A Mechanistic Pharmacokinetic Approach to the Development of Predictive Models in HIV-malaria Co-infection in Children Accounting for Induction of CYPs 3A4 and 2B6 – a Lumefantrine and Efavirenz Case Study

Zaril Harza Zakaria[1] Gavin Woodhall[2] Raj Singh Badhan[1]

[1]Aston Pharmacy School, Aston University, Birmingham, B4 7ET, UK
[2]Aston Brain Centre, School of Life and Health Sciences, Aston University, Birmingham, B4 7ET, UK

Introduction

Malaria and human immunodeficiency virus infection (HIV) represent a considerable and overlapping healthcare burdens. The World Health Organization (WHO) estimated 200 million malaria cases and 600 000 malaria-related deaths in 2013. Artemether-lumefantrine (AL) with the 3-day treatment regimen is one of the most widely used antimalarials, and many countries adopted it as first line therapy for uncomplicated falciparum malaria, including children with HIV co-infection. True recrudescence is usually uncommon in AL therapy. However, for patients within whom pharmacokinetic exposure to AL may be reduced i.e. in the context of enzyme inducers such as efavirenz in HIV co-infection, recrudescence rates may increase. In addition, there is a need to evaluate these interactions in young children, who may be at higher risk of treatment failure if treated with efavirenz due to a lower level of acquired immunity.

Aim: Optimal therapeutic doses in children

Objectives:

- To develop a physiologically-based pharmacokinetic (PBPK) model describing PK relationships between efavirenz and lumefantrine specifically in paediatrics population (3-10 years old).
- Understanding the complex drug interaction between efavirenz, an ART for treatment of HIV, and antimalarial agent, lumefantrine to develop new strategies for optimal treatment for malaria in children.

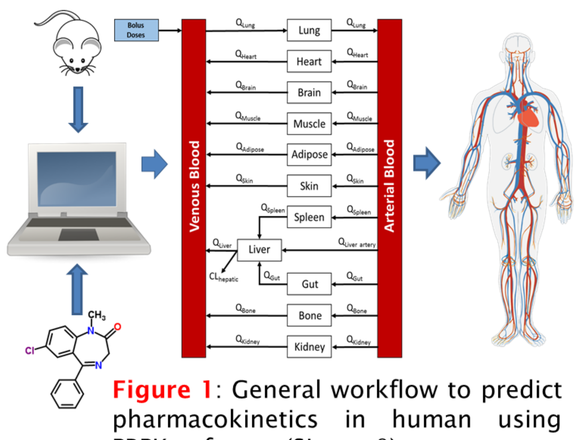


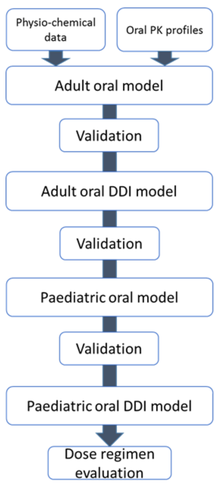
Figure 1: General workflow to predict pharmacokinetics in human using PBPK software (Simcyp®).

Table 1: Coartem and efavirenz dosing regimen in accordance with the WHO weight-bands in children (3-10 years old).

		Total mg per dose	
Body weight	**Tablets per dose**	**Lumefantrine**	**Artemether**
5 to < 15 kg	1	120	20
15 to < 25 kg	2	240	40
25 to < 35 kg	3	360	60
		Efavirenz	
10 to < 15 kg	-	200	
15 to < 20 kg	-	250	
20 to < 25 kg	-	300	
25 to < 35 kg	-	350	

Therapeutic Efficacy Marker:
Lumefantrine target 7-day post-dosing concentration ~280 ng/mL

Methods



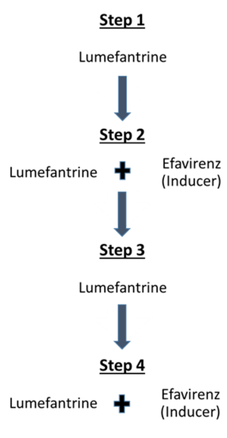


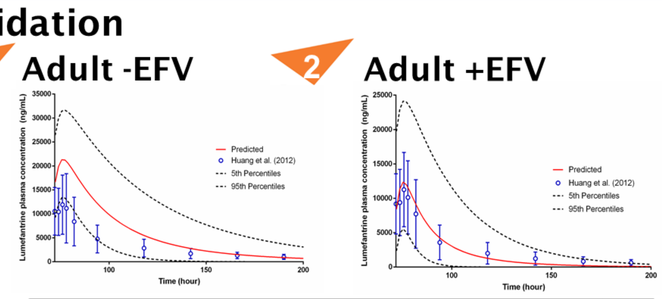
Figure 2: Stepwise approach in developing the PBPK model.

