Physiologically-based Pharmacokinetic (PBPK) Modeling for Prediction of the Optimal Dose Regimens of Quinine and Phenobarbital Co-administration in Adult Patients with Cerebral Malaria and Seizures

Teerachat Saeheng
Thammasat University
Juntra Karbwang
Thammasat University
Rajith Kumar Reddy Rajoli
University of Liverpool
Marco Siccardi
University of Liverpool
Kesara Na-Bangchang (kesaratmu@yahoo.com)
Chulabhorn International College of Medicine https://orcid.org/0000-0001-6389-0897

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Title page

Physiologically-based pharmacokinetic (PBPK) modeling for prediction of the optimal dose regimens of quinine and phenobarbital co-administration in adult patients with cerebral malaria and seizures

Teerachat Saeheng[1], Juntra Karbwang[1,2], Rajith Kumar Reddy Rajoli[3], Marco Siccardi[3], and Kesara Na-Bangchang[1,2*]

1. Center of Excellence in Pharmacology and Molecular Biology of Malaria and Cholangiocarcinoma, Chulabhorn International College, Thammasat University, Pathumthani, Thailand
2. Drug Discovery and Development Center, Office of Advanced Science and Technology, Thammasat University, Thailand
3. Department of Molecular and Clinical Pharmacology, University of Liverpool, United Kingdom

Correspondence

K Na-Bangchang, Chulabhorn International College of Medicine, Thammasat University, Rangsit Campus, 99 Moo 18 Phaholyothin Road, Klong Luang District, Pathumthani 12121, Thailand

Email: kesaratmu@yahoo.com

Abstract

Background: Cerebral malaria is a fatal disease. Patients with cerebral malaria are at risk of seizure development, therefore, the co-administration of antimalarial and antiepileptic drugs are needed. Quinine and phenobarbital are standard drugs for the treatment of cerebral malaria with seizures. However, there is no information on the optimal dosage regimens of both drugs when used concomitantly.T he study applied physiologically-based pharmacokinetic (PBPK) modeling for prediction of the optimal dose regimens of quinine and phenobarbital when co-administered in patients with cerebral malaria and concurrent seizures who carry wild type and polymorphic cytochrome P450 (CYP450) *2C9/2C19*.

Methods: The whole-body PBPK models for quinine and phenobarbital were constructed based on the previously published information using Simbiology®. One hundred virtual population were simulated. Four published articles were used for model verification. Sensitivity analysis was carried out to determine the effect of the changes in model parameters on $AUC_{0–72h}$. Simulation of optimal dose regimens was based on standard drug-drug interactions (DDIs), and actual clinical use study approaches.

Results: Dose adjustment of the standard regimen of phenobarbital is not required when co-administered with quinine. The proposed optimal dose regimen for quinine, when co-administered with phenobarbital for patients with a single or continuous seizure in all malaria-endemic areas regardless of *CYP2C9/CYP2C19* genotypes, is a loading dose of 1,500 mg IV infusion over 8 hours, followed by 1,200 mg infusion over 8 hours given three times daily, or multiple doses of 1,400 mg IV infusion over 8 hours, given three times daily. In areas with quinine resistance, the dose regimen should be increased as a loading dose of 2,000 mg IV infusion over 8 hours, followed by 1,750 mg infusion over 8 hours given three times daily.

Conclusion: The developed PBPK models are reliable, and successfully predicted the optimal doses regimens of quinine-phenobarbital co-administration with no requirement of *CYP2C9/CYP2C19* genotyping.

Keywords

Physiologically-based pharmacokinetic (PBPK) modeling, quinine, phenobarbital, cerebral malaria, seizure, cytochrome P450, drug-drug interactions

Background

Cerebral malaria remains a high burden neurological problem in sub-Saharan African countries with an increased risk of seizures [1]. Quinine is the standard antimalarial drug for the treatment of severe malaria, including cerebral malaria [1]. Phenobarbital, a cost-effective antiepileptic drug, is the standard treatment for cerebral malaria patients with seizures [2, 3]. Phenobarbital-induced severe cutaneous adverse reactions are, however, an issue of concern for clinical use of this drug [4]. Information on the contribution of host genetics on such reactions in cerebral malaria patients with seizures has been limited. Since phenobarbital induces xenobiotic drug-metabolizing enzymes cytochrome P450 (CYP450), the situation is further complicated when it is co-administered with drugs that are also metabolized by CYP450 enzymes. Phenobarbital is metabolized mainly in the livers by the polymorphic isoforms -- CYP2C9 and CYP2C19 [5, 6]. Quinine, on the other hand, is metabolized by CYP3A4 and UDP-glucuronosyltransferase 1A1 (UGT1A1) enzymes [7]. The activity of both enzymes is induced by phenobarbital [8, 9]. Cerebral malaria patients with polymorphic *CYP2C9/CYP2C19* genotypes who receive concomitant treatment with quinine and phenobarbital are, therefore, at risk of inadequate or toxic therapeutic drug concentrations due to metabolic drug interactions. To our knowledge, there have been few reports on the optimal phenobarbital dose for patients with epilepsy [5, 6], but not for cerebral malaria patients with seizures who carry polymorphic *CYP2C9* and *CYP2C19*. Besides, the optimal dosage of quinine when co-administered with phenobarbital has not been reported in this group of patients.

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 [10]. The present study aimed to apply PBPK modeling

and simulation for optimization of quinine and phenobarbital co-administration in adult patients with cerebral malaria and seizures, with consideration of genetic polymorphisms of *CYP2C9/CYP2C19* and DDIs.

Methods

Model construction

The whole-body PBPK models for quinine and phenobarbital (alone and co-administration) were constructed based on the previously published information [11, 12] using Simbiology® (version 5.8.2), the product of MATLAB® (version 2019a) (MathWorks, Natick, MA, USA). The physicochemical and biochemical properties (model parameters) of each drug, including human physiological parameters, were obtained from the published articles are available in the supplementary material of this article [9, 11, 13-25] (Additional file 1).

Model assumptions included the limitation of blood-flow, immediate dissolution of each drug in the gastrointestinal tract, absence of drug absorption in the stomach and large intestine, absence of enterohepatic recirculation, and absence of effect of 3-hydroxyquinine (quinine metabolite) on quinine disposition.

