Population Pharmacokinetics of Intramuscular Quinine in Children with Severe Malaria

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We present the first population pharmacokinetic analysis of quinine in patients with Plasmodium falciparum malaria. Ghanaian children (n = 120; aged 12 months to 10 years) with severe malaria received an intramuscular loading dose of quinine dihydrochloride (20 mg/kg of body weight). A two-compartment model with first-order absorption and elimination gave post hoc estimates for pharmacokinetic parameters that were consistent with those derived from non-population pharmacokinetic studies (clearance [CL] = 0.05 liter/h/kg of body weight; volume of distribution in the central compartment [V1] = 0.65 liter/kg; volume of distribution at steady state = 1.41 liter/kg; half-life at β phase = 19.9 h). There were no covariates (including age, gender, acidemia, anemia, coma, parasitemia, or anticonvulsant use) that explained interpatient variability in weight-normalized CL and V1. Intramuscular quinine was associated with minor, local toxicity in some patients (13 of 108; 12%), and 11 patients (10%) experienced one or more episodes of postadmission hypoglycemia. A loading dose of intramuscular quinine results in predictable population pharmacokinetic profiles in children with severe malaria and may be preferred to the intravenous route of administration in some circumstances.

Although quinine is one of the oldest drugs in the pharmacopoeia, the optimum usage of quinine in children with severe malaria is still debated (12, 29). The choice of route and dose of quinine for children with severe malaria will vary depending on circumstances and particularly on the capability of administering intravenous infusions reliably. Quinine is the drug of choice for the management of severe malaria in most areas of the world, and it is frequently deployed in conditions where intravenous infusions cannot be rapidly established or reliably monitored.

Recent pharmacokinetic studies using African children have revived the intramuscular route as an alternative, cheaper, practicable, and potentially safer route for quinine administration (15, 25, 27). However, classical pharmacokinetic studies are not always applicable to populations at highest risk of death from Plasmodium falciparum infection. One of the most important risk factors that identify these children is the complication of lactic acidosis (plasma or whole blood lactate concentration of ≥5 mmol/liter) (11). Dichloroacetate (DCA) is a potential treatment for malaria-associated lactic acidosis (7). We recently conducted a randomized, double-blind, placebo-controlled investigation to test the hypothesis that treatment with the lactate-lowering drug DCA, given with quinine, significantly improved morbidity and mortality in Ghanaian children with lactic acidosis due to severe P. falciparum malaria infection. This report describes the population pharmacokinetics of a loading dose of intramuscular quinine dihydrochloride (20 mg/kg of body weight) in 120 patients. The size of this study also allows assessment of covariables that may be important in influencing quinine kinetics. The major clinical results of the study will be presented elsewhere.

MATERIALS AND METHODS

Patients. The study was carried out at the Komfo-Anokye Teaching Hospital in Kumasi, Ghana, and was approved by the Committee of Research and Ethics of the School of Medical Sciences, University of Science and Technology, Kumasi, Ghana, and the Institutional Review Board at the University of Florida. Between June 1997 and February 1999, 1,654 children with a suspected case of malaria were referred to the study team. Patients were examined by a member of the team, and samples were taken to measure glucose or lactate (100 µl of whole blood or plasma), hematocrit, and parasitemia. After written, informed consent from parents or guardians was obtained, children were entered into this study if they fulfilled the following inclusion criteria: age of 12 months to 10 years inclusive, positive blood film for asexual stages of P. falciparum, and plasma venous or capillary blood lactate concentration of ≥5 mmol/liter. Exclusion criteria were pregnancy, assessed by a urine β-human chorionic gonadotropin test in patients aged 10 years, and brain death, determined by clinical examination. Cerebral malaria was defined using the Blantyre Coma Score (BCS) (≥2 on a 5-point scale) (16). A lumbar puncture was performed on all patients with coma (BCS ≤ 2) to exclude the possibility of meningitis or encephalitis. The cerebrospinal fluid was analyzed immediately by microscopy and cultured.

