Statistical Power Analysis to Detect Drug-Drug Interaction between Lorezapam and Probenecid in Healthy and Renal-impaired Populations Using PBPK Modelling and the Simcyp R Package

Theresa Cain, Janak Wedagedera, Masoud Jamei
SIMCYP (a Certara Company), Sheffield, UK

Background

When designing a clinical study, it is important to calculate the sample size required to achieve adequate power in the study. A tool is already available within the Simcyp Simulator to calculate the power of studies to correctly detect the difference between PK parameters in two populations. [1] We have developed an R library package where the Simcyp simulator can be run from within R. This facilitates various scenarios [2] such as constrained sensitivity analysis or parameter estimation, and parameter estimation using multiple substrates or populations. It can also be used for compliance and bioequivalence studies. We aim to extend the power calculation tool in Simcyp and use the Simcyp V16 R package to calculate the power of a drug-drug interaction (DDI) study using model compounds Lorezapam and Probenecid.

Methods

The Version16 R package was first used to calculate the power of correctly detecting the difference in AUC values after a single dose of Lorezapam between a healthy volunteer and a renal impaired (GFR<30) population, given a set of sample sizes and a significance level of 0.05. These values were then compared with results using the Simcyp power calculation tool [1].

We then extended the power calculation to consider a DDI study, which is not currently available in the Simcyp power calculation tool but can be calculated using the Simcyp Version 16 R package[2]. The physiologically-based PK (PBPK) model for a DDI between Lorezapam and Probenecid has previously been verified [3]. Simcyp simulations of 1000 individuals were run from R for the DDI using both the healthy volunteers and renal impaired (GFR<30) populations. The null hypothesis being tested is:

H_0: Mean AUC Lorezapam=Mean AUC Lorezapam (+Probenecid)

The mean and variance of the AUC was then calculated for both populations. If the AUC values are assumed to be sampled from a normal distribution,

$$AUC_L \sim N(\mu_L, {\sigma_L}^2)$$

$$AUC_{LP} \sim N(\mu_{LP}, {\sigma_{LP}}^2)$$

then given a sample size, n, the distribution of the sample mean AUCs is also normal:

$$\overline{AUC}_L \sim N\left(\mu_L, \frac{{\sigma_L}^2}{n}\right)$$

$$\overline{AUC}_{LP} \sim N\left(\mu_{LP}, \frac{{\sigma_{LP}}^2}{n}\right)$$

Given the distribution of the two mean AUCs, the power can then be derived for a significance level of 0.05.

The power to correctly detect the difference in mean AUC after taking Lorezapam alone and in combination with Probenecid was then determined using the Simcyp R package for the sample sizes 4, 6, 8, 10 and 12, assuming a significance level of 0.05.

Results

Using the R package, a sample size of 50 achieved a power of 85.54% to correctly determine a difference between the healthy volunteer and renal impaired (GFR<30) mean AUC after a single Lorezapam dose, which is the same as derived using the Simcyp power calculation tool.

Figure 1: Calculating Power using Simcyp Simulations in R

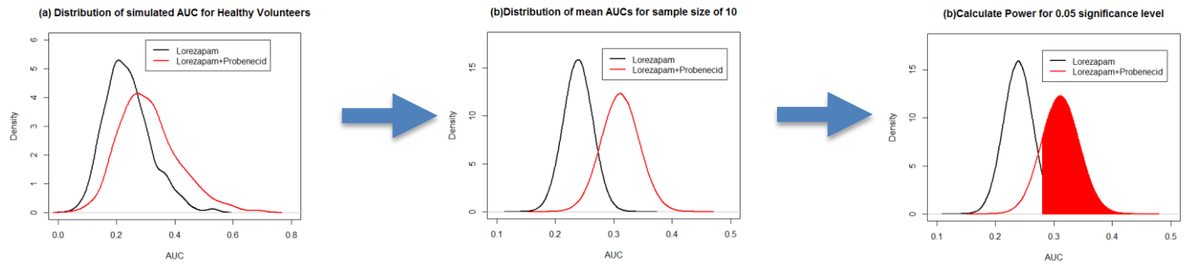

Table 1: Power of detecting a DDI by sample size for Healthy Volunteers and Renal impaired(GFR<30) populations

Sample size	Power (%)	
	Healthy Volunteers	Renal (GFR<30)
4	55.18	61.58
6	67.21	74.23
8	76.16	82.9
10	82.78	88.77
12	87.64	92.7

Figure 1 shows the process of calculated power using the Simcyp R package comparing the mean AUC between taking Lorezapam alone and in combination with Probenecid for a health volunteers population. Figure 1(a) presents the density of the two scenarios after running simulations of 1000 individuals. Figure 1(b) presents the density of the mean AUC of the two scenarios for a sample size of 10. The shaded area in Figure 1(c) represents the power obtained to detect the difference between the two scenarios using a sample size of 10.

Table 1 lists the power achieved for each sample size used in the DDI study between Lorezapam and Probenecid. For each sample size the renal impaired(GFR<30) population achieves a greater power of detecting a difference between the mean AUCs, and therefore a greater power of correctly determining a DDI between the two drugs. Therefore, using the renal impaired (GFR<30) population a smaller sample size is required to achieve the equivalent power as the healthy volunteer population.

Conclusions

This work shows that Simcyp's power calculation tool can be extended to calculate the power to correctly identify a DDI using the Simcyp V16 R package. The results indicate that in the studied scenario a smaller sample size is required to correctly determine a DDI in the renal impaired(GFR<30) population than a healthy volunteers population for a given power. The reduced renal function in the renal-impaired population results in a lower renal clearance and therefore a greater DDI than for the healthy volunteers. Therefore a smaller sample size is needed in the renal impaired population to obtain the same power as the healthy volunteers.

References

[1] Emami Riedmaier et al, More Power to OATP1B1: An evaluation of Sample Size in Pharmacogenetics Studies Using a Rosuvastatin PBPK Model for Intestinal, Hepatic, and Renal Transporter-mediated Clearances. The Journal of Clinical Pharmacology. 2016

[2] Cain et al. Application of Simcyp's R Library Package in Simulation and Prediction of Metoprolol Compliance Using a Single Plasma Concentration Sample. 24th PAGE meeting, Crete, 2nd-5th June 2015 (poster presentation).

[3] Neuhoff et al, Application of a physiologically based pharmacokinetic (PBPK) model for prediction of the drug-drug interaction (DDI) between Lorazepam and Probenecid. 19th North American ISSX/29th JSSX Meeting, 19th October 2014 (poster presentation)