Model verification

Four published articles for quinine [26-29] and one article for phenobarbital [30] were used for model verification. The published data were extracted using Plot digitizer® version 2.6.8 (Free Software Foundation, Inc., Boston, MA, USA). The area under the plasma concentration-time curve (AUC) was calculated based on the trapezoidal rule using the Excel spreadsheet. The simulated results from the developed models were compared against the published data, using the accepted criterion --absolute average-folding errors (AAFEs) of $\pm$ 2-fold [31]. The mathematical equation for AAFEs is given below:

$$AAFE=10^{(\Sigma abs(\log(prediction/observation))/n)}$$

Where n is the number of samples. The prediction is the simulated results from the developed model, and the observation is the published clinical data.

Sensitivity analysis (the study of the uncertainty of certain model input parameters on the model output)

Sensitivity analysis was performed to determine the effect of the changes in model parameters on the AUC during the first 72 hours ($AUC_{0–72h}$) following the standard intravenous (IV) regimen of quinine (quinine model) or phenobarbital (phenobarbital model) or quinine and phenobarbital co-administration (DDIs model). The model parameters for sensitivity analysis of the quinine model were a fraction of unbound drug (f_u), a fraction of UGT1A1 on total metabolism ($f_{m,UGT1A1}$), a fraction of CYP3A4 on total metabolism ($f_{m,CYP3A4}$), inhibitor concentration that produces half-maximal inhibition (Ki3A4), and blood-to-plasma partition ratio (R_{bp}). The model parameters for phenobarbital were f_u, R_{bp}, half-maximal effective concentrations ($EC_{50,2C9}$), maximum effect at the maximum concentration ($EC_{max,2C9}$), a fraction of CYP2C9 on total metabolism ($f_{m,CYP2C9}$), and a fraction of CYP2C19 on total drug metabolism ($f_{m,CYP2C19}$). The model parameters for DDIs included E_{max3A4}, $EC_{50,3A4}$, $EC_{50,UGT1A1}$, and $E_{max,UGT1A1}$. The effect of the changes in model parameters on the $AUC_{0–72h}$ was determined by the change of each model parameter within ±20%. The mathematical equation for sensitivity analysis is given below:

Sensitivity coefficient = %Y/%X

Where %Y is the percent change of the $AUC_{0–72h}$ and %X is the percent change of the model parameter.

Virtual population simulation

One hundred virtual population (50 males and 50 females, aged 18-60 years, weighing 60 kg, fasting state) were simulated in (i) seizure patients with polymorphic *CYP2C9/CYP2C19* (phenobarbital model), (ii) patients with cerebral malaria (quinine model), and (iii) patients with cerebral malaria and seizures with polymorphic *CYP2C9/CYP2C19* (DDIs model). The intrinsic clearance of phenobarbital in each genotype was obtained from the published clinical data for wild type [*CYP2C9* extensive metabolizer (EM)/*CYP2C19*EM] [6], *CYP2C9*1/*1CYP2C19*1/*3* [*CYP2C9*EM/*CYP2C19* poor metabolizer (PM)] or *CYP2C9/CYP2C19*2/*2* (*CYP2C9*EM/*CYP2C19*PM) or *CYP2C9*/*CYP2C19*3/*3* (*CYP2C9*EM/*CYP2C19*PM) [5, 6], and *CYP2C9*1/*3/CYP2C19*1/*1* (*CYP2C9*PM/*CYP2C19*EM) [32].

Quinine and phenobarbital dose regimens used in simulations

The standard regimen of quinine for severe malaria is the loading dose of 20 mg kg^{-1} (1,000 mg base total dose for the average 60 kg body weight) IV infusion over 4 hours, followed by the maintenance dose of 10 mg kg^{-1} (500 mg base total dose for the average 60 kg body weight) IV infusion over 4 hours, given three times daily (every 8 hours) [1] for 72 hours. The simulation time used was based on the average time for patients with cerebral malaria to regain consciousness (72 hours) [28].

DDIs model simulation

Simulation based on standard DDIs study approach: For standard DDIs study approach, plasma concentration-time profiles of phenobarbital and quinine following the co-administration of standard dose regimen of phenobarbital and quinine were simulated. Phenobarbital is given at 2 mg $kg^{-1}day^{-1}$ (1-3 $mg.kg^{-1}.day^{-1}$) or 120 mg total dose for the

175 average 60 kg body weight) IV infusion over 30 minutes for 17 consecutive days. The
176 standard dose regimen of quinine for three days (described above) was given on day 14 of
177 phenobarbital administration when steady-state plasma concentration was achieved.
178 *Simulation based on actual clinical use approach:* For the PBPK simulation based on actual
179 clinical use study approach, two simulated scenarios were applied with the total simulation
180 time of 72 hours. The scenario-I applies for patients who have only a single seizure;
181 phenobarbital (15 mg kg^{-1} or 900 mg total dose for the average 60 kg body weight, IV
182 infusion over 30 minutes) is given as a single dose 6 hours after the first dose of quinine
183 (average time of occurrence of seizure after admission) [33]. The scenario-II applies for
184 patients who have continuous seizures; phenobarbital at a loading dose of 15 mg kg^{-1} or 900
185 mg total dose for the average 60 kg body weight IV infusion over 30 minutes, followed by
186 the maintenance dose of 1.5 mg $kg^{-1}day^{-1}$ (1-3 $mg.kg^{-1}$ day^{-1}) or 90 mg total dose for average
187 60 kg body weight IV infusion over 30 minutes [33] is given every 24 hours, starting 6 hours
188 after the first dose of quinine until 72 hours. The time of simulation and seizure frequency
189 was based on the clinical report [34]. The predicted optimal dosage regimens were presented
190 as amount of quinine base.
191
192 **Criteria for optimal dose regimens**
193 The optimal dose regimens of quinine for adult patients with cerebral malaria with seizures
194 were proposed based on the therapeutic range of quinine, *i.e.,* maximum plasma
195 concentration (C_{max}) ≤ 20 $mg.L^{-1}$, and trough plasma concentration (C_{trough}) ≥ 10 $mg.L^{-1}$ [35].
196 The optimal dosage of phenobarbital were proposed based on the therapeutic rage of
197 phenobarbital: C_{max} ≤ 40 $mg.L^{-1}$ [36], and C_{trough} ≥ 15 $mg.L^{-1}$ [33]. The predicted
198 pharmacokinetic parameters are presented as mean (95% confidence interval or CI).
199

Results

Model verification

The AAFEs for quinine and phenobarbital, quinine alone, and phenobarbital alone ranged from 1.17 (1.03-1.21) [26-30], 1.14 (1.03-1.21) [26-29], and 1.20 [30], respectively. All were within accepted ranges [31], indicating the reliability of the PBPK models (Table 1). Visual Predictive Checks (VPCs) between predicted results and published data are shown in Additional file 2.

