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Population-Pharmacokinetics of the Artesunate-Mefloquine (ASMQ) Fixed Dose Combination for the Treatment of Uncomplicated Falciparum Malaria in African children

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Background

- WHO recommends fixed-dose artemisin-based combinations therapies (ACTs) to treat uncomplicated *Plasmodium falciparum* malaria.
- In Africa, there is limited data available on the artesunate-mefloquine (ASMQ) fixed-dose combination (FDC) and no data on MQ pharmacokinetics in children.

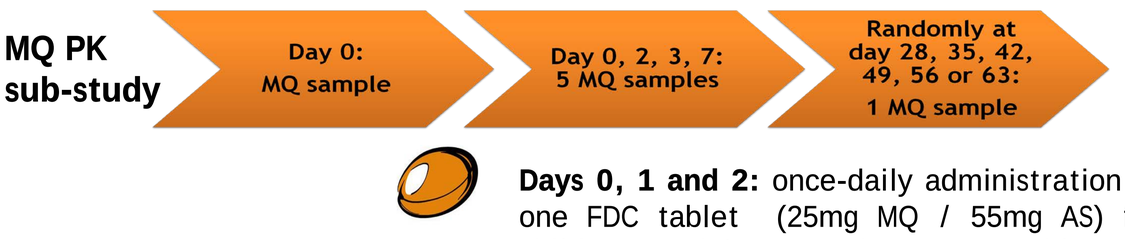
Objectives

- To characterize the population pharmacokinetics (PK) of mefloquine following administration of ASMQ FDC in children.
- To test the influence of co-administered drugs as well as of demographic and physiological characteristics on mefloquine PK.

Methods

Study design

- A randomized clinical study evaluating the efficacy and safety of artesunate-mefloquine vs arthemether-lumefantrine combinations is being conducted in children under 5 years of age in Kenya, Tanzania and Burkina Faso.



Days 0, 1 and 2: once-daily administration of one FDC tablet (25mg MQ / 55mg AS) for children aged 6-11 months, or two tablets for children aged 12-59 months.

Analytical methods

- Plasma drug levels have been determined by reverse phase liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) with an electrospray ionization interface using an adaptation of the multiplex method for the simultaneous analysis of antimalarials developed previously in our laboratory[1].
- The Laboratory participates in the External Quality Control program for antimalarial drugs organized by the WorldWide Antimalarial Resistance Network (WWARN)[2] where our Laboratory performs well.

Patients characteristics

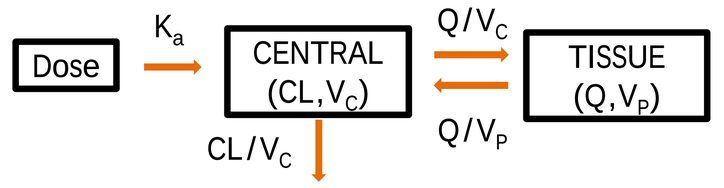
Baseline characteristics	Value	% or range
Demographic characteristics		
Sex (male/female) (no.)	19/29	40/60
Median age (yr)	2.60	0.55-4.95
Median body weight (kg)	12.6	6.6-17
Median height/length (cm)	89.2	66-114
Physiological characteristics		
Hematocrit (%)	30.9	16.8-49.1
Hemoglobin (g/dl)	9.5	5.3-15.2
Co-administered drugs		
CYP3A4 inducers (no.)	7/41	15/85
CYP3A4 inhibitors	0	0

Data

- A total of 216 MQ samples were collected from 48 Kenyan children with *Plasmodium falciparum* malaria.

Data analysis

- The analysis was performed using the NONMEM® (non-linear mixed effect modelling) program[3].
- A two-compartment model with first-order absorption and elimination best describes mefloquine pharmacokinetics.
- Estimated parameters were: systemic clearance (CL), intercompartmental clearance (Q), volumes of distribution of the central and peripheral compartment (V_C and V_P) and absorption rate constant (K_a).
- Interpatient variability (IIV) was associated with CL, V_c and K_a.



Covariates analyses

- Linear models were used to model the effect of demographic and physiological characteristics (centered on their median value) as well as for comedications (coded as 0 or 1) on MQ pharmacokinetics.
- Allometric power model was also tested to model body weight impact on volume of distribution and clearance.
- Treatment day (1 vs. 2 and 3), considered as a marker of health improvement due to the first dose of ASMQ intake, was evaluated for its impact on the absorption rate constant.

1 Hodel EM, Zanolari B, Mercier T, Biollaz J, Keiser J, Olliaro P, Genton B, **Decosterd LA**. A single LC tandem MS method for the simultaneous determination of 14 antimalarials and metabolites in human plasma. **J Chromatog B** 877, 867–886 **(2009)**
2 WorldWide Antimalarial Resistance Network (WWARN) http://www.wwarn.org/toolkit/qaqc.
3 Beal, S.L., et al., *NONMEM User's Guides (1989-2009)*, 2009, Icon Development Solutions: Ellicot City, MD, USA.

Results

- The volume of distribution of the central compartment was found to increase significantly with patients body weight.
- Age and treatment day were found to respectively decrease and increase the absorption rate constant.
- None of the tested covariates was associated with MQ clearance.

Parameter	Population mean			
	Estimate	RSE(%)	IIV(%)	RSE(%)
CL (L/h)	0.20	7	41	14
V_c (L)	45.2	6	32	16
K_a(h^{-1})	0.19	20	95	12
Q (L/h)	0.10	16		
V_P (L)	21.2	9		
$\theta_{AGE,Ka}$	-0.70	21		
$\theta_{DAY,KA}$	0.49	21		

IIV: Interpatient variability; RSE: Relative standard error

$TVVc = Vc^* BW/MBW$
allometric power function, BW: patients' body weight; MBW: median population BW

$TVK_a = K_a*(1+\theta_{AGE,Ka} * ((AGE-MAGE)/AGE)) *(1+\theta_{Day,Ka}*Q1)$
with Q1=0 if treatment day = 0, 1 otherwise; MAGE: median population AGE

- High interindividual variability is associated with MQ pharmacokinetics
- Median (range) MQ elimination half-life is estimated to be 12.6 days (9-33 days)
- Visual predictive check of the dose-normalized observed MQ plasma concentration with mean population prediction (solid lines) and 90% confidence intervals (dotted lines):

Conclusions

- MQ pharmacokinetics present large inter-patient variability in children treated with fixed dose regimen.
- Clearance and volume of distribution of MQ in children is lower than in adult patients of African, Caucasian or Asian origin, but the terminal elimination half-life and mean absorption time are of similar magnitude.
- These results will be further analyzed in light of efficacy and tolerance data.