The Impact of Genetic Polymorphism in CYP3A5 on the Pharmacokinetics of the Mixed 3A4/5 Substrates Midazolam and Tacrolimus Assessed by Clinical Trial Simulation (CTS)

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INTRODUCTION

- Substrates of CYP3A show large inter-individual variability in their kinetics which may be partly explained by genetic polymorphisms.
- The overlapping substrate specificities of CYP3A4 and CYP3A5[1,2] may confound the detection of differences in CYP3A5 genotype, particularly in studies with inadequate numbers of subjects.
- Inconsistency in the outcomes of studies reported in the literature has generated debate over the importance of CYP3A5 genotype in the metabolism of drugs such as midazolam (MDZ) and tacrolimus (TAC).

AIMS

- To assess the effect of sample size on the power of studies to detect differences in MDZ and TAC kinetics between CYP3A5 genotypes.
- To investigate the effect of the contribution of CYP3A5 to overall CYP3A metabolism on study power using a series of virtual compounds (MDZ analogues).

METHODS

- Physicochemical and *in vitro* metabolic data on TAC and MDZ obtained from the literature were entered into Simcyp® V7.01 (www.simcyp.com).
- The virtual analogues of MDZ differed only in the ratio of CYP3A5:CYP3A4 intrinsic metabolic clearances (ratios: 1 for MDZ and 10, 2, 0.5 and 0.1 for analogues; i.e. fm_{CYP3A5} varied from 6 to 78% of total CYP3A metabolism, Figure 1).
- Substrate plasma concentration – time profiles were simulated in virtual individuals selected randomly from Caucasian populations within the Simcyp Population Library. Twenty trials of varying sizes (n = 4 - 500) were simulated.

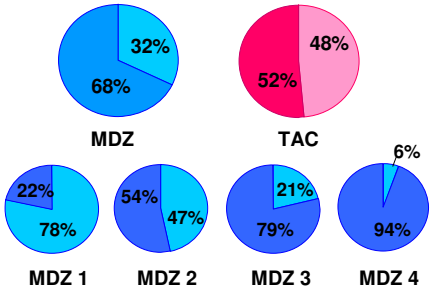

Figure 1: % contribution of CYP3A4 and CYP3A5 to MDZ and TAC intrinsic metabolic clearance (fm).

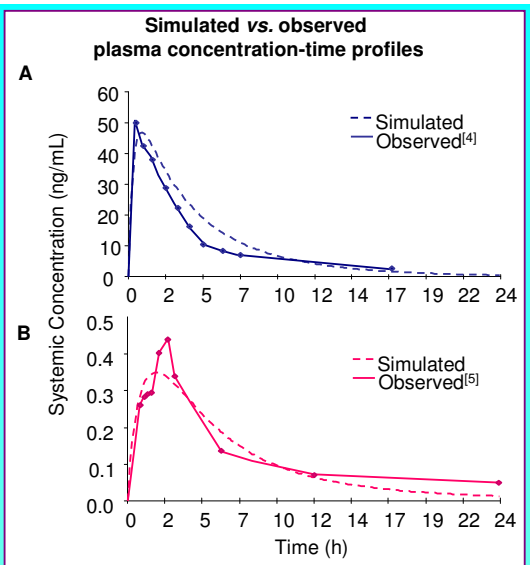

Figure 2: Simulated (- -) and observed (—) plasma concentration-time profiles of A) MDZ and B) TAC. Dotted lines represent the mean profile generated from a population of 100 virtual individuals with a CYP3A5 PM frequency of 0.83.

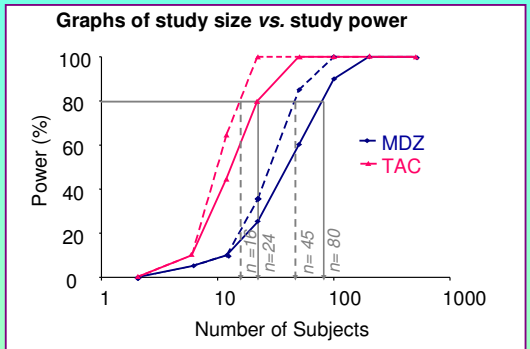

Figure 3: Influence of the number of subjects on the power of simulated pharmacogenetic studies of MDZ and TAC metabolism in normal (83% CYP3A5 PM ~~) and~~ EM enriched (50% CYP3A5 PM) ~~populations~~

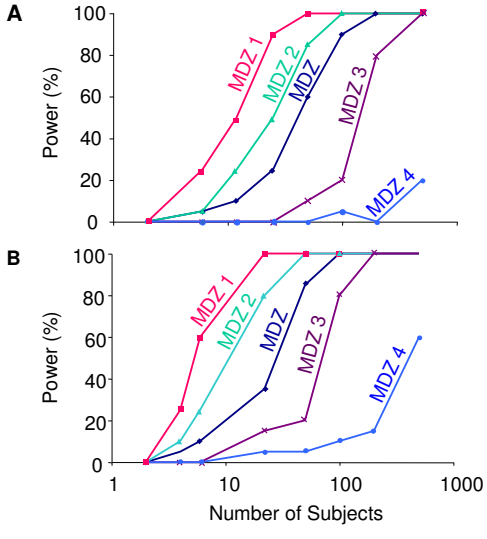

Figure 4: Influence of the number of subjects on the power of simulated pharmacogenetic studies of MDZ and four midazolam analogues (MDZ 1-4) in (A) a normal population (83% PM) and (B) an EM enriched population (50% PM).

- Genotype frequencies of CYP3A5 were those assigned to a Caucasian population within the library (derived from a meta-analysis of the literature; extensive metabolisers [EM] (*1*1 and *1*3) = 17% and poor metabolisers [PM] (*3*3) = 83%).
- The percentage of 20 trials showing a significant difference in AUC between CYP3A5 phenotypes (t – test ; $p < 0.05$) indicated study power.
- The sensitivity of study power to the effects of population 'enrichment' (equal numbers of EMs and PMs) was also investigated.
- Simulations focused on differences in metabolic clearance (active transporter processes were not considered).

RESULTS

- Simulated plasma drug concentration – time profiles of MDZ and TAC were consistent with those reported in clinical studies (Figure 2).
- Without enrichment, the numbers of subjects required to achieve 80% power were 80 and 24 for MDZ and TAC, respectively (Figure 3). The use of an enriched population decreased these numbers to 45 and 16, respectively.
- As expected, detection of the influence of CYP3A5 genotype in virtual MDZ analogues having a greater contribution of CYP3A5 to overall metabolism required fewer subjects.

DISCUSSION

- The simulations indicate that CYP3A5 genotype does influence the metabolism of TAC and MDZ.
- However, the number of subjects required to detect differences between CYP3A5 genotypes varies greatly depending on the ratio of CYP3A5:CYP3A4 contribution to the metabolism of the substrate.
- The lower the contribution of CYP3A5, the greater the importance of adequate study size.

CONCLUSION

- Simulations based on a knowledge of *in vitro* metabolism, as indicated in this study, can assist in determining appropriate study size to assess the influence of CYP3A5 polymorphism *in vivo*.

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