Sensitivity analysis

Sensitivity coefficient analysis values for $AUC_{0\text{-}72h}$ of quinine, phenobarbital, and quinine and phenobarbital co-administration ranged from -0.72 to +0.14, -0.02 to +0.10, and -0.48 to +0.12, respectively. All values were less than one, indicating no significant impact of the model parameters on model construction.

Simulation of standard dose regimen of phenobarbital in patients with seizures with polymorphic *CYP2C9* and *CYP2C19*

Simulation based on standard DDIs study approach: Results of the simulation of optimal dose regimens of phenobarbital (C_{max}, C_{trough}, and clearance) in patients with wild type (*CYP2C9*EM/*CYP2C19*EM) and polymorphic *CYP2C9*EM/*CYP2C19*PM, and *CYP2C9*PM/*CYP2C19*EM are summarized in Table 2**.** The average values of all parameters in all genotypes were within the therapeutic range.

Simulation based on actual clinical use study approach: Results of the simulation of optimal dose regimens (single and multiple dosing) of phenobarbital (C_{max}, C_{trough}, and clearance) in patients with wild type (*CYP2C9*EM/*CYP2C19*EM) and polymorphic

*CYP2C9*EM/*CYP2C19*PM, and *CYP2C9*PM/*CYP2C19*EM are summarized in Table 3. The average values of all parameters in all genotypes were within the therapeutic range.

Simulation of the optimal dose of quinine when co-administered with phenobarbital in cerebral malaria patients with concomitant seizures and polymorphic *CYP2C9/CYP2C19*

Results (C_{trough}, C_{max}, AUC ratio or AUCR, and C_{max} ratio or $C_{max}R$) of the simulation of the standard dose of quinine, when co-administered with phenobarbital in cerebral malaria patients with concomitant seizures (*scenario I:* single seizure, and *scenario II:* continuous seizures) and polymorphic CYP2C9/CYP2C19 based on DDI and actual clinical use study approaches, are summarized in Table 4.

Simulation based on standard DDIs study approach: Standard dose regimen of quinine provided inappropriate plasma drug concentrations when co-administered with phenobarbital (C_{trough} < 10 $mg.L^{-1}$) (Table 4). The initially proposed quinine (*regimen-1*: a loading dose of 2,200 mg IV infusion over 4 hours, followed by maintenance doses of 1,200 mg IV infusion over 4 hours given three times daily) in patients with wild type and polymorphic *CYP2C9/CYP2C19* provided 2.2-fold lower plasma drug concentrations compared with standard quinine regimen, with AUCR ranging from 0.42 to 0.45. This 2.2-fold increase of quinine standard dose provided the C_{max} exceeding 20 $mg.L^{-1}$, but the C_{trough} lower than 10 $mg.L^{-1}$ both in patients with wild type and polymorphic *CYP2C9/CYP2C19* (Fig. 1, and Fig. 2 for wild type and polymorphic *CYP2C9/CYP2C19,* respectively) (Table 5). The time to reach therapeutic concentration ranged from 2 to 3 hours. The three subsequent dose regimens were therefore simulated, *e.g.,* a loading dose of 2,200 mg IV infusion, followed by 2,000 mg IV infusion (*regimen-2*), a loading dose of 2,000 mg IV infusion, followed by 1,500 mg IV infusion (*regimen-3*), and a loading dose of 1,750 mg IV infusion, followed by 1,500 mg IV infusion (*regimen-4*). All regimens were given as IV infusion over 8 hours, and

the maintenance doses were given three times daily. The average C_{max} and C_{trough} (95%CI) for each regimen (-2, -3, and -4) are shown in Fig. 1 (wild type), and Fig. 2 (polymorphic *CYP2C9/CYP2C19*) (Table 5). The time to reach therapeutic concentration ranged from 4 to 6 hours.

Simulation based on actual clinical use study approach: Standard dose regimen of quinine provided inappropriate plasma drug concentrations when co-administered with phenobarbital (C_{trough} < 10 mg.L^{-1}) (Table 4). Dose adjustment in both clinical scenarios based on standard dosage regimen of quinine provided the AUCR of quinine when co-administered with phenobarbital in patients with wild type genotype, and polymorphic *CYP2C9/CYP2C19* ranging from 0.47 to 0.53 (Table 4). The 2-fold increase of quinine standard dose (*regimen-5*: a loading dose of 2,000 mg IV infusion over 4 hours, followed by maintenance doses of 1,000 mg IV infusion over 4 hours given three times daily) provided the concentrations out of therapeutic range (C_{max} > 20 mg.L^{-1}, and C_{trough} < 10 mg.L^{-1}) both in patients with wild type and polymorphic *CYP2C9/CYP2C19* (Fig. 3 (scenario I and II), Fig. 4 (scenario I), and 5 (scenario II) for wild type and polymorphic *CYP2C9/CYP2C19,* respectively) (Table 6 and 7 for scenario I and scenario II, respectively). The three subsequent dose regimens for the scenario I (single seizure) and II (multiple seizures) were therefore simulated, *i.e..,* a loading dose of 2,000 mg IV infusion, followed by 1,750 mg IV infusion three times daily (*regimen-6*), a loading dose of 1,500 mg IV infusion, followed by 1,200 mg IV infusion three times daily (*regimen-7*), and multiple doses of 1,400 mg IV infusion three times daily (*regimen-8*). The IV infusion duration in all regimens was 8 hours, and the maintenance doses were given three times daily. The average C_{max}, and C_{trough} (95%CI) of quinine for wild type genotype in each simulation are shown in Fig. 3**,** and those for polymorphic *CYP2C9/CYP2C19* for the *scenario I* and *scenario II* are presented in Fig. 4 and Fig. 5, respectively. Table 5, 6, and 7 summarize the parameters predicted based on standard DDI and actual clinical use (single

and continuous seizures) study approach, respectively. Time to reach therapeutic quinine levels ranged from 4 to 6 hours. Plasma quinine concentrations following *regimen-7* and *-8* except *regimen-5 and -6* were within the therapeutic range for both *scenarios I* and *scenario II.* The C_{max} of quinine following *regimen-6* in both scenarios ranged from 21-23 $mg.L^{-1}$.

