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ARTICLE

Physiologically based pharmacokinetic modeling for dose optimization of quinine–phenobarbital coadministration in patients with cerebral malaria

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Abstract

Patients with cerebral malaria with polymorphic *Cytochrome P450 2C19* (*CYP2C19*) genotypes who receive concurrent treatment with quinine are at risk of inadequate or toxic therapeutic drug concentrations due to metabolic drug interactions. The study aimed to predict the potential dose regimens of quinine when coadministered with phenobarbital in adult patients with cerebral malaria and complications (e.g., lactic acidosis and acute renal failure) and concurrent with seizures and acute renal failure who carry wild-type and polymorphic *CYP2C19*. The whole-body physiologically based pharmacokinetic (PBPK) models for quinine, phenobarbital, and quinine–phenobarbital coadministration were constructed based on the previously published information using Simbiology®. Four published articles were used for model validation. A total of 100 virtual patients were simulated based on the 14-day and 3-day courses of treatment. using the drug–drug interaction approach. The predicted results were within 15% of the observed values. Standard phenobarbital dose, when administered with quinine, is suitable for all groups with single or continuous seizures regardless of *CYP2C19* genotype, renal failure, and lactic acidosis. Dose adjustment based on area under the curve ratio provided inappropriate quinine concentrations. The recommended dose of quinine when coadministered with phenobarbital based on the PBPK model for all groups is a loading dose of 2000 mg intravenous (i.v.) infusion rate 250 mg/h followed by 1200 mg i.v. rate 150 mg/h. The developed PBPK models are credible for further simulations. Because the predicted quinine doses in all groups were similar regardless of the *CYP2C19* genotype, genotyping may not be required.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Quinine is a drug of choice for severe malaria, including cerebral malaria, in cases when injectable artesunate and/or parenteral artemether are not available.

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Phenobarbital is the standard treatment for cerebral malaria with concurrent seizures. Patients with cerebral malaria with polymorphic *Cytochrome P450 2C19 (CYP2C19)* genotypes who receive concurrent treatment with quinine are at risk of inadequate or toxic therapeutic drug concentrations as a result of metabolic drug interactions.

WHAT QUESTION DID THIS STUDY ADDRESS?

Does patients carrying polymorphic *CYP2C19* with cerebral malaria with concurrent seizures require quine-phenobarbital co-administered dose optimization? If so, what are the optimal dose regimens of both drugs when coadministered?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The recommended dose of quinine and phenobarbital coadministration with phenobarbital based on the physiologically based pharmacokinetic (PBPK) model for all patients is a loading dose of 2000 mg i.v. infusion rate 250 mg/h followed by 1200 mg i.v. rate 150 mg/h. *CYP2C19* genotyping and phenobarbital dose optimization are not required when coadministered with quinine.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

The developed PBPK models are credible for further simulations of optimal dose regimens of quinine in patients with cerebral malaria with concurrent seizures and complications.

INTRODUCTION

Cerebral malaria remains a high burden neurological problem not only in children aged younger than 5 years but also in adults.[1–3] Quinine is a drug of choice for severe malaria, including cerebral malaria in cases when injectable artesunate and/or parenteral artemether are not available (the recommended regimen is a loading dose of 20 mg/kg salt intravenous [i.v.] infusion for 4 h followed by 10 mg kg^{-1} salt i.v. infusion for 4 h given every 8 h).[4] Phenobarbital, a cost-effective antiepileptic drug, is the standard treatment for cerebral malaria with concurrent seizures (the recommended regimen is a loading dose of 15 mg/kg given i.v. infusion for 30 min followed by 1–3 mg kg^{-1} given i.v. infusion for 30 min every 12 h).[5,6] Phenobarbital-induced severe cutaneous adverse reactions are, however, of critical concern for clinical use of this drug.[7] Information on the contribution of host genetics on such reactions in adult patients with cerebral malaria with concurrent seizures has been limited. Because phenobarbital induces the xenobiotic drug-metabolizing cytochrome P450 (CYP450) enzymes, the situation is further complicated when it is coadministered with drugs that are also metabolized by CYP450 enzymes. Phenobarbital is metabolized mainly in the livers by the polymorphic CYP450 isoforms: CYP2C9[8,9] (fraction of metabolized [f_m] of CYP2C9 or $f_{m,CYP2C9} = 0.1$) and CYP2C19[8,9] ($f_{m,CYP2C19} = 0.9$). Quinine, on the other hand, is metabolized by CYP3A4 and uridine diphosphate-glucuronosyltransferase1A1 (UGT1A1)[10] ($f_{m,CYP3A4} = 0.44$ and $f_{m,UGT1A1} = 0.56$). The activities of both CYP3A4 and UGT1A1 enzymes are induced by phenobarbital.[11,12] In addition, phenobarbital also induces CYP1A2, CYP2B1, CYP2B2, CYP2B6, CYP2C9, UGT1A4, UGT1A8, and UGT1A9.[13,14] Patients with cerebral malaria with polymorphic *CYP2C19* genotypes (altered phenobarbital clearance) who receive concurrent treatment with quinine are, therefore, at risk of inadequate or toxic therapeutic drug concentrations as a result of metabolic drug interactions. In addition, quinine is a narrow therapeutic drug (therapeutic range 10–20 mg L^{-1}, therapeutic index 2).[15] To our knowledge, there have been a few reports on the optimal phenobarbital dose for patients with epilepsy,[8,9] but not for patients with cerebral malaria with seizures who carry polymorphic *CYP2C19* as well as the wild-type genotypes. Also, the optimal dose(s) of quinine when coadministered with phenobarbital has never been reported in this group of patients. This is of concern as approximately 17.3% of adult patients with malaria had severe malaria, where 70.7% of the patients developed convulsions and the overall mortality rate was up to 14% of severe malaria cases.[16]

Physiologically based pharmacokinetic (PBPK) modeling and simulation are accepted by various regulatory authorities as a promising tool to support dose optimization in the clinical phase of drug development, particularly for the investigation of drug–drug interactions (DDIs) and non-DDIs.[17] The present study aimed to apply PBPK modeling and simulation for the optimization of quinine and phenobarbital coadministration in adult patients with cerebral malaria with concurrent seizures. The optimal dose(s) was

predicted with consideration of genetic polymorphisms of CYP2C19, malarial complications (i.e., lactic acidosis and acute renal failure), and the propensity of DDIs.

