European Journal of Pharmaceutical Sciences 119 (2018) 90–101

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

# The impact of CYP2B6 polymorphisms on the interactions of efavirenz with lumefantrine: Implications for paediatric antimalarial therapy

Zaril Zakaria[a,b], Raj K.S. Badhan[a,c,*]

[a] Aston Health Research Group, Aston Pharmacy School, Aston University, Birmingham B4 7ET, United Kingdom
[b] Ministry Of Health Malaysia, Block E1, E3, E6, E7 & E10, Parcel E, Federal Government Administration Centre, 62590 Putrajaya, Malaysia
[c] Aston Pharmacy School, Aston University, Birmingham B4 7ET, United Kingdom

ARTICLE INFO

*Keywords:*
Physiologically-based pharmacokinetics
Malaria
HIV
Paediatrics
Africa

ABSTRACT

Lumefantrine is a widely used antimalarial in children in sub-Saharan Africa and is predominantly metabolised by CYP3A4. The concomitant use of lumefantrine with the antiretroviral efavirenz, which is metabolised by CYP2B6 and is an inducer of CYP3A4, increases the risk of lumefantrine failure and can result in an increased recrudescence rate in HIV-infected children. This is further confounded by CYP2B6 being highly polymorphic resulting in a 2–3 fold higher efavirenz plasma concentration in polymorphic subjects, which enhances the potential for an efavirenz-lumefantrine drug-drug interaction (DDI). This study developed a population-based PBPK model capable of predicting the impact of efavirenz-mediated DDIs on lumefantrine pharmacokinetics in African paediatric population groups, which also considered the polymorphic nature of CYP2B6. The validated model demonstrated a significant difference in lumefantrine target day 7 concentrations ($C_{d7}$) in the presence and absence of efavirenz and confirmed the capability of efavirenz to initiate this DDI. This was more apparent in the *6/*6 compared to *1/*1 population group and resulted in a significantly lower ($P < 0.001$) lumefantrine $C_{d7}$. A prospective change in dosing schedule from 3-days to 7-days resulted in a greater number of *6/*6 subjects (28–57%) attaining the target $C_{d7}$ across age bands (0.25–13 years), with the greatest increase evident in the 1–4 year old group (3-day: 1%; 7-day: 28%).

## 1. Introduction

Malaria represents a considerable healthcare burden, with the World Health Organisation (WHO) attributing an estimated 212 million malaria cases and 429,000 malaria-related deaths in 2015. Out of those malaria cases and deaths, 92% are from African regions and predominantly occur in children aged under 5 years (World Health Organisation, W.H.O., 2016a, 2016b, 2016c).

Lumefantrine, often combined with artemether, is one of the most widely used antimalarials in sub-Saharan Africa, and many countries adopted it as first line therapy for uncomplicated *falciparum malaria*, including children with HIV co-infection (Flateau et al., 2011). Typical treatment regimens for lumefantrine in children include a 3 day six-dose regimen which is 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, with each tablet providing 120 mg lumefantrine (World Health Organisation, 2016a).

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) and is predominantly metabolised by CYP2B6 (Ogburn et al., 2010) and is an inducer of CYP3A4 (Hariparsad et al., 2004; Shou et al., 2008). It is a common first-line treatment in paediatrics or pregnancy population groups (2013) (Dybul et al., 2002). Lumefantrine is predominantly metabolised by CYP3A4 and, although lumefantrine therapy has a wide therapeutic window (Bharti et al., 2016), patients who are exposed to CYP3A4 inducers, such as efavirenz, may demonstrate reduced lumefantrine exposure which can lead to increased recrudescence rates and therapeutic failure (Maganda et al., 2016a). However, this process is further confounded by the fact that CYP2B6 is highly polymorphic with at least 37 distinct star-alleles (Zanger and Klein, 2013) with *1/*1 carriers considered as wild-type. The most common variant alleles result in two amino acid changes, Q172H and K262R, and is termed *CYP2B6*6*, and which has been reported to lead to a 65% reduction in protein expression and 50% reduction in mean enzyme activity in the homozygous state (Lang et al., 2001).

