A), and weight-for-height (W//H). The anthropometric data were calculated for each child by use of the anthropometry software package developed by the US Centers for Disease Control.[5] The standard deviation scores (Z-scores), percentiles, and percent-of-median values for each child were calculated from the median of the reference population. For inclusion in malnutrition groups, the cutoff point was a Z-score of –2 (ie, 2 standard deviations below the reference mean) of at least 2 of these anthropometric indices.[6,7] All children with clinical manifestations of Kwashiorkor were excluded.

Malarial inclusion criteria were a combination of coma from which the child could not be roused, as assessed with the Glasgow coma scale adapted to children by Molyneux et al[8] and defined by the World Health Organization,[9] and more than 1000 *P. falciparum* parasites per microliter of peripheral blood. Exclusion criteria were other causes of coma or infection, circulatory collapse or shock (systolic blood pressure <50 mm Hg), severe anemia (hematocrit <15%), and renal impairment. Children who had been treated with antimalarial drugs <1 week before the study were excluded. Absence of blood quinine was confirmed retrospectively on blood samples obtained at inclusion.

Four groups of children were formed. Group 1 consisted of 10 well-nourished children (Z-score for anthropometric indices more than -2σ) with negative blood films for plasmodia. All of these children were apyretic and were admitted to hospital for minor surgery (hernia or benign fracture). Group 2 consisted of 10 well-nourished children (Z-score for anthropometric indices more than -2σ) who met the inclusion criteria for cerebral *falciparum* malaria. Group 3 included 10 severely malnourished children (Z-score less than -2σ for at least 2 anthropometric indices) with negative blood films for plasmodia and no clinical signs of systemic infection. These children were admitted to the hospital for nutritional rehabilitation and were studied in the acute phase of malnutrition. Group 4 consisted of 10 malnourished children (Z-score less than -2σ for at least 2 anthropometric indices) with cerebral *falciparum* malaria.

Study design. After inclusion, all the children received 8 mg/kg Quinimax as a slow infusion in 5% glucose (20 mL/kg) over 4 hours through an electric syringe. Quinimax solution is a combination of cinchona alkaloids that contains 96.1% quinine, 2.5% quinidine, 0.68% cinchonine, and 0.67% cinchonidine; 8 mg/kg of Quinimax corresponds to 4.7 mg/kg quinine base (Quinimax, Sanofi, Gentilly, France). A single infusion of Quinimax was given to uninfected children (groups 1 and 3), and infusions were repeated every 8 hours for children with cerebral malaria (groups

Table I. Anthropometric characteristics of control children (group 1), children with malaria (group 2), malnourished children (group 3), and malnourished children with malaria (group 4) at admission to the study

	Group 1	*Group 2*	*Group 3*	*Group 4*
Sex				
Male	9	3	4	4
Female	1	7	6	6
Age (mo)	44.8 ± 20.9	36.5 ± 10.1	34.2 ± 7.8	41.8 ± 9.0
Height (cm)	100.0 ± 15.4	92.6 ± 6.6	82.6 ± 8.5*†	92.9 ± 8.8‡
Weight (kg)	15.4 ± 5.4	13.2 ± 1.8	7.8 ± 1.4*†	11.5 ± 2.0*‡
Height for age (Z-scores)	–0.84 ± 1.13	–0.47 ± 1.32	–2.85 ± 1.76*†	–1.34 ± 1.62
Weight for age (Z-scores)	–1.14 ± 1.27	–0.84 ± 0.84	–4.29 ± 0.88*†	–2.34 ± 0.86*†‡
Weight for height (Z-scores)	–0.75 ± 0.91	–0.56 ± 0.57	–3.39 ± 0.72*†	–2.07 ± 0.56*†‡

Data are mean values ± SD.
*$P < .05$ versus group 1.
†$P < .05$ versus group 2.
‡$P < .05$ versus group 3.

2 and 4). Once the child was able to swallow, 10 mg/kg oral quinine was given to complete a 5-day course. Symptomatic treatment of malaria (convulsions, hyperthermia, and hypoglycemia) was started immediately after the first examination. Nutritional rehabilitation was started immediately (group 3) or when children were able to swallow (group 4).

At inclusion and at each parasitemia determination, physical signs, consciousness, and rectal temperature were recorded by the physician. A heparinized Teflon catheter was inserted in a superficial arm vein. Blood was withdrawn for measurements of hematologic and biochemical parameters, parasitemia, and quinine concentrations.

Bioanalytical methods. Before treatment, full blood cell counts, hematocrit, and hemoglobin were determined (Coulter counter). Total and fractionated (serum albumin and globulin) proteins were assayed by the Biuret reaction and electrophoresis, respectively. Specific proteins were measured by immunodiffusion (M-Partigen for prealbumin and NOR-Partigen for α_1-acid glycoprotein and α_1-antitrypsin, Dade Behring, Paris, France).

