Individualized dosing with high inter-occasion variability is correctly handled with model-informed precision dosing

UPPSALA UNIVERSITET

Lina Keutzer and Ulrika S.H. Simonsson

Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Correspondance: lina.keutzer@farmbio.uu.se, +46 18 471 4000

Introduction

Rifampicin has a high inter-individual variability (IIV) in pharmacokinetics (PK) which leads to variation in exposure between patients given the same dose even if weight-based dosing is used. Model-informed precision dosing (MIPD) could overcome this by optimising a dose based on individual concentrations together with a pharmacometric model. However, high inter-occasional variability (IOV) in PK, i.e. variability within an individual between visits (occasions), makes it more difficult to predict the AUC and subsequently the next dose correctly (Fig.1). Therefore, it is important to take IOV for AUC prediction into account.

Objective

In this simulation-based study we investigated the magnitude of IOV in rifampicin's PK, the impact of not acknowledging IOV when performing model-informed precision dosing and the number of sampling occasions needed to predict the AUC.

Methods

One thousand patients with drug-susceptible TB were simulated from a population pharmacokinetic (popPK) model previously developed by Svensson et al. [1] using the covariate distribution from the population of the HIGHRIF1 trial [2]. Rifampicin plasma concentrations pre-dose and at times 2 h and 4 h post-dose [3] in the dose-range between 10 - 35 mg/kg were simulated.

To compare the magnitude of IOV and IIV in PK, the $AUC_{0\text{-}24h}$ distribution within the population was derived by simulating including either only IOV or IIV.

The impact of ignoring IOV for $AUC_{0\text{-}24h}$ prediction was investigated by using a model-based approach and neglecting IOV in the model. The individual prediction error was compared to a model-based approach including IOV.

To assess the number of sampling occasions needed to predict the $AUC_{0\text{-}24h}$, the performance of three different sampling schemes, including concentration data from one (day 1), two (days 1, 7) or three (days 1, 7, 14) occasions were evaluated in terms of bias [mean absolute percentage error (MAPE)] and imprecision [relative root mean square error (rRMSE)].

The analysis was carried out in NONMEM 7.4.3 [4].

Results

The distribution of the simulated $AUC_{0\text{-}24h}$ was comparable when either IOV or IIV was included in the simulations (Fig. 3), i.e. IOV is as large as IIV in rifampicin PK.

A popPK model including IOV performed better than a model neglecting IOV, comparing the individual prediction error (Fig. 4). The imprecision (rRMSE) and bias (MAPE) in predicted $AUC_{0\text{-}24h}$ using an IOV approach decreased with increasing numbers of sampling occasions used to obtain individual PK parameters. The MAPE was 13.3%, 5.6% and 5.5% and the rRMSE 19.3%, 10.2% and 10.1% for one, two and three occasions included, respectively.

A workflow about how MIPD of rifampicin could be performed in the clinic has been proposed in Fig. 2.

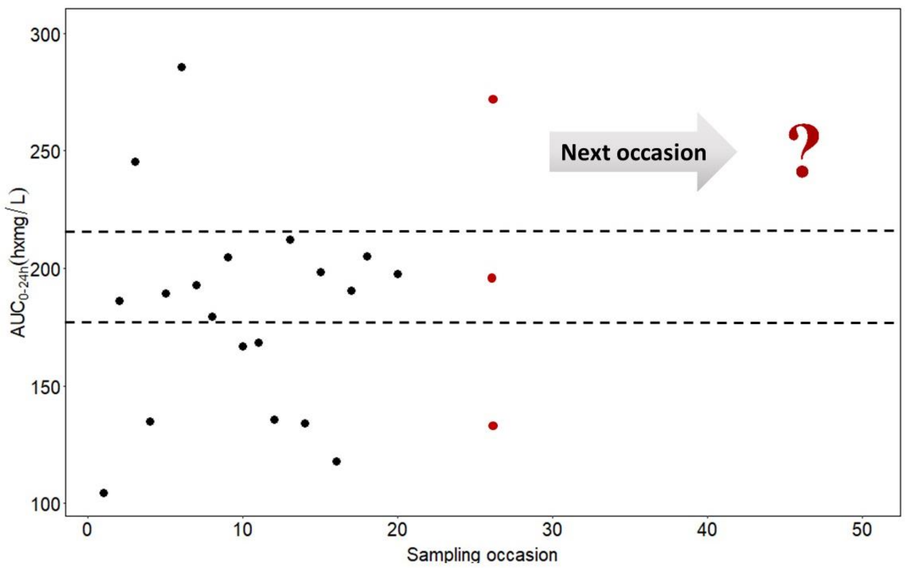

Fig. 1: $AUC_{0\text{-}24h}$ of the typical patient at different sampling occasions at steady state. The dashed lines represent the Bayesian $AUC_{0\text{-}24h}$ target range [5]. The difficulties in decision making using only observed exposure is illustrated at the 25th sampling occasion (red circles). There are three possible decisions; no dose change (within target range), decrease the dose (exposure above target range), or increase dose (exposure below target range). The question mark illustrates the difficulties in decision making using a non-model based approach ignoring IOV.

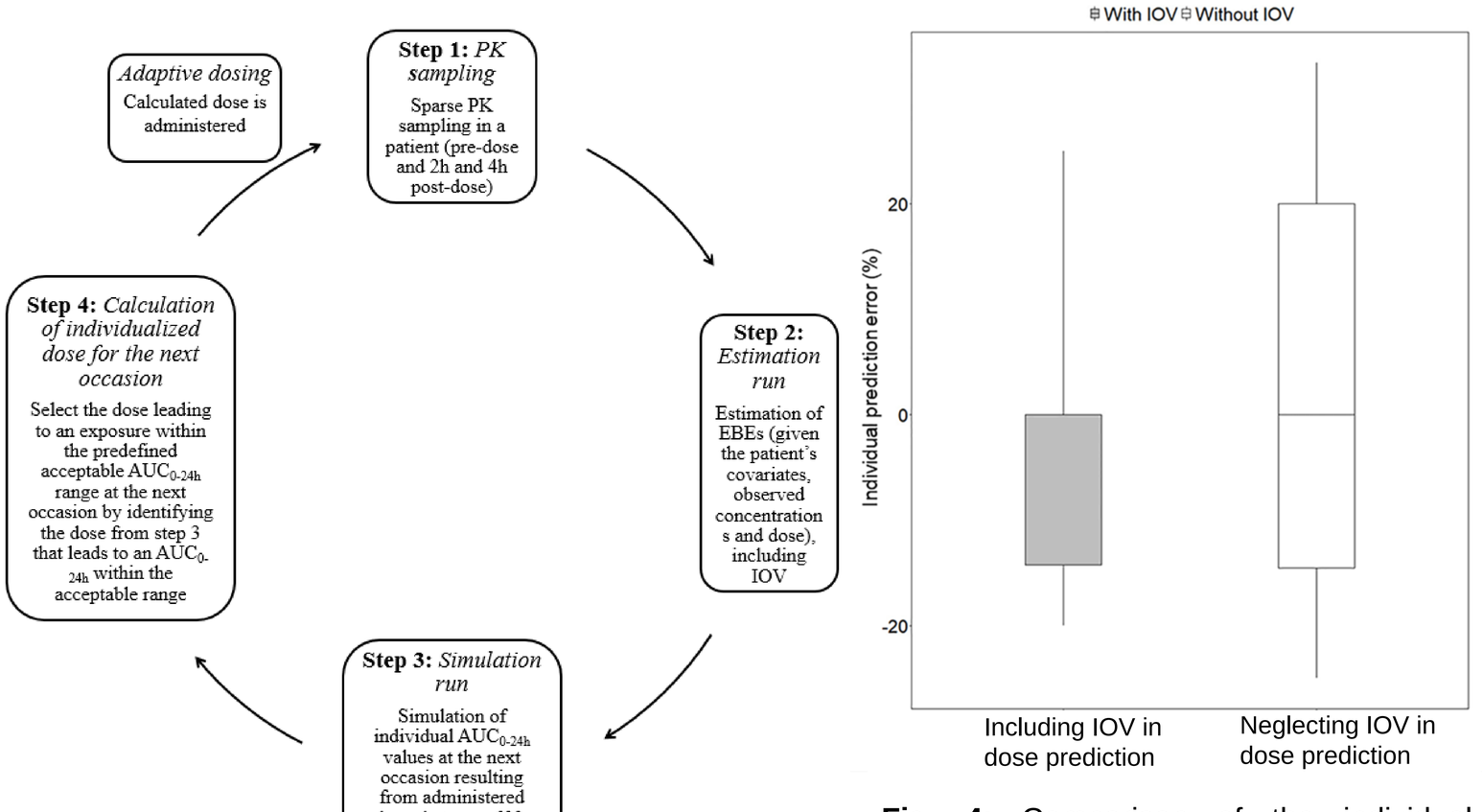

Fig. 2: Suggested workflow for performance of the MIPD approach in the clinic.

Conclusions

A large variability between occasions in rifampicin exposure within individuals was shown in this work.

To forecast the next dose with a low individual prediction error, IOV must be acknowledged in individual $AUC_{0\text{-}24h}$ predictions.

In order to fully capture IOV in PK, at least two sampling occasions are necessary, since the imprecision and bias decreased when a second occasion was added, but only marginally including information from a third occasion.

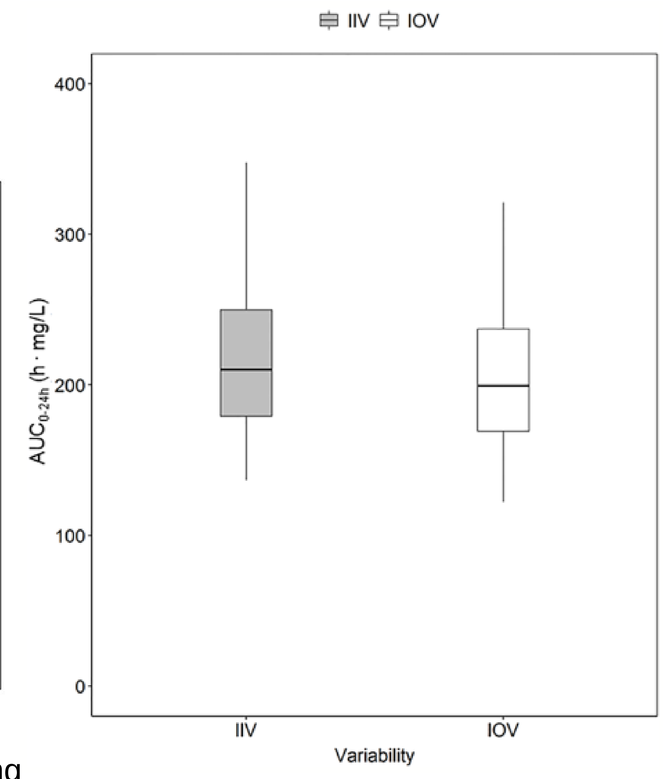

Fig. 3: Magnitude of IIV (grey) and IOV (white) in $AUC_{0\text{–}24h}$. The $AUC_{0\text{–}24h}$ distribution between subjects due to IIV shown in this plot was derived by simulating for 1,000 individuals with only IIV at steady state and for IOV by simulating the typical patient at 1,000 sampling occasions with only IOV at steady state. The box range represents the 50th percentile and the whiskers the 2.5th and 97.5th percentiles.

Fig. 4: Comparison of the individual prediction error (%) between predicting the next dose based on a popPK model neglecting IOV and therefore inflating IIV and residual variability, and a model including IOV. The boxplot body represents the 50th percentile and the whiskers the 75th percentile.

References

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