

Development of PBPK drug models to support antimalarial combination strategy

Nada Abila (1), Lisa Almond (2), Maurice Dickins (2), Nathalie Gobeau (1), Susan A. Charman (3), Karen Rowland-Yeo (2), Zoe Barter (2), Jörg Möhrle (1), David Wesche (4)(5) and Jeremy Burrows (1)

(1) Medicines for Malaria Venture, Geneva, Switzerland, (2) Simcyp Limited (a Certara Company), Sheffield, UK, (3) Monash University, Australia, (4) Bill & Melinda Gates Foundation, Seattle, USA, (5) Great Lakes Drug Development (a Certara Company), Grand Rapids, USA

INTRODUCTION

The current WHO recommendation for the treatment of uncomplicated falciparum malaria is artemisinin-based combination therapies (ACTs)[1]. Different ACTs are available and a better understanding of the pharmacokinetic behavior and potential drug-drug interactions (DDIs) of each individual drug is needed in order to **optimize the doses for new combinations** of ≥ 2 drugs, and potentially **adapt the doses** in children, who receive sub-optimal doses in some cases [2].

Malaria remains a public health imperative

Estimated 445 000 deaths worldwide in 2016 [1]



70% deaths occur in children <5 years

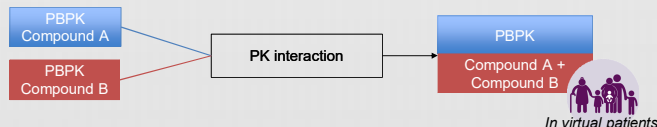
Major ACTs:

Treatment of uncomplicated malaria

- Artemether + Lumefantrine
- DHA + Piperaquine
- Artesunate + Pyronaridine
- Artesunate + Mefloquine
- Artesunate + Amodiaquine
- Artesunate + Sulfadoxine + Pyrimethamine

OBJECTIVES

- To develop PBPK models for the major antimalarial compounds currently in use.
- To make these models publicly available to researchers to support:
 - Development of new combinations of ≥ 2 antimalarials
 - Dose optimization of existing combinations in children
 - Evaluation of DDI risk with co-administered drugs (eg: anti-HIV, anti-TB drugs)



METHODS

In vitro data

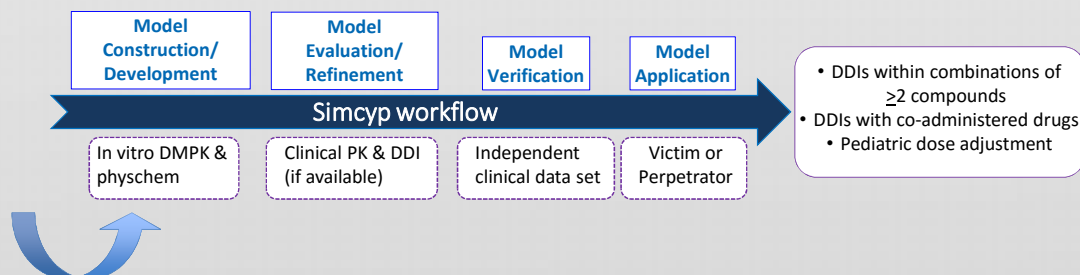
❖ Centre for Drug Candidate Optimisation, Monash University, Australia:

- Log $D_{7.4}$
- pKa
- P_{app} (Caco-2); Efflux Ratio
- Plasma protein binding
- B:P ratio
- $F_{u,mic}$
- CL_{int} in HLM
- Aqueous solubility @ pH7.4
- Solubility in FaSSIF, FeSSIF, FaSSGF
- CYP inhibition (direct + TDI)



❖ External CRO:

- CYP and UGT reaction phenotyping



RESULTS

Antimalarial compounds for which PBPK files are available, and potential DDIs related to CYP2D6 (←-----→) and CYP3A4 (←-----→) based on in vitro data, to be confirmed by M&S and/or clinical studies.

