Introduction

- Predictions of OATP1B1-mediated interactions have tended to report a discrepancy between in vitro and in vivo Ki [1]. This could be due to multiple factors (e.g. absence of absolute transporter abundances and their corresponding activities).
- Rifampicin administered as a single dose is an FDA recommended OATP1B1 inhibitor [2].
- Recently, the rifampicin-glyburide drug-drug interaction (DDI) has been simulated assuming that glyburide is transported only by OATP1B1 and using an in vitro determined Ki for rifampicin [3].
- Given the observed range of reported Ki values for in vitro OATP1B1 inhibition by rifampicin (0.28-11µM) and the involvement of OATP2B1 in hepatic uptake of glyburide [3], a modelling and simulation exercise was undertaken to assess the impact of incorporating multiple hepatic uptake pathways for glyburide over a range of rifampicin OATP Ki values on the predicted DDI (Figure 1).
- Sensitivity of predicted DDI when a permeability-limited liver model for both glyburide and rifampicin was used was also investigated.

Aims

- Assess the sensitivity of rifampicin OATP1B1 inhibition to sinusoidal hepatic uptake of glyburide over a range of Ki values.
- Assess the impact an additional glyburide sinusoidal hepatic uptake transporter pathway on the predicted rifampicin-glyburide DDI.
- Investigate the impact of a rifampicin permeability-limited liver model on DDI predictions.

Methods

- Full-PBPK models were constructed for glyburide and rifampicin using the Simcyp Simulator (V13R2). Tissue-to-plasma partition coefficients were predicted by the methods described by Rodgers and co-workers [3]. A permeability-limited liver model was used for glyburide to incorporate passive and active hepatic uptake of 5 and 25µmol/min/liver cells, respectively.
- Metabolism of glyburide was described by in vitro in vivo extrapolation from human recombinant CYP3A4, CYP2C8, CYP2C9 and CYP2C19 enzymes [4].
- Absorption of glyburide was described using intestinal permeability scaled from Caco-2 data [4] within the advanced dissolution, absorption and metabolism (ADAM) model [5].
- Inhibition of OATP2B1 [Ki=80µM] by rifampicin was considered [6]. A 7-fold reduction in Ki of OATP2B1 was also assessed.
- Inhibition of CYP3A4 [Ki=18.5µM] and CYP2C8 [Ki=30.2µM] by rifampicin was also considered [7].
- Induction was assumed to be negligible in these simulations.
- The DDI between glyburide (1.25 mg oral) and rifampicin (600 mg single dose 30 minutes i.v. infusion) was simulated by matching the trial design [6].
- A rifampicin permeability limited model was constructed, assuming a passive diffusion clearance of 100µl/min/liver hepatocytes after performing a sensitivity analysis.
- The sensitivity of the predicted AUC ratio to varying both the rifampicin OATP1B1 Ki (over the range of literature reported values), and the contribution of OATP2B1 to total active hepatic uptake transport of glyburide was evaluated, using both perfusion-limited and permeability-limited rifampicin models.

Results

- The glyburide concentration-time profiles for oral and intravenous dosing are shown in Figure 2. The impact of incorporating rifampicin within a permeability limited model is shown in Figure 3.
- The observed AUC ratio could be recovered using a rifampicin Ki value of 1µM in the absence of glyburide OATP2B1 active uptake.
- The predicted magnitude of DDI changed from ~6 - ~1-fold as the active contribution of OATP2B1 to glyburide uptake increased from 0-100% (Figure 4).
- An OATP1B1 Ki value of 0.3µM was required to recover the clinical data when the OATP2B1 contribution to glyburide active uptake was 25%.
- If the contribution of OATP2B1 was >40%, a rifampicin OATP1B1 Ki as low as 0.01µM failed to recover the observed AUC ratio.

Conclusions

- In this glyburide example, if only a single uptake pathway is considered, a less potent Ki value is required to recover the observed DDI.
- For a substrate of active uptake transporters into the liver, consideration of additional hepatic uptake routes that play only minor roles in total hepatic uptake (~10%, with low inhibition potency) can have a significant impact on the predicted AUC ratio over a relatively small range of inhibitor Ki values (0.1-1µM).
- Understanding the relationship between in vitro and in vivo transporter Ki values warrants further examination.

References


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