ABSTRACT

Objectives: Cytochrome P450 3A (CYP3A) is a major human drug-metabolizing enzyme and several medically important drug-drug interactions (DDIs) are known to result from CYP3A induction. The bioactivation of cortisol to 6-beta hydroxycortisol is selectively catalyzed by CYP3A, and prototypic CYP3A inducing drugs have been shown to increase the urinary 6-beta hydroxycortisol/cortisol molar ratio (CMR), a non-invasive biomarker of hepatic CYP3A induction. Although the value of CMR measurements for qualitative diagnosis of CYP3A induction has been widely recognized, an understanding of the relationship between changes in this biomarker and clinical pharmacokinetic correlations of CYP3A induction is currently not available. Additionally, unlike CYP2C inhibition for which a classification to guide DDI risk assessment is established, there is no comparable classification of CYP3A inducers. These factors have precluded the utilization of CMR as an objective biomarker for quantitative DDI risk assessment in early clinical development. In this communication we describe a Bayesian model of the fold-increase in CMR to percent decrease in total exposure of midazolam and demonstrate its application in the context of a proposed classification of CYP3A inducers to guide DDI risk assessment.

Methods: We have collated literature data on eight prototypic CYP3A inducers including in vivo data on compounds in clinical development to fit a Bayesian meta-analytic model relating percent decrease in midazolam AUC (Y) to the log fold-increase in CMR (x). The Bayesian model incorporates weakly informative prior distributions for all parameters in the model, to enhance boundary conditions and utilize historical data on placebo variability. A case study describing application of this model to predicting the effects of Compound X on oral midazolam pharmacokinetics from Bayesian dose-response modeling of CMR data collected in a multiple dose toleration study was used to illustrate the proposed methodology. The application of a Bayesian approach to the modeling permitted fine-tuning of the probability of observing clinically meaningful levels of CYP3A induction (≥60% decrease in midazolam exposure), DDI risk and associated therapeutic index, where viewed in context of a proposed classification of CYP3A inducers.

Results: Posterior predictive checks and cross-validation demonstrated that the model fits the CMR-midazolam data well and gives good predictive performance. Combining Bayesian dose-response modeling for effect of Compound X on fold-change CMR with the predictive model above, we have predicted the effects of Compound X on midazolam AUC. The low dose shows a high probability of having effects less than pioglitazone (~30% decrease) while the high dose shows a high probability of having effects larger than St. John’s Wort (~60% decrease). The middle doses have effects in-between.

Integration of predictions from the dose-response model into the relationship described by the Bayesian meta-analytic model permitted prediction of the effects of Compound X on MDZ AUC. Posterior distributions of model-predicted mean effects of 2-25 mg doses of Compound X on CMR and MDZ AUC were used to estimate:

- Pr (|% decrease in MDZ AUC| ≥ 60%) to represent CYP3A induction of potential clinical relevance (≥ mean S/W effect)
- Pr (|% decrease in MDZ AUC| ≥ 30) to represent CYP3A induction unlikely to be clinically relevant (compared to or less than pioglitazone’s affect)

RESULTS

Posterior summary of model relating CYP3A inducer to effects on MDZ AUC

METHODS

Data collection

• A review of the literature and in-house studies yielded data on the effects of prototypic CYP3A inducers on CMR and MDZ AUC.

• CMR and MDZ AUC data reported together in only one study

Inducer

<table>
<thead>
<tr>
<th>Inducer</th>
<th>Fold-in CMR (p of studies)</th>
<th>% decrease in MDZ AUC (p of studies)</th>
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</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>4.06 (1.51, 10.00)</td>
<td>60% (1.7, 19.0)</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>1.20 (1.51, 1.20)</td>
<td>26 (1.7, 12.1)</td>
</tr>
<tr>
<td>Compound C</td>
<td>750 mg/d 2.0 (1.05, 3.11)</td>
<td>94 (0.35, 2.0)</td>
</tr>
<tr>
<td>Compound D</td>
<td>250 mg/d 1.11 (0.64, 1.88)</td>
<td>12.1 (0.37, 0.8)</td>
</tr>
<tr>
<td>Compound E</td>
<td>60 mg/d 0.35 (0.15, 1.3)</td>
<td>6.7 (0.15, 0.6)</td>
</tr>
<tr>
<td>Compound F</td>
<td>6 mg/d 0.91 (0.09, 1.06)</td>
<td>0.76 (0.5, 0.5)</td>
</tr>
<tr>
<td>Compound G</td>
<td>25 mg/d 2.0 (1.05, 3.11)</td>
<td>94 (0.35, 2.0)</td>
</tr>
<tr>
<td>Compound H</td>
<td>2 mg/d 0.35 (0.15, 1.3)</td>
<td>6.7 (0.15, 0.6)</td>
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Bayesian meta-analytic model

An empirical meta-analysis model was used to relate % decrease in MDZ AUC (Y) to log-fold change in CMR (x) using the following Bayesian sigmoid Emax model

\[ y_{ij} = \delta_0 + \delta_1 x_i + \epsilon_{ij} \]

\[ \delta_0 \sim N(0, \sigma^2_0) \]

\[ \delta_1 \sim N(0, \sigma^2_1) \]

\[ x_i \sim N(0, \sigma^2) \]

\[ y_{ij} \sim A \left[ 1 - \exp \left( -B y_i \right) \right] + \delta_0 + \delta_1 x_i \]

Likelihood

\[ y_{ij} = \theta_i + \eta_i + \epsilon_{ij} \]

\[ \eta_i \sim N(0, \sigma^2) \]

\[ \theta_i \sim N(0, \sigma^2) \]

\[ y_{ij} \in (0,100) \]

Priors

\[ \theta_i \sim N(-0.1,0.1) \]

\[ i = 1, \ldots, 12 \]

\[ A \sim U(1, 100) \]

\[ B \sim \text{Gamma}(4, 4) \]

\[ \gamma \sim U(0.5) \]

\[ \sigma^2 \sim U(0.2, 1.0) \]

\[ \sigma^2, \sigma^2 \sim \text{Gamma}(0.01, 0.01) \]

Model evaluation

Model evaluation was performed using cross validation and posterior predictive checks.

Both approaches demonstrate the model fits reasonably well, particularly for the NMEs. There is some indication that Rifampin is an outlier in this model (cluster with positive residuals).