

Assessing the Relevance of Genetic Polymorphism in CYP3A5 on the Kinetics of Midazolam and Tacrolimus: The Importance of Adequate Study Size

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INTRODUCTION

- Studies of tacrolimus (TAC) kinetics suggest that CYP3A5 genotype is important in its elimination [1-6], while reports on the effect of this genotype on the kinetics of midazolam (MDZ) have been inconsistent [7-10].
- There are adequate *in vitro* data to indicate differential metabolism of TAC and MDZ by CYP3A4 and CYP3A5.

AIMS

- The aim was to investigate the power of studies reported in the literature to assess the influence of CYP3A5 genotype on MDZ and TAC kinetics.
- To determine whether study design (size and frequency of CYP3A5 genotypes) could explain the inconsistency in reported outcomes.

METHODS

- Physicochemical and *in vitro* metabolic data for MDZ and TAC were entered into Simcyp[®] Clinical Trial Simulation software V7.01 (www.simcyp.com).
- The simulations mimicked actual trial designs with respect to numbers of subjects, the demography of the subjects (age, sex) and frequency of CYP3A5 genotypes.
- Each study was simulated 20 times and the percentage of simulations showing a significant difference in AUC between genotypes (t-test, $p < .05$) was used to indicate study power.
- Studies with greater than 50% power were assumed to be more likely to differentiate the impact of genotype.
- The observed outcomes of the clinical studies (4 MDZ & 6 TAC) were compared with those predicted by simulation (χ^2 test).

RESULTS

- Simulated plasma drug concentration – time profiles of MDZ and TAC were consistent with those reported from *in vivo* studies (Perrett *et al.*, this meeting).
- All of the reported *in vivo* studies on the influence of CYP3A5 on TAC kinetics included sufficient subjects to give a greater than 50% probability of observing an effect (Figure 2B), as found in the reported outcomes (Table 1, Figure 3).
- In contrast, simulated MDZ studies indicated that none of the studies had sufficient numbers of subjects to achieve statistical significance in showing the influence of CYP3A5 genotype (Figure 2A). Nonetheless, one of these studies [10] reported an association between the kinetics of MDZ and CYP3A5 (Figure 3). The power of this study by simulation was 30%.

Table 1: Comparison between actual and simulated outcomes of studies of the influence of CYP3A5 genotype on MDZ and TAC kinetics.

Midazolam Studies	N	% CYP3A5 PM	Study Outcome		Simulation Predicted Outcome
			Not Significant (X)	Significant (✓)	
Eap <i>et al.</i> , (2004)	21	81%	X	15	X
Lepper <i>et al.</i> ,(2005)	58	85%	X	20	X
He <i>et al.</i> , (2004)	26	81%	X	5	X
Wong <i>et al.</i> ,(2004)	52	88%	✓	30	X

Tacrolimus Studies	N	% CYP3A5 PM	Study Outcome		Simulation Predicted Outcome
			Not Significant (X)	Significant (✓)	
Macphee <i>et al.</i> , (2002)	120	87%	✓	90	✓
Goto <i>et al.</i> , (2004)	180	74%	✓	100	✓
Haufroid <i>et al.</i> , (2004)	50	78%	✓	70	✓
Hesselink <i>et al.</i> , (2003)	154	89%	✓	85	✓
Zheng <i>et al.</i> , (2003)	54	78%	✓	80	✓
Zheng <i>et al.</i> , (2004)	81	90%	✓	50	✓

Simulated plasma drug concentration-time profiles

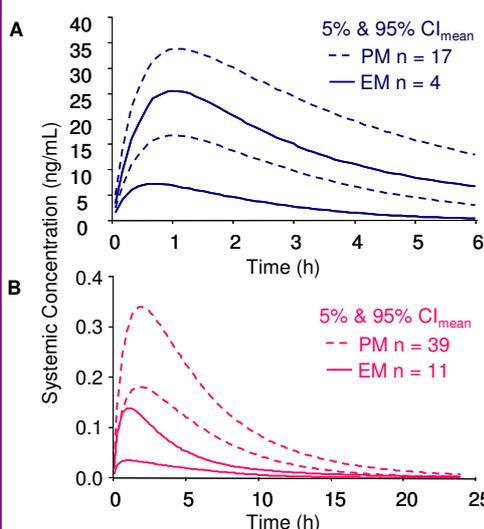


Figure 3: 95% Confidence Intervals of mean simulated plasma concentration-time profiles of (A) MDZ and (B) TAC based on studies by:

A) Eap *et al.*, MDZ 7.5 mg p.o.; n=17 PM, AUC_{0-6hr} 107 ± 46; n=4 EM AUC_{0-6hr} 48 ± 28 $p > 0.05$ NSD

B) Haufroid *et al.*, TAC 2 mg p.o.; n=39 PM, AUC_{0-24hr} 4.9 ± 4.1; n=11 EM, AUC_{0-24hr} 1.0 ± 0.7 $p < 0.001$

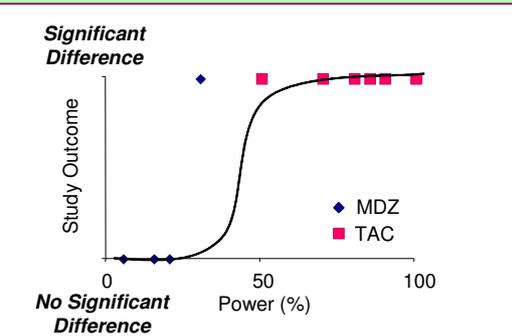


Figure 3: Relationship between the outcome of the effect of CYP3A5 genotype on TAC and MDZ kinetics as reported in the literature vs. calculated power from simulations of the same studies.

RESULTS cont.

- Only one study outcome was not consistent with the simulated prediction (Table 1, Figure 3).
- Previous simulations (Perrett *et al.*, this meeting) predicted that study sizes of 80 and 24 with a PM frequency of 83% would be required to detect any influence of CYP3A5 genotype on the kinetics of MDZ and TAC, respectively.
- Overall, the Simcyp[®] simulations predicted the outcome of 90% of the published studies accurately with no significant difference between simulated and actual results (χ^2 test).

DISCUSSION

- Simulations of TAC and MDZ pharmacogenetic studies predicted actual outcomes in the majority of cases.
- The simulations indicate that most of the MDZ studies were underpowered.

CONCLUSIONS

- Simulations can provide a quantitative framework to extrapolate *in vitro* data on variability in metabolism by CYP3A4 and CYP3A5 to predict the likely impact of CYP3A5 genotype on *in vivo* drug kinetics.
- In vitro* - *in vivo* extrapolation is useful to optimise the design of pharmacogenetic studies to avoid inconclusive outcomes.

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