For quinine analysis, blood samples (500 μL) were collected into tubes that contained ethylenediaminetetraacetic acid before and 2, 4, 6, and 8 hours after the start of Quinimax infusion. In the children with malaria (groups 2 and 4), additional blood samples were drawn 12, 16, and 24 hours after drug administration. After centrifugation at 1500*g* for 15 minutes, the upper two-thirds of the plasma and the lower two-thirds of erythrocytes were separated and stored at –20°C until analysis. In addition, plasma (1.0 mL) was saved for measurement of total and free quinine 4 and 8 hours after drug administration. Free quinine concentrations were measured using the Amicon MPS-1 micropartition system with YMT membranes. Because of the supraphysiologic pH of stored plasma, pH was adjusted to 7.40 by overnight exposure to 95% air/5% carbon dioxide at 37°C. A protein-free ultrafiltrate was then obtained by centrifugation at 2000*g* for 20 minutes at room temperature.[10] Binding was recorded as the ratio of bound quinine to the total quinine concentration. Quinine concentrations were determined by HPLC with fluorometric detection.[11] Calibration curves were linear in the range from 0.01 to 10 mg/L. At quinine concentrations of 1 and 10 mg/L, extraction recoveries from plasma were 87% and 91%, respectively, and extraction recoveries from erythrocytes were 78% and 73%, respectively. Coefficients of variation were 5.1% and 6.2% (within day) and 6.3% and 7.1% (day to day) in plasma and 6.7% and 8.3% (within day) and 8.4% and 9.3% (day to day) in erythrocytes at concentrations of 1 and 10 mg/L, respectively.

In children with malaria (groups 2 and 4), densities of parasites were assessed by counting asexual parasites in thick and thin blood films stained with May Grünwald Giemsa before, at 2, 4, 6, 12, 24, 40, and 48 hours, and then daily until 2 consecutive blood smears were negative.

Pharmacokinetics and statistical analysis. Plasma quinine concentrations were fitted with an iterative least-squares curve-fitting program (APIS).[12] The best fit of concentration–time data was obtained with use of a 1-compartment model. Peak concentrations were observed values. The area under the plasma concentration–time curve [AUC(0-8)] was estimated using the trapezoidal rule for the first 8 hours. The elimination half-life values, apparent volume of distribution, and total plasma clearance were calculated with standard procedures.[13]

Results are presented as mean values ± SD, except for parasitemia, which is given as geometric means with

Table II. Biochemical and hematologic characteristics of control children (group 1), children with malaria (group 2), malnourished children (group 3), and malnourished children with malaria (group 4) at admission to the study

	Group 1	*Group 2*	*Group 3*	*Group 4*
Proteinemia (g/L)	75.0 ± 8.9	73.9 ± 8.8	66.8 ± 9.9	69.0 ± 6.1
Albuminemia (g/L)	35.7 ± 2.4	35.5 ± 3.9	30.5 ± 5.2*†	31.8 ± 2.2*
Prealbuminemia (g/L)	0.15 ± 0.05	0.10 ± 0.04	0.07 ± 0.03*	0.06 ± 0.02*
α_1-Antitrypsin (g/L)	2.22 ± 0.35	3.81 ± 0.69*	2.72 ± 0.92*†	4.07 ± 0.79*‡
α_1-Glycoprotein (g/L)	1.10 ± 0.29	1.78 ± 0.38*	2.00 ± 0.57*	1.72 ± 0.27*
α_1-Globulin (g/L)	2.76 ± 0.72	4.51 ± 0.80*	3.43 ± 0.69†	5.04 ± 0.53*‡
Erythrocytes (10^6 per μL blood)	4.6 ± 0.6	3.2 ± 0.8*	4.9 ± 1.3†	3.4 ± 0.8*‡
Hemoglobin (g/100 mL)	11.9 ± 1.2	8.5 ± 2.0*	11.4 ± 3.1†	8.9 ± 1.9*‡
Hematocrit (%)	37.4 ± 1.1	25.8 ± 5.9*	35.2 ± 10.5†	27.8 ± 6.2*‡
White blood cells (per μL blood)	7,521 ± 1,023	8,667 ± 1,928	12,880 ± 13,600	12,614 ± 5,144
Parasitemia (per μL blood)	ND	120,201 (36,700-466,200)	ND	132,276 (18,350-362,600)

Data are mean values ± SD (parasitemia is expressed as geometric mean and range).
*P < .05 versus group 1.
†P < .05 versus group 2.
‡P < .05 versus group 3.
ND, Not detectable.

