RESPONSE LETTER TO THE EDITOR

Response to "Pharmacometric Approach to Evaluate Drug Dosing Adherence"

Junjie Ding[1,2,3], Richard M. Hoglund[1,2] and Joel Tarning[1,2,3,*]

We appreciate the comments sent by Dr. Qi *et al*. regarding our article.[1]

The population pharmacokinetic (PK)-based Bayesian approach developed by Barrière and colleagues was proven to be successful in estimating the probability of adherence/nonadherence in different adherence scenarios.[2] We used this developed Bayesian approach, with small modifications (see **Supplementary Materials**), and evaluated the predictive performance of different nonadherence scenarios associated with seasonal malaria chemopreventive treatment. The Bayesian approach resulted in a higher cutoff concentration value, suggesting a higher sensitivity but lower specificity, compared to the percentile method (**Table S1**). The overall predictive performance of the Bayesian approach, defined by Youden's index, was slightly inferior to the percentile method in both the first-dose directly observed therapy (DOT) and the first-dose non-DOT scenarios.

The magnitude of interindividual variability (IIV) affects the distribution of PK concentrations. Generally, high IIV results in a wider distribution of concentrations, although the median level would be unaffected. We conducted a sensitivity analysis by altering the IIV levels in the final population PK model. The simulations were based on a typical child described in our paper (i.e., 36 months old, 11.5 kg, receiving 153 mg amodiaquine for 3 days). The results suggested that the predictive performance of nonadherence for the percentile method decreased with increasing IIV, ranging from completely distinguishable when IIV was zero (100% sensitivity and specificity) to clinically unusable at very high IIV (**Table 1**). When IIV increased by 100%, the area under the receiver operating characteristic (ROC) curves were < 0.7 at the majority of days in the DOT scenario, suggesting poor nonadherent predictive performance (no discriminating capacity). The nonadherence results presented in our article, using the percentile method were robust, even in a scenario where IIV increased by 50%. As shown in **Table 1**, the area under the ROC curve were above 0.7 at most of days and the cutoff concentration values were similar (differences were within ± 20%).

Finally, the specificity of the percentile approach was based on the selected optimal percentile value, derived from simulated fully adherent individuals (e.g., 20% percentile value resulted in 80% specificity). The

Table 1 The predictive performance at different magnitude of IIVs using the percentile approach

	Current IIV			IIV increased by 50%			IIV increased by 100%		
	AUC ROC	Optimal cutoff percentile	DEAQ cutoff concentration, nmol/L	AUC ROC	Optimal cutoff percentile	DEAQ cutoff concentration, nmol/L	AUC ROC	Optimal cutoff percentile	DEAQ cutoff concentration, nmol/L
First-dose DOT									
Day 3	0.826	20	1,451	0.761	25	1,348	0.704	30	1,200
Day 7	0.795	20	576	0.736	30	625	0.693	35	546
Day 14	0.778	25	255	0.713	35	260	0.669	40	226
Day 21	0.780	25	155	0.708	35	145	0.661	40	140
Day 28	0.754	30	101	0.685	40	98	0.644	45	81
First-dose non-DOT									
Day 3	0.856	20	1,451	0.801	20	1,206	0.752	25	1,049
Day 7	0.835	20	576	0.782	25	557	0.743	25	480
Day 14	0.829	20	233	0.768	25	206	0.727	30	194
Day 21	0.831	20	141	0.766	25	114	0.721	30	102
Day 28	0.807	25	90	0.744	30	77	0.706	40	71

AUC ROC, area under the receiver operating characteristic curve; DEAQ, desethylamodiaquine; DOT, directly observed therapy; IIV, interindividual variability. IIV was estimated for six pharmacokinetic parameters in final amodiaquine (AQ) and DEAQ population pharmacokinetic model. Current IIV variance estimates were; 3.00 for the absorption rate constant, 0.141 for the relative bioavailability of AQ, 0.0492 for the clearance of AQ, 0.646 for the central volume of AQ, 0.0231 for the clearance of DEAQ, and 0.466 for the peripheral volume of DEAQ.

sensitivity was derived from the comparison of the concentrations from simulated nonadherent individuals with the optimal percentile cutoff value defined in the table above (e.g., 20% percentile concentration value), which was not associated with the simulated adherent individuals. Therefore, the sensitivity and specificity were not changed if the proportion of the adherent and nonadherent individuals varied in the simulation.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

All authors declared no competing interests for this work.

1. Ding, J. *et al*. Adherence and population pharmacokinetic properties of amodiaquine when used for seasonal malaria chemoprevention in African children. *Clin. Pharmacol. Ther.* **107**, 1179–1188 (2020).
2. Barriere, O., Li, J. & Nekka, F. A Bayesian approach for the estimation of patient compliance based on the last sampling information. *J. Pharmacokinet. Pharmacodyn.* **38**, 333–351 (2011).

[1]Mahidol Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; [2]Centre for Tropical Medicine and Global Health, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK; [3]The WorldWide Antimalarial Resistance Network, Oxford, UK. *Correspondence: Joel Tarning (joel@tropmedres.ac)

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