Assessing Drug–drug Interactions Associated with Antimalarial Treatment in Paediatrics Co-infected with Tuberculosis: A PBPK Case Study with Lumefantrine and Rifampicin.

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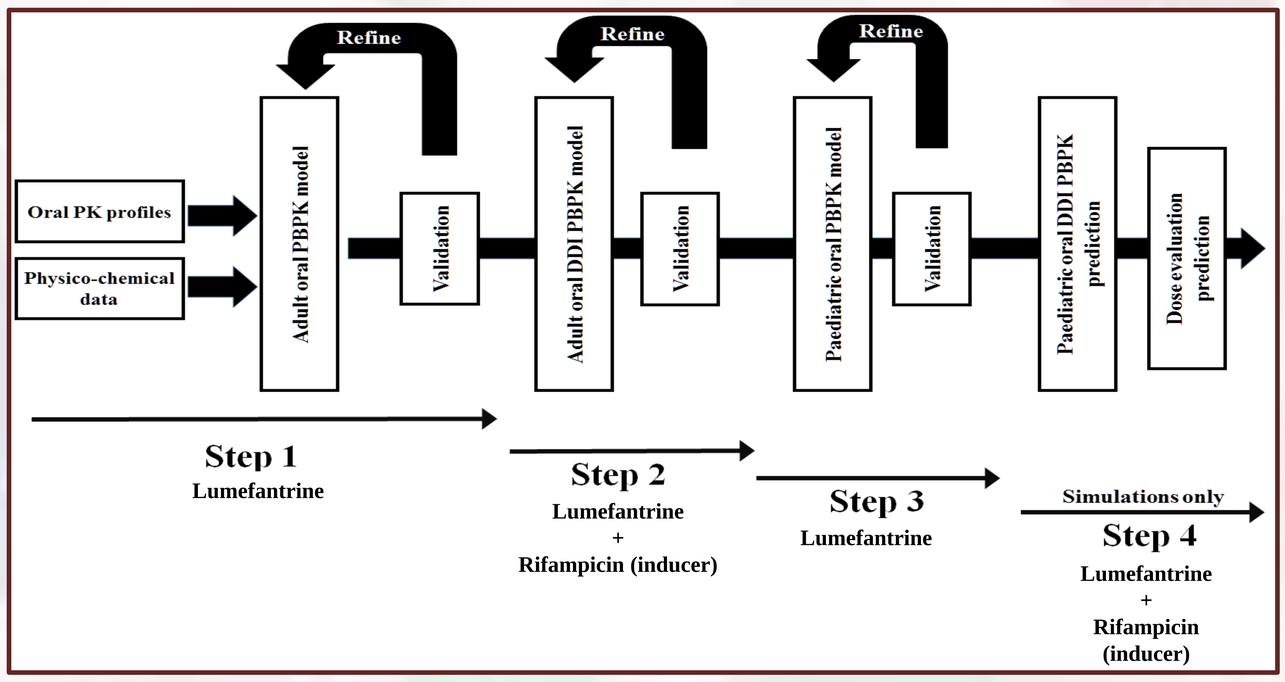
Introduction

Breakthroughs in antimalarial treatment with artemisinin based combination therapy (ACT) development may have contributed to a 60% reduction in mortality rate from year 2000 to 2015, however, mortality rate due to malaria infections remains higher in children compared to adults [1]. Artemether/lumefantrine (AL) is recommended for the treatment of malaria and the standard dosing in children is weight based whereby children 5–15 kg receive 1 tablet per dose; 15–25 kg, 2 tablets per dose; 25–35 kg, 3 tablets per dose and > 35 kg 4 tablets per dose. Each dose containing 20/120mg AL and taken at 0, 8, 24, 36, 48 and 60h [1]. It is reported that AL systemic exposure is reduced when administered with rifampicin (a CYP3A4 inducer) in adults [2]. However, developmental physiology and the ontogeny of metabolising enzymes may alter the way DDI effects are presented in paediatric. Population-based physiologically-based pharmacokinetic (PBPK) modelling may be used to explore DDI between AL and rifampicin in paediatrics due to the sparsity of recruitment of malaria-infective children into clinical trials during drug development [3].

