Simulations to assess the propagation of the impact of genetic polymorphism in CYP enzymes into PK and PD outcomes: Warfarin and dextromethorphan as examples

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ABSTRACT

Background: Due to an increase in interindividual variability in response compared to the metabolism/PK of drugs it is expected that most studies of the impact of genetic polymorphism in drug metabolism will be more successful in assessing PK rather than PD outcome (e.g. dextromethorphan (DEX)) (figure 1). However, some studies have linked PD to enzyme phenotype/genotype but fail to establish a relationship between phenotype/genotype and PK (e.g. warfarin). A simulation approach may help to clarify the reasons for these contrasting outcomes.

Methods: Simcyp® algorithms (www.simcyp.com) were used to simulate virtual populations with respect to: (1) the PK of DEX and its antitussive response in CYP2D6 phenotypes, and (2) the relationship between CYP2C9 genotype and the PK and PD of S-warfarin. To mimic the design of studies reported in the literature, the populations in case (1) were enriched with the poor metaboliser phenotype, and, in case (2), subjects unselected for CYP2C9 genotype were studied.

Results*: While 5 subjects of each phenotype were required to achieve 80% power to discriminate the PK of DEX between extensive and poor metabolisers (EMs and PMs respectively), the corresponding number to detect the difference in antitussive effects >1000. With a study size of 550, the power to detect a difference in warfarin clearance between CYP2C9 wild type (*1/*1) and some of the less frequent genotypes was higher than that for the more frequent genotypes (e.g. 90% power for *2/*3 vs 45% power for *1/*2). This is because of the combined effects of relative enzyme activity (*2/*3 = 40%; *1/*2 = 85% of wild type activity) and genotype frequency (*2/*3 = 1.4%; *1/*2 = 20.4% in Caucasians).

Conclusions: The simulations explain the failure of reported studies with regard to defining relationships between genetic polymorphism of drug metabolising enzymes and PK and PD. Integration of prior information on enzyme kinetics is helpful in optimising study design and in avoiding costly and unsuccessful clinical studies.

* Please note that results have been updated since submission of abstract and numbers in results section (lines 1, 3, 5 and 6).

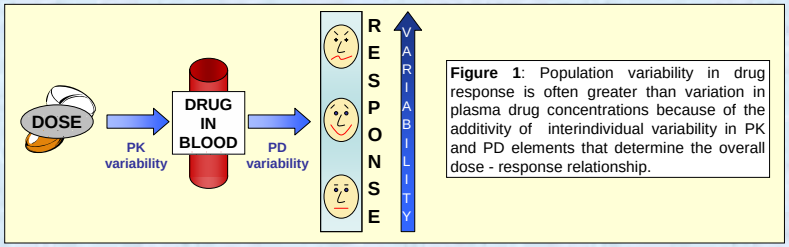


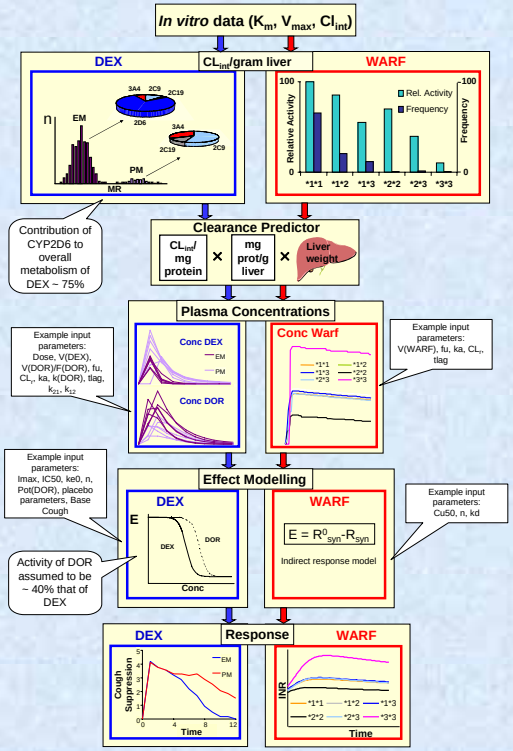
Figure 1: Population variability in drug response is often greater than variation in plasma drug concentrations because of the additivity of interindividual variability in PK and PD elements that determine the overall dose - response relationship.