Table III. Distribution ratios of quinine in whole blood in the control children (group 1), children with malaria (group 2), malnourished children (group 3), and malnourished children with malaria (group 4)

	Group 1	*Group 2*	*Group 3*	*Group 4*
Erythrocyte to total plasma quinine concentrations				
H4	0.5 ± 0.2	0.3 ± 0.1*	0.3 ± 0.1*	0.2 ± 0.1*
H8	0.6 ± 0.2	0.2 ± 0.1*	0.3 ± 0.1*	0.2 ± 0.1*
Erythrocyte to free plasma quinine concentrations				
H4	4.3 ± 0.8	4.2 ± 1.3	5.1 ± 1.4	6.0 ± 1.2
H8	4.9 ± 2.4	5.1 ± 1.4	5.9 ± 1.9	5.7 ± 1.4
Protein-bound plasma to free quinine concentrations				
H4	9.5 ± 5.0	13.2 ± 2.7*	23.0 ± 13.6*	21.6 ± 10.2*
H8	9.2 ± 4.9	25.6 ± 13.4*	18.4 ± 11.1*	29.0 ± 15.7*

Data are mean values ± SD.
The ratios were calculated at 4 and 8 hours after an intravenous infusion of 8 mg/kg Quinimax.
*P < .05 versus group 1.

ranges in parentheses, and in figures in which the points are plotted as mean values ± SEM. Homogeneity of variance was evaluated with the Bartlett test, and normally distributed data were analyzed with ANOVA and the Student *t* test with the Bonferroni correction. The Kruskal-Wallis test and the Dunn test were used for non-normally distributed data. The Spearman correlation coefficient was used to evaluate the relationship between variables. A *P* value below .05 was considered to be statistically significant.

RESULTS

Characteristics of the children at admission. The main anthropometric characteristics of the children in the 4 groups are given in Table I. All the children were comparable in age. No difference was observed between the control subjects and the children with malaria. The heights and weights of the malnourished children (group 3) were lower than those of the other 3 groups. Only the weights of the children with both malaria and malnutrition (group 4) were lower than those of the control children. The standard deviation scores for groups 1 and 2 were above the cutoff point of -2σ calculated from the median of the reference population. The Z-score values for W//H, W//A, and H//A of children in group 3 were lower than -2σ and lower than those of children in groups 1 and 2. Children in group 4 had Z-score values below the cutoff point of -2σ for only W//A and W//H. These latter 2 parameters were lower than those in groups 1 and 2 but remained higher than in group 3. Similar results were obtained with percentiles and percent-of-median values for these anthropometric indicators (data not shown).

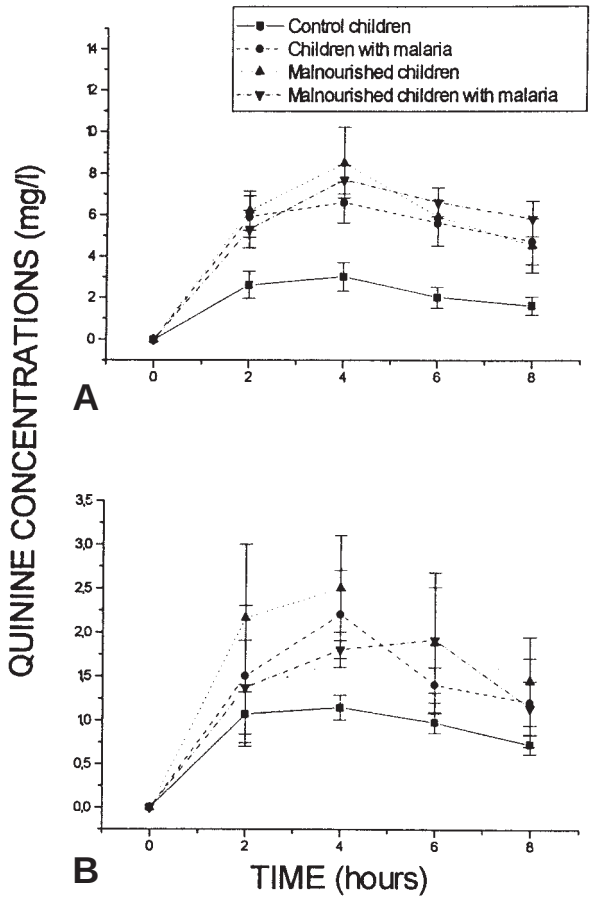

Figure 1. Mean ± SD plasma **(A)** and erythrocytes **(B)** quinine concentration versus time profiles in control children (group 1), children with malaria (group 2), malnourished children (group 3), and malnourished children with malaria (group 4) after a 4-hour intravenous infusion of 8 mg/kg Quinimax.

Falciparum malaria and malnutrition altered both biochemical and hematologic parameters (Table II). Total proteinemia was similar in the 4 groups, but both albuminemia and prealbuminemia were lower in the malnourished children (groups 3 and 4) than in the control group. The prealbumin and albumin plasma concentrations correlated with Z-scores for W//H (n = 40, r = 0.420, P = .008, and n = 40, r = 0.338, P = .01, respectively) but not with Z-scores for W//A and H//A. In the children with malaria (groups 2 and 4), levels of inflammatory proteins (α_1-acid glycoprotein, α_1-antitrypsin, and total α_1-globulin) were higher than those in the control children (group 1). In the malnourished children (group 3), α_1-acid glycoprotein levels were similar to those in the malaria groups, but α_1-antitrypsin and α_1-globulin concentrations were lower than in the malaria groups (groups 2 and 3) and higher than those in the control subjects (group 1). The geometric mean of parasitemia values were similar in the 2 groups of children with malaria (groups 2 and 4), and all the children in the other 2 groups had negative blood smears. The hematologic parameters were similar in groups 1 and 3, but the 2 groups of children with malaria had a similar decrease in erythrocyte numbers, hemoglobin, and hematocrit. Because of the broad variability in white blood cells counts, no difference was observed among the 4 groups.

