Prediction of Rosiglitazone compliance from last sampling information using Population based PBPK modelling and Bayes theorem: Comparison of prior distributions for compliance scenarios.

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Introduction

Drug compliance can have an impact on drug efficacy and safety, and is often difficult to determine. Barriere *et al*. [1] proposed a method to predict the compliance scenario of a patient given their last sampled concentration. This involved calculating the probability $P(w_j|C)$ of a compliance scenario given the last concentration using Bayes theorem:

$$P(w_j|C) = \frac{P(w_j)P(C|w_j)}{P(C)} \qquad (1)$$

where $P(w_j)$ is the prior probability of compliance scenario w_j, $P(C|w_j)$ is the probability of the final concentration given compliance scenario w_j and $P(C) = \sum_j P(C|w_j)P(w_j)$ is the probability of concentration C. The predicted compliance scenario for a given final concentration was determined by maximising the probability $P(w_j|C)$ over all compliance scenarios.

Objectives

To predict the compliance scenario of Rosiglitazone from a patient's last sampled concentration using PBPK modelling and Bayes theorem, and to compare the predictability when compliance scenarios are assumed equally likely and when they are generated randomly.

Methods

We applied the Barriere *et al.* [1] method to predict patient's compliance when taking a 4 mg daily dose of Rosiglitazone (ROS) for 5 days. Prior in vitro and physicochemical parameters for ROS and the Healthy Volunteer population of Simcyp (V12 R2) were used to generate the plasma concentration profiles of 500 patients. In all patients the first three doses were taken and the final two doses were varied over five compliance scenarios: full compliance (11), missing the first dose (01), missing the second dose(10), taking both doses at the final doing time (02) and missing both doses (00).

Two prior distributions were investigated, the first a uniform prior distribution where each compliance scenario is equally likely, and the second where compliance is generated randomly and therefore each scenario has a different prior probability. For the uniform prior, 100 plasma concentration profiles were simulated for each compliance scenario using the Simcyp custom trial design option. For the second prior, a compliance scenario was generated for each of the 500 patients using an algorithm written in an R script. Concentration profiles were then simulated for each of the generated compliance scenarios using the simulation option within the Simcyp parameter estimation tool.

Given the last simulated plasma concentrations and the known compliance scenarios, the probability of each compliance scenario given the last plasma concentration $P(w_j|C)$ was calculated for both priors using equation (1).

For a given concentration, C, the predicted compliance scenario was determined using Bayes decision theory, where compliance scenario w_i is predicted if

$$P(w_i|C) > P(w_j|C) \; for \; all \; j \neq i \quad (2)$$

The reliability of the predictions was assessed by calculating for each compliance scenario and prior distribution, the probability of correctly predicting the compliance scenario (true positive) and the probability of correctly rejecting the compliance scenario (true negative).

Results

Plasma concentration profiles of 100 patients were simulated for each compliance scenario when assuming a uniform prior. Predicted mean concentration profiles over the second 60 hours of the trial are presented in Figure 1, where the predicted mean profile for full compliance (11) is compared with the predicted mean of each of the other scenarios (01, 10, 02 and 00).

For the random compliance prior, a compliance scenario was randomly generated in R for each of the 500 patients. Figure 2 presents the mean concentration profile for the randomly generated compliance compared with the mean concentration profile if all doses were taken.

Using equation (1), posterior probabilities were calculated for each compliance scenario and prior distribution. For the uniform prior distribution, each compliance scenario has a prior probability $P(w_j) = 0.2$. The prior probabilities for the randomly generated compliance scenarios are presented in Table 1. The prior probability for the full compliance scenario (11) is greater in the case of the random compliance than when a uniform prior is assumed, while for the other scenarios the prior probability is greater when a uniform prior is assumed. The probability of the two scenarios 02 and 00 are fairly small for the randomly generated compliance, at 0.04 and 0.03 respectively.

The probabilities of correctly predicting a compliance scenario (true positive) and of correctly rejecting a compliance scenario (true negative) given the final concentration, are presented in Tables 2 and 3, for the uniform prior and the prior for randomly generated compliance scenarios respectively.

The probabilities of a true positive and a true negative using a uniform prior are between 0.41 to 0.95, and between 0.78 and 0.98 respectively. For the randomly generated compliance these probabilities are between 0.65 and 0.99, and between 0.91 and 1 respectively. In both cases the scenarios for full compliance, two missed doses and taking both doses together had the greatest probabilities of a true positive.