Although CYP2B6 contributes towards between 2 and 10% of total CYP content (Wang and Tompkins, 2008), the impact of the *6/*6 genotype can often result in a 2- or 3-fold higher efavirenz plasma concentration (Haas et al., 2004; Rodriguez-Novoa et al., 2005; Rotger et al., 2005; Tsuchiya et al., 2004). A consequence of this alteration in efavirenz plasma concentration would be a greater ability of efavirenz

* Corresponding author at: Aston Pharmacy School, Life and Health Sciences, Aston University, Birmingham, B4 7ET, United Kingdom.
*E-mail address:* r.k.s.badhan@aston.ac.uk (R.K.S. Badhan).

https://doi.org/10.1016/j.ejps.2018.04.012
Received 10 October 2017; Received in revised form 8 February 2018; Accepted 5 April 2018
Available online 07 April 2018
0928-0987/ 

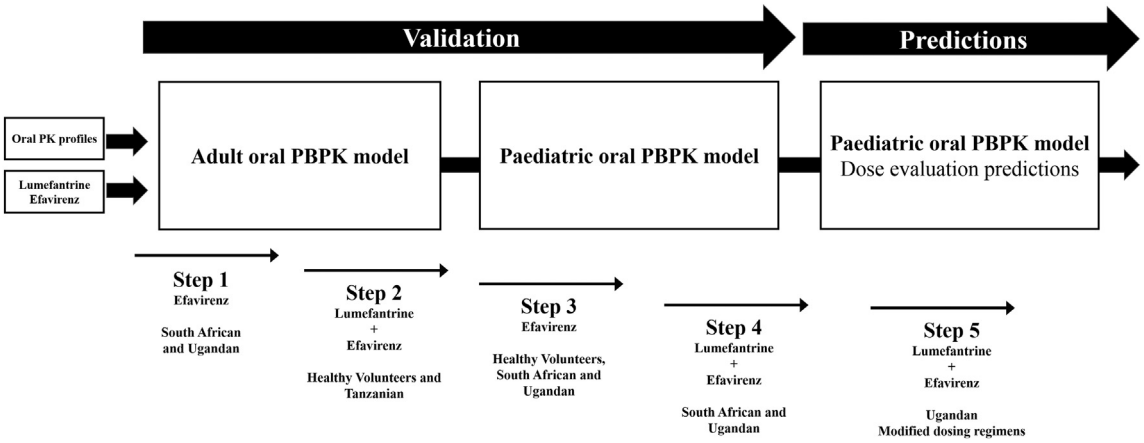


**Fig. 1.** Model development strategy.

to induce CYP3A4 (Habtewold et al., 2013; Hariparsad et al., 2004; Mouly et al., 2002) and thereby enhance the potential for an efavirenz-lumefantrine DDI.

Importantly, the *6/*6 polymorphism is more frequent in African population groups than Caucasian population groups (King and Aberg, 2008; Klein et al., 2005), and this places a considerable risk-burden on this geographic population group. However, the impact of CYP2B6 polymorphisms in antiretroviral-antimalarial mediated DDIs in African paediatric populations is lacking, and warrants investigation as it may contribute to significantly increased the risk of recrudescence especially in highly endemic regions and potential resistance towards these antimalarial treatments (Achan et al., 2012; Barnes et al., 2008; Khoo et al., 2005; World Health Organisation, W.H.O., 2016a, 2016b, 2016c). This is further confounded by the risk of placental transfer of HIV (Drake et al., 2014) and/or malaria (World Health Organisation, 2016b), and the lack of naturally acquired immunity towards children, often puts paediatric population groups at significant risk of succumbing to either infection or being exposed to complex DDIs (Doolan et al., 2009).