Rectal temperature did not differ between the 2 groups of children with malaria (39.0°C ± 1.1°C and 39.0°C ± 0.8°C in groups 2 and 4, respectively) but was higher than in the control group (37.2°C ± 0.4°C) and group 3 (37.8°C ± 1.2°C). The frequency of distribution of the modified Glasgow coma score was similar in groups 2 and 4: score 1 (1 and 2 children, respectively), score 2 (8 and 5 children, respectively), and score 3 (1 and 3 children, respectively).

Quinine blood distribution. Mean plasma and erythrocyte quinine concentration–time profiles in the 4 groups are shown in Figures 1, *A* and *B*, respectively. At all the kinetic time points, quinine plasma concentrations were similar in groups 2, 3, and 4, and higher than in the control group. Erythrocyte quinine concentrations were similar in groups 2, 3 and 4 at each time point, but tended to be higher at 2 and 8 hours and were significantly higher at 4 and 6 hours than the concentrations in the control group. The erythrocyte-to-total plasma quinine concentration ratio in the control group was higher than the ratio in groups 2, 3, and 4 at 2 hours (0.6 ± 0.6 versus 0.2 ± 0.1, 0.3 ± 0.1, and 0.2 ± 0.03, respectively), 4 hours (0.5 ± 0.2 versus 0.3 ± 0.1, 0.3 ± 0.1, and 0.2 ± 0.1, respectively), 6 hours (0.6 ± 0.1 versus 0.25 ± 0.1, 0.3 ± 0.06, and 0.25 ± 0.05, respectively), and 8 hours (0.6 ± 0.2 versus 0.2 ± 0.1, 0.3 ± 0.1, and 0.2 ± 0.1, respectively). In each group the plasma protein binding of quinine was similar at 4 and 8 hours, but values in the control group (87.5% ± 3.8% and 88.9% ± 5.8%) were lower than those in children with cerebral malaria (92.4% ± 1.4% and 96.4% ± 1.3%), malnourished children (94.6% ± 2.7% and 94.5% ± 3.9%), and children with cerebral malaria and malnutrition (94.8% ± 3.5% and 95.8% ± 2.3%) at 4 and 8 hours, respectively.

To evaluate quinine distribution in whole-blood fractions, distribution ratios were calculated for each group at 4 and 8 hours (Table III). Compared with the control group, the erythrocyte-to-total plasma quinine concentrations ratios were lower in groups 2, 3, and 4. The ery-

Table IV. Pharmacokinetic parameters of total plasma quinine in control children (group 1), children with malaria (group 2), malnourished children (group 3), and malnourished children with malaria (group 4) after a 4-hour intravenous infusion of 8 mg/kg Quinimax

	Group 1	*Group 2*	*Group 3*	*Group 4*
C_{max} (mg/L)	3.0 ± 2.1	6.6 ± 3.0*	8.5 ± 4.7*	7.7 ± 2.0*
Total plasma clearance (mL/min/kg)	4.0 ± 2.1	1.1 ± 0.7*	1.7 ± 1.5*	0.8 ± 0.7*
Volume of distribution (L/kg)	1.63 ± 1.05	0.53 ± 0.10*	0.56 ± 0.28*	0.58 ± 0.22*
$t_{½}$ (h)	5.1 ± 2.6	8.9 ± 7.6*	7.2 ± 5.9*	15.6 ± 12.4*
AUC(0-8) (mg · h/L)	16.7 ± 12.1	40.9 ± 20.8*	43.5 ± 23.9*	43.0 ± 15.9*

Data are mean values ± SD.
C_{max}, Peak concentrations; $t_{½}$, elimination half-life; AUC(0-8), area under the plasma concentration–time curve for the first 8 hours.
*P < .05 versus group 1.

throcyte-to-free plasma quinine concentrations ratios were similar in the 4 groups, but the protein bound-to-free plasma quinine concentrations ratios were higher in groups 2, 3, and 4 than in control group. A correlation was observed between erythrocyte and free quinine concentrations (n = 78, r = 0.934, P < .001). Erythrocyte uptake of quinine, expressed as the erythrocyte-to-total plasma quinine concentration ratio, correlated negatively with α_1-glycoprotein plasma concentrations (n = 79, r = –0.570, P < .001) and the percentage of quinine protein binding (n = 78, r = –0.819, P < .001). No significant relationship was observed between intraerythrocyte quinine concentrations and parasitemia.

