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

Dickinson GL¹, Lennard MS¹, Tucker GT¹, Rostami-Hodjegan A¹²

Correspondence: G.Dickinson@sheffield.ac.uk

(1) - Academic Unit of Clinical Pharmacology, University of Sheffield, S10 2JF, UK ; (2) - Simcyp Limited, Blades Enterprise Centre, John Street, S2 4SU, UK

INTRODUCTION

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

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 while reports on the link with PD have been positive.

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 CYP2C9 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.

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).

METHODS

Clearance values (total and unbound) were simulated for each individual using different population sizes (n = 47, 93, 150, 200, 250, 350, 450, 550, 850, 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.

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).

REFERENCES