METHODS

Model construction

Whole-body PBPK models for quinine and phenobarbital (alone and coadministration) were constructed based on the previously published information[18,19] using Simbiology® (version 5.8.2), the product of MATLAB® (version 2019a; MathWorks, Natick, MA). The physicochemical and biochemical properties (model parameters) of each drug, including human physiological parameters, were obtained from the published articles and are available in the supplementary material of this article.[11,18,20–35] Because quinine is a CYP3A4 inhibitor, the inhibitor constant was taken into account for model construction. Model assumptions included, blood-flow limited, absence of enterohepatic recirculation, and absence of 3-hydroxyquinine (metabolite) on quinine disposition.

Model validation

Four published articles for quinine[32,36–38] and one article for phenobarbital[39] were used for model validation. The published data were extracted using Plot digitizer® version 2.6.8 (Free Software Foundation, Inc., Boston, MA). The area under the plasma concentration–time curve (AUC) was calculated using the trapezoidal rule. The simulated results from the developed models were compared against the published data using the accepted criterion, that is, absolute average-fold errors (AAFEs) of ±2-fold.[40] However, as quinine is a drug with a narrow therapeutic index, the AAFE used in this article was reduced to ±1.25-fold. The following is the mathematical equation for AAFEs:

$$\text{AAFEs} = 10^{\sum_{i=1,\ldots,n}^{n}\left(\left|\log\frac{\text{prediction}}{\text{observation}}\right|\right)/n}$$

where n is the number of observed pharmacokinetic parameters, the prediction is the simulated results from the developed model, and the observation is the published clinical data.

Sensitivity analysis

Sensitivity analysis was performed to determine the effect of the changes in model parameters on the clearance during the first 72 h following the i.v. regimen of phenobarbital and quinine–phenobarbital coadministration (DDI model). The model parameters for sensitivity analysis of the phenobarbital included a fraction of unbound phenobarbital (f_u), acid dissociation constant (pKa) of phenobarbital, LogP of phenobarbital, blood-to-plasma ratio (R_{bp}) of phenobarbital, $f_{m,CYP2C19}$, and $f_{m,CYP2C9}$, maximal effect at high concentrations (E_{max}) of CYP2C19, half-maximal effective concentrations (EC_{50}) of CYP2C19, and hepatic blood flow (Q_{hv}). The model parameters for quinine (quinine–phenobarbital model) included f_u of quinine, acid dissociation constant (pKa) of quinine, LogP of quinine, R_{bp} of quinine, $f_{m,CYP3A4}$, $f_{m,UGT1A1}$, E_{max} of CYP2C19, UGT1A1, CYP3A4, and EC_{50} of CYP2C19, UGT1A1, CYP3A4, Q_{hv}, and the relative effect of *CYP2C19* polymorphisms (wild-type, *2C19*1/*2*, *2C19*1/*3*, *2C19*2/*2*, and *2C19*3/*3*). The effect of the changes in model parameters on the clearance was determined by the change of each model parameter within ±20%. The following is the mathematical equation for sensitivity analysis:

$$\text{Sensitivity coefficient} = \frac{\%\nabla Y}{\%\nabla X}$$

where $\%\nabla Y$ is the percent change of the clearance, and $\%\nabla X$ is the percent change of the model parameters.

Virtual population

A total of 100 virtual patients (50 males and 50 females aged 18–60 years and weighing 60 kg during the fasting state) were simulated in (i) seizure patients with polymorphic *CYP2C19* (phenobarbital model), (ii) patients with cerebral malaria (quinine model), (iii) patients with cerebral malaria with concurrent seizures and polymorphic *CYP2C19* (DDI model), and (iv) patients with cerebral malaria with concurrent seizures and acute renal failure (corrected with lactic acidosis) and polymorphic *CYP2C19*. The intrinsic clearance of phenobarbital in each genotype was obtained from the published clinical data for the wild-type *CYP2C19*1/*1* (extensive metabolizer [EM]),[8] *CYP2C19*1/*2* (intermediate metabolizer [IM]), and *CYP19*1/*3*, *CYP2C19*2/*2*, or *CYP2C19*3/*3* (poor metabolizer [PM]).[9] The intrinsic clearance values in *CYP2C19*1/*2* (IM) and *CYP2C2C19*1/*3* or *CYP2C19*2/*2* or *CYP2C19*3/*3* (PM)[9] were estimated as a relative clearance compared with wild-type. Acute renal failure or acute kidney injury (AKI) was classified based on the risk, injury, failure, loss of kidney function and end-stage kidney disease (RIFLE) criteria, that is, AKI (≤25% decrease of estimated glomerular filtration rate [eGFR]), RIFLE-R (risk; >25%–50% decrease of eGFR), RIFLE-I

(injury; > 50%–75% decrease of eGFR), or RIFLE-F (failure; >75% decrease of eGFR).[41]

Quinine dose regimen used in simulations

The standard regimen of quinine for severe malaria is the loading dose of 20 mg kg^{-1} (1000 mg base total dose for an average body weight of 60 kg) i.v. infusion for 4 h followed by the maintenance dose of 10 mg kg^{-1} (500 mg base total dose for an average body weight of 60 kg) i.v. infusion for 4 h given three times daily for 72 h (assuming that the patients respond to quinine treatment).[2]

DDI model simulations

Simulation based on standard DDI study approach

For the standard DDI study approach, plasma concentration–time profiles of phenobarbital and quinine following the coadministration of the standard dose regimen of phenobarbital and quinine were simulated. Phenobarbital is given at 1.5 mg kg^{-1} day^{-1} (1–3 mg kg^{-1} day^{-1}) or 90 mg total dose for an average body weight of 60 kg with i.v. infusion for 30 min for 17 consecutive days. The standard dose regimen of quinine for 3 days (described previously) was given on day 14 of phenobarbital administration when steady-state plasma concentration was achieved.

Simulation based on actual clinical approach

For the PBPK simulation based on an actual clinical use approach, two simulated scenarios were applied with the total simulation time of 72 h. Scenario I applies to patients who have only a single seizure; phenobarbital (15 mg kg^{-1} or 900 mg total dose for an average body weight of 60 kg with i.v. infusion for 30 min) is given as a single dose 6 h after the first dose of quinine (average time of occurrence of seizure after admission).[42] Scenario II applies to patients who have continuous seizures; phenobarbital at a loading dose of 15 mg kg^{-1} or 900 mg total dose for an average body weight of 60 kg with i.v. infusion for 30 min followed by the maintenance dose of 1.5 mg kg^{-1} day^{-1} (1–3 mg kg^{-1} day^{-1}) or 90 mg total dose for an average body weight of 60 kg with i.v. infusion for 30 min[42] is given every 24 h, starting 6 h after the first dose of quinine until 72 h. The time of simulation and seizure frequency was based on a previous clinical report.[43] The predicted optimal dosage regimens were presented as the amount of quinine base.