Aim of study

To investigate the impact of DDIs between lumefantrine and rifampicin in paediatrics age 2-5 years old with tuberculosis co-infected with malaria using the virtual clinical trials simulator **Simcyp®**

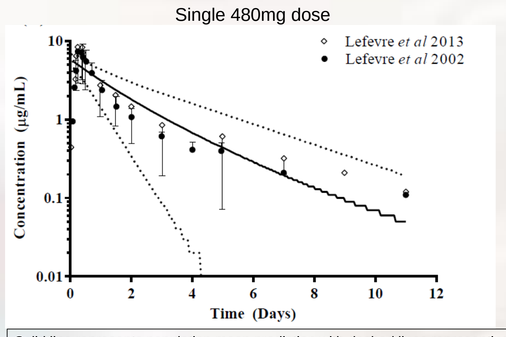
Methods



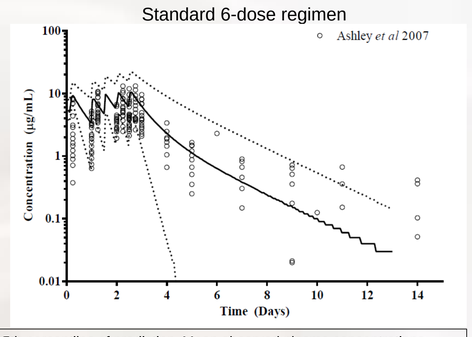
Results and Discussion

1. Validation of lumefantrine concentration time profile in adults

Single 480mg dose



Standard 6-dose regimen



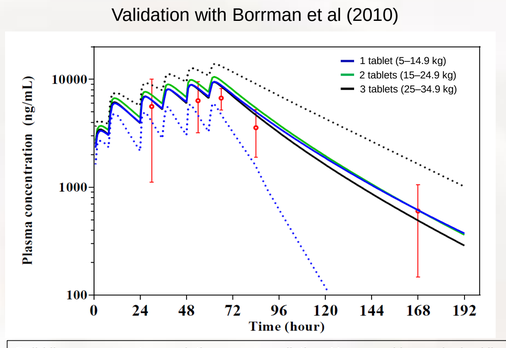
Solid line represents population mean prediction with dashed lines representing the 5th and 95th percentiles of prediction. Mean observed plasma concentrations represented by the diamond and circles.

		Prediction	Lefevre et al 2013	Lefevre et al 2002	Ashley et al 2007
Artemether	Dose (mg)	80	80	80	
	Population size (n)	100	58	16	
	C_{max} (µg/ml)	139.1 ± 70.2	113 ± 69.5	104 ± 40	
	AUC_{last} (µg/mL.h)	521.2 ± 254.1	408 ± 209	302 ± 135	
Lumefantrine	Dose (mg)	480	480	480	
	Population size (n)	100	58	16	
	C_{max} (µg/ml)	6.31 ± 1.45	8.92 ± 3.18	7.91 ± 3.49	
	AUC_{last} (µg/mL.h)	251.4 ± 112.3	236 ± 93	195 ± 119	
Lumefantrine	Dose (mg)	6 dose regimen			6 dose regimen
	Population size (n)	100			17
	C_{max} (µg/ml)	9.56 (5.67-16.78)			6.89 (3.69-13.19)
	C_{24h} (pre-dose)	3.39 (1.98-9.28)			2.53 (0.68-9.8)
	C_{48h} (pre-dose)	5.81 (1.48-13.14)			3.84 (1.91-6.80)
	C_{72h} (pre-dose)	5.84 (1.12-12.75)			3.91 (2.15-9.64)
	C_{d7}	0.32 (0.11-0.78)			0.35 (0.20-0.87)
	$AUC_{0-\infty}$ (µg/mL.h)	387.4 (98-1157)			432 (308-991)

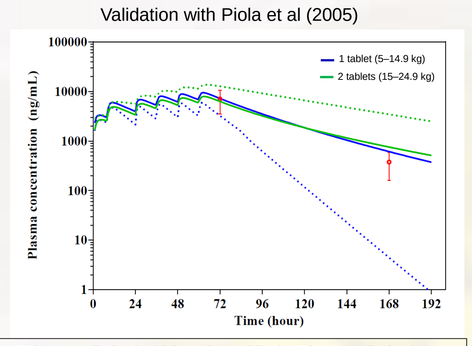
A visual check of the predicted concentration time profiles of lumefantrine showed **congruence with the reported profiles,** also it reflected the wide interindividual variation in the absorption phase of the drug. In addition, the **model appropriately predicted the pharmacokinetic parameters of lumefantrine including the day 7 concentration (>280 ng/ml)** and these values were all within two folds of reported values.

