Use of a test dose of efavirenz to predict the likelihood of individual patients experiencing serious adverse reactions to a standard dose

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Background

Serious adverse reactions to a standard 600mg dose of efavirenz have been reported in poor metabolizers (PMs) of CYP2B6, the major enzyme responsible for efavirenz metabolism.[1] These involve mainly the central nervous system and affect drug compliance. Dosage adjustments based on genotyping to identify PMs prior to treatment has been recommended. However, genotyping is not economically feasible in developing countries. The objective of this study was to determine whether a standard test dose of efavirenz can be useful as a probe drug in identifying PMs.

Methods

- **Physiologically based pharmacokinetic (PBPK) models to simulate the pharmacokinetics of a single 600mg dose of efavirenz in extensive metabolizers (EMs), intermediate metabolizers (IMs) and poor metabolizers (PMs) of CYP2B6, based on the models published by Xu et al[2], 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 categories were simulated. Bayes theorem was then used to calculate the probability of each phenotype given the concentration value at a sampling time. Sampling times of 2hr, 4hr, 8hr, 12hr and 24 hr 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 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 a concentration at a given sampling time 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 time point.

- **Predicted phenotype for a given observed concentration was 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**

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

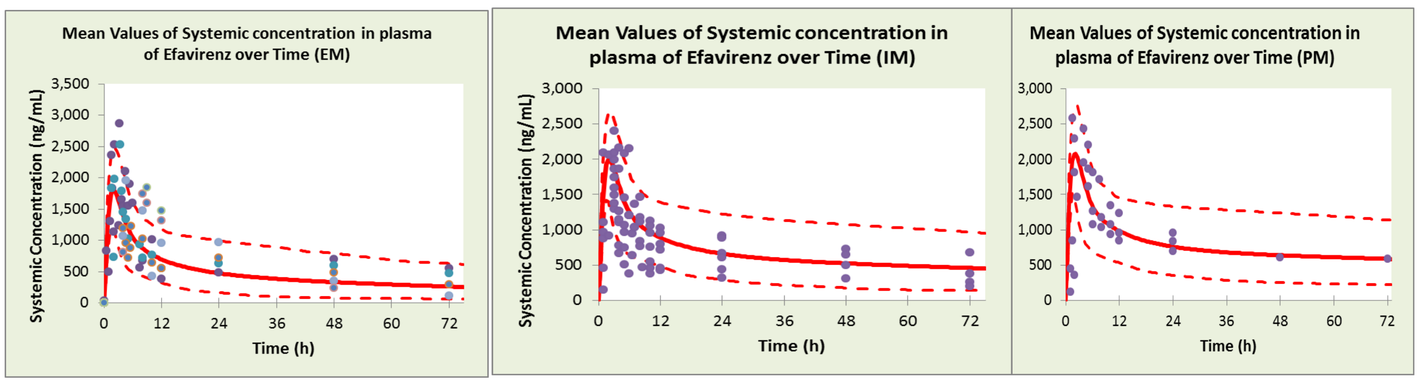

Figure 1: Comparison of predicted (mean=solid line with dashed line showing CI) and observed[2] concentration-time profiles in the EM, IM and PM groups .

Figure 2 shows a graph of the posterior probability of each phenotype by concentrations at 24 hours 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 PM or EM phenotype are fairly good, at 0.57 and 0.82 respectively (Table 3).

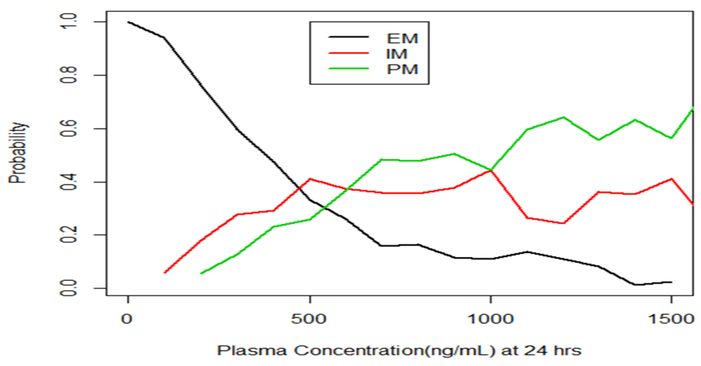

Figure 2: Probability of identifying the EM, IM and PM phenotypes using the 24 hour plasma concentrations

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 recommended daily dose of 200mg in PMs has been shown to be effective and tolerable.[4] Since clinical data were available for a limited number of patients, more patient data are required to fully validate the model.

References

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2. Xu et al. DMD, 2013, 41: 2004-2011
3. Haas et al. JID, 2009, 199:872-881
4. Siccardi et al. CPT, 2012. 92:494-502