Population pharmacokinetics and cardiovascular safety of piperaquine in African patients with uncomplicated malaria

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Background & Objective

- Piperaquine has been documented to prolong the electrocardiographic QT interval and may have significant adverse clinical effects in susceptible individuals. Safety data on repeated treatment courses of piperaquine is limited and there might be a potential toxicity risk associated with piperaquine accumulation.
- The aim of this study was to develop a PK/PD model to describe the relationship between piperaquine exposure and QT-prolongation in order to evaluate the cardiovascular safety in patients with uncomplicated *falciparum* malaria.

Methods

- PK samples and electrocardiogram (ECG) measurements were obtained from a total of 1,000 uncomplicated P. falciparum malaria patients, enrolled in a multi-centre safety trial in Burkina Faso, Mozambique, Ghana, and Tanzania[1-3]. All patients received a standard 3-day treatment of dihydroartemisinin-piperaquine.
- Nonlinear mixed-effects modelling (NONMEM v.7.3) was used to evaluate PK/PD properties of piperaquine. Both QTc-prolongation (ΔQTc) and absolute QTc-intervals (QTc) were evaluated. Direct exposure-response models with linear and Emax relationships were investigated to describe the effect of piperaquine on ΔQTc/QTc intervals.

Conclusions

- The developed PK/PD model described the relationship between piperaquine concentrations and ΔQTc/QTc intervals accurately.
- The model demonstrated that an increased piperaquine concentration was directly related to a prolongation of the QTc interval.
- Simulations showed that the maximum QTc-prolongation was less than 60 ms in all scenarios. The proportion of simulated patients having a maximum absolute QTc interval of >500 ms were less than 0.006% in each body weight strata.
- Children weighting 5 to 12 kg had the highest probability (0.015 and 0.024% for old and new regimen, respectively) of having a maximum QTc intervals >500 ms.
- Modelling and simulation suggested that piperaquine has an acceptable safety profile in a clinical setting of life-saving malaria treatment.

Results

Pharmacokinetics of piperaquine

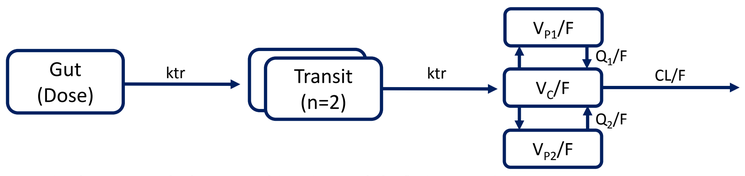

Figure 1. Final structural pharmacokinetic model of piperaquine

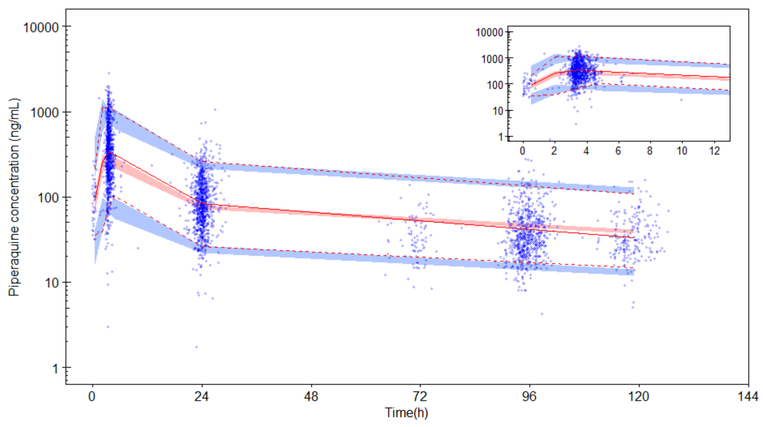

Figure 2. Visual predictive check (n=1,000)

Piperaquine effect on ΔQTc interval

Table 1a. ΔQTc-PQ concentration linear relationship using different correction methods

Parameter	QT correction methods			
	Fridericia correction α = 0.333 (%RSE)[a]	Bazett correction α = 0.500 (%RSE)[a]	Day1 correction α = 0.476 (%RSE)[a]	Day1-3-7 correction α = 0.476, 0.442, 0.435 (%RSE)[a]
OFV	27,224	26,530	26,263	26,340
ΔOFV	-	-694	-961	-884
Baseline	0 fixed	0 fixed	0 fixed	0 fixed
IIV on Baseline (ms)	15.5 (12.8)	14.0 (18.3)	13.7 (18.3)	14.0 (17.7)
Slope (ms/100 ng/ml)	7.97 (4.4)	5.30 (5.0)	5.90 (4.0)	4.11 (4.5)
IIV on slope	0.253 (20.0)	0.122 (30.2)	0.128 (25.3)	0.076 (34.4)
Residual variability (ms)	15.5 (5.6)	14.8 (6.1)	14.1 (6.2)	14.6 (5.9)