2. Validation of lumefantrine concentration time profile in paediatrics

Validation with Borrman et al (2010)



Validation with Piola et al (2005)

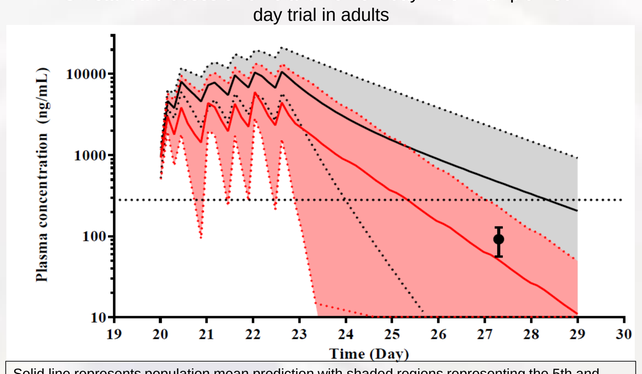


Solid lines represents population mean prediction. Upper and lower dashed lines represent the 95th percentile for the highest dose while the 5th percentile for the lowest dose. Mean observed plasma concentrations represented red circles.

The standard weight-based dosing of lumefantrine in paediatrics was simulated with the model and the model **gave good predictions for the concentration time points including the day 7 lumefantrine concentrations on the profile** for each published study. The scare data points for visual validation checks of the predicted profile was due to unavailability robust data for the concentration time profiles of lumefantrine in paediatrics.

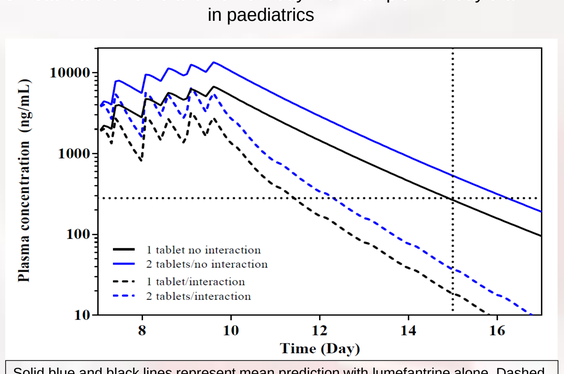
3. Simulated plasma concentration-time profile of lumefantrine in the absence and presence of rifampicin in adults and paediatrics

Six standard doses of lumefantrine from day 20 of rifampicin 30-day trial in adults



Solid line represents population mean prediction with shaded regions representing the 5th and 95th percentiles of prediction (grey: no interaction; red: interaction). Dashed horizontal lines represents minimum effective parasite clearance plasma concentration for lumefantrine (280 ng/mL)

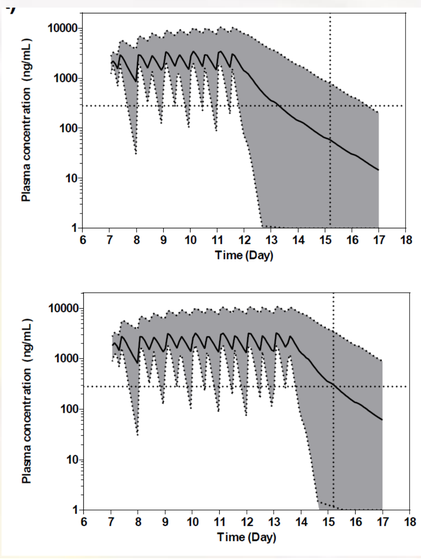
Six standard of lumefantrine from day 7 of rifampicin 20-day trial in paediatrics