Quinine pharmacokinetics. Table IV compares the pharmacokinetic variables of quinine in plasma among the 4 groups of children. No difference in kinetic variables was observed among groups 2, 3, and 4. Compared with control values, the observed peak concentrations of plasma quinine, the AUC(0-8) and the half-life value estimated over 8 hours were higher, and both total plasma quinine clearance and volume of distribution were similarly smaller in malaria (group 2), malnutrition (group 3), and malaria-malnutrition (group 4). None of the anthropometric parameters correlated with the pharmacokinetic variables. Prealbumin plasma concentrations correlated with total plasma clearance (n = 39, r = 0.511, P < .001) and the volume of distribution of quinine (n = 38, r = 0.6226, P < .001). The total plasma clearance and volume of distribution values correlated negatively with α_1-acid glycoprotein plasma concentrations (n = 39, r = –0.717, P < .001, and n = 38, r = –0.634, P < .001, respectively) and with the protein binding of quinine at 4 hours (n = 37, r = –0.481, P = .008, and n = 36, r = –0.6248, P = .002, respectively) and at 8 hours (n = 39, r = –0.7806, P < .001 and n = 39, r = –0.714, P < .001).

Clinical and parasitologic responses to treatment. Among the children with cerebral malaria, the mean full coma recovery times (35 ± 9 hours versus 39 ± 11 hours) and the time required to be able to eat (38 ± 12 hours versus 41 ± 13 hours) were similar in the groups of normally nourished children and undernourished children, respectively. No differences were observed in the times required for temperature to return to normal values (36 ± 8 hours and 44 ± 15 hours, respectively). Figure 2 illustrates the decrease in parasitemia in the 2 groups of children with malaria. This decrease in parasitemia tended to be slower in malnourished children (group 4) than in normally nourished children (group 2), but the mean (±SD) times to achieve 50% of initial parasitemia were not significantly different (29 ± 21 hours and 18 ± 12 hours, respectively; P = .176). No correlation was observed between these times and indicators of malnutrition.

The estimated pharmacokinetic parameters were used to simulate multiple 4-hour infusions of 8 mg/kg Quinimax every 8 hours in children with cerebral malaria. The peak and trough plasma quinine concentrations obtained with multiple doses were in agreement with the mean observed plasma quinine concentrations at 12, 16, and 24 hours (Figure 3). Simulated peak plasma concentrations at 12 hours (10.5 and 10.7 mg/L) and residual values at 16 hours (6.8 and 6.0 mg/L) and 24 hours (7.7 and 6.5 mg/L) were similar in children of groups 2 and 4, respectively. These values were also in agreement with measured values at 12 hours (9.8 ± 2.3 and 9.6 ± 2.7 mg/L), 16 hours (7.6 ± 4.0 and 6.8 ± 2.6 mg/L), and 24 hours (7.7 ± 2.6 and 7.8 ± 2.4 mg/L). These 2 quinine plasma profiles fluctuated similarly in the range from 5 to 12 mg/L.

DISCUSSION

The pharmacokinetics and the whole-blood distribution of quinine can be influenced by 2 frequent childhood diseases: malaria and malnutrition. In this study quinine disposition was assessed in childhood cerebral malaria, severe malnutrition, and malaria with malnutrition, relative to children without malaria and with standard nutritional status.

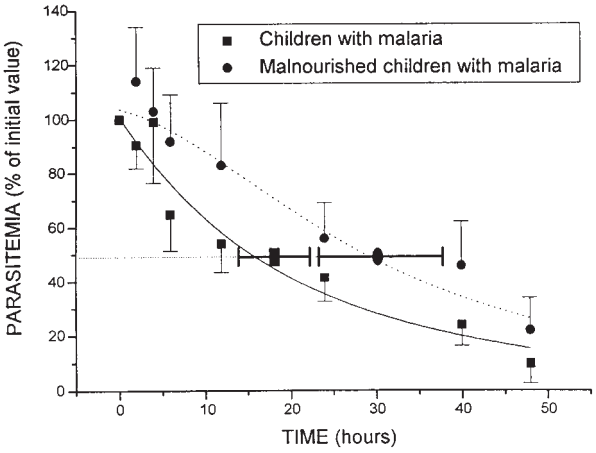

Figure 2. Changes in parasitemia expressed as mean values ± SEM of percentage of initial values in children with cerebral malaria without malnutrition (group 2) and with malnutrition (group 4) after a 4-hour intravenous infusion of 8 mg/kg Quinimax. The mean ± SEM times to achieve 50% of initial parasitemia (18 ± 4 and 29 ± 7 hours, respectively) are illustrated for the 2 groups.

