R6387

SIMULATION OF VIRTUAL HUMAN SUBJECTS TO INVESTIGATE THE IMPACT OF CYP2C19*17/*17 ON OMEPRAZOLE EXPOSURE

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BACKGROUND

- There are an increasing number of clinical reports describing the importance of the *17 allelic variant of CYP2C19. This polymorphism has been associated with a 2-fold increase in transcriptional activation leading to an ultrarapid metabolizer (UM) phenotype and decreased in exposure of CYP2C19 substrates, such as omeprazole[1].

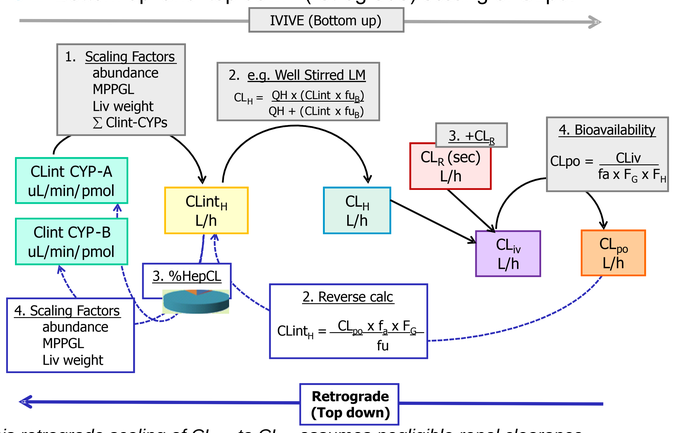
PURPOSE

- We previously developed an approach to investigate the impact of CYP2C9 polymorphisms within a population[2,3], which was also adopted by other investigators[4]. The objective of this study was to extend this approach using prior *in vitro* and *in vivo* information the on metabolism and kinetics of omeprazole in order to evaluate the likely impact of the *17/*17 genotype on the pharmacokinetics (AUC) of omeprazole in a virtual population.

METHODS

- A meta-analysis was carried out to determine the frequency of CYP2C19*17/*17 within an unselected European Caucasian population.
- In the absence of genotypic-specific abundance data, the CYP2C19 abundance for extensive metabolisers was increased 2-fold for *17/*17 (28 pmol/mg microsomal protein) to reflect the increased transcriptional activation. Equivalent variability (106%) was assumed.
- The intrinsic clearance (CL_{int}) for omeprazole was extrapolated from *in vivo*[5] (Figure 1) and apportioned to CYP2C19 (87%) and CYP3A4 (13%), based on the reported fractional contribution of the enzymes to hepatic clearance[6]. The resulting CL_{int} for CYP2C19 and CYP3A4 (21.3 and 0.33 µL/min/pmol rCYP) were then used in all simulations.
- Multiple virtual trials (VTs) matched to the clinical trial (number of subjects, ethnicity, sex, age range, dosing regimen) were simulated using the Simcyp Population-based Simulator (Version 10.0).

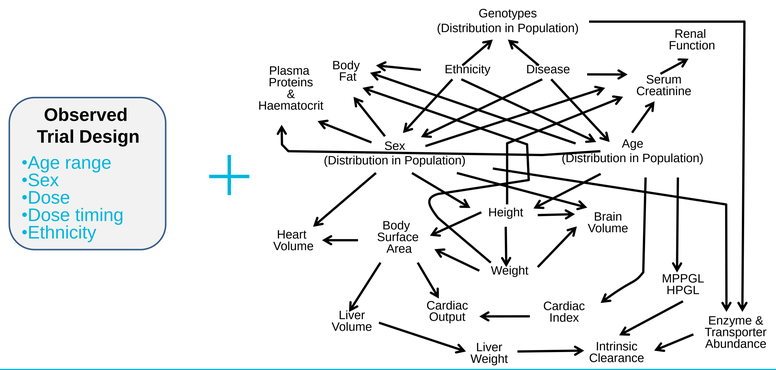
Figure 1 'Bottom up' and 'top down' (retrograde) scaling of CLpo.



NB This retrograde scaling of CL_{po} to CL_{int} assumes negligible renal clearance

- Each virtual subject was assigned physiological characteristics based on covariation built into the Simulator algorithms (Figure 2).
- Predicted AUCs and fold difference in virtual individuals with the genotype *17/*17 *vs.* *1/*1 were compared to corresponding *in vivo* data reported by Baldwin *et al*., 2008[7], which were extracted using GetData Graph Digitizer.

