TIME VARIATION IN THE FRACTIONAL CONTRIBUTION OF AN ENZYME TO ELIMINATION OF A VICTIM DRUG CAN EXPLAIN DIFFERENCES IN DDI SUSCEPTIBILITY FOLLOWING SINGLE AND MULTIPLE DOSING

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Introduction

- The fractional contribution of an enzyme to systemic elimination (fm) is an important determinant of the drug-drug interaction (DDI) potential of a victim drug. In static DDI predictions, fm is assumed to be constant.
- However, this assumption is not valid for victim drugs that show for example saturation of metabolism, or time-dependent inhibition (autoinhibition) of one or more of their own metabolic pathways[1].
- Time variation in the fm of CYP2D6 and CYP3A4 was investigated for paroxetine, which is both a substrate and a potent mechanism-based inhibitor (MBI) of CYP2D6. It is also a weak MBI for CYP3A4 (Figure 1).
- CYP2D6 is a polymorphic enzyme where mutations cause a lack of expression occurring in around 8% of Caucasians resulting in a poor metaboliser (PM) phenotype[2]. This results in no CYP2D6 metabolic capability in comparison to normal extensive metabolisers (EM).

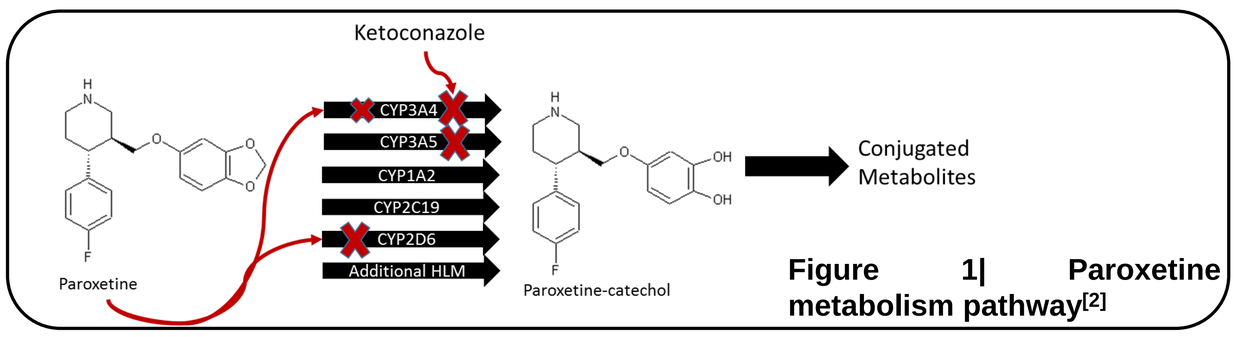

Figure 1| Paroxetine metabolism pathway[2]

Aims

- To examine the impact of changes in fm pathway contributions after repeated dosing of the MBI paroxetine.
- To investigate the impact of genetic polymorphisms (PM and EM) on time variant fm for paroxetine.
- To predict the impact on fm in the presence of a strong CYP3A4 inhibitor, ketoconazole.

Methods

- Multiple daily dosing of 30 mg paroxetine for 21 days was simulated in the Simcyp Simulator V15.1 for CYP2D6 extensive metabolisers (EMs) and poor metabolisers (PMs) using the built-in Sim-Healthy Volunteer population library and SV-Paroxetine compound file. Simulations were run as 10 trails of 10 individuals, 50% female, 20-50 years old.
- The paroxetine model includes MBI for both CYP2D6 and CYP3A4. DDI with ketoconazole (400mg QD for 8 days) was simulated for paroxetine from day 15 to day 21.
- The model automatically considers dynamic variation in fm for CYP2D6 and CYP3A4 for paroxetine, assuming a well-stirred liver model and accounting for multiple metabolism routes (Figure 1) and the minor contribution of renal elimination.
- Simulations were undertaken taking into account the presence and absence of daily doses of the CYP3A4 inhibitor ketoconazole administered from as a single dose on day one and multiple doses from day 15.