Because of possible errors in the determination of age and measurement of height in the supine position, inclusion criteria for malnutrition were based on a cut-off point of -2σ for at least 2 of the anthropometric indices: W//H, H//A, and W//A.[14] Children of group 3 had deficits in the 3 indicators and had severe malnutrition with a combination of wasting and stunting. All of these children had no obvious evidence of infectious disease and malaria, but the increase in the acute-phase proteins, such as α_1-acid glycoprotein, confirms the high prevalence of subclinical inflammatory process during the course of malnutrition.[15] Children with cerebral malaria and malnutrition (group 4) had deficits in both W//A and W//H but not in H//A, suggesting an acute deficiency in fat and muscle rather than a long-term growth deficiency. These clinical anthropometric indicators were consistent with the decrease in prealbumin and albumin plasma levels, which correlate strongly with the severity of malnutrition.[15,16] For groups 2 and 4 (with cerebral malaria), the severity of the disease was similar in terms of coma scores, parasitemia, anemia, and inflammatory markers (α_1-acid glycoprotein, α_1-antitrypsin, and total α_1-globulin).

Like many other basic drugs, quinine binds to the low-affinity, high-capacity binding protein albumin, but α_1-acid glycoprotein is the major determinant of variation in quinine protein binding.[17] Malnutrition decreased albumin plasma concentrations, and both cerebral malaria and malnutrition were associated with an increase in α_1-acid glycoprotein plasma concentrations. Compared with control children, a similar increase in quinine protein binding was observed in the 3 groups of children with cerebral malaria or malnutrition or both. The lack of relationship between plasma albumin concentrations and quinine binding and the correlation between quinine binding and α_1-acid glycoprotein concentrations confirm that free plasma quinine concentrations are regulated by changes in plasma concentrations of this acute-phase reactant.[18] As previously shown, quinine protein binding correlated with the α_1-acid glycoprotein plasma concentrations, and the free quinine fraction in control children (11% to 12%) was larger than that in children with cerebral malaria (4% to 7%). These values are consistent with those of previous studies in healthy subjects[19] and during the acute or recovery phase of *falciparum* malaria.[20-23] In addition, during malnutrition and during malaria, the high α_1-acid glycoprotein plasma concentrations are associated with a lower free quinine fraction (5% to 6%) than that in the control children.

In whole blood, quinine is highly bound not only to plasma α_1-acid glycoprotein but also to erythrocytes in a parasitemia-dependent manner.[24] The erythrocyte-to-plasma total quinine concentration ratio is generally used to show the extensive erythrocyte uptake of 4-aminoquinolines.[25] In our control children without parasitemia, red blood cell quinine concentrations were about 50% of those in plasma. This erythrocyte-to-plasma ratio remained constant during the first 8 hours after drug infusion and was similar to that previously observed after oral or intravenous administration of quinine to healthy African adults.[26] In patients with cerebral malaria, this ratio, which is initially constant, has been showed to gradually fall from the second day (0.50) to the sixth day (0.26) of quinine treatment. In addition, a positive correlation between this ratio and parasitemia on admission has been described, pointing to increased uptake of quinine by parasitized cells.[24] In our study the increase in quinine concentrations was stronger in plasma than in erythrocytes, resulting in a lower erythrocyte-to-plasma ratio in cerebral malaria than in the healthy control group. A similar red cell-to-plasma quinine ratio (0.26) has been reported by Mansor et al[27] in Malawian children with *falciparum* malaria. Malnourished children (group 3) without parasitized erythrocytes exhibited similar modifications of plasma and erythrocyte concentrations to those in children with cerebral malaria, suggesting that quinine uptake by erythrocytes is not dependent on the presence of parasites, contrary to that which has been shown

