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Development of a paediatric physiologically based pharmacokinetic model to assess the impact of drug-drug interactions in tuberculosis co-infected malaria subjects: A case study with artemether-lumefantrine and the CYP3A4-inducer rifampicin

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ABSTRACT

The fixed dosed combination of artemether and lumefantrine (AL) is widely used for the treatment of malaria in adults and children in sub-Sahara Africa, with lumefantrine day 7 concentrations being widely used as a marker for clinical efficacy. Both are substrates for CYP3A4 and susceptible to drug-drug interactions (DDIs); indeed, knowledge of the impact of these factors is currently sparse in paediatric population groups. Confounding malaria treatment is the co-infection of patients with tuberculosis. The concomitant treatment of AL with tuberculosis chemotherapy, which includes the CYP3A4 inducer rifampicin, increases the risk of parasite recrudescence and malaria treatment failure. This study developed a population-based PBPK model for AL in adults capable of predicting the pharmacokinetics of AL under non-DDI and DDI conditions, as well as predicting AL pharmacokinetics in paediatrics of 2–12 years of age. The validated model was utilised to assess the concomitant treatment of rifampicin and lumefantrine under standard body-weight based treatment regimens for 2–5 year olds, and demonstrated that no subjects attained the target day 7 concentration (C_{d7}) of 280 ng/mL, highlighting the importance of this DDI and the potential risk of malaria-TB based DDIs. An adapted 7-day treatment regimen was simulated and resulted in 63% and 74.5% of subjects attaining the target C_{d7} for 1-tablet and 2-tablet regimens respectively.

1. Introduction

Malaria is a deadly parasitic disease spread by female *anopheles* mosquitoes infected with *Plasmodium falciparum* (Gomes, 1993; World Health Organisation, 2016a). The World Health Organisation's (WHO) target is to eliminate malaria in 35 countries by 2030 and this has led to several measures being taken over the past few decades directed towards malaria prevention and treatment in order to reduce its prevalence and mortality rates (World Health Organisation, 2016a). At the turn of the millennium, the global estimate of malaria cases averaged 262 million which, by 2015, had fallen to 214 million, reflecting a decrease of 18% (World Health Organisation, 2015). Furthermore, 88% of these malaria cases were reported in the sub-Saharan African region. Alarmingly however, within the paediatric population group 70% of the total malaria related deaths were attributed to children under five years of age (World Health Organisation, 2016a).

In 2006, artemisinin or artemisinin derivatives were recommended by the WHO for the first line treatment of malaria in endemic areas. During every 48 h *P. falciparum* replication period, artemether and its active metabolite dihydroartemisinin (DHA) decreases parasite load by approximately 10,000 fold (Byakika-Kibwika et al., 2010; Mwesigwa et al., 2010). Artemether's oral absorption and onset of action are both rapid, with an approximate t_{max} following oral administration of 2 h (White et al., 1999; Ezzet et al., 1998). Furthermore, oral absorption is improved following a fat-rich meal (Borrmann et al., 2010a), with bioavailability increasing by 2-fold compared to a fasted-state in healthy volunteers (Ezzet et al., 2000). Hepatic metabolism of artemether is rapid and predominantly mediated by CYP3A4, as well as CYP2B6 (Mwesigwa et al., 2010; Hietala et al., 2010; Siccardi et al., 2013). Lumefantrine is a racemic fluorine mixture possessing a chemical structure related to the arylaminoalcohol group of antimalarials such as quinine, halofantrine and mefloquine (Cui & Su, 2009). Lumefantrine is well orally absorbed but, as with artemether, demon-

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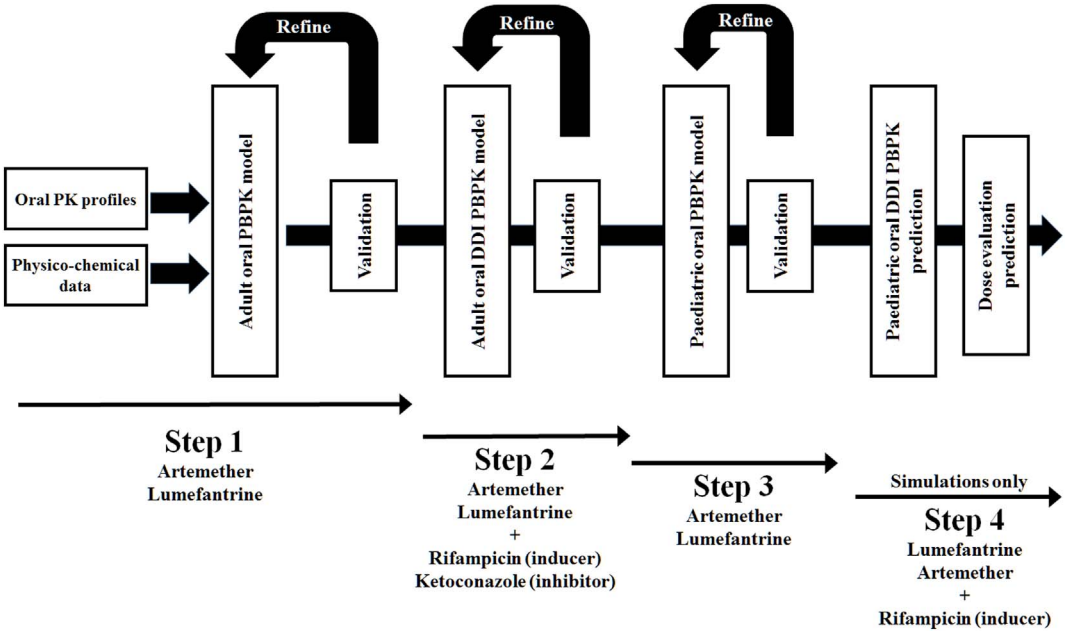