Quinine and DCA treatments. Quinine (20 mg/kg as a loading dose; diluted 1:1 [vol/vol] in water for injection, giving a final concentration for quinine dihydrochloride of 150 mg/ml) (Rotomed [Rotex, Trittau, Germany] or quinine...
individual-parameter estimates. These two steps are iterated up to convergence.

Bayesian approach, given the present population parameters and the individual
maximization analysis is an iterative two-step process suitable for computing
concentrations.

The inter- and intrabatch bias and relative standard deviation were
,
, and retention times for quinine and quinidine were 5.2 and 4.5 min, respec-

The flow rate was kept at 1 ml/min. Quinine and quinidine were detected at 254

graphic separation with a mobile phase consisting of acetonitrile and 1% trieth-

HPLC. HPLC was performed with a Hewlett-Packard 1100 Series system (Palo

chloride (500

solution), ammonia (60

m

aqueous layer was separated, and sample (5

l) was injected and analyzed by

The model was validated for standardized concentration prediction error (SCPE) and standardized parameter prediction error (SPPE) for clearance (CL), intercompartmental clearance (Q), volume of distribution in the central compartment (Vc), and volume of distribution in the peripheral compartment (Vp). SCPE for each concentration was calculated using the relationship:

where

represents the observed concentrations, and SD (Cpop) represents the esti-
mated standard deviation on the expected values computed, using all sources of
random variability including residual error. For each pharmacokinetic parameter
(CL and Vp), the normalized SPPEs were computed as

and

is the population pharmacokinetic parameter, and SD (Ppop) is the corre-
sponding standard deviation. To assess the posterior distribution properties of
the residuals and the individual parameters, a t test was used to compare the
mean of SCPE and SPPE to zero and the Kolmogorov-Smirnov test was used to compare the sampled distribution to the expected one [n (0.1)].

RESULTS

Patients. Patients with malaria-associated lactic acidosis (n = 124) were enrolled. Sixteen patients (12.9%) died, the majority of them (11 of 16; 69%) within 24 h of admission. Demographic, clinical admission, and laboratory features of patients are summarized in Table 1. All patients had one or more defining features of severe malaria, including hyperlac-
tatemia, cerebral malaria (n = 38; 31%), acidemia (39 of 81; 48%), or respiratory distress (n = 67; 56%). Fifteen patients who did not have cerebral malaria on admission became comatose during the first 24 h of quinine treatment. Half the patients (n = 62) were randomized to receive DCA. More detailed descriptions of these patients’ clinical courses will be published elsewhere. Ninety-two patients (74%) had a history of antimalarial treatment (1 with amodiaquine, 1 with artesunate, 10 with an unspecified antimalarial, and the remainder with chloroquine).

Population modeling of quinine pharmacokinetics. Each pa-
tient contributed 1 to 3 plasma samples, depending on the actual time of blood sampling. Five patients with a history of prior quinine pretreatment had measurable baseline quinine levels. Three patients with baseline quinine levels above 2

µg/ml (range, 6.6 to 13.4 µg/ml) and one patient without mea-
surable quinine levels for up to 1 h after admission were ex-
cluded from the population analysis. The patient without mea-
survivable quinine survived. Another surviving patient’s quinine concentration was >60 μg/ml (0.5-h sample), and this time point was also excluded from analysis. Plasma samples (n = 282) from 120 patients were available for population pharmacokinetic analysis of quinine. Based on earlier analysis and published reports (12), a two-compartment model with first-order absorption and elimination was used to develop a population pharmacokinetic model for quinine. Total CL, Q, V₁, V₂, and absorption rate constant (kₐ) were used as the model parameters. The parameter kₐ was fixed at 3.5/h (absorption half-life of 12 min) (8) to arrive at reliable estimates of CL and V₁. Intersubject variability in CL had a log-normal distribution, while the values for intersubject variability for Q, V₁, and V₂ showed normal distributions. The distribution of residual errors was best explained by a multiplicative (proportional to the observed concentration) error model.

The population mean and post hoc estimates of pharmacokinetic parameters are summarized in Table 2. Figure 1a displays the base population pharmacokinetic model fitted to 282 samples obtained from patients in this study and the correlation between observed plasma quinine levels and Bayesian estimates predicted by the model. Six values for quinine lie at or above 30 μg/ml. These plasma samples were reassayed, and the initial measurements were confirmed. All these patients survived. The mean (± standard deviation) terminal elimination half-life for quinine was 19.9 ± 4.4 h. Figure 1b compares observed plasma quinine concentrations with those predicted from population modeling.

