

Semi-mechanistic Pharmacokinetic and Pharmacodynamic Modeling of Piperaquine in a Volunteer Infection Study with *P. falciparum* Blood-Stage Malaria

Thanaporn Wattanakul¹, Mark Baker², Joerg Mohrle³, Brett McWhinney⁴, Richard M. Hoglund^{1,5}, James S. McCarthy^{6,7}, Joel Tarning^{1,5}

¹Mahidol Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, ²Department of Clinical Pharmacology, ViiV Healthcare, Geneva, Switzerland, ³Medicine for Malaria Venture, Meyrin, Switzerland, ⁴Analytical Chemistry Unit, Pathology Queensland, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia, ⁵Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom, ⁶QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia, ⁷School of Medicine, The University of Queensland, Brisbane, QLD, Australia

Background

Pharmacokinetic (PK) properties of piperaquine have been studied extensively, its pharmacodynamic (PD) properties in humans are less well studied. The knowledge of key PD parameters of piperaquine in humans would provide information to improve current treatments using artemisinin-combination therapies (ACTs) and assist dose selection for the new antimalarial therapies. The induced blood-stage malaria (IBSM) model has been extensively used to investigate the activity of antimalarial drugs in humans. The IBSM model, allows for an evaluation of the activity of antimalarial drugs against the asexual blood stages of the parasites, both before and after the antimalarial drug treatment, which is not possible with data from field studies.

Aims

To develop a PK/PD model describing the parasite dynamics in healthy volunteers inoculated with blood-stage *P. falciparum* parasites using the IBSM model. The developed PK/PD model was then used to predict treatment failures in the presence of multidrug-resistant infections and characterize the ideal partner drug for triple-combination therapy for these infections.

Methods

The PK/PD model was developed using data from a previously reported dose-ranging study where 24 healthy volunteers were inoculated with 1,800 blood-stage *P. falciparum* parasites. All volunteers received a single oral dose of piperaquine (960 mg, 640 mg, or 480 mg) on day 7 or day 8 after parasite inoculation in separate cohorts. Parasite densities were measured by quantitative PCR (qPCR), and piperaquine levels were measured in plasma samples. We used nonlinear mixed-effect modeling to characterize the PK properties of piperaquine and the parasite dynamics associated with piperaquine exposure.

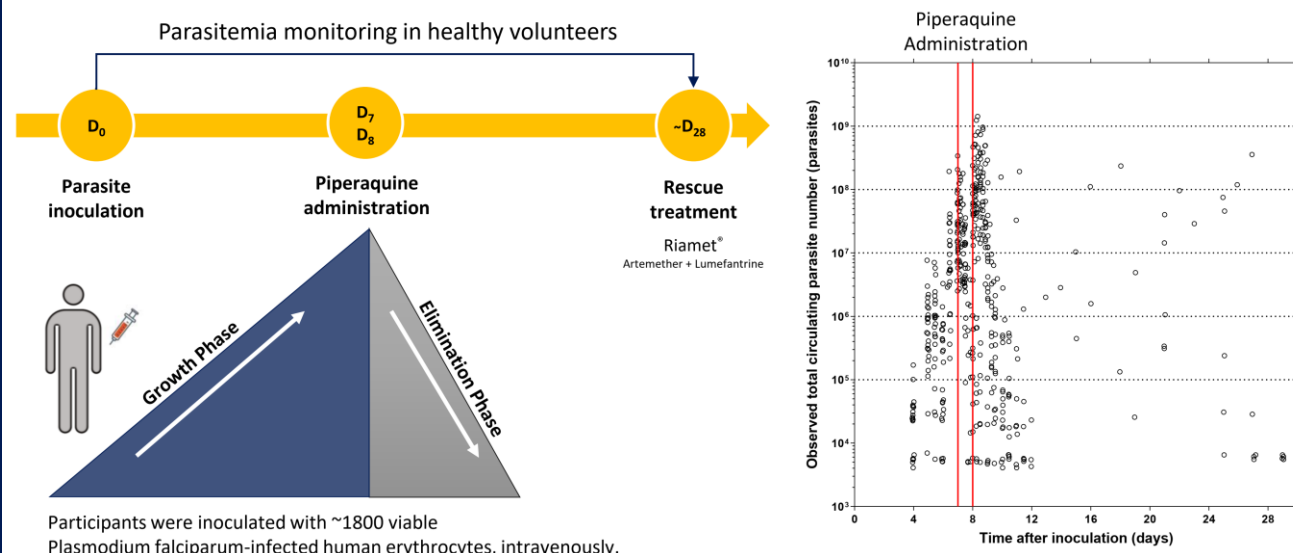


Figure 1. Induced blood-stage malaria infection and data used in PK/PD analysis.

Results

PK model of piperaquine

PK model of piperaquine was best described by three-disposition compartment model with two-transit absorption model. Body weight was a significant covariate, implemented with an allometric function.