Table 1b. Final PK/PD model for ΔQTc-PQ concentration relationship (Day1 correction)

Parameter	Population estimate[a] (% RSE)[b]	95% CI[b]
Baseline	0 fixed	-
IIV on Baseline (ms)	15.1 (6.72)	13.3-17.2
E_{max} (ms)	57.2 (7.03)	50.7-66.3
EC_{50} (ng/ml)	473 (14.1)	366-630
Effect of age on EC_{50} (%)	3.10 (33.5)	1.25-5.21
Residual variability (ms)	14.8 (2.64)	14.1-15.6

[a] Population mean values estimated by NONMEM
[b] The relative standard error (%RSE) was calculated from the non-parametric bootstrap results (n=1,000)

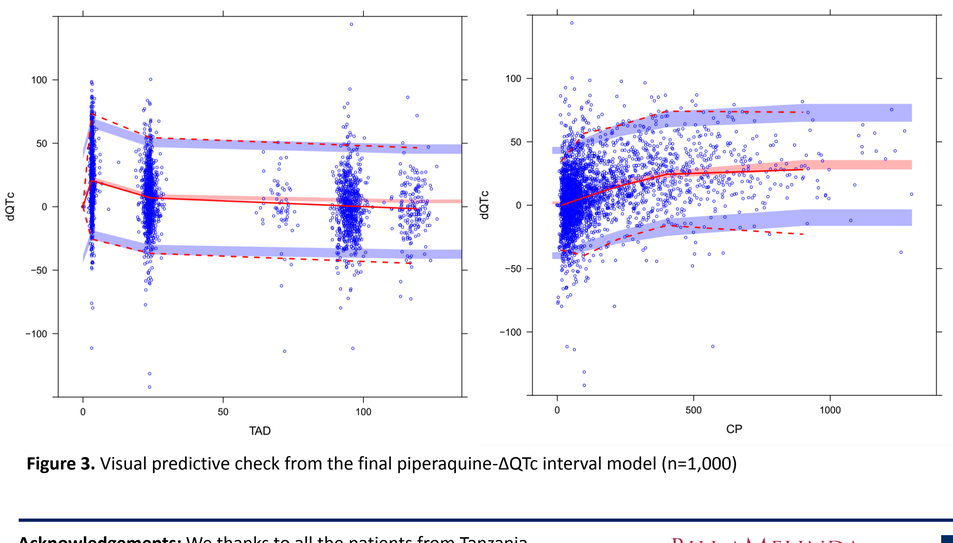

Figure 3. Visual predictive check from the final piperaquine-ΔQTc interval model (n=1,000)

Piperaquine effect on absolute QTc interval

Table 2. Final PK/PD model for absolute QTc-PQ concentration relationship (Day1 correction)

Parameter	Population estimate[a] (% RSE)[b]	95% CI[b]
QTc_{ss} (ms)	421 (0.143)	420-423
IIV baseline (ms)	16.2 (2.67)	15.4-17.1
E_{max}	50.5 (6.16)	45.3-57.2
EC_{50} (ng/mL)	363 (12.7)	285-466
Effect of age on EC_{50} (%)	3.69(24.9)	1.96-5.56
Residual variability (ms)	14.7 (3.70)	13.7-15.8

[a] Population mean values estimated by NONMEM
[b] The relative standard error (%RSE) was calculated from the non-parametric bootstrap results (n=1,000)

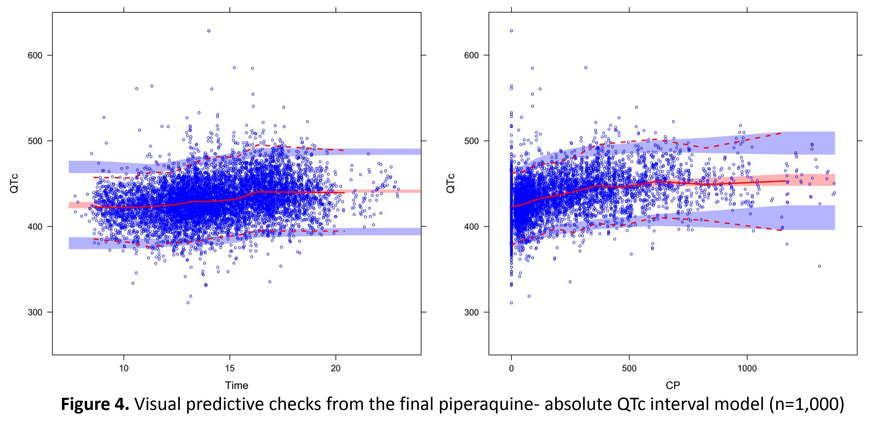

Figure 4. Visual predictive checks from the final piperaquine- absolute QTc interval model (n=1,000)