Discussion

Results of the current study based on PBPK modeling and simulation raise a concern about the potential DDIs between quinine and phenobarbital in patients with cerebral malaria who have seizures and require concurrent treatment with both drugs. 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 pose the patients at risk of treatment failure and/or severe complication. The PBPK modeling approach, on the other hand, has proved a promising tool for dose optimization of quinine and phenobarbital co-administration.

Optimal phenobarbital dose regimens in patients with seizures with polymorphic *CYP2C9* and *CYP2C19*

Simulation of the optimal phenobarbital dose regimens in patients with seizures who carry polymorphic *CYP2C9/CYP2C19* was investigated using dose regimens based on the two approaches, *i.e.,* the standard DDIs 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 of the present study supported the previous report of the decrease in total clearance of phenobarbital by 48.2% [32] and 20% [5, 6] in patients carrying *CYP2C9*PM/*CYP2C19*EM and *CYP2C9*EM/*CYP2C19*PM genotypes, respectively. The reported frequencies of the wild type, *CYP2C9*PM/*CYP2C19*EM, and

300 *CYP2C9*EM/*CYP2C19*PM genotypes in the Thai population are 42% [37], 2.8% [38], and
301 13% [37], respectively. Based on the results of PBPK modeling using both DDIs and actual
302 clinical use study approaches, however, dosage adjustment of phenobarbital may not be
303 required as plasma drug concentrations were maintained within the therapeutic range ($C_{max} \leq$
304 40 $mg.L^{-1}$ [36], and $C_{trough} \geq 15$ $mg.L^{-1}$ [33]) (Table 2 and 3). The proposed phenobarbital
305 dosage regimens are optimal for the treatment of patients with single seizure (single dose of
306 900 mg or 15 mg. kg^{-1}), as well as patients with cerebral malaria who have continuous
307 seizures (a loading dose of 15 mg. $kg^{-1}.day^{-1}$, followed by 1.5 $mg.kg^{-1}.day^{-1}$ once-daily)
308 regardless of patients' *CYP2C9/CYP219* genotypes. Genotyping is therefore not necessary,
309 which is practical both in developed and developing countries. Besides, the advantage of
310 using phenobarbital over other anticonvulsants is its relatively low cost [2].
311
312 **Optimal quinine dose regimens when co-administered with phenobarbital in cerebral**
313 **malaria patients with concomitant seizures and polymorphic *CYP2C9/CYP2C19***
314 Similarly to phenobarbital, simulation of the optimal quinine dose regimens in patients with
315 concurrent cerebral malaria and seizures with polymorphic *CYP2C9/CYP2C19* were
316 investigated using dose regimens based on standard DDIs study and actual clinical use
317 (scenario I and II) study approaches. Dose optimization based on AUCR yielded undesirable
318 plasma quinine concentrations when co-administered with phenobarbital.
319 *Simulations based on standard DDIs approach:* The three proposed quinine dosage
320 regimens, *i.e., regimen-2, -3* and *-4*) provided adequate C_{trough} above 10 $mg.L^{-1}$ in both
321 wildtype genotype (Fig 1B, C, D for *regimen-2, 3,* and *-4,* respectively) and polymorphic
322 *CYP2C9/CYP2C19* (Fig 2B, C, D for *regimen-2, -3*, and *-4,* respectively). Nevertheless,
323 *regimen-2* (a loading dose of 2,200 mg IV infusion over 8 hours, followed by 2,000 mg IV
324 infusion over 8 hours given three times daily) is not appropriate for clinical use due to high

drug concentrations above 20 $mg.L^{1}$ in individuals with both wild type and polymorphic *CYP2C9/CYP2C19* and thus, the possibility of toxicity. Since the reported minimum inhibitory concentration (MIC) of quinine in quinine-resistant areas has been rising to over 10 $mg.L^{-1}$ [39], the most optimal dose regimen would be *regimen-3* (a loading dose of 2,000 mg IV infusion over 8 hours, followed by 1,500 mg IV infusion over 8 hours given three times daily). In low quinine resistant malaria-endemic areas, *regimen-4* (a loading dose of 1,750 mg IV infusion over 8 hours, followed by 1,500 mg IV infusion three times daily) could be an alternative regimen. It is noted, however, that the infusion duration of 8 hours might result in the delay of time to reach therapeutic level compared with the recommended standard regimens (4-6 and 2-3 hours for the recommended and standard regimens, respectively). Since the critical clinical period for treatment of patients with cerebral malaria is during the first 24 hours [27], such delay is unlikely to pose the patients at risk of complicated manifestation or death. These quinine regimens can be co-administered with phenobarbital without consideration of *CYP2C9/CYP2C19* genotypes.