Criteria for optimal dose regimens

All regimens for quinine and phenobarbital were evaluated based on the criteria for optimal dose regimens. The optimal dose regimens of quinine for adult patients with cerebral malaria with seizures were proposed based on the therapeutic range of quinine, that is, maximal plasma concentration (C_{max}) ≤20 mg L^{-1} and minimal plasma concentration (C_{min}) ≥10 mg L^{-1}.[15] The optimal dosage of phenobarbital was proposed based on the therapeutic range of phenobarbital, that is, C_{max} ≤40 mg L^{-1},[44] and C_{min} ≥15 mg L^{-1}.[42] The predicted pharmacokinetic parameters are presented as mean ± standard deviation (SD).

RESULTS

Model validation

The AAFEs for overall (both quinine and phenobarbital), quinine, and phenobarbital ranged from 1.08 ± 0.07,[36] 1.07 ± 0.076,[32,36–38] and 1.13,[39] respectively. The overall AAFEs were within accepted ranges[40] (Table S1). In addition, the overall errors were within 20% of the published data. The virtual predictive checks between the predicted results and published data are shown in the supplementary material file (Figure S1).

Sensitivity analysis

None of the sensitivity coefficient analysis values for phenobarbital clearance (phenobarbital model) in the wild-type *CYP2C19*EM, CYP*2C19*1/*3*PM, and *CYP2C19*PM were lower than 1 (Figure S2a,b,d). However, the coefficients in 3 of 18 in *CYP2C19*1/*2*IM were higher than 1 (Figure S2c). The visual comparative figures between *CYP2C19*EM (wild-type) and *CYP2C19*PM are shown in Figure S2e. For quinine (DDI model), only 2 of 34 model parameters in Scenario I were higher than 1 (Figure S3). The sensitivity coefficient over 1 indicates the high sensitivity of quinine clearance in the DDI model to these model parameters.

Simulation of standard dose regimen of phenobarbital in patients with seizures with polymorphic *CYP2C19*

Simulation based on standard DDI study approach

Results of the simulation of potential dose regimens (multiple dosing) of phenobarbital (C_{max}, C_{min}, and clearance)

in patients with wild-type *CYP2C19*EM and *CYP2C19*IM (*CYP2C19*1/*2* and *CYP2C19*1/*3*) and CYP2C19PM are summarized in Table S2. Phenobarbital plasma concentrations for individuals with all *CYP2C19* genotypes are shown in Figure S4A–D). The average values of all parameters in all genotypes were within the therapeutic range.

Simulation based on actual clinical use only

Results of the simulation of potential dose regimen (single and multiple dosing) of phenobarbital (C_{max}, C_{min}, and clearance) in patients with *CYP2C19*EM, *CYP2C19*IM, and *CYP2C19*PM are summarized in Table S3. Phenobarbital plasma concentrations for all genotypes are shown in Figure S5 and Figure S6 for Scenarios I and II, respectively. The average values in all genotypes were within the therapeutic range.

Simulation of the potential dose of quinine when coadministered with phenobarbital in patients with cerebral malaria with concurrent seizures and polymorphic *CYP2C19*

Results (C_{min}, C_{max}, area under the curve ratio [AUCR], and C_{max} ratio) of the simulation of the standard dose of quinine when coadministered with phenobarbital in patients with cerebral malaria with concurrent seizures (Scenario I, single seizure; Scenario II, multiple seizures) and polymorphic *CYP2C19* based on the standard DDI and actual clinical use study approaches are summarized in Table S4.

Simulation based on standard DDI study approach

The standard dose regimen of quinine did not provide optimal plasma drug concentrations when coadministered with phenobarbital (C_{min} < 10 mg L^{-1}; Table S4). The initial regimen (Regimen 1: a loading dose of 2000 mg i.v. infusion for 4 h followed by maintenance doses of 1000 mg i.v. infusion for 4 h given three times a day) in patients with wild-type and polymorphic *CYP2C19* provided a twofold increase of quinine concentrations compared with standard quinine regimen. Regimen 1 provided C_{max} exceeding 20 mg L^{-1} but C_{min} less than 10 mg L^{-1} both in wild-type and polymorphic *CYP2C19* (Figure S7A and Figure S6B–D for *CYP2C19*EM, *CYP2C19*1/*2*, and *CYP2C19*1/*3*, *CYP2C19*2/*2*, or *CYP2C19*3/*3*, respectively). The time to reach therapeutic concentration ranged from 2 to 3 h. Another subsequent dose regimen was simulated (Regimen 2: a loading dose of 2000 mg i.v. for 8 h followed by maintenance doses of 1200 mg continuous infusion until day 3 [72 h]). Plasma quinine concentration-time profiles in are shown in Figure 1A–D for the wild-type CYP2C19EM, *CYP2C19*1/*2*IM, and

