**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.

**PURPOSE**

We previously developed an approach to investigate the impact of CYP2C9 polymorphisms within a population\(^2\), 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 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\(^6\) (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 mumol/min per g of liver) were then used in all simulations.

Multiple virtual trials (VTs) matched the clinical trial (number of subjects, ethnicity, sex, age range, dosing regimen) were simulated using the Simcyp Population-based Simulator (Version 10.0).

**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.

**CONCLUSIONS**

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

**REFERENCES**