Simulations based on actual clinical use study approach: Optimal C_{max} and C_{trough} of quinine were achieved with the two proposed quinine dose regimens (*regimen-7* and *-8)* when co-administered with phenobarbital in both clinical scenarios (scenario I for a single seizure and scenario II for continuous seizures) using PBPK modeling and simulation, but not the AUCR, resulted in adequate plasma concentrations (Fig. 3, Fig. 4, and Fig. 5 for wild type, the scenario I in polymorphic *CYP2C9/CYP2C19,* and scenario II in polymorphic *CYP2C9/CYP2C19,* respectively). With the administration time of quinine 6 hours prior to phenobarbital in actual clinical study approach, the optimal quinine dosage regimens can be reduced as a loading dose of 2,000 mg IV infusion over 8 hours, followed by 1,750 mg IV infusion three times daily (*regimen-6*), or alternatively, 1,500 mg IV infusion, followed by 1,200 mg IV infusion (*regimen-7*), or 1,400 mg IV infusion over 8 hours given three times

daily (*regimen-8*). These quinine regimens can be co-administered with phenobarbital without consideration of *CYP2C9/CYP2C19* genotypes since plasma quinine concentrations in patients with wild type, and polymorphic *CYP2C9/CYP2C19* were comparable. There is no influence of CYP2C9/CYP2C19 genotypes on the inducing effect of quinine metabolism since the steady-state drug concentrations are not achieved with a short duration of phenobarbital dosing. The possibility of dose reduction could be due to the lack of CYP450 enzyme-inducing effect of phenobarbital during this period (6 hours). In the case of quinine resistant malaria, particularly with the contribution of large interindividual variability in quinine clearance, quinine *regimen-6* would be the best option. The higher C_{max} of 1-3 $mg.L^{-1}$ above the therapeutic range is unlikely to cause toxicity due to high plasma protein binding during the acute phase of malaria infection. It is noted that the recommended optimal dose regimens of quinine and phenobarbital co-administration apply for cerebral malaria patients with seizures who have normal hepatic function but not in those with impaired function. Therapeutic drug monitoring for quinine in those patients is recommended.

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 [11].

In summary, PBPK models are a potential tool for dose optimization of quinine in patients with cerebral malaria in resource-limited countries. The developed PBPK models for phenobarbital and quinine-phenobarbital co-administration are reliable, and successfully predicted the optimal doses regimens of phenobarbital in cerebral malaria patients with single or continuous seizures with no requirement of *CYP2C9/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 co-administered with quinine. The proposed optimal dose regimen for quinine when co-administered with phenobarbital for patients with a single seizure (scenario I), and continuous seizures (scenario II) in all malaria-endemic areas regardless of *CYP2C9/CYP2C19* genotypes is a loading dose of 1,500 mg IV infusion over 8 hours, followed by 1,200 mg IV infusion over 8 hours given three times daily (*regimen-7*), or multiple doses of 1,400 mg IV infusion over 8 hours, given three times daily (*regimen-8*). In areas with quinine resistance, the dose regimen should be increased as a loading dose of 2,000 mg IV infusion over 8 hours, followed by 1,750 mg IV infusion over 8 hours given three times daily (*regimen-6*).

Abbreviations

95%CI: 95% confident interval; AAFEs: absolute average-folding errors; AUC: the area under the plasma concentration-time curve; AUCR: AUC ratio; C_{max}: peak plasma concentration; C_{max}R: C_{max} ratio; C_{trough}: trough plasma concentration; CYP450: cytochrome P450; DDIs: drug-drug interactions; EC_{50}: half-maximal effective concentrations; EM: extensive metabolizer; E_{max}: maximum effect at the maximum concentration; f_m: fraction of metabolism; f_u; fraction of unbound drug; IV: intravenous; K_i: inhibitor concentration that produces half-maximal inhibition; R_{bp}: blood-to-plasma ratio; PM: poor metabolizer; UGT1A1: UDP-glucuronosyltransferase 1A1; VPC: visual predictive check.

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Authors's contributions

T.S., J.K., M.S., and K.N. designed the study. M.S., T.S., and R.K.R. collected the information. T.S., R.K.R., and M.S. performed research. T.S., J.K., and K.N. wrote the manuscript. All authors had accessed and interpreted the data. All authors approved the final version.

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Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Ethical approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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554

555 **Figures**

556 **Figure 1** Prediction of quinine dose regimens in wild type *CYP2C9/CYP2C19* based on
557 standard DDIs approach. Prediction of quinine dosage regimens when co-administered with
558 phenobarbital based on standard DDIs study approach in cerebral malaria patients with
559 seizures who carry wild type *CYP2C9/CYP2C19.* Data are presented as mean (95%CI). Set
560 criteria for dose optimization are $C_{max} \leq 20$ mg.L^{-1}, and $C_{trough} \geq 10$ mg.L^{-1} (therapeutic range
561 of quinine).

562

563 **Figure 2** Prediction of quinine dose regimens in polymorphic CYP2C9/CYP2C19 based on
564 standard DDIs approach. Prediction of quinine dosage regimens when co-administered with
565 phenobarbital based on standard DDIs study approach in cerebral malaria patients with
566 seizures who carry polymorphic *CYP2C9/CYP2C19.* Data are presented as mean (95%CI).

Set criteria for dose optimization are $C_{max} \leq 20$ mg.L^{-1}, and $C_{trough} \geq 10$ mg. L^{-1} (therapeutic range of quinine).

Figure 3 Prediction of quinine dose regimens in wild type *CYP2C9/CYP2C19* based on actual clinical use approach. Prediction of quinine dosage regimens when co-administered with phenobarbital based on actual clinical use study approach in cerebral malaria patients with seizures (scenario I: single, and scenario II: continuous) who carry wild type *CYP2C9/CYP2C19.* Data are presented as mean (95%CI). Set criteria for dose optimization are $C_{max} \leq 20$ mg.L^{-1}, and $C_{trough} \geq 10$ mg.L^{-1}(therapeutic range of quinine).

Figure 4 Prediction of quinine dose regimens in polymorphic *CYP2C9/CYP2C19* based on actual clinical use approach (scenario-I). Prediction of quinine dosage regimens when co-administered with phenobarbital based on actual clinical use study approach in cerebral malaria patients with a single seizure (scenario I) who carry polymorphic *CYP2C9/CYP2C19.* Data are presented as mean (95%CI). Set criteria for dose optimization are $C_{max} \leq 20$ mg.L^{-1}, and $C_{trough} \geq 10$ mg.L^{-1}(therapeutic range of quinine).