PK/PD model of piperaquine

The semi-mechanistic growth model was developed using only the growth phase data. The parasite life-cycle length was fixed to 38.8 hours based on previous study using IBSM model¹. The parasite model consisted of 3 compartments describing the maturation, sequestration, and multiplication of parasites. Parasites in P1 and P2 are assumed to be visual. The parasitocidal effect of piperaquine (EFF) was added as a direct effect to the mature parasite compartments (P2 and P3), describing the drug-dependent parasite elimination adequately.

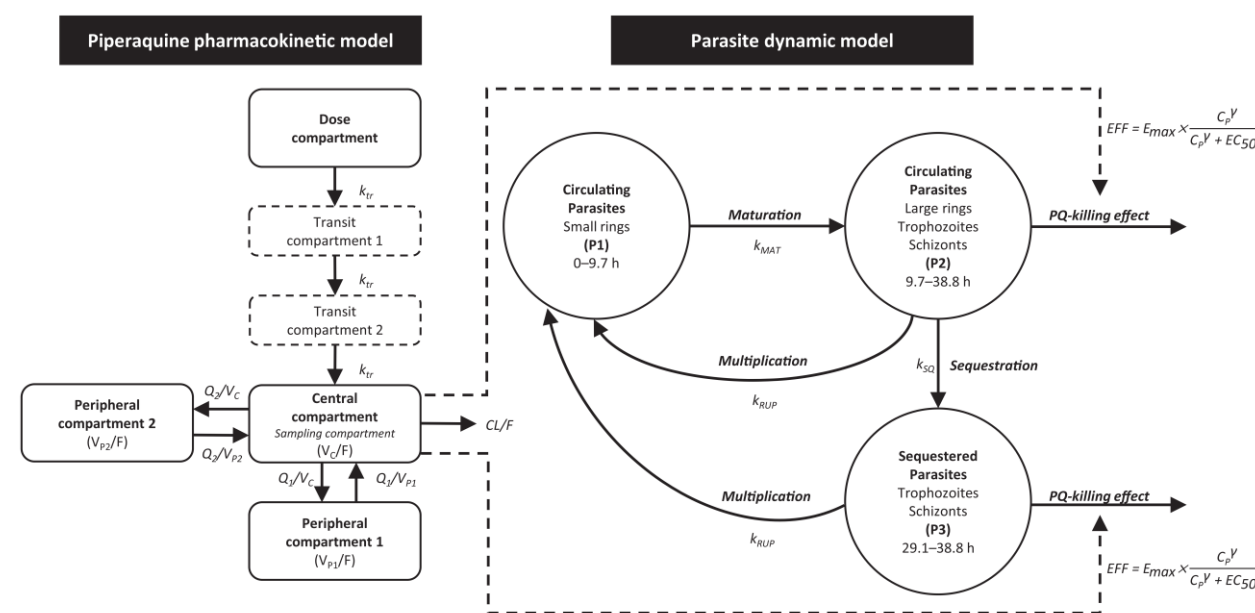


Figure 2. Final semi-mechanistic model describing *P. falciparum* malaria parasites and the final pharmacokinetic model of piperaquine.

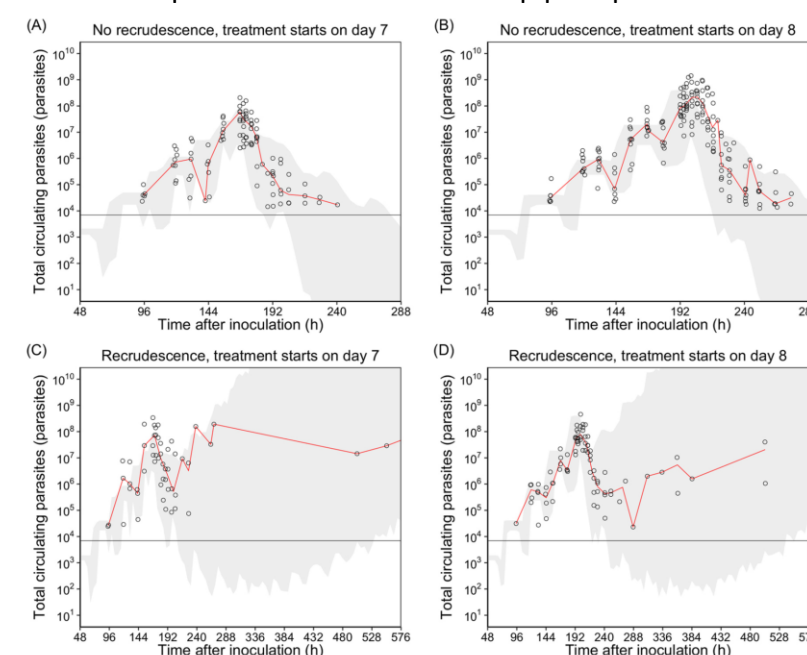


Figure 3. The simulated 90% prediction interval from the final PK/PD model (n = 1,000).