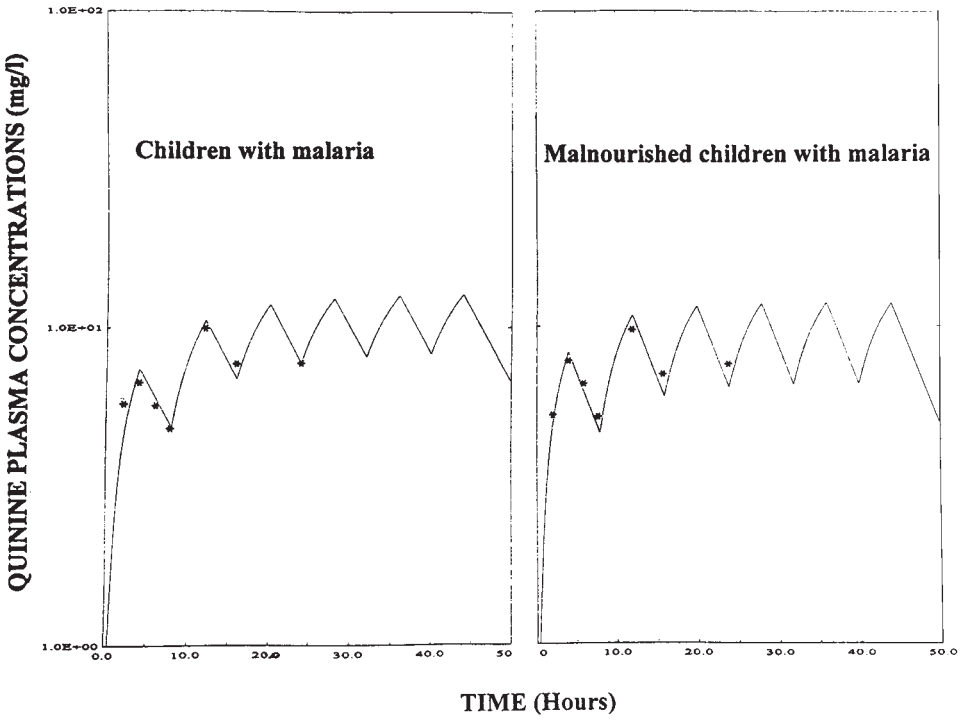

Figure 3. Quinine plasma concentrations profiles in children with cerebral malaria without malnutrition (group 2) and with malnutrition (group 4) after repeated 4-hour intravenous infusions of 8 mg/kg Quinimax every 8 hours during 3 days.

for 4-aminoquinolines.[25] Moreover, erythrocyte uptake of quinine is related to variations in α_1-acid glycoprotein plasma concentrations and not to the degree of parasitemia. The erythrocyte quinine concentrations increased similarly in cerebral malaria (group 2) and malnutrition (group 3). Independently of the presence of *P. falciparum* parasites, the ratio of erythrocyte-to-free plasma quinine concentrations was similar in all 4 groups of children (Table III), suggesting that quinine uptake by erythrocytes is influenced more by free plasma quinine concentrations through a simple diffusion mechanism than by an active uptake caused by the parasite (Figure 4).

For ethical reasons, the kinetic parameters of quinine could be determined only during the 8 hours after intravenous infusion of Quinimax. Optimal fitting of the plasma concentrations profile was obtained according a 1-compartment model. Nevertheless, the volume of distribution of quinine observed in our control group was in keeping with values previously described in convalescent children,[28] healthy adults,[19,26,29] and adults studied after they recovered from malaria.[30] Compared with the control children, plasma total quinine concentrations and AUC(0-8) values were approximately 2- to 3-fold higher during cerebral malaria and malnutrition (groups 2, 3, and 4). Simultaneously, the total volume of distribution observed in these 3 groups represented about one-third of that in control group. This contraction of the volume of distribution of quinine has been described during the acute and recovery phases of malaria and is directly proportional to the disease severity.[22,30] In cerebral malaria these changes in distribution might be related to dehydration or to a decrease in tissue blood flow (obstruction of the capillary bed by parasitized erythrocytes). Severe malnutrition is associated with changes in the protein-to-fat ratio, an imbalance in body water distribution, and a reduced volume of distribution of various drugs.[2] Moreover, cerebral malaria and malnutrition could induce similar modifications of the equilibrium between tissue and plasma binding (Figure 4). There is a relationship between the decrease in distribution volume and α_1-acid glycoprotein plasma concentrations, suggesting that the increase in the α_1-acid glycoprotein plasma concentrations, rather than malaria or malnutrition themselves, could explain the contraction of the volume of distribution. A similar correlation between α_1-acid glycoprotein and the volume of distribution has been described by Tre-

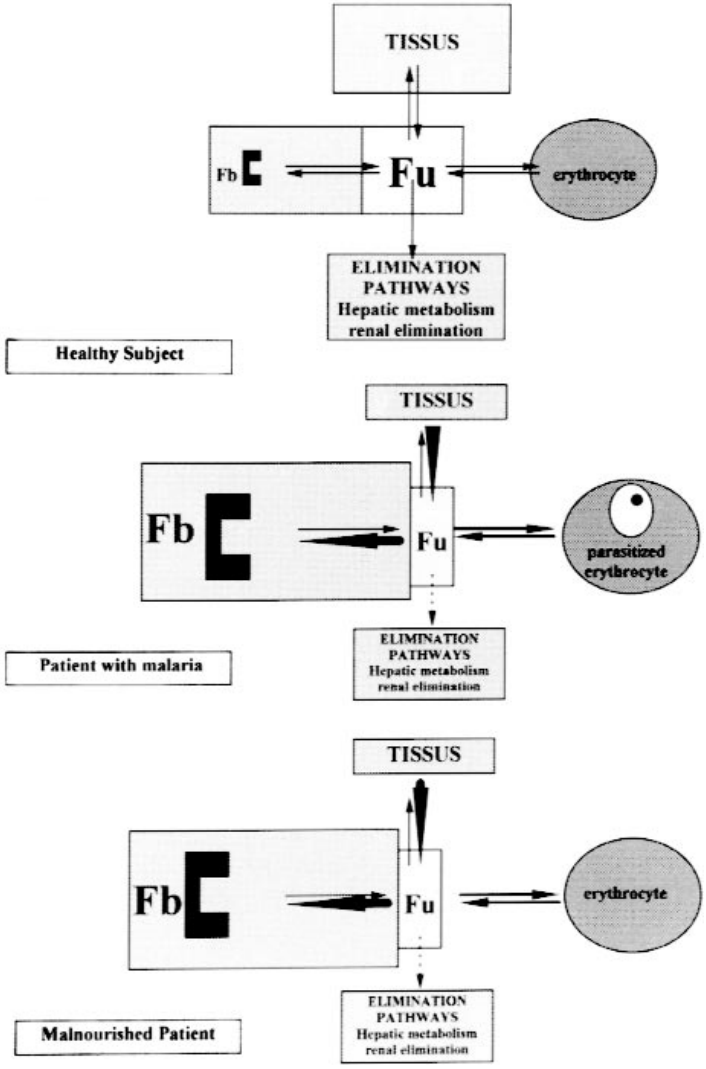

Figure 4. Proposed models for quinine distribution in healthy subjects and in patients with malaria or malnutrition. Fu, Unbound fraction of quinine; Fb, protein bound fraction of quinine.