Simulations using the final PK/PD model

- **Acute treatment: old vs new treatment regimen**

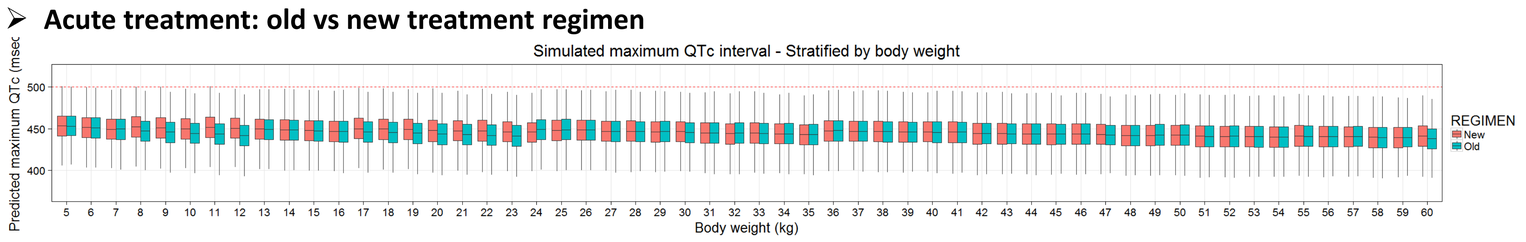

Figure 5. The box plots represent the simulated maximum QTc stratified by body weight after receiving the old and new dosing regimen (5,000 simulated individuals per body weight)

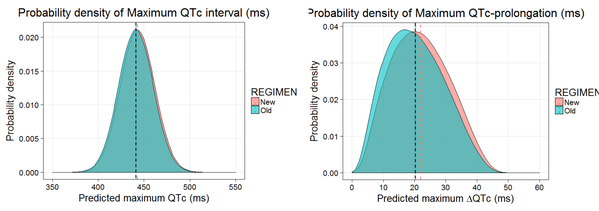

Figure 6. Distribution of simulated maximum QTc intervals and ΔQTc from 480,000 simulated patients per dosing regimen

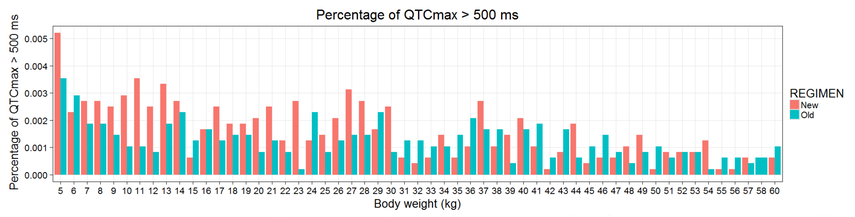

Figure 7. The bar charts represent the probability of having maximum QTc of >500 ms, based on 480,000 simulated patients (5,000 simulated individuals per body weight)