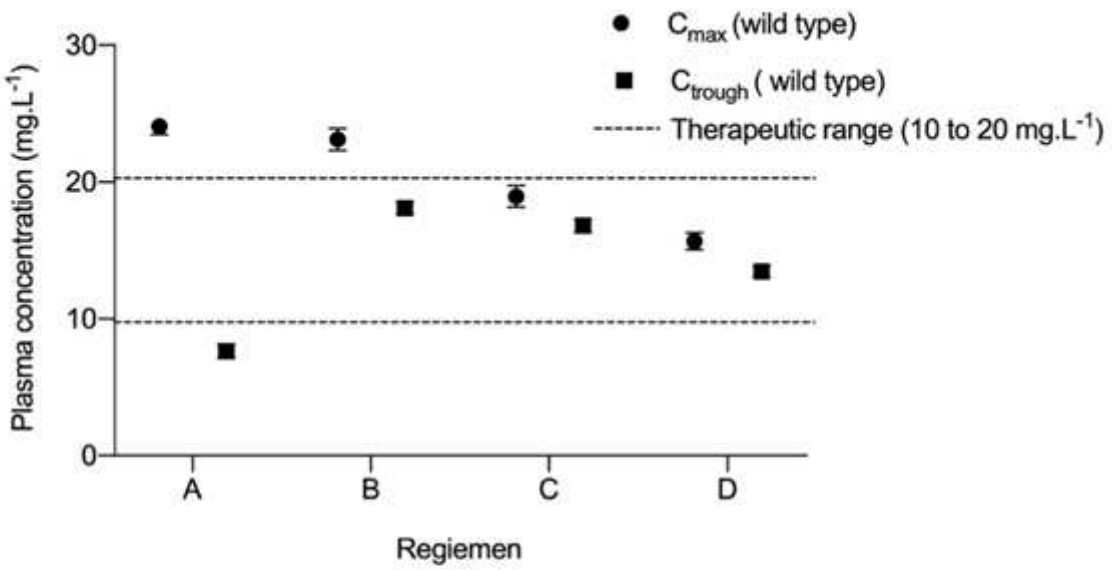
Figure 5 Prediction of quinine dose regimens in polymorphic *CYP2C9/CYP2C19* based on actual clinical use approach (scenario-II). Prediction of quinine dosage regimens when co-administered with phenobarbital based on actual clinical use study approach in cerebral malaria patients with continuous seizures (scenario II) who carry polymorphic *CYP2C9/CYP2C19.* Data are presented as mean (95%CI). Set criteria for dose optimization are $C_{max} \leq 20$ mg.L^{-1}, and $C_{trough} \geq 10$ mg.L^{-1}(therapeutic range of quinine).

Tables

592 **Table 1** Model verification of quinine and phenobarbital in cerebral malaria, severe malaria,
593 and healthy adults. Comparisons of quinine and phenobarbital between predicted results and
594 published data in patients with cerebral malaria, severe malaria, and healthy adults.
595 **Table 2** Simulated standard dose regimens of phenobarbital based on standard DDI study
596 approach. Simulation of standard dose regimens of phenobarbital in patients with seizures
597 with wild tyle and polymorphic *CYP2C9/CYP2C19* based on standard DDI study approach.
598 **Table 3** Simulated standard dose regimens of phenobarbital based on actual clinical use
599 DDI study approach. Simulation of standard dose regimen of phenobarbital in patients with
600 seizures with wild type and polymorphic *CYP2C9*/*CYP2C19* based on actual clinical use
601 study approach
602 **Table 4** Simulated standard dose regimens of quinine when co-administered with
603 phenobarbital based on actual clinical use approach. Simulation of the standard dose of
604 quinine when co-administered with phenobarbital in cerebral malaria patients with
605 concomitant seizures with wild type and polymorphic *CYP2C9/CYP2C19*.
606 **Table 5** Prediction of quinine dose regimens when co-administered with phenobarbital
607 based on standard DDI study approach. Prediction of quinine dosage regimens when co-
608 administered with phenobarbital in cerebral malaria patients with concomitant seizures and
609 polymorphic CYP2C9/CYP2C19 based on standard DDI study approach.
610 **Table 6** Prediction of quinine dose regimens when co-administered with phenobarbital based
611 on scenario-I. Prediction of quinine dosage regimen when co-administered with
612 phenobarbital in cerebral malaria patients with concomitant seizures with wild type and
613 polymorphic CYP2C9/CYP2C19 based on actual clinical study approach (*scenario I: single*
614 *seizure*).
615 **Table 7** Prediction of quinine dose regimens when co-administered with phenobarbital based
616 on scenario-II. Prediction of quinine dosage regimen when co-administered with

617 phenobarbital in cerebral malaria patients with concomitant seizures with wild type and
618 polymorphic CYP2C9/CYP2C19 based on actual clinical study approach (*scenario II:*
619 continuous seizures).
620
621 **Additional files**
622 **Additional file 1: Table S1.** PBPK model input parameters for quinine and phenobarbital.
623 **Additional file 2: Figure S1.** A comparison of 500 mg quinine IV infusion over 4 hours in
624 African healthy adults between predicted result and published data. **Figure S2.** A comparison
625 of 10 mg kg^{-1} body weight quinine IV infusion over 4 hours in adult Thai patients with
626 cerebral malaria between predicted result and published data. **Figure S3.** A comparison of 4
627 mg kg-1 body weight quinine IV infusion over 4 hours in adult Thai patients with severe
628 malaria between predicted result and published data. **Figure S4.** A comparison of loading
629 dose of 20 mg kg^{-1} body weight quinine IV infusion over 4 hours, followed by 10 mg kg^{-1}
630 body weight IV infusion over 4 hours given 3 times daily in adult Thai patients with cerebral
631 malaria between predicted result and published data. **Figure S5.** A comparison of 10 mg kg^{-1}
632 body weight IV infusion over 4 hours given 3 times daily in adult Thai patients with cerebral
633 malaria between predicted result and published data. **Figure S6.** A comparison of 5 mg kg^{-1}
634 body weight IV infusion over 4 hours given 3 times daily in adult Thai patients with cerebral
635 malaria between predicted result and published data. **Figure S7.** A comparison of 2.6 mg kg^{-1}
636 (218 mg) phenobarbital IV infusion over 6 minutes given in healthy male subjects between
637 predicted result and published data.
638

Figures



A (Regimen 1): Loading dose of 2200 mg IV infusion over 4 hours, followed by 1200 mg IV infusion over 4 hours (given every 8 hours daily)
B: (Regimen 2): Loading dose of 2200 mg IV infusion over 8 hours, followed by 2000 mg IV infusion over 8 hours (given every 8 hours daily)
C (Regimen 3): Loading dose of 2000 mg IV infusion over 8 hours, followed by 1500 mg IV infusion over 8 hours (given every 8 hours daily)
D (Regimen 4): Loading dose of 1750 mg IV infsuion over 8 hours, followed by 1500 mg IV infusion over 8 hours (given every 8 hours daily)

Figure 1

Prediction of quinine dose regimens in wild type CYP2C9/CYP2C19 based on standard DDIs approach. Prediction of quinine dosage regimens when co-administered with phenobarbital based on standard DDIs study approach in cerebral malaria patients with seizures who carry wild type CYP2C9/CYP2C19. Data are presented as mean (95%CI). Set criteria for dose optimization are Cmax ≥ 20 mg.L-1, and Ctrough ≥ 10 mg.L-1 (therapeutic range of quinine).