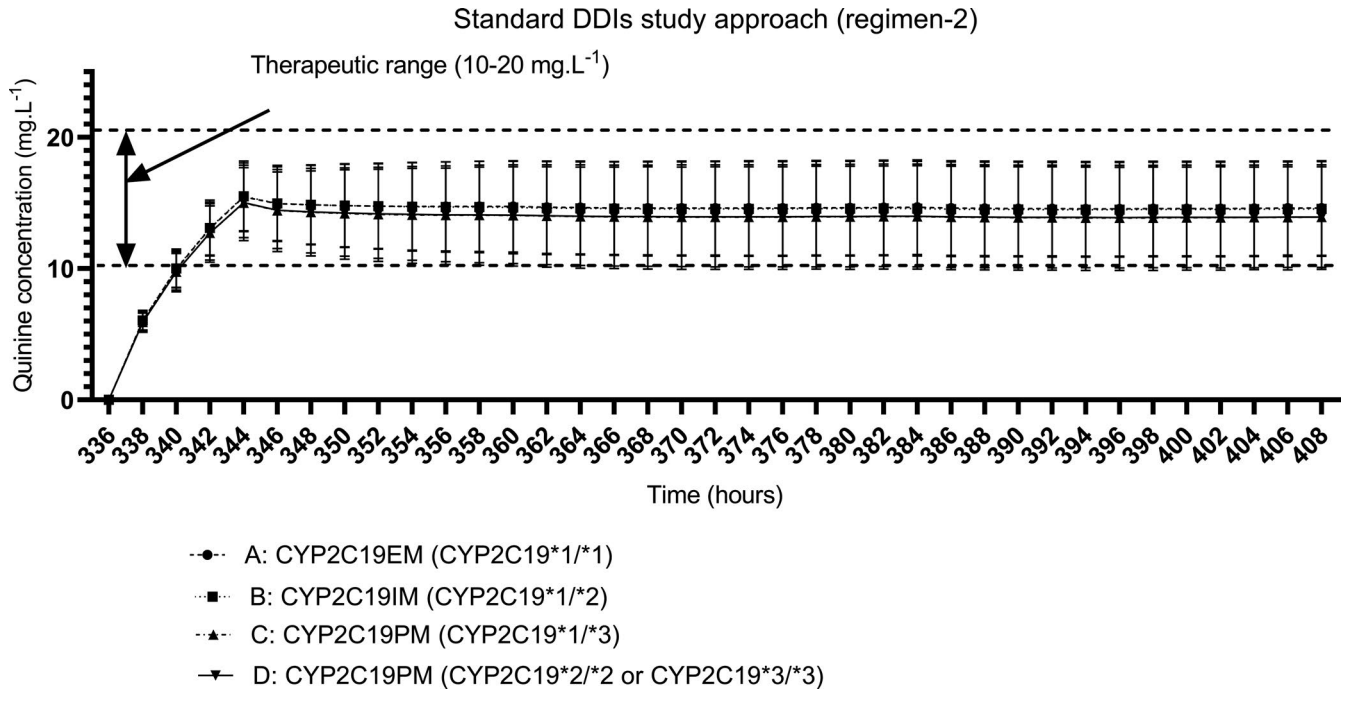

FIGURE 1 Prediction of quinine dose Regimen 2 in all genotypes based on a standard drug–drug interaction (DDI) study approach. CYP2C19EM, extensive metabolizer of CYP2C19; CYP2C19PM, poor metabolizer of CYP2C19; CYP2C19IM, intensive metabolizer of CYP2C19

*CYP2C19*1/*3* or *CYP2C19*PM, respectively). The time to reach therapeutic concentrations ranged from 4 to 6 h. The pharmacokinetic parameters (C_{max}, C_{min}, and clearance) for Regimens 1 and 2 are summarized in Table S5.

Simulation based on actual clinical use study approach

The standard dose regimen of quinine provided inappropriate plasma concentrations when coadministered with phenobarbital (C_{min} < 10 mg L^{-1}; Table S4). The twofold increase of quinine standard dose regimen (based on AUCR; Regimen 1: a loading dose of 2000 mg i.v. infusion for 4 h followed by 1000 mg i.v. for 4 h given three times a day) provided C_{max} exceeding 20 mg L^{-1} and C_{min} less than 10 mg L^{-1} in all genotypes in both scenarios. Plasma quinine concentration-time profiles in Scenarios I and II in the wild-type *CYP2C19*EM, *CYP2C19*1/*2*IM, and CYP2C19PM are shown in Figure S8 and Figure S9, respectively. Another subsequent dose regimen for Scenario I (single seizure) and Scenario II (multiple seizures) were simulated (Regimen 2: a loading dose of 2000 mg i.v. infusion for 8 h followed by 1200 mg i.v. continuous infusion until day 3 [72 h]). Plasma quinine concentration-time profiles for wild-type and polymorphic *CYP2C19* in Scenarios I and II are presented in Figure 2 and Figure 3, respectively. The pharmacokinetic parameters (C_{max}, C_{min}, and clearance) for Regimens 1 and 2 are summarized in Tables 1 and 2, respectively. Time to reach therapeutic quinine levels ranged from 4 to 6 h.

Simulation of the potential dose of quinine when coadministered with phenobarbital in patients with cerebral malaria with concurrent seizures and acute renal failure with lactic acidosis

Simulation based on actual clinical use study approach

The potential quinine dosage regimen (Regimen 2) when coadministered with phenobarbital in patients with different degrees of eGFR from Scenarios I and II was simulated. Plasma concentration–time profiles of quinine in patients in all groups were within the therapeutic range (Figure 4 and Figure 5 for Scenarios I and II, respectively). Therefore, no further subsequent dose regimens were simulated.

DISCUSSION

The current study successfully developed the DDI PBPK models. Although the sensitivity coefficients of some parameters were greater than 1, these parameters were obtained from experimental studies with low variability.