When model validation was carried out (as detailed in Materials and Methods), results showed that the distributions of the residuals and the normalized parameters were normal and not significantly different from expected. These results are represented as histograms and cumulative distribution curves in Fig. 2.
Analysis of covariates. Based on a preselected critical percentage (5%) of the F distribution to assess the contribution of a covariate in multiple, stepwise, linear regression, none of the following covariates influenced weight-normalized CL and $V_1$: age, sex (0 = male, 1 = female), admission arterial pH, pO$_2$, pCO$_2$, body temperature, parasite count, cerebral malaria (0 = no, 1 = yes), phenobarbital treatment, diazepam treatment (0 = no, 1 = yes), and previous antimalarial treatment (0 = no, 1 = yes). When all of these factors were forcibly included as covariates and the data set was reanalyzed, weight, sex, age, hematocrit, and DCA (0 = placebo, 1 = DCA) treatment were selected as covariates for CL. Covariates for other parameters were weight for $V_1$, hematocrit and cerebral malaria for Q; and cerebral malaria, DCA, and hematocrit for $k_p$. Intersubject variability estimates of all the parameters were lower with the covariate model (Table 3). However, there were no significant changes in the ML ratio and AIC. Analysis of the diagnostic graphs also did not indicate any improvements in the predictions. Hence, it was inferred that none of these patient-specific factors could be used reliably as covariates to explain inter-patient variability in CL and $V_1$.

Values for pH, pO$_2$, and pCO$_2$ were not available for 38 patients. The influence of these blood gas variables on the parameters was therefore assessed separately in a subgroup of 82 patients with all potential covariates. The base model parameters (without covariables) were similar to those for the data set containing 120 patients. In this subgroup also, none of these additional factors (pH, pO$_2$, and pCO$_2$) were selected as covariables. Hence, results from the complete data set with 120 patients were retained. Table 3 summarizes a model that includes covariates and goodness-of-fit parameters. There were no significant differences in estimates for pharmacokinetic parameters between survivors and fatal cases.

Efficacy and tolerability of quinine. Figure 3a represents parasite CL data following quinine as a survival curve. The time taken for half the patients to clear parasites completely is 43 h. Figure 3b shows normalized parasite CL kinetics (median PC$_{50}$ = 16 h and PC$_{90}$ = 27 h, where PC$_{50}$ is the time taken for parasite numbers to fall by 50% of baseline values and PC$_{90}$ is the time required for parasite numbers to fall by 90% of baseline values). The median (interquartile range) parasite clearance time was 48 (36 to 54) h.

Ninety-five (88%) patients from among 108 survivors had normal injection sites when discharged from the hospital. Twelve (11%) patients had mild, mainly unilateral induration, and one (1%) had unilateral swelling on discharge. Four (3%) of 68 patients who returned for follow-up examination 28 days after admission had evidence of local toxicity (two with induration and two with small [≤2 cm] fluctuant swellings). These patients were reexamined 1 to 2 weeks later, and local toxicity had resolved without specific therapy. It is not possible to attribute all local toxicity to quinine injections, as patients also received other intramuscular medication.

Hypoglycemia (blood sugar level of ≤ 2.2 mmol/liter) was present in 19 (15%) patients prior to quinine treatment.

<table>
<thead>
<tr>
<th>TABLE 3. Analysis of covariates for population pharmacokinetic parameters of quinine*</th>
<th>Values for:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>Base model</td>
</tr>
<tr>
<td>Mean</td>
<td>CV</td>
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<tr>
<td>CL (liter/kg/h)</td>
<td>0.050</td>
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<tr>
<td>$V_1$ (liter/kg)</td>
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<tr>
<td>Q (liter/kg/h)</td>
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<tr>
<td>$V_p$ (liter/kg)</td>
<td>0.764</td>
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<tr>
<td>$k_p$ (h$^{-1}$)</td>
<td>3.5</td>
</tr>
<tr>
<td>$t_{1/2b}$ (h)</td>
<td>19.9 ± 4.4</td>
</tr>
<tr>
<td>ML</td>
<td>$-861.1$</td>
</tr>
<tr>
<td>AIC</td>
<td>3.082</td>
</tr>
<tr>
<td>Sigma</td>
<td>$0.912 \times y$</td>
</tr>
</tbody>
</table>