Parameter	Population estimate ^a (% RSE) ^b	95% CI ^b	IIV ^a (% RSE) ^b	95% CI ^b	Shrinkage (%)
Semi-mechanistic growth model					
F _{SUR} (%)	5 fixed				
T _{PC} (h)	38.8 fixed		6.00 (24.8)	5.11–8.50	34.5
k _{MAT} (h ⁻¹)	2 fixed				
T _{SO} (h)	29.1 (4.84)	27.7–29.7			
F _{SO} (%)	90 fixed				
k _{RUP} (h ⁻¹)	2 fixed				
PMR _{LC}	15.7 (8.43)	14.1–19.9	18.3 (27.7)	15.4–33.3	14.6
In vivo parasitocidal effect of piperaquine					
E _{max} (h ⁻¹)	0.289 (5.31)	0.262–0.321	23.6 (26.0)	5.20–30.0	18.7
EC ₅₀ (ng/ml)	5.43 (29.4)	1.77–7.33	114 (38.6)	67.0–760	30.6
γ	2.8 fixed				
σ	4.69 (4.80)	3.81–5.55			7.69

^a Population mean parameters estimated from NONMEM. ^b Based on nonparametric bootstrap diagnostics (n = 1,000). Abbreviations: F_{SUR}, fraction of parasite survival after inoculation; T_{PC}, duration of parasite life cycle; k_{MAT}, first-order rate constant for parasite maturation; T_{SO}, onset of parasite sequestration; F_{SO}, fraction of parasites sequestration; k_{RUP}, first-order rate constant of schizont rupture; PMR_{LC}, parasite multiplication rate given as fold increase per life cycle; E_{max}, maximum parasite killing rate of piperaquine; EC₅₀, plasma concentration of piperaquine associated with half of maximum parasite killing rate; γ, hill factor; and σ, residual unexplained variability.

Simulations of drug resistance scenarios

In order to simulate treatment scenarios of drug resistant infections, dihydroartemisinin (DHA) was used as a representative of artemisinin derivative. The parasitocidal effect of DHA was adjusted based on the observed parasite clearance half-life from previous study². Additionally, simulations to inform on suitable PK/PD characteristics for candidate partner drugs used in triple-combination therapy demonstrated that the addition of a hypothetical drug with a PRR_{LC} of ≥10² and total therapeutic duration of ≥ 2 weeks had a 99% probability of successful treatment.

Drug resistant scenario		DHA + PQ ^a	PRR _{LC}	Probability of treatment failure (%)					
				Hypothetical drug characteristics					
				Duration of action (weeks)					
1	DHA-resistant (E _{max} = 0.216)	8.1	10 ¹	4.19	2.79	2.27	2.29	2.23	
	PQ-resistant (2 × EC ₅₀ = 10.9 ng/ml)		10 ²	1.42	< 1.00	< 1.00	< 1.00	< 1.00	
			10 ³	< 1.00	< 1.00	< 1.00	< 1.00	< 1.00	
2	DHA-resistant (E _{max} = 0.216)	15.2	10 ¹	9.35	5.60	5.31	5.46	5.46	
	PQ-resistant (3 × EC ₅₀ = 16.3 ng/ml)		10 ²	3.65	< 1.00	< 1.00	< 1.00	< 1.00	
			10 ³	< 1.00	< 1.00	< 1.00	< 1.00	< 1.00	
3	DHA-resistant (E _{max} = 0.216)	23.6	10 ¹	15.3	10.7	10.0	9.96	9.94	
	PQ-resistant (4 × EC ₅₀ = 21.7 ng/ml)		10 ²	6.02	< 1.00	< 1.00	< 1.00	< 1.00	
			10 ³	1.25	< 1.00	< 1.00	< 1.00	< 1.00	

The hypothetical drug was added to the standard 3-day dose of DHA-PQ (120/960 mg). ^a Initial total parasite biomass for symptomatic infection of 10⁶ parasites. PRR_{LC}, parasite reduction ratio per parasite life cycle (38.8 h) of the simulated hypothetical drug.

Conclusions

An *in vivo* semi-mechanistic PK/PD model of piperaquine in participants inoculated with *P. falciparum* malaria, and model parameters associated with piperaquine PK/PD effects were successfully characterized. This semi-mechanistic parasite model provides important insights and could be an important tool in the development of novel triple-combination therapies and for dose optimization of piperaquine and other antimalarial drugs.

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References: (1) Wockner LF, et al. 2019. Growth rate of Plasmodium falciparum: analysis of parasite growth data from malaria volunteer infection studies. J Infect Dis 221:963–972. (2) Ashley EA, et al. Spread of artemisinin resistance in Plasmodium falciparum malaria. N Engl J Med 371:411–423.