luyer et al,[4] but the lack of parasitologic status in the normally nourished and the malnourished children in that study explains the similar α_1-acid glycoprotein plasma concentrations and distribution volumes of quinine found in the 2 groups.

The total plasma clearance of quinine observed in our control children is consistent with the values previously observed in healthy African children,[3] children studied during recovery of *falciparum* malaria,[28] and healthy adults.[19,26] Cerebral malaria induces a 75% reduction in systemic quinine clearance. This reduction is related to the severity of the disease and contributes to the higher quinine plasma concentrations observed in cerebral malaria.[28,30] Similarly, the clearance of oral quinine measured in adults in the acute phase of *falciparum* malaria was lower than during the convalescence phase.[22] A 50% decrease in total plasma clearance was also observed in our children with severe global malnutrition. Similarly, in African children with Kwashiorkor, the total clearance of oral quinine was lower than the clearance in control children.[3] In contrast, faster total plasma clearance of quinine associated with increased metabolism was described in children with global protein-energy deficiency compared with normally nourished children. However, the parasitologic status of these children was not determined and probably interfered with the determination of quinine pharmacokinetics.[4] The primary mechanism of quinine

clearance is hepatic biotransformation by cytochrome P450 (CYP 3A) 3A4 into the major 3-hydroxylated metabolite.[1] Malaria impairs this oxidase activity, leading to a reduction in systemic clearance and an increase in the elimination half-life of quinine and antipyrine (INN, phenazone).[31] Similar changes in quinine disposition are observed in etiocholanolone-induced fever.[32] Drug oxidation rates are often impaired in severe malnutrition: In Indian and African children with protein-calorie malnutrition, a decrease in plasma clearance of antipyrine was shown and was corrected after nutritional rehabilitation.[33] Severe malnutrition alters antipyrine clearance, which is an indicator of hepatic mixed-function oxidase activity, suggesting a similar mechanism for the decrease in quinine clearance. Moreover, malaria and malnutrition were also associated with increased α_1-acid glycoprotein plasma concentrations, suggesting that the avid protein binding of quinine limits its hepatic extraction.

Thus, cerebral malaria (group 2) and severe malnutrition with subclinical infections (group 3) similarly impair the distribution and elimination pathways of quinine. Malaria is frequently associated with mild and moderate forms of malnutrition characterized by growth retardation rather than very severe malnutrition. This moderate malnutrition, as in the children in group 4, does not significantly potentiate the cerebral malaria–induced alterations of quinine disposition. The simulated pharmacokinetic profiles were similar in the 2 groups of children with cerebral malaria and are in good agreement with the plasma concentrations of total quinine measured at 12, 16, and 24 hours (Figure 3). All the trough quinine plasma concentrations were higher than 5 mg/L, the minimum quinine plasma concentration described to be effective in West Africa.[34] In addition, plasma concentrations of peak total quinine were similar (approximately 10 to 12 mg/L) in the 2 groups and were below the theoretical 15 to 20 mg/L threshold of toxicity.[34] Among the children with cerebral malaria, the lower and upper plasma concentrations of free quinine were 0.18 and 0.76 mg/L respectively, suggesting that free concentrations are maintained within the effective range of 0.2 to 2.0 mg/L.[21] In this restricted number of children, wide variability was observed in clinical and parasitologic outcome. The times to coma recovery and to be able to eat were similar in the 2 groups and were consistent with previous reports.[35,36] The decrease in parasitemia tended to be slower in malnourished children with malaria, but the difference in the times required to obtain 50% of initial parasitemia did not reach significance. This trend might be related to the nutritional status of the children which, by influencing immunity, could decrease parasite clearance. The restricted number of patients and the low consecutive statistical power cannot support the possible modifications in clinical efficacy and disposition of quinine that occur in association with various degrees of malnutrition and malaria. Further studies based on population kinetics approach may provide additional information.

In conclusion, this study shows that severe malnutrition and cerebral malaria impair quinine pharmacokinetics in a similar manner—by increasing plasma binding of the drug and decreasing the volume of distribution and total plasma clearance. Nevertheless, only minor changes in the pharmacokinetics of quinine were observed in children with both cerebral malaria and mild to moderate malnutrition. Therefore current therapeutic quinine regimens should not require major adjustment in these patients.

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