Fig. 1. Model development strategy.

strates absorption pharmacokinetics which are highly variable in malaria patients (Ezzet et al., 2000). As with artemether, the administration of food increases the bioavailability by 16-fold when compared to the fasted state in healthy volunteers (Ezzet et al., 2000). CYP3A4 is primarily responsible for the metabolism of lumefantrine. As a result of low hepatic intrinsic clearance and negligible renal excretion, lumefantrine possess a prolonged half-life (Borrmann et al., 2010a) of up to six days in healthy volunteers (Lefevre et al., 2002a) (Davis et al., 2016). Artemether is recommend for dosing in conjunction with lumefantrine (AL) as a fixed dose combination (FDC) of 20 mg/120 mg respectively, in six doses usually over three days (commonly at 0, 8, 24, 26, 48 and 60 h). Typical treatment regimens for children include a similar 3 day six-dose regimen stratified based on body weight: 5–15 kg 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 (World Health Organisation, 2016), with the latter dose primarily being the default adult dose.

Contrary to adults who possess naturally acquired immunity, children often do not, this puts them at risk of succumbing to the infection (Doolan et al., 2009) and this is further complicated by possible trans-placental transmission in pregnant women leading to congenital malaria (World Health Organisation, 2016a). Whilst malaria is endemic to many areas of sub-Sahara Africa, other communicable diseases such as tuberculosis are also commonplace, and particularly impacts upon paediatric population groups. In 2015, there were an estimated 10 million new TB cases worldwide of which 10% were children (World Health Organisation, 2016b). Worryingly, the mainstay treatments for tuberculosis, namely a FDC of rifampicin (10–20 mg/kg), isoniazid (10–15 mg/kg), pyrazinamide (30–40 mg/kg) and ethambutol (15–25 mg/kg), can directly affect CYP3A4 activity through primarily rifampicin being a strong inducer (Niemi et al., 2003; FDA, 2006) or isoniazid being a modrate inhibitor (FDA, 2006; Wen et al., 2002). Thus, drug-drug interactions are commonplace in patients who are likely to present with both malaria and tuberculosis making dosing strategies in paediatrics complex. Although data is sparse and the connection between malaria and tuberculosis co-infection has not been widely investigated (in contrast to HIV and tuberculosis coinfection), one study in Angola reported that the presence of malaria in patients admitted for tuberculosis as 37.5% (Valadas et al., 2013). Furthermore, the risk of rifampicin-mediated induction in CYP3A4 expression/activity would have the potential to significantly increase the clearance of AL, as has been demonstrated in adult populations (Lamorde et al., 2013a) and has further been contraindicated when used with strong inducers such as rifampicin (Norvartis, 2012).

However, the magnitude of this induction effect on AL pharmacokinetics has not been investigated. DDIs between antimalarials and other drugs in paediatrics are not well studied and this may impact on the clinical efficacy, and safety of antimalarial drug therapy. *In-lieu* of complex clinical studies, physiologically-based pharmacokinetic (PBPK) modelling has been used to explore the potential risk of DDIs in adults (Feng & Varma, 2016; Johansson et al., 2016) and paediatric populations (Salem et al., 2013a; Salem et al., 2013b; Johnson et al., 2014).

The objective of the current study was to demonstrate the application of PBPK modelling to the prediction of DDI risks in malaria-tuberculosis co-infection paediatric population groups. Specifically, the potential for a DDI between the CYP3A4 inducer rifampicin and AL will be explored over 2–5 year old population groups.

2. Methods

All population based PBPK modelling was conducted using the virtual clinical trials simulator Simcyp® (Simcyp® Ltd., a Certara company, Sheffield, UK, Version 16) using either the pre-validated in-built 'Healthy Volunteer' or 'Paediatric' population groups. The latter population group accounts for age-related changes in systems-parameters such as organ volumes, organ perfusion and ontogeny of drug metabolising enzymes (Johnson, 2005) (Johnson, 2008) (Small et al., 2017) and allows for the prediction of drug behaviour in paediatric population groups. In the case of both models, population variability is accounted for by the inclusion of a variability metric (% coefficient variability) having been established from public health data bases such as the US National health and Nutrition Examination Survey (https://www.cdc.gov/nchs/nhanes/).

2.1. Study design

A four stage strategy was employed for model development and validation (Fig. 1).

Step 1: this step focussed on the development of Simcyp® compound files and validation of simulations with published clinical studies. For artemether and lumefantrine, these included a study conducted in 120 adult subjects who were orally dosed the branded combination