Figure 2 Virtual subjects are generated based on the relationships of covariates affecting ADME defined within the Simulator databases and user-defined trial design.



RESULTS

- The weighted mean frequency for *17/*17 was 6.0% in the North European Caucasian population (5 independent studies, 2493 subjects; Table 1)[1,8-11].
- The predicted AUCs (median 2121 and 1524 nmol.h/L) were in good agreement with the observed data for both *1/*1 (3226 nmol.h/L) and *17/*17 (2097 nmol.h/L) genotypes, respectively (Figure 3).
- The predicted fold decrease in AUC (*17/*17 *vs.* *1/*1) also compared well with the observed data (ratio of overall medians 1.39 *vs.* observed 1.54; Figure 3).
- The variability in *1/*1 individuals across 10 VTs (Figure 4a) was in reasonable agreement with that observed, however, the variability in *17/*17 individuals was over predicted compared to observed (Figure 4b). This could be an indication that the low subject number in the clinical trial (n=5) caused underestimation of the 'true' variation in a *17/*17 population or indicate that the assumed CV of 106% for the *17/*17 abundance requires refinement.

Table 1 Meta-analysis for the frequency of CYP2C19*17/*17 in the Caucasian population.

		CYP2C19*17/*17		
	Nationality	Total n	*17/*17 n	% *17/*17
Sim *et al*., 2006	Swedish	107	4	3.74
Kurzawski *et al*., 2006	Polish	125	8	6.40
Rudberg *et al*., 2008	Norwegian	166	7	4.22
Justenhoven *et al*., 2009	German	1989	119	5.98
Grabar *et al*., 2008	Slovenian	106	12	11.3
Weighted Mean %				***6.02***

Figure 3 The AUC of omeprazole in *1/*1 and *17/*17 individuals in observed (shaded) and virtual (open) clinical trials. Data are expressed as median with box (25-75th percentile) and whisker (range).

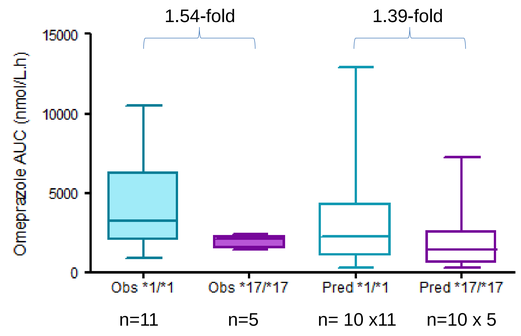
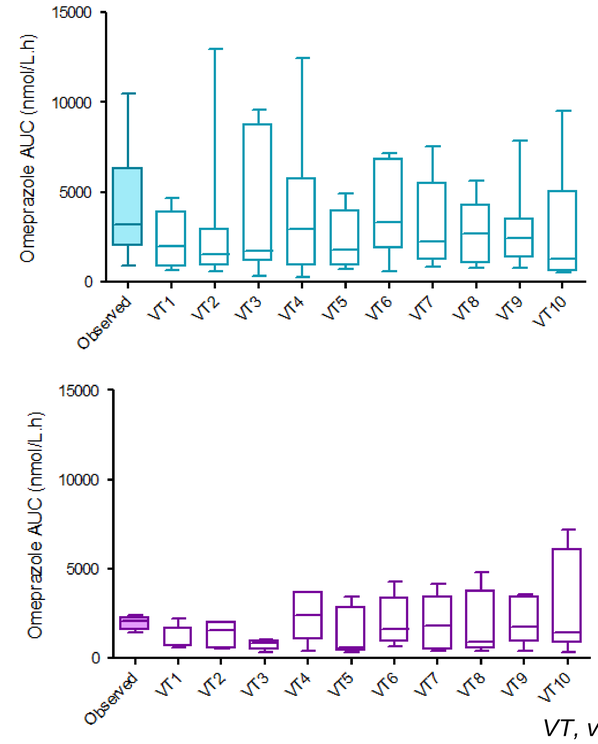


Figure 4 The AUC of omeprazole in a) *1/*1 (n=11) and b) *17/*17 (n=5) observed (shaded) and virtual (open) clinical trials. Data are expressed as median with box (25-75th percentile) and whisker (range).



VT, virtual trials

CONCLUSIONS

- Mechanistic physiologically based modelling approaches are useful for the assessment of genotypic differences in the context of other sources of physiological variability.

REFERENCES

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