Results

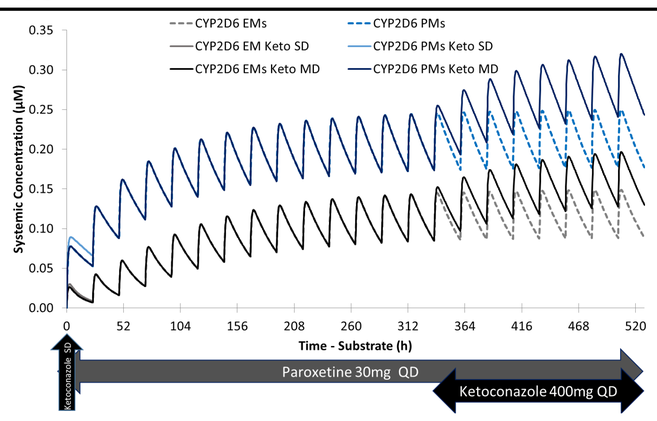

Figure 2| Mean Paroxetine systemic concentration for CYP2D6 EM and PM phenotypes, with and without Ketoconazole. Ketoconazole was administered as a single dose on day one and multiple doses from day 15.

Paroxetine + Ketoconazole DDI	AUC Ratio (Static)	AUC Ratio day 1 (Dynamic)	AUC Ratio day 21 (Dynamic)
CYP2D6 EMs	1.07 (1.02-1.30)	1.16 (1.04-1.75)	1.38 (1.09-2.23)
CYP2D6 PMs	1.64 (1.26-3.01)	1.20 (1.06-1.49)	1.33 (1.14-1.82)

Table 1| Impact of CYP2D6 polymorphism on static and dynamic AUC ratio predictions for MD Paroxetine and Ketoconazole. Regimen as shown in Figure 2. Geomean (range)

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Results continued

- For CYP2D6 EMs, the mean fm CYP2D6 was 0.94 for the first dose paroxetine and it decreased to 0.49 on day 21 as a result of MBI reducing CYP2D6 active enzyme levels (Figure 3A).
- The reported range of fm values for EMs reflect concentration sensitivity of MBI, as well as a progressive change in fm over time (Figure 3B).
- The mean fm CYP3A4 was 0.02 for the first dose and increased to 0.15 on day 21 (Figure 3B), which corresponded to an increase in the predicted AUC ratio in the presence of ketoconazole from 1.16 (day 1) to 1.38 (day 21) (Table 1).
- For CYP2D6 PMs, the fm CYP3A4 was relatively unchanged from day 1 (0.32) to day 21 (0.29) (Figure 3C). The AUC ratio with ketoconazole was 1.20 (day 1) to 1.33 (day 21) (Table 1).
- Based on static predictions the day 21 AUC ratios were lower for EMs (1.07) and higher for PMs (1.64).