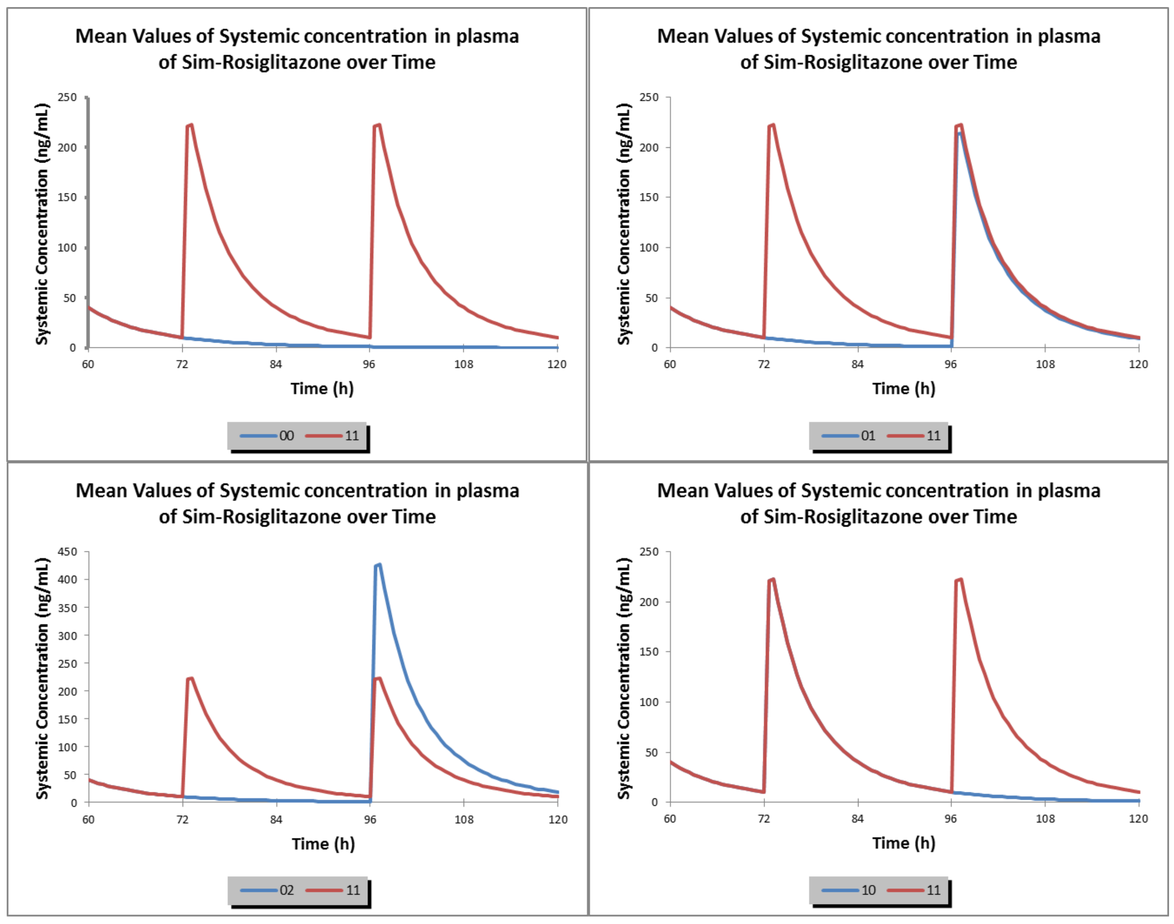

Figure 1: Mean Plasma Concentration profiles over last 60 hours for fixed compliance scenarios, comparing full compliance with other scenarios.

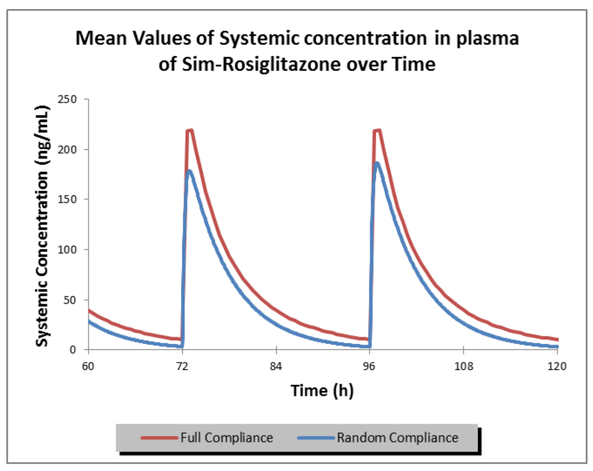

Figure 2: Mean Plasma concentration profiles for random compliance compared with full compliance.

Compliance Scenario	Prior Probability
11	0.60
10	0.19
01	0.14
02	0.04
00	0.03

Table 1: prior probabilities of randomly generated compliance scenarios

Compliance Scenario	P(+|+)	P(-|-)
11	0.78	0.95
10	0.41	0.96
01	0.68	0.98
02	0.83	0.98
00	0.95	0.78

Table 2: Probability of true positive and true negative by compliance scenario, for equally likely compliance scenarios.

Compliance Scenario	P(+|+)	P(-|-)
11	0.97	0.91
10	0.99	1
01	0.65	0.99
02	0.94	1
00	0.97	1

Table 3: Probability of true positive and true negative by compliance scenario, for randomly generated compliance scenarios.

Discussion

The probabilities of both true positive and true negative for each compliance scenario are greater when assuming the randomly generated compliance scenario, which is arguably more representative of the true population. Compliance scenarios where only one dose was taken tended to be the hardest to predict from the final concentration. This is particularly the case for compliance scenario 01 where the probability is low for both prior distributions, and it can be observed in Figure 1 that the mean concentration profile for scenario 01 after the final dose is very similar to that for full compliance. The lowest probability was the probability of correctly predicting the scenario 10 for the uniform prior distribution. In this case the final concentrations could be similar to those where both doses were missed (00).

These results demonstrate the value of population PBPK modelling in identifying potential predictive compliance indicators. This work can be expanded to include other PK outcomes, drug response, and to investigate the compliance predictive power for different prior distributions.

References

[1] Barriere O et al., J Pharmacokinet Pharmacodyn. 2011 Jun 1;38:333-351.