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 paediatrics. 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-infected 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®

Results and Discussion

1. Validation of lumefantrine concentration time profile in adults

2. Validation of lumefantrine concentration time profile in paediatrics

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

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

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 cases.

References:


