APPLICATION OF PBPK AND BAYESIAN MODELLING FOR PREDICTION OF THE LIKELIHOOD OF INDIVIDUAL PATIENTS EXPERIENCING SERIOUS ADVERSE REACTIONS TO A STANDARD DOSE OF EFAVIRENZ

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Background

A standard 600mg dose of efavirenz has been associated with serious adverse reactions in poor metabolizers (PMs) of CYP2B6, necessitating a reduction in dose.[1] The objective of this study was to determine whether a single plasma concentration can be useful in identifying PMs when genotyping is unavailable.

Methods

- **A Physiologically based pharmacokinetic (PBPK) model, based on the models published by Xu et al[2], and Siccardi et al [3], was used to simulate the pharmacokinetics of a 600mg single and multiple doses of efavirenz in extensive metabolizers (EMs), intermediate metabolizers (IMs) and poor metabolizers (PMs) of CYP2B6. The models were implemented using the Simcyp population-based simulator (V13 R2) and verified using clinical data.**
- **Concentration-time profiles of 5000 virtual individuals in each of the EM, IM and PM phenotypes were simulated. Bayes theorem was then used to calculate the probability of identifying the individuals phenotype based on the concentration at a specific sampling time. Sampling times of 2hr, 4hr, 8hr, 12hr and 24 hr for single doses and 8 hr and 12 hr at steady state were tested to determine which sampling time was associated with the highest probability of identifying PMs and hence individuals with a high risk for serious adverse reactions.**
- **The probability $P(e_j|C)$ of a phenotype e_j given concentration C at a particular sampling time is calculated using Bayes theorem:**

$$P(e_j|C) = \frac{P(e_j)P(C|e_j)}{P(C)}$$

where $P(e_j)$ is the prior probability of phenotype e_j; $P(C|e_j)$ is the probability of concentration C given phenotype e_j and $P(C) = \sum_j P(C|e_j)\,P(e_j)$ is the probability of concentration C at a given sampling time point.

- **Predicted phenotypes for given observed concentrations were determined by maximising the probability $P(e_j|C)$ over all phenotypes. For a given concentration, C, the predicted phenotype was determined using Bayes decision theory, where phenotype e_i is predicted if:**

$$P(e_i|C) > P(e_j|C)\ for\ all\ j \neq i$$

- **Reliability of the predictions was assessed by calculating the probability of correctly predicting each phenotype (true positive) and the probability of correctly rejecting each phenotype (true negative). Clinical data on genotyping in 34 HIV patients [2,4] who had taken a single dose of efavirenz and 46 HIV patients[3] at steady state were used in the analysis.**

Results

A favourable comparison between the predicted and observed PK parameters for efavirenz was seen following simulations with the developed PBPK models for EMs, IMs and PMs, suggesting that the models were acceptable (Table 1; Figure 1).

Table 1: Comparison of predicted and observed PK parameters in the EM, IM and PM phenotypes.

Parameter	Predicted (Mean and CI)	Observed[2] (Mean ±SD)	Observed[3] (Mean and CI)	CYP2B6 Phenotype
$AUC_{(0-t)}$ ng/mL.h	66.8 (51.4-61.9)	79.8 ± 28.4	68 (47 – 102)	EM
$AUC_{(0-t)}$ ng/L.h	108.4 (105.2-90.7)	81.6 ± 33.7	77 (63–99)	IM
$AUC_{(0-t)}$ ng/L.h	153.2 (131.8-150.2)	101.7 ± 7.9	123 (102–128)	PM
Cmax ng/mL	1850 (1755-1871)	2300 ± 700	1642 (1469–1916)	EM
Cmax ng/mL	1952 (1965-2077)	1700 ± 500	1878 (1376–2404)	IM
Cmax ng/mL	2135 (2048-2161)	2400 ± 200	2344 (1780–2522)	PM
CL L/h	12.8 (9.7-11.7)	8.5 ± 3.4	7.57 (4.89–12.53)	EM
CL L/h	6.9 (5.7-6.6)	8.3 ± 2.8	7.14 (5.47–8.38)	IM
CL L/h	4.7 (3.9-4.6)	5.9 ± 0.5	4.09 (3.90–4.55)	PM

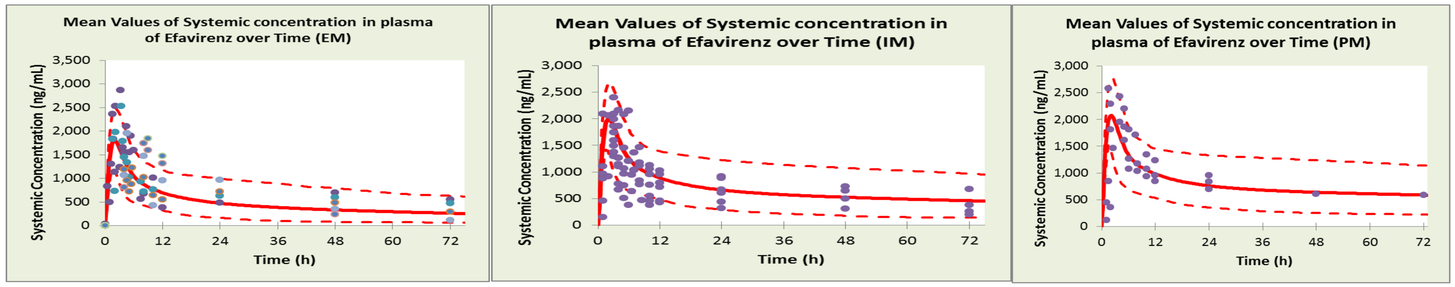

Figure 1: Comparison of predicted (mean=solid line with dashed line showing CI) and observed[2] concentration-time profiles in the EM, IM and PM groups after a single dose .

Predictability of PMs using a 24 hour sample after a single dose appeared to be better than the other sampling times tested and was also better than sampling at steady state. Figure 2 shows a graph of the posterior probability of each phenotype by concentrations at 24 hours after single dose and suggests that an EM would tend to be predicted for concentrations less than 500 ng/mL and a PM is likely to be predicted for concentrations greater than 500 ng/mL There is only a narrow range around 500 ng/mL where the probability of an IM has the greatest probability and therefore this phenotype is unlikely to be correctly identified using a single dose. Table 2 shows the probabilities of predicting each phenotype given the true phenotype. Using clinical data, the probabilities of correctly predicting either a EM or PM phenotype are fairly good, at 0.57 and 0.82 respectively (Table 3).

Figure 2: Probability of identifying the EM, IM and PM phenotypes using the 24 hour plasma concentrations

Table 2: Probability of correctly identifying the EM, IM and PM phenotypes using clinical data

True Phenotype	Observed Phenotype		
	EM	IM	PM
EM	0.57	0.36	0.07
IM	0.33	0.33	0.33
PM	0	0.18	0.82

Table 3: Probability of true positive or true negative by phenotype

Phenotype	P(+|+)	P(-|-)
EM	0.57	0.85
IM	0.33	0.64
PM	0.82	0.87

Conclusion

The results of this study are promising and suggest that there is a high probability (0.82 for PM) that a test dose of efavirenz may be useful in identifying patients who are at risk of experiencing serious adverse reactions. The reduced daily dose of 200mg in PMs has been shown to be effective and tolerable.[3] Since clinical data were available for a limited number of patients, more patient data are required to fully validate the model.

References

1. Marzolini et al. *AIDS*, 2001, 15: 71-75
2. Xu et al. DMD, 2013, 41: 2004-2011
3. Siccardi et al. CPT, 2012. 92:494-502
4. Haas et al. JID, 2009, 199:872-881