* Sigma, residual variability; $k_p$, fixed at 3.5; $t_{1/2b}$, half-life at β phase, estimated using post hoc parameters; y, observed concentration of quinine (Table 1); CV, intersubject variability.

* Distribution models and equations: CL, log-normal distribution. CL = $-0.008965 \times 0.006 \times \text{weight} - 0.0161 \times \text{sex} + 0.0006 \times \text{age} + 0.00098 \times \text{PCV} - 0.03013 \times \text{cerebral} + 0.0075 \times \text{DCA}$. $V_1$, Q, $V_p$, normal distribution. $V_1 = 0.3158 + 0.0232 \times \text{weight}$. Q = $2.041 - 0.028 \times \text{PCV} - 0.0949 \times \text{cerebral}$. $V_p = 0.585 - 0.1637 \times \text{cerebral} + 0.161 \times \text{DCA} + 0.00883 \times \text{PCV}$. 

FIG. 2. Histograms and cumulative distribution graphs for normalized residuals (A), CL (B), $V_1$ (C), Q (D), and $V_p$ (E).
 Debate about the best way to administer quinine has continued since it was first used to treat severe malaria (12, 13, 29). Ross and others, working in India (14, 19), cautioned against using “strong” quinine solutions, because they might cause necrosis at the intramuscular injection site and might not be adequately absorbed. Diluted quinine was advocated as it was “practically painless and rapidly effective” (3). Fletcher provided a lucid review of clinical and laboratory experience on intramuscular quinine and suggested that it should be reserved for “patients who are most dangerously ill with malaria” (5). More recent studies have examined absorption of undiluted (300-mg/ml) (27) and diluted (150-mg/ml) (8) quinine and 60-mg/ml (18) quinine following a loading dose (20 mg of salt/kg). Dilution of quinine decreases the absorption half-life (mean ± standard deviation) from 38 ± 25 min to 10.4 ± 9 min (for 150-mg/ml quinine) and 8.7 ± 7.8 min (60-mg/ml quinine). There was no evidence of major local or systemic toxicity in these studies. A larger prospective evaluation of intramuscular (n = 57) versus intravenous (n = 47) quinine confirmed similar efficacy, safety, and blood levels of quinine for both routes (21) but did not include a pharmacokinetic analysis. Parasite CL estimates after quinine in our population are similar to those reported for children with cerebral malaria in The Gambia: median (with the interquartile range in parentheses) parasite CL time was 48 (36 to 54) h in our study, compared with 60 (48 to 72) h in the study from The Gambia (26).

This study on the pharmacokinetics of intramuscular quinine in children with severe malaria exceeds other reports in size and detail. Population estimates for pharmacokinetic parameters presented here are consistent with previous, smaller, classical pharmacokinetic studies. For example, quinine CL is estimated here as equal to 0.05 liter/h/kg. In previous studies, estimates ranged from 0.027 to 0.0816 liter/h/kg (reviewed in reference 12). In this study kₐ was fixed in order to obtain reliable estimates for other parameters. The suitability of distribution models is reflected in Fig. 1b, which shows the correlation between observed plasma concentrations of quinine and those predicted by Bayesian analysis.

Quinine (20 mg/kg) is absorbed rapidly and reliably after dilution and intramuscular injection into both anterior thighs. Mean peak plasma concentration versus time profiles between 15 and 20 μg/ml (Fig. 1a) are within the notional “therapeutic range” for quinine (12). The relatively broad confidence intervals around this value may reflect heterogeneity in quinine disposition rather than variability due to disease, as children were selected for study by strict and objective entry criteria and represent patients with the highest mortality (9, 11). The absence of any identifiable relationship between clinical and laboratory variables and population pharmacokinetic indices supports this suggestion. In particular, it is reassuring that intramuscular quinine is reliably absorbed, even in patients who may have severe acidemia, cerebral malaria, or anemia. Concomitant use of other medications (DCA, phenobarbital, and diazepam) also did not affect first-dose pharmacokinetics of quinine. Quinine is metabolized to 3-hydroxyquinine predominantly by the hepatic CYP4503A4 system (12). Since the expression of this enzyme system exhibits considerable interindividual variation (ranging from between 10 and >60% total hepatic cytochrome P450 activity) (6), genetic factors may contribute to quinine’s variable disposition.

