THE PROPAGATION OF GENETIC POLYMORPHISM IN CYP2C9 INTO WARFARIN PHARMACOKINETICS: AN INTEGRATED MODEL

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INTRODUCTION

Functional allelic variants of cytochrome P450 2C9 (*CYP2C9*) contribute to inter-individual variation in clinical response to warfarin[1-4]. However, studies attempting to correlate this genetic variability with the kinetics (PK) of (S)-warfarin have largely been unsuccessful[5,6].

Interindividual variability occurs in both PK and pharmacodynamics (PD). Thus, variability in response is expected to be greater than that in plasma drug concentration (Figure 1).

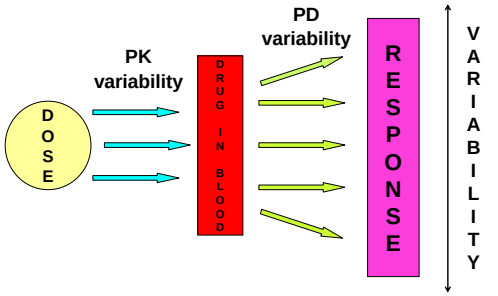

Figure 1: Population variability in drug response is often greater than variation in plasma drug concentrations.

In theory, higher variability in PD may mask the expected relationship between *CYP2C9* and warfarin effects (or dose requirements), while the link between warfarin PK and genotypic differences in metabolism is likely to be more discernable. However, this is in contrast with a failure of literature reports to establish a relationship between *CYP2C9* and warfarin PK[5,6] while reports on the link with PD have been positive[1-4].

The inconsistency between theoretical expectations and observed results may relate to differences in study size between PK and PD studies. PK studies tend to be more costly, time-consuming and invasive, while PD studies simply relate dose to observed effects, and often use larger numbers of subjects.

In this study we have used clinical trial simulation (CTS) as a tool to investigate the impact of CYP genotype on warfarin PK by extrapolating known information on *in vitro* drug metabolism to *in vivo* drug clearance. The ultimate aim was to assess the effect of sample size on the power of studies to detect differences in warfarin PK between different *CYP2C9* genotypes.

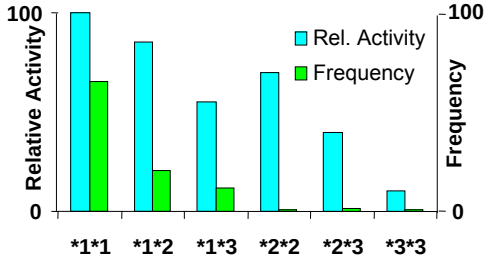

Figure 2: The frequency and relative activity of *CYP2C9* genotypes, derived from a meta-analysis of the literature.

METHODS

A literature review was conducted to determine the frequency of established *CYP2C9* genotypes in Caucasians. The activity of each genotype relative to wild type was assessed from published *in vitro* data (Figure 2).

A physiologically-based model (Figure 3), Simcyp®, which incorporates *in vitro* metabolic values and variability in genetic, physiological and demographic features was adapted to integrate information on the frequency and relative activity of *CYP2C9* genotypes.

Clearance values (total and unbound) were simulated for each individual using different population sizes (n = 47, 93, 150, 200, 250, 350, 450, 550, 650, 1000), some of them mimicking those reported in the literature. Overall, 200 trial simulations were carried out and the probability of detecting a statistically significant difference in PK between *CYP2C9* genotypes was assessed using ANOVA. The power of each study (of different size) was assessed based on the percentage of trials that yielded a significant difference in PK between genotypes.

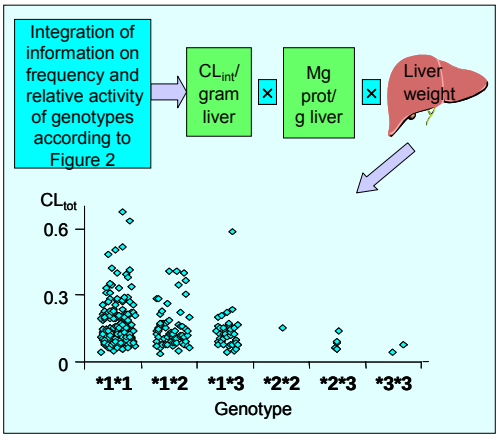

Figure 3: Model propagating genetic variation in *CYP2C9* activity and genotype frequency into (S) - warfarin clearance.

RESULTS

Figure 4A shows the power to detect a difference in clearance between wild type (*1*1) and other genotypes as a function of study size.

Figure 4B shows the power of studies comparing each genotype with the *1*2 genotype.

Other comparisons did not lead to adequate power (≤ 5%) to distinguish between different genotypes (data not shown).

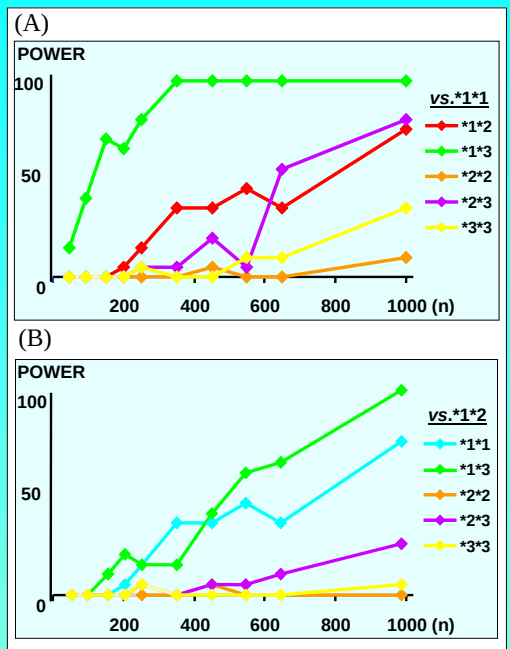

Figure 4: Power (% studies showing a significant difference in response between different genotypes and the reference genotype (A - *1*1; B - *1*2) *vs* number of subjects in each study (n).

DISCUSSION

The results indicate that both the relative activity of the allelic variant and its population frequency contribute to the ability of studies to detect a difference in clearance between genotypes. For example, *3*3 has the lowest activity of all the genotypes with only 10% the activity of the wild-type. This should lead to a pronounced difference in clearance between *3*3 and the other genotypes. However, the power of studies to detect such a difference rarely reached more than 10%, even when study sizes as large as 1000 were used. This is due to the rarity of this genotype. As its prevalence is only 0.4% of the Caucasian population, there are insufficient subjects with *3*3 genotype in the study to demonstrate statistical significance.

The study of Takahashi *et al*[6], which was unsuccessful in demonstrating a difference in the clearance of warfarin between *CYP2C9* genotypes using a study size of 47, was grossly underpowered (power = 0 - 10%). That of Scordo *et al*[5] (n = 93) could detect clearance differences between *1*3 and *1*1 subjects (power = 40%), but had zero power for other genotype contrasts.

To overcome the issue of inadequate power, genotypically-enriched populations need to be studied.

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