Due to the complexity and ethical issues of recruitment of paediatrics into complex DDI studies in HIV-infected malaria subjects, population-based physiologically-based pharmacokinetic (PBPK) modelling can be used to explore the potential risk of DDIs in adults (Feng and Varma, 2016; Johansson et al., 2016; Olafuyi et al., 2017a) and paediatric populations (Johnson et al., 2014; Olafuyi et al., 2017b; Salem et al., 2013a; Salem et al., 2013b). The benefit of this approach is both the ability to model population variability in physiology (Jamei et al., 2009a; Jamei et al., 2009b; Jamei et al., 2009c; Olafuyi et al., 2017a, 2017b), but to also specifically develop a modelling approach that is tailored towards a specific geographical population group of interest rather than a standard healthy (Caucasian) adult male.

The objectives of the present study were 2-fold: (i) to predict efavirenz pharmacokinetics in African population groups (adults and paediatrics) and (ii) to assess the impact of efavirenz in the attenuation of lumefantrine pharmacokinetics through a CYP3A4 induction effect. In all cases, it was important also to address the impact of the *6/*6 CYP2B6 phenotype on efavirenz pharmacokinetic and the effect of this to alter lumefantrine pharmacokinetics following a DDI.

## 2. Methods

Population based PBPK modelling was conducted using the virtual clinical trials simulator Simcyp (Simcyp Ltd., a Certara company, Sheffield, UK, Version 16). For all simulations, doses for both lumefantrine and efavirenz were employed according to the standard weight-based dose regimen (See supplementary materials table S1), unless stated otherwise. Further, for all lumefantrine simulations, dosing occurred under fed-conditions unless otherwise indicated.

### 2.1. Model development

A five-stage stepwise approach was implemented for model development, validation and model refinement (Fig. 1) which is fully described below. Unless otherwise stated, efavirenz was dosed for 20 days prior to initiation of a DDI (and throughout the study). Lumefantrine was dosed at over 3 days at 0, 8, 24, 36, 48 and 60 h.

#### 2.1.1. Step 1: adult simulations with efavirenz

The Simcyp library compound efavirenz was selected, having already been developed and pre-validated by Simcyp (Ke et al., 2016). The metabolism of efavirenz was modelled using the application of allele-specific intrinsic clearance (CLint) for *1/*1 and *6/*6 genotypes, as described by Xu et al. (Xu et al., 2013). Subsequently, when simulating either entirely *1/*1 (EM) or *6/*6 (PM) genotypes, the frequency of CYP2B6 genotype was set at 1 for either *1/*1 or *6/*6. For efavirenz, unless otherwise stated, doses were administered to steady state or beyond (at least 20 days) prior to the initiation of lumefantrine dosing.

Step 1 attempted to apply the compound file to model predictions in Healthy Volunteer (Caucasian), South African and Ugandan population groups, which were generally the focus of clinical studies identified.

Clinical studies selected included: (i) A single 600 mg oral dose to healthy adult volunteers with results genotyped for *1/*1 and *6/*6 (Xu et al., 2013) and (ii) a 600 mg once daily multi-dose study over 32 weeks in Ugandan adults (Mukonzo et al., 2014).

The Ugandan population group was developed from reported age-weight relationships for Ugandan males and females (Hayes et al., 2015), and are detailed in the supplementary materials. A similar approach was reported and applied in PBPK modelling by our group (Olafuyi et al., 2017a). In the absence of literature reported abundance of CYP2B6 in Ugandan subjects, we fixed *1/*1 and *6/*6 genotype abundances to 6.9 and 2.4 pmol/mg protein, respectively, based upon adaptations found in a South African population group developed by Simcyp as part of the Critical Path to TB Drug Regimens (CPTR) (Critical Path to TB Drug Regimens, 2016) and which is available from population library repository of Simcyp. The South African population group includes appropriate age-weight-height distributions, CYP expression and blood biochemistry changes compared to standard (Caucasian) Healthy Volunteer population group (Gardner, 2016). All simulations replicated the study design reported by the validation clinical studies cited above.

#### 2.1.2. Step 2: adult simulations with lumefantrine-efavirenz drug-drug interactions

The validation of the lumefantrine-efavirenz DDI was conducted using two published clinical studies: (i) dosing of a single oral dose of