The Propagation of Genetic Polymorphism in CYP2C9 into Tolbutamide Pharmacokinetics: Assessment Using an Integrated Model

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INTRODUCTION

- Polymorphisms in cytochromes P450 (CYPs) contribute to inter-individual variation in plasma drug concentrations.
- The consequences of these genetic variations for pharmacological response are unclear (1), and literature reports are often conflicting.
- This may be due to difficulty in determining the power of such studies *a priori*, which requires a combination of estimates of pharmacokinetic (PK) and pharmacodynamic (PD) variability.
- Current examples of clinical trial simulation rely on data collected from preliminary clinical studies and do not incorporate biological variability related to drug metabolizing enzymes, receptor abundance etc.

AIMS & OBJECTIVES

- To use mechanistic-based clinical trial simulation as a tool to investigate the influence of *CYP2C9* genotype on tolbutamide (TOL) PK and PD by extrapolating known information on its *in vitro* metabolism to *in vivo* drug clearance.
- To assess the effect of sample size on the power of studies to detect differences in TOL PK and PD between different *CYP2C9* genotypes.

METHODS

- A meta-analysis was conducted to assess the activity of *CYP2C9* genotypes relative to the wild type from *in vitro* data (2-6) (Fig 1.). The genotype frequencies were taken from the literature (7) (Fig 1.).
- The above information and the *in vitro* metabolic data, were entered into Simcyp® algorithms (www.simcyp.com), which also account for other physiological and demographic features. The simulated population PK of TOL in the different genotypes (Fig. 2) was then integrated into a PK/PD model derived from *in vivo* studies (8).
- TOL concentration- and effect (insulin secretion) - time profiles were simulated for each individual in a population using different study sizes (n = 5 to 300).
- Twenty clinical trial simulations were carried out for each n value. The percentage of trials showing a significant difference between *CYP2C9* genotypes (by ANOVA) was taken as the power of that particular simulation.
- Since some reported studies have used an "enriched" design (*i.e.* deliberately recruiting rare *CYP2C9* genotypes), the proportions of genotypes were modified in the simulations to mimic these studies.

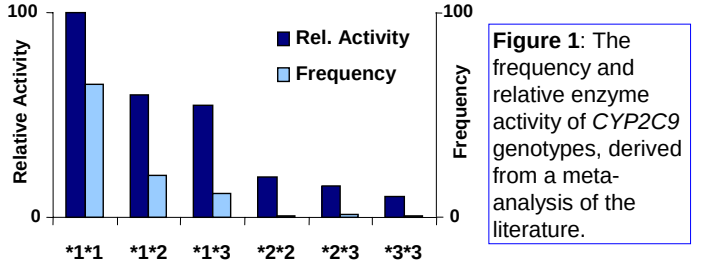

Figure 1: The frequency and relative enzyme activity of *CYP2C9* genotypes, derived from a meta-analysis of the literature.

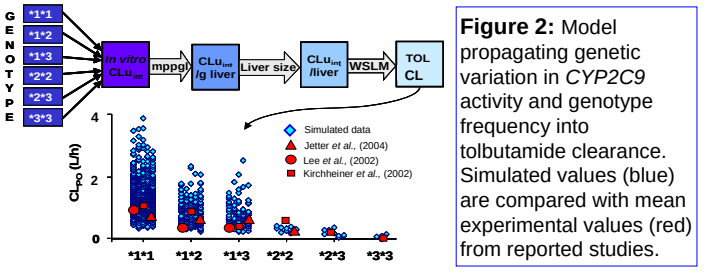

Figure 2: Model propagating genetic variation in *CYP2C9* activity and genotype frequency into tolbutamide clearance. Simulated values (blue) are compared with mean experimental values (red) from reported studies.

RESULTS

- Figure 3 (A) shows the power to detect differences in the area under the concentration-time curve (AUC) between wild type (*1*1) and a 'combination' of the other genotypes as a function of study size. The power to detect differences between the wild-type and any other single genotype is also shown.
- Figure 3 (B) shows the corresponding powers for differences in the area under the effect – time curve (AUEC).
- A summary of the results of published studies and their powers (as estimated by the current study) is shown in Table 1.

Table 1: Estimated powers of published studies which have attempted to identify an influence of CYP2C9 genotype on the PK or PD of TOL (9-13).

Study	Sample Size	Difference seen in PK?	Difference seen in PD?	Power – PK (%)	Power – PD (%)
Shon *et al.*	18	✓	✓	40	40
Jetter *et al.*	23	✓	N/A	45	40
Wang *et al.*	63	✓	N/A	75	50
Kirchheiner *et al.*	23	✓	×	100	50
Lee *et al.*	16	✓	N/A	35	30

N/A = not assessed

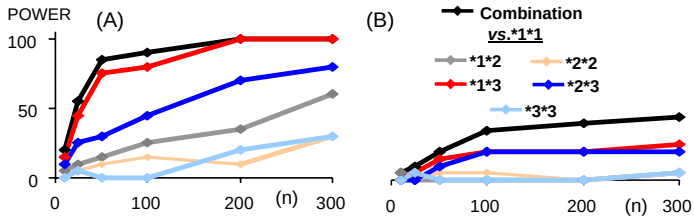

Figure 3: Power (% studies showing a significant difference in (A) - AUC; (B) - AUEC between different genotypes and the wild type genotype) *vs.* number of subjects in each virtual study (n).

DISCUSSION

- Both the relative enzyme activity of the allelic variant and its population frequency influence the ability of studies to detect a difference in TOL clearance between genotypes. (*e.g.* for the *1*1 *vs.* *3*3 comparison, *3*3 subjects are too rare to allow high power despite the low catalytic activity associated with this genotype).
- The five studies that compared the PK of tolbutamide between *CYP2C9* genotypes used between 16 and 63 subjects. The power of these studies was high (between 40 and 100%) and all identified significant differences between genotypes (8-12).
- The power of the PD studies of Shon *et al.* (9) and Kirchheiner *et al.* (12) was 40 and 50%, respectively. Therefore, they had approximately equal chances of achieving a positive or negative result. Our calculations are consistent with the outcomes of these studies.
- Our findings are consistent with our studies of *(S)*-warfarin and dextromethorphan, indicating that enriched study designs (including more individuals with rare genotypes) are more powerful in detecting potential differences between genotypes.
- Simulations such as those described here should, whenever possible, be used *a priori* to determine the likelihood of success of clinical studies, thereby making best use of time and money (14).

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