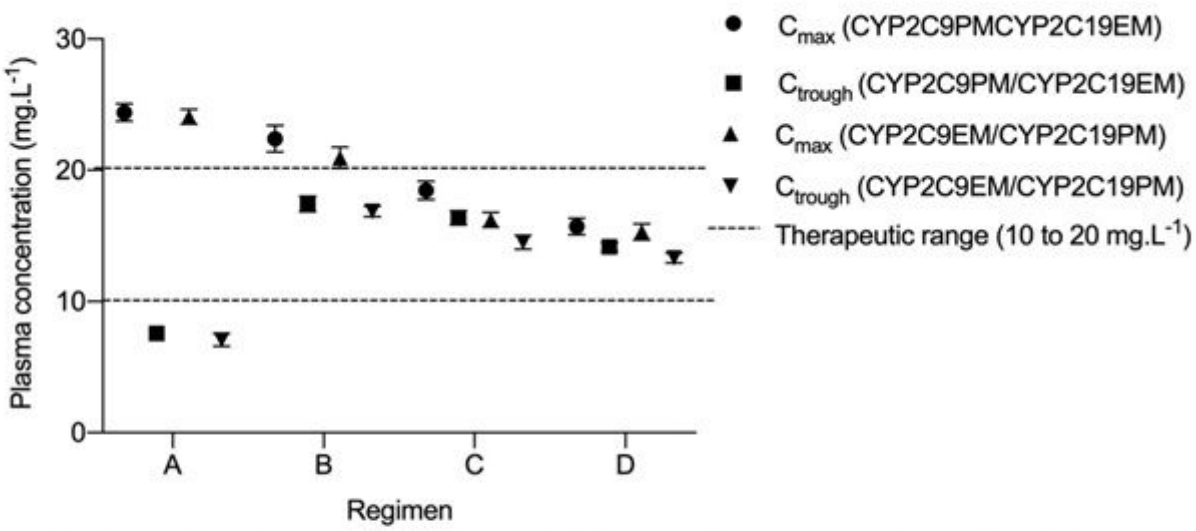


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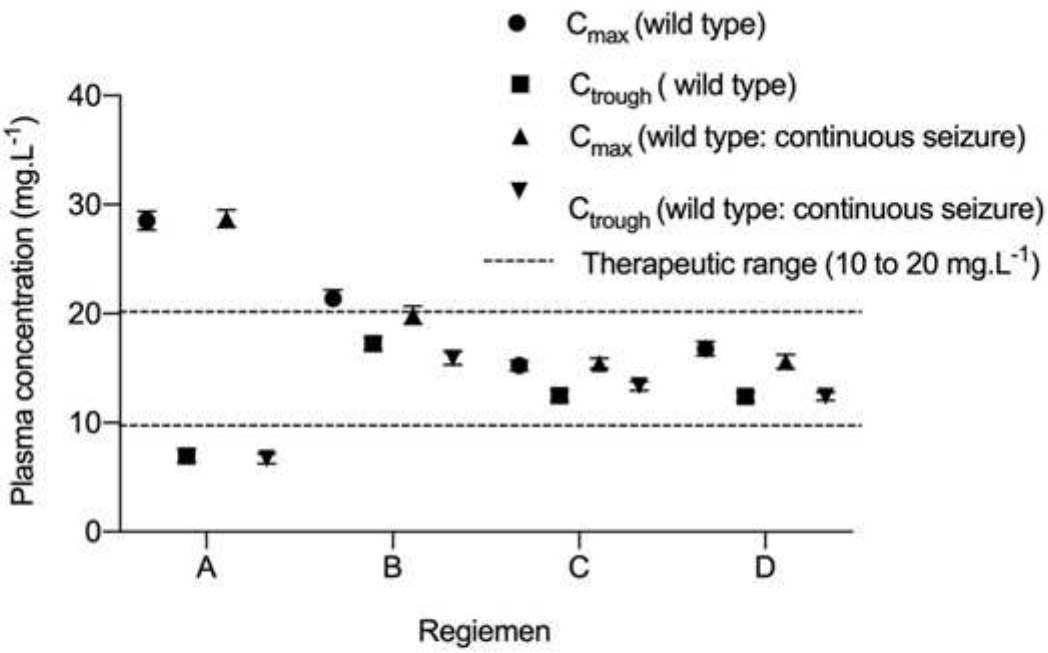
Figure 2

Prediction of quinine dose regimens in polymorphic CYP2C9/CYP2C19 based on standard DDIs approach. Prediction of quinine dosage regimens when co-administered with phenobarbital based on standard DDIs study approach in cerebral malaria patients with seizures who carry polymorphic CYP2C9/CYP2C19. Data are presented as mean (95%CI). Set criteria for dose optimization are Cmax ≥ 20 mg.L-1, and Ctrough ≥ 10 mg. L-1 (therapeutic range of quinine).



A (Regimen 5): Loading dose of 2000 mg IV infusion over 4 hours, followed by 1000 mg IV infusion over 4 hours (given every 8 hours daily)
B: (Regimen 6): Loading dose of 2000 mg IV infusion over 8 hours, followed by 1750 mg IV infusion over 8 hours (given every 8 hours daily)
C (Regimen 7): Loading dose of 1500 mg IV infusion over 8 hours, followed by 1200 mg IV infusion over 8 hours (given every 8 hours daily)
D (Regimen 8): Multiple doses of 1400 mg IV infusion over 8 hours (given every 8 hours daily)

Figure 3

Prediction of quinine dose regimens in wild type CYP2C9/CYP2C19 based on actual clinical use approach. Prediction of quinine dosage regimens when co-administered with phenobarbital based on actual clinical use study approach in cerebral malaria patients with seizures (scenario I: single, and scenario II: continuous) who carry wild type CYP2C9/CYP2C19. Data are presented as mean (95%CI). Set criteria for dose optimization are Cmax ≥ 20 mg.L-1, and Ctrough ≥ 10 mg.L-1(therapeutic range of quinine).