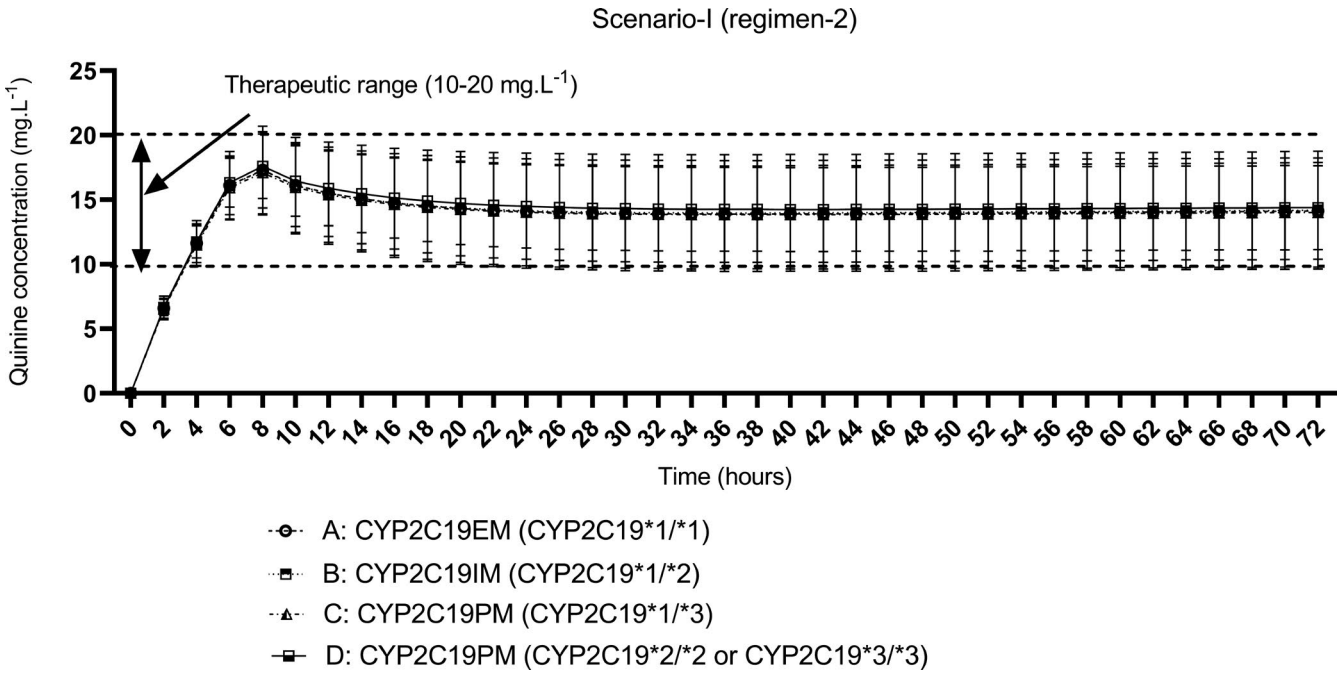

FIGURE 2 Prediction of quinine dose regimens in polymorphic CYP2C19 based on actual clinical use approach (Regimen 2; Scenario I). CYP2C19EM, extensive metabolizer of CYP2C19; CYP2C19PM, poor metabolizer of CYP2C19; CYP2C19IM, intensive metabolizer of CYP2C19)

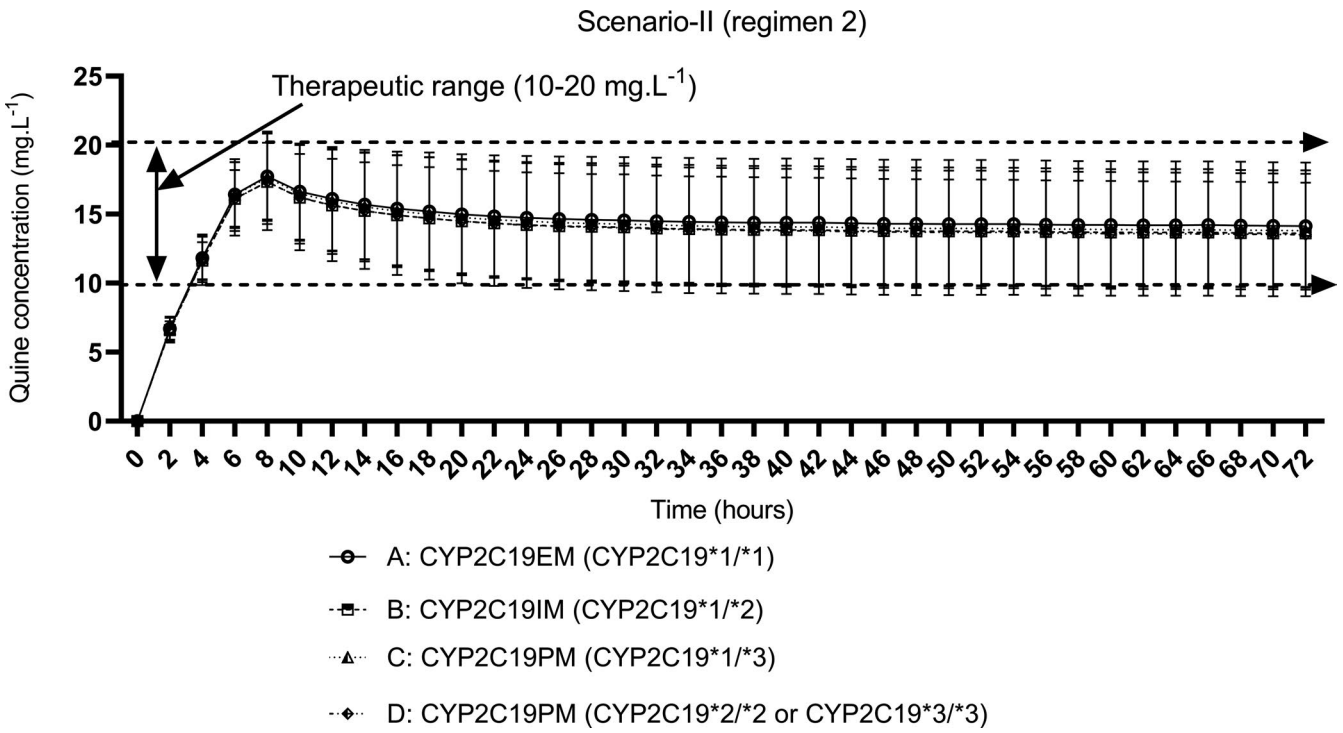

FIGURE 3 Prediction of quinine dose regimens in polymorphic CYP2C19 based on actual clinical use approach (Regimen 2; Scenario II). CYP2C19EM, extensive metabolizer of CYP2C19; CYP2C19PM, poor metabolizer of CYP2C19; CYP2C19IM, intensive metabolizer of CYP2C19

TABLE 1 Prediction of quinine dose regimens when coadministered with phenobarbital based on Scenario I

Regimen	C_{max} (mg L^{-1})	C_{min} (mg L^{-1})	Clearance (L h^{-1})
CYP2C19EM (*CYP2C19*1/*1*)			
Regimen 1 (loading dose of 2000 mg i.v. infusion for 4 h followed by 1000 mg i.v. infusion for 4 h [given every 8 h daily])	23.92 ± 3.32	9.13 ± 3.65	9.61 ± 2.82
Regimen 2 (loading dose of 2000 mg i.v. infusion for 8 h followed by 1200 mg i.v. infusion [given every 8 h daily])	17.33 ± 2.99	15.07 ± 3.92	10.19 ± 2.78
CYP2C19IM *(CYP2C19*1/*2)*			
Regimen 1 (loading dose of 2000 mg i.v. infusion for 4 h followed by 1000 mg i.v. infusion for 4 h [given every 8 h daily])	23.48 ± 3.97	8.97 ± 3.02	10.41 ± 3.17
Regimen 2 (loading dose of 2000 mg i.v. infusion for 8 h followed by 1200 mg i.v. infusion [given every 8 h daily])	17.33 ± 3.58	14.23 ± 4.15	10.36 ± 3.11
CYP2C19PM (*CYP2C19*1/*3*)			
Regimen 1 (loading dose of 2000 mg i.v. infusion for 4 h followed by 1000 mg i.v. infusion for 4 h [given every 8 h daily])	23.32 ± 3.33	9.03 ± 3.38	10.18 ± 3.03
Regimen 2 (loading dose of 2000 mg i.v. infusion for 8 h followed by 1200 mg i.v. infusion [given every 8 h daily])	17.18 ± 3.26	14.34 ± 4.21	10.40 ± 3.24
CYP2C19EM (*CYP2C19*2/*2* or *CYP2C19*3/*3*)			
Regimen 1 (loading dose of 2000 mg i.v. infusion for 4 h followed by 1000 mg i.v. infusion for 4 h [given every 8 h daily])	23.50 ± 3.32	8.97 ± 3.66	10.05 ± 3.21
Regimen 2 (loading dose of 2000 mg i.v. infusion or 8 h followed by 1200 mg i.v. infusion [given every 8 h daily])	17.59 ± 2.49	14.37 ± 4.12	9.71 ± 2.25

