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Validation of Computational Approaches for Antiretroviral Dose Optimization

Marco Siccardi, Laura Dickinson, Andrew Owen

Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, United Kingdom

Strategies for reducing antiretroviral doses and drug costs can support global access, and numerous options are being investigated. Efavirenz pharmacokinetic simulation data generated with a bottom-up physiologically based model were successfully compared with data obtained from the ENCORE (Exercise and Nutritional Interventions for Cardiovascular Health) I clinical trial (efavirenz at 400 mg once per day versus 600 mg once per day). These findings represent a pivotal paradigm for the prediction of pharmacokinetics resulting from dose reductions. Validated computational models constitute a valuable resource for optimizing therapeutic options and predicting complex clinical scenarios.

Global access to treatment would result in a more effective strategy against the HIV pandemic, but there are several challenges in terms of drug production and distribution. Antiretroviral dosing strategies have been selected to inhibit 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 for these medications is greatest.

Alternative strategies for lowering doses and drug costs 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 results from large clinical studies.

Drug distribution can be quantitatively investigated through computational approaches using data from clinical studies to provide a top-down description and its variability in populations (i.e., population pharmacokinetic [popPK] modeling) or integrating drug-specific *in vitro* data in models to predict bottom-up pharmacokinetics (PK) in populations of virtual patients (i.e., physiologically based pharmacokinetic [PBPK] modeling). PBPK modeling is based on the mathematical representation of absorption, distribution, and elimination processes that define pharmacokinetics (2). Drug-specific factors (lipophilicity, apparent permeability, *in vitro* clearance, induction, and inhibition potential) and patient-specific factors (demographics, enzyme expression, organ volume, and blood flows) are integrated 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 covariances.

A pharmacokinetic assessment after administration of efavirenz (EFV) at 400 mg once daily (q.d.) versus 600 mg q.d. conducted as part of the ENCORE (Exercise and Nutritional Interventions for Cardiovascular Health) I study was recently published (6). Three years before this clinical analysis, we published a prediction about the 400-mg exposure of this drug that was made by using PBPK modeling (7).

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

The frequency of the *CYP2B6*(G516T) genotype (the G-to-T change at position 516 encoded by *CYP2B6*) from our previously published PBPK model was amended to match that in the population of the ENCORE I trial to provide a more realistic description of interpatient variability. The medians of pharmacokinetic variables, such as maximum concentration of drug in serum (C_{max}) and concentration of drug at 12 and 24 h ($C_{12\ h}$ and $C_{24\ h}$, respectively), obtained through the PBPK simulations, and their variabilities were compared with model-predicted PK parameters from ENCORE I. As shown in Fig. 1, the key pharmacokinetic descriptors of EFV were accurately predicted by the PBPK model after correcting the frequency of *CYP2B6*(G516T). The predicted pharmacokinetic variables (C_{max}, $C_{12\ h}$, and $C_{24\ h}$) were in satisfactory agreement with the data observed for the dose reduction to 400 mg. These findings can be viewed as a paradigm for predicting the pharmacokinetic consequences of dose reduction. While PBPK modeling cannot help establish the accuracy of existing pharmacokinetic therapeutic cutoff 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 labor-intensive prospective clinical trials. Therefore, integration of PBPK modeling prior to or during the 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 modeling can act as a bridge from drug development through *in vitro* data to the clinical scenario and reduce the number of clinical studies required to optimize therapies. This modeling approach can support the design of clinical studies in terms of sample size, timing of doses, and sampling, as recently indicated in several regulatory

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Address correspondence to Marco Siccardi, siccardi@liverpool.ac.uk.

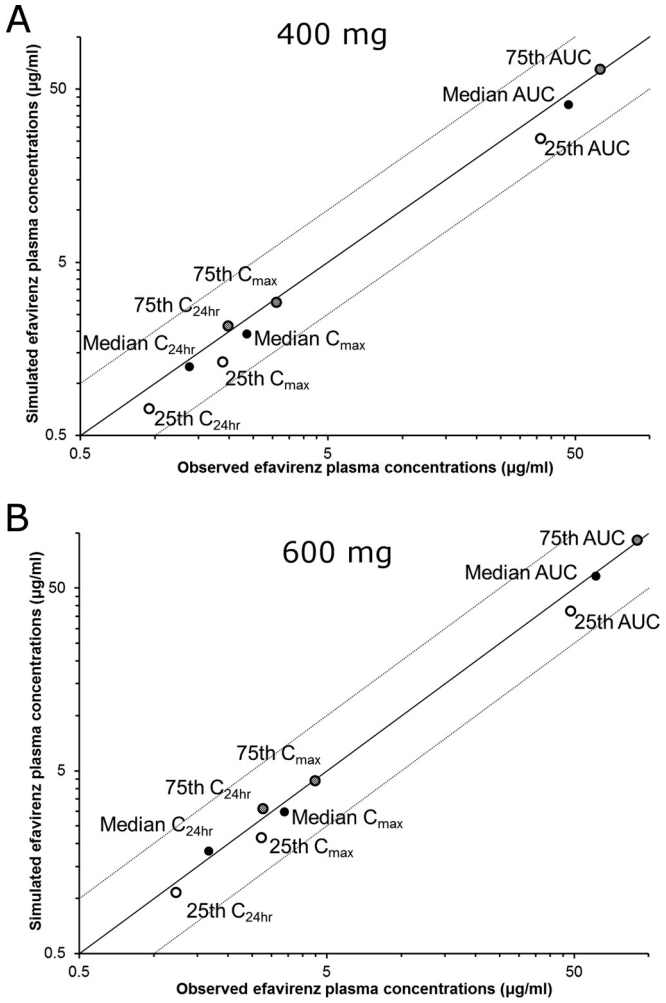

FIG 1 Scatter dot plot representing the main pharmacokinetic descriptors (area under the curve [AUC], C_{max}, and $C_{24\ h}$) simulated through the PBPK model (7) and the population PK model developed for ENCORE I (6) for EFV at 400 mg q.d. (A) or 600 mg q.d. (B). The 25th percentiles (white circles), the medians (black circles), and the 75th percentiles (patterned circles) are presented. The solid line represents the identity line, and the dotted lines represent the 50% to 200% range.

guidelines and documents (8–10). Our findings demonstrate the utility of PBPK modeling for dose optimization, and a comparison between bottom-up and top-down approaches can build the basis for a future wider application of this modeling approach (11–13). The pharmacology of antiretrovirals and other anti-infective drugs is based on the coadministration of complex regimens, and these drugs are often administered to patients with specific characteristics that result in challenging clinical scenarios (14, 15). Computational predictive models, such as the PBPK model, can represent a pivotal resource from which to answer questions that cannot otherwise be examined in preclinical or clinical development, can support the rational design of therapeutic options and can identify strategies for maximizing the efficiency and safety of therapies in various populations of patients.

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