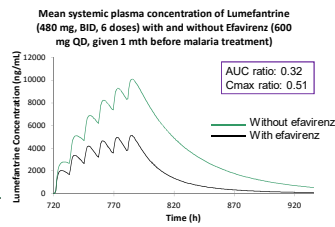
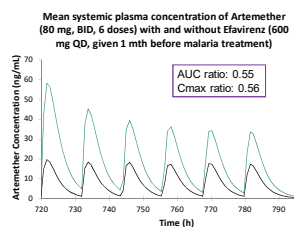
Available Simcyp files	Risk as a victim	Risk as a perpetrator
Artemether	CYP2B6, 3A4	CYP2B6 induction
DHA (eg from artesunate)	UGT1A9, 2B7	CYP1A2 inhibition
Lumefantrine	CYP3A4	CYP2D6 inhibition
Piperaquine	CYP3A4, 2C9, 2C19	CYP3A4 TDI
Pyronaridine	CYP1A2, 2B6, 2C8, 2D6, 3A4	CYP2D6 inhibition
Mefloquine	CYP3A4	CYP2D6 inhibition
Amodiaquine (+desethylamodiaquine)	CYP2C8	CYP2D6 inhibition
Sulfadoxine	Renal clearance (90%)	None
Pyrimethamine	Incomplete information (very low clearance)	No CYP inhibition
Atovaquone	Mainly biliary clearance	BCRP inhibition
Proguanil (+cycloguanil)	CYP2C19, 3A4	CYP2D6 inhibition
Chloroquine	CYP2C8, 3A4, renal (50%)	CYP2D6 inhibition
Azithromycin	Information missing	CYP3A4 TDI
Doxycycline	Renal + biliary clearance	None
Quinine	CYP3A4 mainly	CYP2D6 inhibition
Primaquine (+carboxyprimaquine)	MAO (89%) → carboxyprim. CYP2D6 (11%)	CYP1A2 inhibition

CONCLUSION

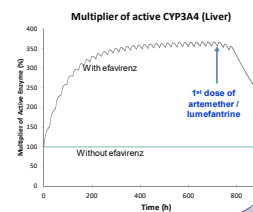
PBPK models for **16 antimalarial drugs** are available and ready to be shared with researchers in the malaria field who are interested in using them for different applications. This is the first step of an effort to establish a library of PBPK models for antimalarial compounds. The next step will be the development of PBPK files for new compounds at different stages of the research and development pipeline, to support the development of new combination therapies for malaria.

Example of an application:

Artemether (CYP2B6, $f_m=0.35$ + 3A4, $f_m=0.65$, substrate [3]) / Lumefantrine (CYP3A4 substrate, $f_m=0.6$ [4]) + Efavirenz (anti-HIV drug, CYP2B6 and 3A4 inducer [5])



- Administration with efavirenz leads to lower exposures of both artemether and lumefantrine.
- Prior chronic dosing with efavirenz reduces the effect of artemether auto-induction.
- Dose adjustment may be needed to reduce risk of treatment failure.
- In line with published clinical observations, at the same dose [6], [7], [8].



REFERENCES

- [1] WHO. World Malaria Report 2017. Geneva, World Health Organization, 2017
- [2] Hoglund RM et al. PLoS Med. 2017;14:1
- [3] Honda M et al., DMD 2011; 39:1860
- [4] Lefevre G et al., BJCP 2002; 54:5; 485
- [5] Ke A et al., CPT Pharmacometrics Syst. Pharmacol. 2016; 5; 367
- [6] Hoglund RM et al., BJCP 2014; 79:4; 636
- [7] Kajubi R et al., OFID 2016; 3:4; 1
- [8] Byakika-Kibwika P et al., JAC 2012; 67; 2213

ACKNOWLEDGEMENTS

This work was funded by the Bill and Melinda Gates Foundation (BMGF). The authors thank Dr. P. Zhao and Dr. S. Kern (BMGF), as well as Dr. D. Smith and Dr. S. Obach (Pfizer Inc) for constructive discussions and scientific support.

