Validation of computational approaches for antiretroviral dose optimisation

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Abstract

Strategies to reduce antiretroviral doses and drug cost can support global access and numerous options are being investigated. Efavirenz pharmacokinetic simulation generated with a bottom-up physiologically based model were successfully compared with data obtained from the Encore I clinical trial (Efavirenz 400mg qd versus 600mg qd). These findings represent a pivotal paradigm for the prediction of pharmacokinetics resulting from dose reductions. Validated computational models constitute a valuable resource to optimise therapeutic options and predict complex clinical scenarios.

Main text

The global access to treatment will favour a more effective strategy against the HIV pandemic but defines several challenges in terms of drug production and distribution. Antiretroviral dosing strategies have been selected to warrant inhibition of viral replication but there is growing recognition that some antiretroviral drugs may be administered at doses above those required for efficacy. This may place a higher demand than necessary on medication budgets and manufacturing costs in resource-limited settings where the need is greatest.

Alternative strategies to lower doses and drug cost could effectively support global access and several reduction strategies are being investigated (1). A rational identification of optimal dose reductions is challenging and is commonly based on large clinical studies.

Drug distribution can be quantitatively investigated through computational approaches, utilising data from clinical studies to provide a Top-down description and its variability in populations (i.e population pharmacokinetic modelling, popPK) or integrating drug specific in vitro data in models to predict Bottom-up pharmacokinetics in populations of virtual patients (i.e physiologically based pharmacokinetic modelling, PBPK). PBPK modelling is based on the mathematical representation of absorption, distribution and elimination processes defining pharmacokinetics (2). Drug specific (lypophilicity, apparent permeability, in vitro

clearance, induction and inhibition potential) and patient specific factors (demographics, enzyme expression, organ volume and blood flows) are integrated in order to provide a realistic description of pharmacokinetics (3-5). A virtual population of patients can be simulated by considering anatomical and physiological characteristics, and their covariance.

The pharmacokinetic assessment after administration of efavirenz (EFV) 400mg once daily (qd) versus 600mg qd conducted as part of the Encore I study was recently published (6). Prior to this clinical analysis we made a prediction of the drug exposure from 400mg using PBPK modelling that we also published 3 years previously (7).

The purpose of this work is to exemplify the utility of PBPK modelling in exploration of the pharmacokinetic consequences of dose reduction by reporting a formal comparison of the previous PBPK prediction against the popPK model (top down) that was constructed with the clinical data from Encore I (6).

The frequency of the *CYP2B6* 516 G>T genotype from our previously published PBPK model were amended to match the population of the Encore I trial to provide a more realistic description of the inter-patient variability. The median of pharmacokinetic variables such as C_{max} , C_{12hr} and C_{24hr} obtained through the PBPK simulations and their variability were compared with model predicted PK parameters from Encore I. As shown in Figure 1 the key pharmacokinetic descriptors of EFV were accurately predicted by the PBPK model after correcting the frequency of *CYP2B6* 516G>T. The predicted pharmacokinetic variables (C_{max} , C_{12hr} and C_{24hr}) were in satisfactory agreement with the data observed for the dose reduction to 400 mg. These findings can be viewed as a paradigm for prediction of the pharmacokinetic consequences of dose reduction. While PBPK modelling cannot help establish the accuracy of existing pharmacokinetic therapeutic cut-off values (which Encore I has shown is likely to be inaccurate for EFV), it can certainly help define the potential for pharmacokinetic success prior to costly and labour-intensive prospective clinical trials. Therefore, integration of PBPK modelling prior to or during design of prospective studies is warranted to ensure effective deployment of available resources.

It is increasingly evident that computational approaches can assist in answering questions that cannot easily be examined because of prohibitive ethical or logistical barriers. PBPK modelling can bridge from drug development through *in vitro* data into the clinical scenario and reduce the number of clinical studies required to optimise therapies. This modelling approach can support the design of clinical studies in terms of sample size, timing of doses and sampling as recently indicated in several regulatory guidelines and documents (8-10). Our findings demonstrate the utility of PBPK modelling for dose optimisation, and a comparison between Bottom-Up and Top-Down approaches can build the basis for a future wider application of this modelling approach (11-13). The pharmacology of antiretrovirals and other anti-infective drugs is based on the co-administration of complex regimens and often administered to patients with specific characteristics defining challenging clinical scenarios (14, 15). Computational predictive models such as PBPK can represent a pivotal resource in answering questions that cannot otherwise be examined in pre-clinical or clinical development, supporting the rational design of therapeutic options, identifying strategies to maximise the efficiency and safety of therapies in various populations of patients.

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Figure 1 Scatter dot representing the main pharmacokinetic descriptors (AUC_{0-24}, C_{max}, and C_{24hr}) simulated through the PBPK model (7)and population PK model developed for ENCORE I (6) for 400mg qd (A) or 600 mg (B). 25th percentile (open circle), median (black circle) and 75th percentile (patterned circle) are presented. The solid line represents the identity line and dotted lines represent 50-200% range

92 **Conflict of Interest**

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