AIMS

- To incorporate information on the genetics of drug metabolism into PBPK models which integrate *in vitro* enzyme kinetic data on dextromethorphan (DEX) and warfarin (WARF) to generate *in vivo* concentration-time profiles for the relevant drug/metabolites (IVIVE).
- To use these IVIVE models as part of clinical trial simulations (CTS) to explore the power of studies which investigate the impact of CYP phenotype/genotype on the PK/PD of DEX and WARF.
- To explain experimental observations reported in the literature using these simulations.

METHODS

A physiologically-based model Simcyp®, which incorporates *in vitro* metabolic values and variability in genetic, physiological and demographic features was adapted to generate DEX and WARF AUC (**A**rea **U**nder Concentration **C**urve) and AUEC (**A**rea **U**nder **E**ffect **C**urve) values for each individual (Figure 2) in populations of various sizes using relevant *in vitro* and *in vivo* parameters.



References and definitions available on request.

Figure 2: Schematic representation of the PBPK model which was used to assess propagation of phenotypic variation in CYP2D6 CL_{int} and genetic variation in *CYP2C9* activity/genotype frequency into DEX and WARF concentration/response profiles over time in each phenotype/genotype.

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RESULTS

DEX:

The effect of study size on power to detect a difference in the PK and PD of DEX due to the CYP2D6 phenotype is shown in Figure 3a. Around 5 EMs and 5 PMs are required to differentiate the PK between phenotypes while the power to differentiate a difference in response does not reach an acceptable level even at n = 1000.

Figure 3b shows that altering the potency of DOR, increasing the contribution of CYP2D6 to the overall metabolism of DEX and decreasing the PD variability all increase the power for detecting differences in response.

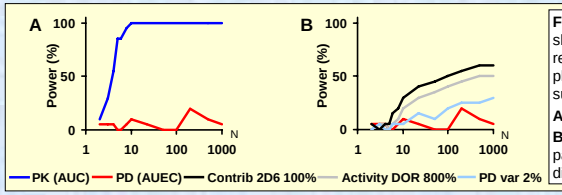

Figure 3: The power (% studies showing a significant difference in response between different phenotypes) *vs.* number of subjects in each study arm (N).

A: PK and PD studies are shown.

B: Shows the influence of various parameters on the ability to detect differences in PD.

WARF:

Figure 4A shows the effect of study size on the ability to differentiate PK and PD response between *CYP2C9* genotypes (subjects are chosen randomly from a Caucasian population). Specific comparisons between wild type (*1*1) and two other genotypes are shown.

Figure 4B shows the effect of study size if subjects are chosen specifically for their genotype (comparing *1*1 with *3*3) as they are in the DEX study.

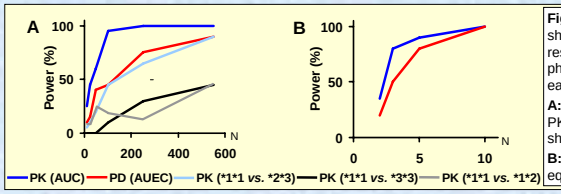

Figure 4: The power (% studies showing a significant difference in response between different phenotypes) *vs.* number of subjects in each study arm (N).

A: PK, PD & Specific comparisons of PK between certain genotypes are shown.

B: Comparing *1*1 with *3*3 only in equal numbers.

DISCUSSION

Both sets of results are consistent with what we see in the literature: Two studies into the effect of the CYP2D6 polymorphism on DEX PK and response used study sizes of 6 and 22[1,2]. Both were able to observe a difference in PK (85 and 100% power respectively) but neither saw a difference in PD between the two phenotypes (both studies had roughly 5% power).

Studies of the effect of *CYP2C9* genotype on warfarin PK are generally unsuccessful[3-5]. They use study sizes of 47 to 120 subjects and have powers of 45 to 90% respectively. Power is even less for distinguishing PK between particular sets of genotypes. PD studies however use 120 to 550 people and have better power (50 to 90%)[6-9]. Enriched populations would solve the problem of underpowered warfarin studies.

The approach used in the studies reported here can help to identify unsuccessful studies *a priori* where the effect of phenotype/genotype on PK or PD is likely to be small and clinically insignificant.

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