Solid blue and black lines represent mean prediction with lumefantrine alone. Dashed blue and black lines represents lumefantrine profiles in the presence of rifampicin. Vertical and horizontal dashed line represents minimum effective parasite clearance plasma concentration for lumefantrine (280 ng/mL)

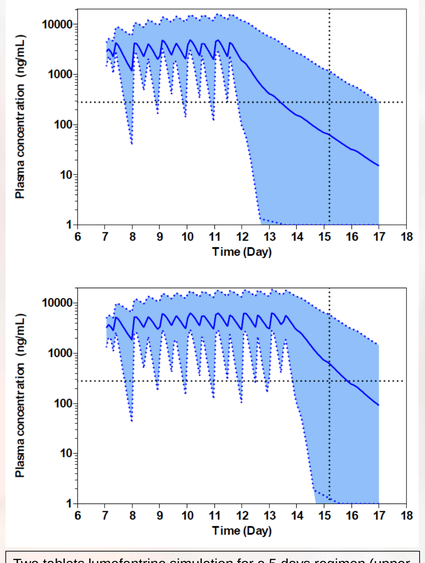
There was a substantial DDI between AL and a rifampicin based anti-tuberculosis agent reported in adult clinical trial study with day 7 lumefantrine concentration drastically falling below the 280ng/ml endpoint. **This DDI was replicated in our model in the adult** population group. There are has been no clinical trial to verify this interaction in paediatric but **our model predicted a similar pattern of interaction in paediatrics between 2 – 5 years old**.

4. Simulated plasma concentration-time profile of lumefantrine in paediatrics in the presence of a DDI 5 and 7-day regimen



One tablet lumefantrine simulation for a 5 days regimen (upper panel) and 7 days regimen (lower panel). Dashed vertical and horizontal lines represents minimum effective parasite clearance plasma concentration for lumefantrine (280 ng/mL).

We showed that lengthening the period of AL treatment in the case of DDI with a rifampicin based anti-tuberculosis treatment can potentially improve the day 7 lumefantrine outcomes in paediatric patients who are being treated for this diseases. **A 7-days treatment period gave better treatment outcomes compared to a 5-days treatment period** with day 7 treatment resulting in 63% and 74% of patients falling within the lumefantrine efficacy target for 2 and 3 tablets regimen respectively.



Two tablets lumefantrine simulation for a 5 days regimen (upper panel) and 7 days regimen (lower panel). Dashed vertical and horizontal lines represents minimum effective parasite clearance plasma concentration for lumefantrine (280 ng/mL).

Conclusion

This is the first study to use PBPK modelling to evaluate DDI of antimalarials in paediatric and this study gives an insight into how this approach can be used in the fight against malaria. We have shown that our PBPK model for lumefantrine in adults and paediatrics reproduces observed clinical data. Also, with this model, DDI between lumefantrine and rifampicin based treatment can be assessed in populations groups where ethical constraints might hinder clinical trial evaluation. From our results, an increase in treatment period of AL in paediatric patients who are simultaneously treated for tuberculosis may improve antimalarial treatment outcomes in these.

References:

1. World Health Organisation, W.H.O. *Malaria: Fact sheets*. 2016 January 2016 [cited 2016 18th April]; Available from: http://www.who.int/mediacentre/factsheets/fs094/en/.
2. Lamorde, M., et al., *Lower artemether, dihydroartemisinin and lumefantrine concentrations during rifampicin-based tuberculosis treatment.* AIDS, 2013. **27**: p. 961-965.
3. Suri, A., et al., *Physiologically Based and Population PK Modeling in Optimizing Drug Development: A Predict-Learn-Confirm Analysis.* Clinical Pharmacology & Therapeutics, 2015. **98**(3): p. 336-344

For more details, kindly refer to full text in the European Journal of Pharmaceutical Sciences https://doi.org/10.1016/j.ejps.2017.05.043 OR contact Dr Raj Badhan: Life and Health Science, Aston University, Birmingham, UK. Email: r.k.s.badhan@aston.ac.uk; Olusola Olafuyi: Life and Health Science, Aston University, Birmingham, UK. Email: akinyelo@aston.ac.uk