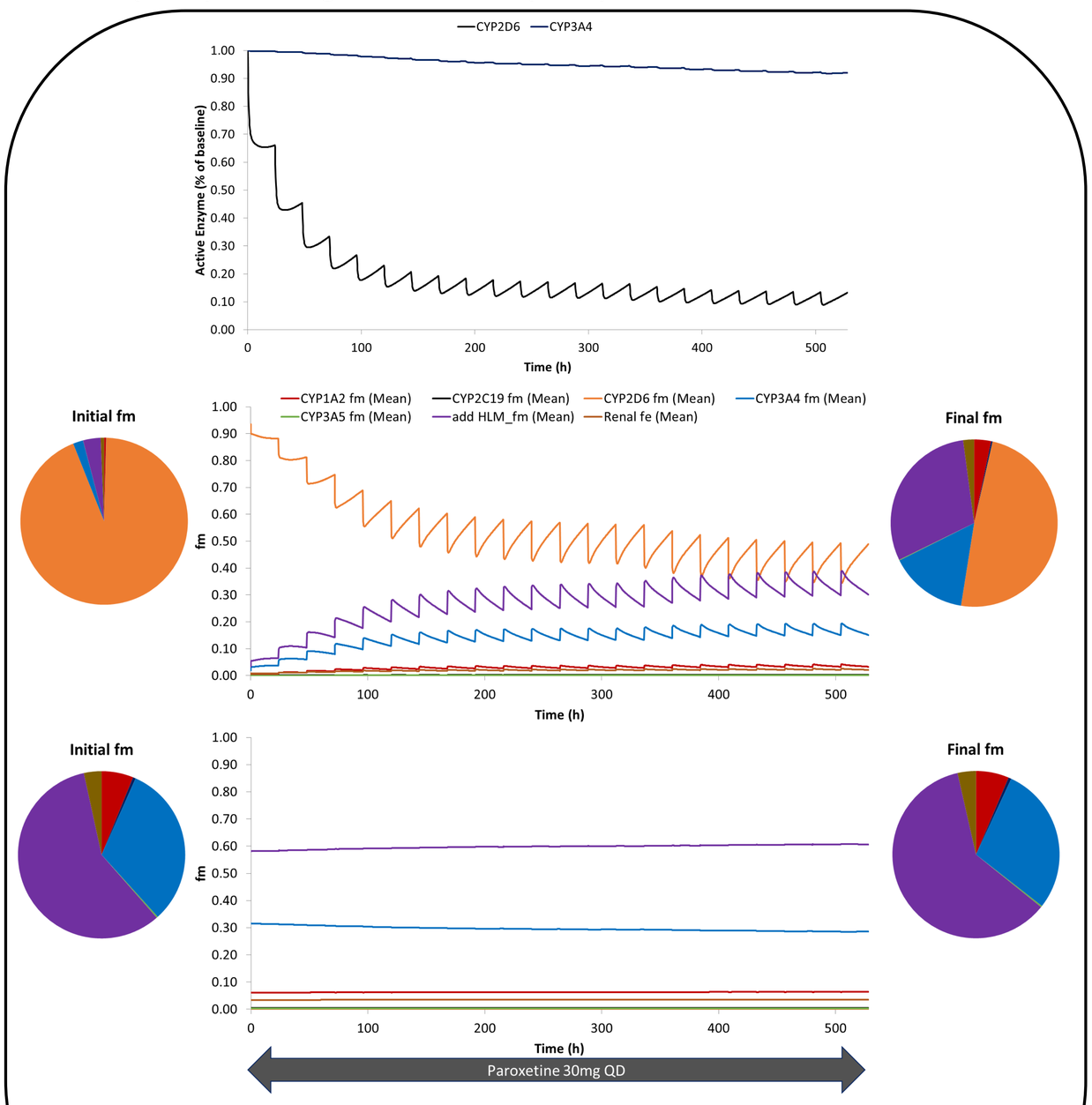

Figure 3| A. (top) Changes in active enzyme levels of CYP2D6 and CYP3A4 over time as a result of Paroxetine MBI. B. (middle) Changes in fm contributions over time for CYP2D6 EMs. C. (bottom) Changes in fm contributions over time for CYP2D6 PMs.

Conclusions

- For paroxetine, autoinhibition of CYP2D6 in EMs results in a decrease in fm CYP2D6 and corresponding increase in CYP3A4 fm following multiple dosing.
- This observation explains an increased susceptibility to DDI with the CYP3A4 inhibitor ketoconazole following multiple dosing for CYP2D6 EMs.
- The absence of CYP2D6 in PMs results in little change in CYP3A4 fm following multiple dosing and a smaller increase in ketoconazole DDI.
- AUC ratios from static predictions under predicted the impact of reductions in the contribution of CYP2D6 for EMs, and overestimate the impact of CYP3A4 fm for PMs.
- Models that incorporate the time variation in fm can predict and explain differences in DDI liability following single and multiple dosing of a victim with autoinhibition, autoinduction or saturation of metabolism; hence better suited for designing clinical studies.

References

1. Jamei *et al.,* (2013) Poster 6337 AAPS Annual Meeting and Exposition San Diego.
2. Jornil *et al.,* (2010) *DMD* **38**:376-386