Note: Data are presented as mean ± SD.

Abbreviations: CYP2C19EM, extensive metabolizer of CYP2C19; CYP2C19PM, poor metabolizer of CYP2C19; CYP2C19IM, intensive metabolizer of CYP2C19; C_{max}, peak plasma concentration; C_{min}, minimal plasma concentration; EM, extensive metabolizer; i.v., intravenous; PM, poor metabolizer.

TABLE 2 Prediction of quinine dose regimens when coadministered with phenobarbital based on Scenario II

Regimen	C_{max} (mg L^{-1})	C_{min} (mg L^{-1})	Clearance (L h^{-1})
CYP2C19EM (*CYP2C19*1/*1*)			
Regimen 1 (loading dose of 2000 mg i.v. infusion for 4 h followed by 1000 mg i.v. infusion for 4 h [given every 8 h daily])	23.73 ± 3.12	8.1 ± 3.29	9.94 ± 2.72
Regimen 2 (loading dose of 2000 mg i.v. infusion for 8 h followed by 1200 mg i.v. infusion [given every 8 h daily])	17.87 ± 3.59	14.00 ± 4.45	9.99 ± 2.69
CYP2C19IM (*CYP2C19*1/*2*)			
Regimen 1 (loading dose of 2000 mg i.v. infusion for 4 h followed by 1000 mg i.v. infusion for 4 h [given every 8 h daily])	23.46 ± 3.18	8.40 ± 2.87	10.17 ± 2.83
Regimen 2 (loading dose of 2000 mg i.v. infusion for 8 h followed by 1200 mg i.v. infusion [given every 8 h daily])	17.42 ± 3.65	14.01 ± 4.94	10.53 ± 3.30
CYP2C19PM (*CYP2C19*1/*3*)			
Regimen 1 (loading dose of 2000 mg i.v. infusion for 4 h followed by 1000 mg i.v. infusion for 4 h [given every 8 h daily])	23.38 ± 3.26	8.23 ± 3.01	10.56 ± 3.09
Regimen 2 (loading dose of 2000 mg i.v. infusion for 8 h followed by 1200 mg i.v. infusion [given every 8 h daily])	17.67 ± 3.37	13.64 ± 3.93	10.28 ± 3.09
CYP2C19EM (*CYP2C19*2/*2* or *CYP2C19*3/*3*)			
Regimen 1 (loading dose of 2000 mg i.v. infusion for 4 h followed by 1000 mg i.v. infusion for 4 h [given every 8 h daily])	23.38 ± 3.17	8.25 ± 3.16	10.47 ± 3.00
Regimen 2 (loading dose of 2000 mg i.v. infusion for 8 h followed by 1200 mg i.v. infusion [given every 8 h daily])	17.37 ± 2.88	13.68 ± 3.94	10.34 ± 2.82

Note: Data are presented as mean ± SD.

Abbreviations: CYP2C19EM, extensive metabolizer of CYP2C19; CYP2C19PM, poor metabolizer of CYP2C19; CYP2C19IM, intensive metabolizer of CYP2C19; C_{max}, peak plasma concentration; C_{min}, minimal plasma concentration; EM, extensive metabolizer; i.v., intravenous; PM, poor metabolizer.