Table 2: Input parameter and predicted PBPK values for use in the simulation for lumefantrine and efavirenz

Parameters	Lumefantrine	Comment	Efavirenz	Comment
Compound type	Diprotic base		Monoprotic acid	
Molecular weight (g/mol)	528.94	Olafuyi, O., et al. (2017)	315.68	Simcyp® default values
Log P	8.70	Huang et al. (2012), Olafuyi, O., et al. (2017)	4.02	
fu	0.003	Colussi, D., et al. (1999), Olafuyi, O., et al. (2017)	0.029	
pKa 1	14.10	Olafuyi, O., et al. (2017)	10.20	
pKa 2	9.80	Olafuyi, O., et al. (2017)	-	
B/P	0.80	Zaloumis et al. (2012), Olafuyi, O., et al. (2017)	0.74	
Vss (L/kg)	0.70	Olafuyi, O., et al. (2017)	14.26	
Peff (10-4 cm/s)	0.97	Olafuyi, O., et al. (2017)	5.68	
Kp scalar	0.50	Parameter estimated	1	
Solubility (mg/mL)	0.002	Kotila et al. (2013), Olafuyi, O., et al. (2017)	-	
CLpo (L/min)	0.25	Ezzet et al. (1998), Olafuyi, O., et al. (2017)	20	
CLint3A4 (µL/min/pmol)	4.60	Parameter estimated	0.0094	
CLint2B6 (µL/min/pmol)	-		1.35	
CYP3A4 Indmax (fold)	-		3	
CYP3A4 IndC50 (µM)	-		3.8	
CYP2B6 Indmax (fold)	-		6.2	
CYP2B6 IndC50 (µM)	-		1.2	
Absorption model	ADAM		1st order	
Distribution model	Full		Full	

Results

Validation

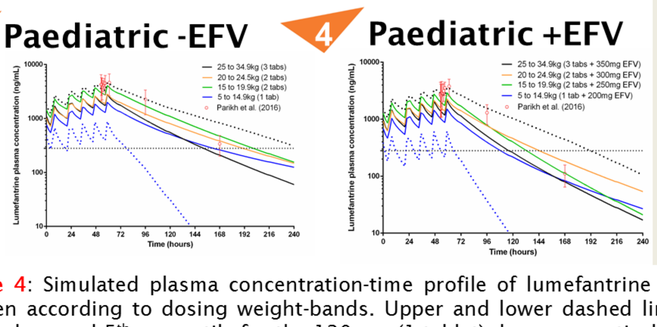


		(-) Efavirenz			(+) Efavirenz		
		C_{max} (ng/mL)	AUC (ng/mL.h)	t_{max} (h)	C_{max} (ng/mL)	AUC (ng/mL.h)	t_{max} (h)
Lumefantrine	Predicted	21302	795191	3.6	12359	276218	3.6
	Observed	11914 ± 6173	484532 ± 275867	4	11261 ± 5401	373205 ± 246468	4

Lumefantrine: AUC (0-last)
Data represent mean ±SD

Figure 3: Simulated plasma concentration-time profile of lumefantrine in the (1) absence and (2) presence of efavirenz in adult. Ideal PK time was used as X-axis. Mean observed plasma concentrations represented by the open circles.

Table 3: Summary of predicted and observed PK parameters of lumefantrine in the absence and presence of efavirenz in healthy adults.



- Validation conducted for the concomitant treatment of efavirenz and lumefantrine under standard body-weight based treatment regimens for 3-10 years old demonstrated that no subjects attained the target day 7 concentration (Cd7) of 280 ng/mL.

Figure 4: Simulated plasma concentration-time profile of lumefantrine in the (3) absence and (4) presence of efavirenz in children according to dosing weight-bands. Upper and lower dashed lines represent the 95th percentile for the 360 mg (3 tablet) dose and 5th percentile for the 120 mg (1 tablet) dose, respectively. Mean observed plasma concentrations represented by the open circles. Dashed vertical line along the x-axis represents the Day 7 lumefantrine plasma concentrations (Cd7) = 280 ng/mL.