- **Mass drug administration (MDA): old vs new treatment regimen**

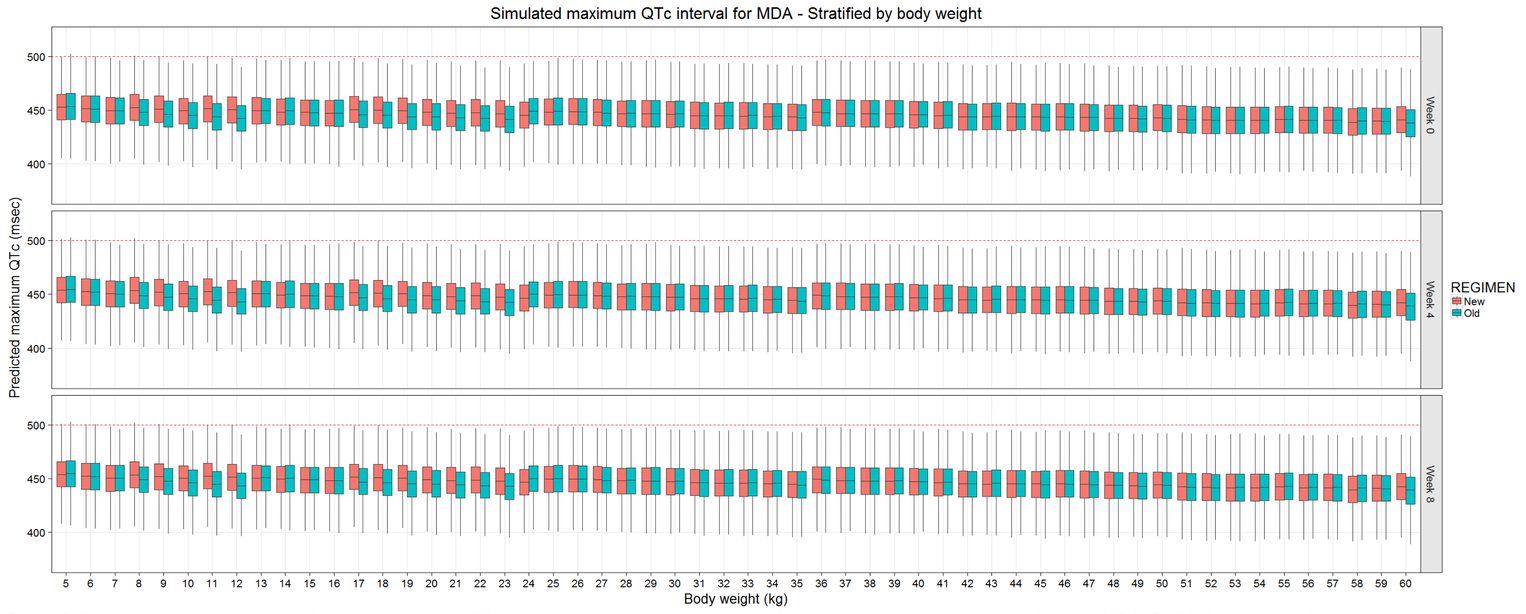

Figure 8. The box plots represent the simulated maximum QTc stratified by body weight after receiving the old and new dosing regimen as MDA (5,000 simulated patients per body weight)

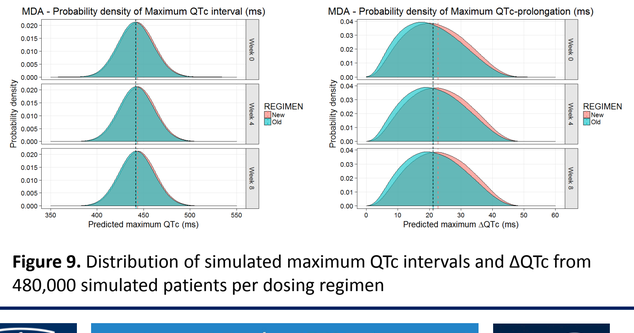

Figure 9. Distribution of simulated maximum QTc intervals and ΔQTc from 480,000 simulated patients per dosing regimen

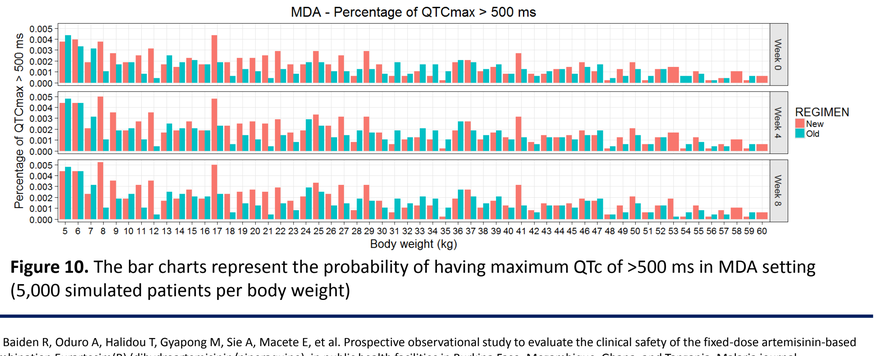

Figure 10. The bar charts represent the probability of having maximum QTc of >500 ms in MDA setting (5,000 simulated patients per body weight)

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[1] Baiden R, Oduro A, Halidou T, Gyapong M, Sie A, Macete E, et al. Prospective observational study to evaluate the clinical safety of the fixed-dose artemisinin-based combination Eurartesim(R) (dihydroartemisinin/piperaquine), in public health facilities in Burkina Faso, Mozambique, Ghana, and Tanzania. Malaria journal. 2015;14:160.
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