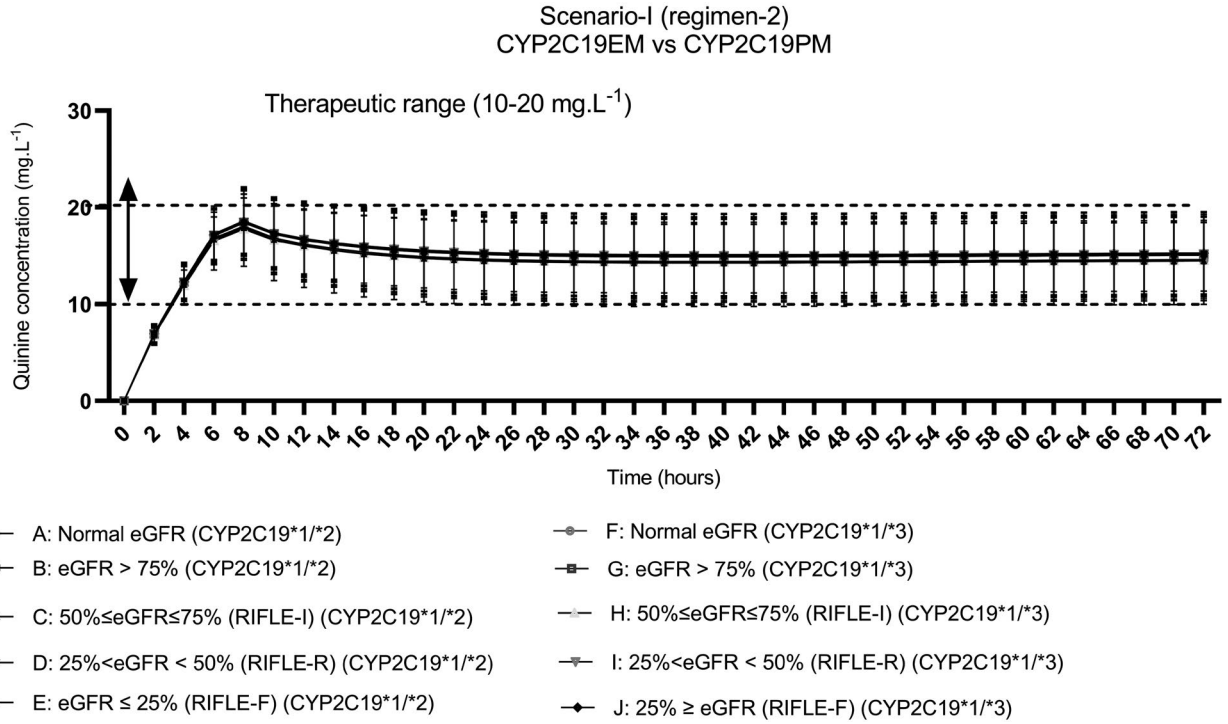

FIGURE 4 Prediction of quinine dose regimens based on actual clinical use approach (Scenario I) in patients with cerebral malaria with concurrent seizures and acute renal failure (corrected with lactic acidosis) who carry polymorphic CYP2C19EM (Regimen 2). CYP2C19EM, extensive metabolizer of CYP2C19; CYP2C19PM, poor metabolizer of CYP2C19; CYP2C19IM, intensive metabolizer of CYP2C19; eGFR, estimated glomerular filtration rate; RIFLE-F, risk, injury, failure, loss of kidney function and end-stage kidney disease–failure; RIFLE-I, risk, injury, failure, loss of kidney function and end-stage kidney disease–injury; RIFLE-R, risk, injury, failure, loss of kidney function and end-stage kidney disease–risk

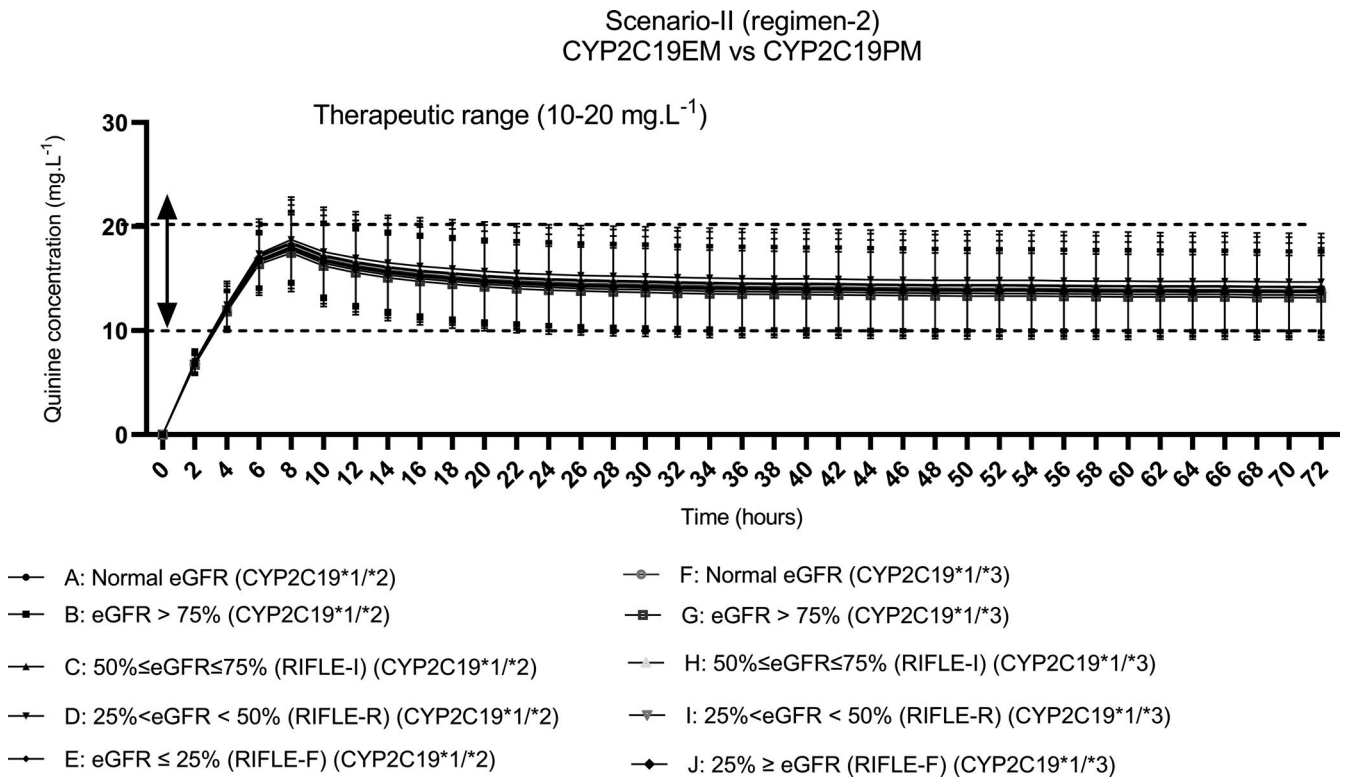

FIGURE 5 Prediction of quinine dose regimens based on actual clinical use approach (Scenario II) in patients with cerebral malaria with concurrent seizures and acute renal failure (corrected with lactic acidosis) who carry polymorphic CYP2C19EM and CYP2C19PM. CYP2C19EM, extensive metabolizer of CYP2C19; CYP2C19PM, poor metabolizer of CYP2C19; CYP2C19IM, intensive metabolizer of CYP2C19; eGFR, estimated glomerular filtration rate; RIFLE-F, risk, injury, failure, loss of kidney function and end-stage kidney disease–failure; RIFLE-I, risk, injury, failure, loss of kidney function and end-stage kidney disease–injury; RIFLE-R, risk, injury, failure, loss of kidney function and end-stage kidney disease–risk

The DDI PBPK models are therefore credible. Results of this study based on PBPK modeling and simulation raise a concern about the potential DDIs between quinine and phenobarbital when were coadministered in patients with cerebral malaria with concurrent seizures. The conventional dose adjustment based on the AUCR of both drugs in different clinical scenarios may provide suboptimal dose regimens with inadequate trough plasma levels, which will pose the patients at risk of treatment failure and/or severe complications. The PBPK modeling approach, on the other hand, has proved a promising tool for dose optimization of quinine and phenobarbital coadministration.