There was no major local toxicity associated with our regimen of intramuscular quinine. Local side effects were self-limiting, and none required surgical intervention, in contrast to findings from The Gambia, where some children (5 of 288) (1.7%) given intramuscular quinine needed drainage of abscesses (26).

Eleven (10%) children had hypoglycemia following quinine treatment; four of these children also had admission hypoglycemia (relative risk for postadmission hypoglycemia was 3.2 [95% confidence interval = 1.02 to 9.75; P = 0.024], if there was preexisting hypoglycemia, when compared with patients who had no admission hypoglycemia).

**DISCUSSION**

There was no major local toxicity associated with our regimen of intramuscular quinine. Local side effects were self-limiting, and none required surgical intervention, in contrast to findings from The Gambia, where some children (5 of 288) (1.7%) given intramuscular quinine (diluted 1:5) needed drainage of abscesses (26).

Patients who had hypoglycemia prior to admission were at highest risk of postadmission hypoglycemia, despite receiving a constant infusion of glucose (3 mg/kg/min). Taken together with observations on glucose kinetics in children with severe malaria receiving quinine (1), children who are hypoglycemic on admission to the hospital may require larger amounts of glucose (up to 6 mg/kg/min) than what we routinely used to
prevent hypoglycemia. In any case, this high-risk group should be monitored particularly carefully. These observations are consistent with studies in Kenyan children, where admission hypoglycemia (n = 27 of 171; 16%) also identified children at risk of postadmission hypoglycemia (n = 9; relative risk = 5.33 [95% confidence interval = 2.33 to 12.2; P < 0.0001]). As in this study, some children who were euglycemic on admission subsequently developed hypoglycemia despite receiving dextrose (4). Postadmission rates of hypoglycemia were ~15% in a large Gambian study (26). These observations contrast with those from Malawi indicating that glucose infusions prevented postadmission hypoglycemia after quinine treatment (23) and confirm that blood glucose should be monitored regularly, whenever practicable, in children with severe malaria.

Figure 4 displays predicted quinine pharmacokinetic profiles of three different doses of quinine, based on our population analysis. Both 10- and 15-mg/kg doses are likely to undertreat a significant proportion of children in areas where parasites are not fully quinine sensitive. The safety of a 20-mg/kg loading dose of quinine and the potential for undertreatment suggest that this dose should be preferred in the management of severe malaria in African children. The risks of undertreatment with quinine were recently highlighted by a retrospective analysis that showed a significantly higher mortality rate in patients who received a 10-mg/kg dose than in those who received a 20-mg/kg dose of quinine (24). A few patients (5%) in our study had quinine levels of >30 μg/mL, but none suffered toxicity. Only one patient had levels below 5 μg/mL 12 h after the first dose of quinine. Many factors must be considered in choosing between intravenous and intramuscular routes for quinine use. Ease of administration, the lack of requirement for immediate intravenous access, more expensive fluid administration sets, predictable pharmacokinetics, usefulness in severe malaria, and safety favor the intramuscular route. However, the intramuscular route has some potential disadvantages, in particular the risk of infection (rarely tetanus or poliomyelitis) that may “seed” to areas of muscle necrosis (2, 5, 30). Both parenteral routes for quinine administration may be associated with hyperinsulinemic hypoglycemia and the risk of transmitting blood-borne infections. The intravenous route incurs a risk of major quinine toxicity if infusion rates cannot be reliably managed. Thus, policies governing selection of one route over another must take into account these considerations. Our findings should increase confidence in the efficacy and safety of intramuscular quinine as the first choice for management of severe malaria in children.

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