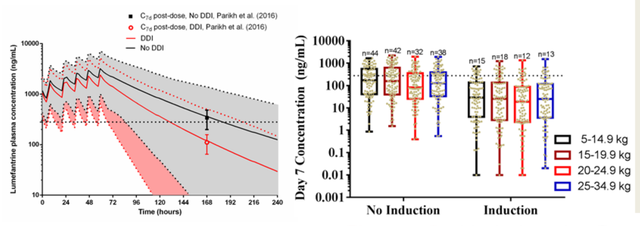
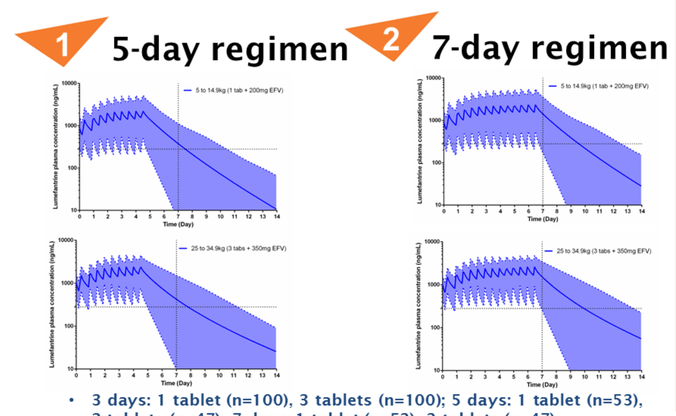


Figure 5: Simulated plasma concentration-time profile of lumefantrine in the absence and presence of efavirenz in children.

Figure 6: Variation in Day 7 lumefantrine plasma concentration in the absence and presence of efavirenz mediated DDI in children. Box and whisker plots represent minimal, 25th percentile, median, 75th percentile and maximum values (n=100). Dashed lines indicate the 280 ng/mL clinical efficacy cut-off. Numbers above the box and whisker are the number (n) of subjects with a predicted concentration of over 280 ng/mL is indicated.

- Predictions for the absence and presence of EFV were within the observed range of day 7 concentration reported by Parikh et al. 2016 (Fig. 5).
- In the presence of EFV, a significant decrease in lumefantrine concentrations was simulated across all weight-band within each population group (Fig. 6).

Paediatric dose regimen prediction



- 3 days: 1 tablet (n=100), 3 tablets (n=100); 5 days: 1 tablet (n=53), 3 tablets (n=47); 7 days: 1 tablet (n=53), 3 tablets (n=47).

Figure 7: The simulated mean plasma concentration-time profile of lumefantrine in paediatrics (3-10 years old) in the presence of a DDI for an adapted 5 and 7-day regimen (100 subjects). Dashed vertical line along the x- and y-axis represents the Day 7 lumefantrine plasma concentrations (Cd7) = 280 ng/mL.

- Current 3-day treatment regimen resulted in 15% and 13% of subjects achieving the target Cd7 for 1-tablet and 3-tablet regimens (Fig. 6).
- Adapted 5-day treatment regimen resulted in 43.3% and 42.6% of subjects achieving the target Cd7 for 1-tablet and 3-tablet regimens (Fig. 7).
- Adapted 7-day treatment regimen resulted in 92.5% and 93.6% of subjects achieving the target Cd7 for 1-tablet and 3-tablet regimens (Fig. 7).

Conclusion

Model suggested optimal therapeutic doses of 5-day regimen Coartem® dosing instead of 7-day regimen (due to possibility of high adverse events e.g. QT interval prolongation) and the current 3-day regimen dosing for treatment with efavirenz in HIV-malaria co-infected paediatric patients 3 to 10 years old.

This approach has significant implications for assessing DDI between efavirenz and lumefantrine as well as provides an opportunity for exploring the relationship between enzyme inducers in HIV-malaria co-infection therapy.

Acknowledgements

Aston University Life & Health Sciences

Ministry of Health Malaysia

References

Ezzet F, Mull R, Karbwang J. Population pharmacokinetics and therapeutic response of CGP 56697 (artemether + benflumetol) in malaria patients. British Journal of Clinical Pharmacology. 1998;46(6):553-561.

Get in touch

Zaril H Zakaria
zakariz1@aston.ac.uk