Potential phenobarbital dose regimens in patients with seizures with polymorphic *CYP2C19*

Simulation of the optimal phenobarbital dose regimens in patients with seizures who carry polymorphic *CYP2C19* was investigated using dose regimens based on the two approaches, that is, the standard DDI study approach (at steady state of phenobarbital level) and the actual clinical use study approach (Scenario I for single seizure and Scenario II for continuous seizures). Results supported the previous report of the decrease in total clearance of phenobarbital by 1% and 21% and 27% in patients carrying the *CYP2C19**1/*2IM, *CYP2C19*1/*3*PM, and *CYP2C19*PM (**2/*2* or **3/*3*) genotypes, respectively.[9] The reported frequencies of the wild-type, *CYP2C19*EM, and *CYP2C19*PM genotypes in the Thai population are 42%,[45] 2.8%,[46] and 13%,[45] respectively. Based on the results of PBPK modeling using both the DDI and actual clinical use study approaches, however, dosage adjustment of phenobarbital may not be required as plasma drug concentrations were maintained within the therapeutic range, that is, $C_{max} \leq 40$ mg L^{-1}[44] and $C_{min} \geq 15$ mg L^{-1}.[44] The proposed phenobarbital dosage regimens are optimal for the treatment of patients with single seizure (single dose of 900 mg or 15 mg kg^{-1}) as well as patients with cerebral malaria who have continuous seizures (a loading dose of 15 mg kg^{-1} day^{-1} followed by 1.5 mg kg^{-1} day^{-1} once daily) regardless of patients' *CYP2C19* genotypes. Genotyping is therefore not necessary, which is practical both in developed and developing countries. Also, the advantage of

using phenobarbital over other anticonvulsants is its relatively low cost.[5]

Potential quinine dose regimens when coadministered with phenobarbital in patients with cerebral malaria with concurrent seizures and polymorphic *CYP2C19*

Similarly to phenobarbital, simulation of the potential quinine dose regimens in patients with concurrent cerebral malaria and seizures with polymorphic *CYP2C19* were investigated using dose regimens based on the standard DDI study and actual clinical use (Scenarios I and II) study approaches. Dose optimization based on AUCR yielded undesirable plasma quinine concentrations when coadministered with phenobarbital. The recommended quinine dosage regimen obtained from the standard DDI approach or actual clinical study use approach was similar. Therefore, the standard DDI approach used could be satisfactorily applied in the real clinical scenarios.

Simulation based on standard approach

The proposed quinine dosage Regimen 2 provided adequate C_{min} above 10 mg L^{-1} and C_{max} under 20 mg L^{-1} in wild-type genotype and polymorphic *CYP2C19* (Figure 1A–D). Therefore, this regimen was considered as the recommended dosage regimen of quinine when coadministered with phenobarbital because it provided plasma quinine concentrations within the therapeutic range. It is noted, however, that the infusion duration of 8 h (continuous infusion) might result in the delay of time to reach therapeutic level compared with the recommended standard regimen (4–6 and 2–3 h for the potentially recommended and standard regimen, respectively). Because the critical period for treatment of patients with cerebral malaria is during the first 24 h,[31] such a delay is unlikely to pose the patients at risk of complicated manifestation or death.

Simulation based on actual clinical use study approach

Optimal C_{max} and C_{min} of quinine were achieved with adequate plasma concentrations following the proposed quinine dose regimen (Regimen 2) when coadministered with phenobarbital in both clinical scenarios (Scenario I for single seizure and Scenario II for continuous seizures) using PBPK modeling and simulation, but not the AUCR, (Figure 2A–D for Scenario I and Figure 3A–D for Scenario II). This quinine regimen can be coadministered with phenobarbital without consideration of *CYP2C19* genotypes because plasma quinine concentrations in patients with wild-type and polymorphic *CYP2C19* were comparable. There is no influence of *CYP2C19* genotypes on the inducing effect of quinine metabolism because the steady-state drug concentrations are not achieved with a short duration of phenobarbital dosing. It is noted that the recommended dose regimens of quinine and phenobarbital coadministration apply to patients with cerebral malaria with seizures who have normal hepatic function but not in those with impaired function. Therapeutic drug monitoring for quinine in those patients is recommended.

Simulation of the potential dose of quinine when coadministered with phenobarbital in patients with cerebral malaria with concurrent seizures and acute renal failure with lactic acidosis

Simulation based on actual clinical use study approach

The recommended quinine dosage regimen in patients with cerebral malaria with seizure without acute renal failure and lactic acidosis can be applied to patients who have acute renal failure and lactic acidosis because plasma quinine concentrations were within the therapeutic range (Figure 4 and Figure 5 for Scenarios I and II, respectively). Thus, no dosage adjustment was needed. It was noted for the absence of influence of the state of acute renal failure (decrease of eGFR) on plasma quinine concentrations due to low renal excretion of quinine and phenobarbital.

The limitations of the study include the exclusion of the contribution of P-glycoprotein transporter on quinine disposition (due to lack of information on in vitro studies) as well as the inhibitory effect of 3-hydroxyquinine metabolite on CYP3A4 activity. Nevertheless, the significant impacts of these two factors on quinine disposition are unlikely.[16] Because of the limited information on phenobarbital i.v. infusion in patients, one publication in healthy volunteers was used for phenobarbital model validation. Relying on the data only from one publication may be insufficient for model validation. Malaria infection may change the pharmacokinetics of phenobarbital through alteration of f_u, although there is no evidence to support such supposition. In addition, most sensitivity

coefficients of the model parameters used for construction of the phenobarbital PBPK models were lower than 1, indicating the insensitivity of the model to the changing of parameters.

In conclusion, PBPK modeling is a promising tool for dose optimization of quinine in patients with cerebral malaria in resource-limited countries. The developed PBPK models for phenobarbital and quinine–phenobarbital coadministration are reliable. They successfully predicted the optimal doses regimens of phenobarbital in patients with cerebral malaria with single or continuous seizures with no requirement of *CYP2C19* genotyping. Dose adjustment based on PBPK modeling but not AUCR provided desirable plasma quinine concentrations. Dose adjustment of the standard regimen of phenobarbital is not required when coadministered with quinine. The proposed potential dose regimen for quinine when coadministered with phenobarbital for patients with a single seizure (Scenario I) and continuous seizures (Scenario II) in all malaria-endemic areas regardless of *CYP2C19* genotypes is a loading dose of 2000 mg i.v. infusion for 8 h followed by 1200 mg i.v. continuous infusion until day 3 (72 h).

CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

T.S., J.K., and K.N. wrote the manuscript. T.S., J.K., M.S., and K.N. designed the research. T.S., R.K.R.R., and M.S. performed research. T.S., R.K.R.R., M.S., and K.N. analyzed the data. T.S., R.K.R.R., and M.S. contributed new reagents/analytical tools.

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SUPPORTING INFORMATION

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