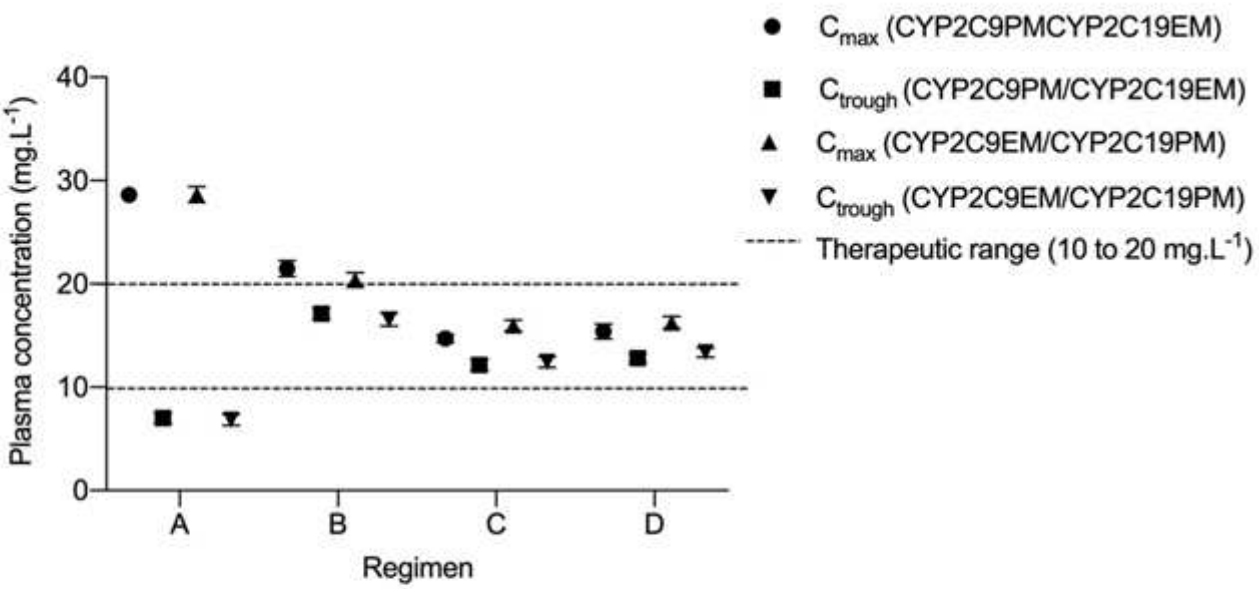


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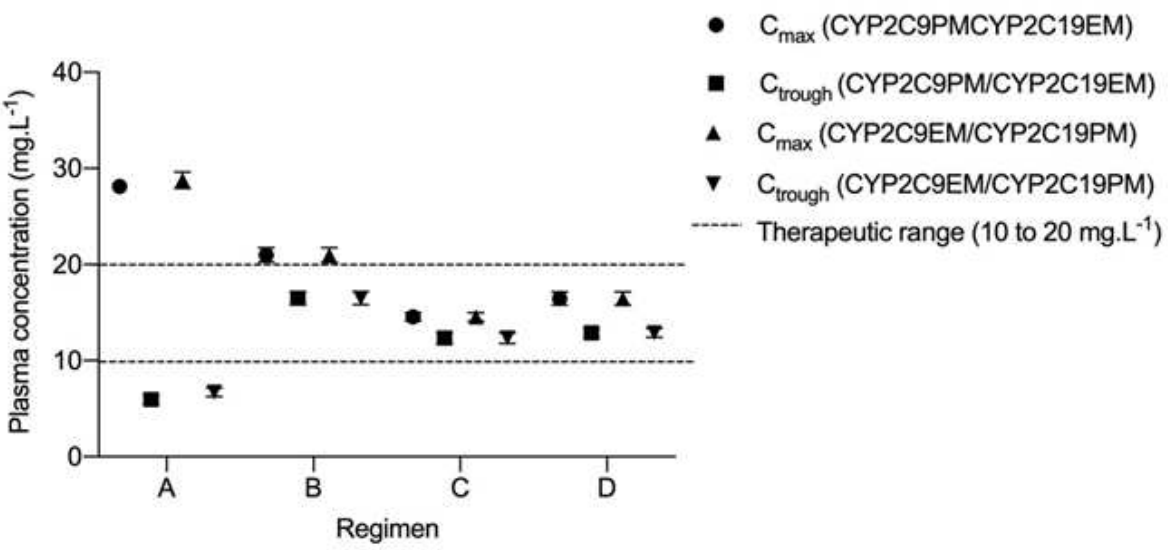
Figure 4

Prediction of quinine dose regimens in polymorphic CYP2C9/CYP2C19 based on actual clinical use approach (scenario-I). Prediction of quinine dosage regimens when co-administered with phenobarbital based on actual clinical use study approach in cerebral malaria patients with a single seizure (scenario I) who carry polymorphic CYP2C9/CYP2C19. Data are presented as mean (95%CI). Set criteria for dose optimization are Cmax 20 mg.L-1, and Ctrough 10 mg.L-1(therapeutic range of quinine).



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D (Regimen 8): Multiple doses of 1400 mg IV infusion over 8 hours (given every 8 hours daily)

Figure 5

Prediction of quinine dose regimens in polymorphic CYP2C9/CYP2C19 based on actual clinical use approach (scenario-II). Prediction of quinine dosage regimens when co-administered with phenobarbital based on actual clinical use study approach in cerebral malaria patients with continuous seizures (scenario II) who carry polymorphic CYP2C9/CYP2C19. Data are presented as mean (95%CI). Set criteria for dose optimization are Cmax 20 mg.L-1, and Ctrough 10 mg.L-1(therapeutic range of quinine).

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