BAYESIAN BIOMARKER-BASED QUANTITATIVE RISK ASSESSMENT FOR CYP3A INDUCTION DDI IN EARLY CLINICAL DEVELOPMENT

Jonathan L. French[a] and Karthik Venkatakrishnan[b]

[a]Global Pharmacometrics, Pfizer Global Research & Development, New London, CT; and [b]Clinical Pharmacology, Millennium Pharmaceuticals, Cambridge, MA

Global Pharmacometrics

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 biotransformation 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 metabolic ratio (CMR), a noninvasive 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 correlates of CYP3A induction is currently not available. Additionally, unlike CYP3A 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 relating 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-house data on compounds in clinical development. We fit a Bayesian meta-analytic model relating percent decrease in midazolam AUC (Y) to the log fold-increase in CMR (Z). The Bayesian model incorporates weakly informative prior distributions for all parameters in the model, to enforce 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 methods. The application of a Bayesian approach to the modeling permitted forecasting of the probability of observing clinically meaningful levels of CYP3A induction (≥ 60% decrease in midazolam exposure), DDI risk and associated therapeutic index, when viewed in context of a proposed classification of CYP3A inducers.

Results: Posterior predictive checks and cross-validation demonstrate 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.

Conclusions: We have described an approach to bridging some key gaps in the current status of clinical pharmacologic approaches to DDI risk assessment for CYP3A inducers via application of Bayesian model-based knowledge management. We offer a quantitative framework that should permit objective utilization of CMR biomarker data from multiple-dose clinical pharmacology studies for early CYP3A induction DDI risk assessment, potentially permitting deferral of the conduct of definitive DDI studies until after demonstration of proof-of-concept and definition of the likely clinical dose range.

INTRODUCTION AND BACKGROUND

Approaches for assessment of risk for CYP3A inhibition DDI have been well characterized, with established guidelines for classification of new molecular entities by strength of inhibition. In contrast, there are no comparable guidelines for CYP3A inducers for DDI risk assessment in clinical drug development. Consequently, we sought to develop a quantitative approach to guide clinical pharmacologic risk assessment for CYP3A induction by NMEs in clinical development.

Urinary 6-β-hydroxycortisol:cortisol metabolic ratio (CMR) is a biomarker of hepatic CYP3A induction and has been widely recognized as having value for qualitative diagnosis of CYP3A induction. One standard approach to assess DDI risk is through a drug interaction study with the orally administered sensitiveCYP3A substrate midazolam (MDZ). We propose using a model-based approach to relate effects on CMR to effects on decreaes in MDZ AUC. This model can then be used to predict DDI risk using CMR data from a standard multiple dose tolerance study.

In this poster we describe a Bayesian model fit to summary-level data collected through a review of the literature and in-house databases. We apply the model to predict the DDI risk for Compound X in the context of a proposed classification of CYP3A inducers.

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	Fold-↑ in CMR [# of studies] (range)	% ↓ in MDZ AUC [# of studies] (range)
Rifampin	4.06 [9] (1.7 – 9.0)	92 [8] (86 – 98)
Troglitazone	2.17 [1]	67 [1]
St. John's Wort	1.70 [4] (1.4 – 2.4)	60 [5] (41 – 79)
Pioglitazone	1.20 [1]	26 [1]
Compound A (25 mg/d)	1.42 [1]	13 [1]
Compound A (100 mg/d)	1.53 [1]	58 [1]
Compound B (40 mg/d)	2.0 [1]	39 [1]
Compound B (120 mg/d)	2.5 [1]	61 [1]
Compound C (50 mg/d)	1.61 [1]	73 [1]
Compound C (750 mg/d)	2.0 [1]	94 [1]
Compound D (250 mg/d)	1.11 [1]	12.1 [1]
Compound D (1000 mg/d)	2.3 [1]	51.4 [1]

Bayesian meta-analytic model

• An empirical meta-analysis model was used to relate % ↓ in MDZ AUC (Y) to log-fold change in CMR (z):

- The model was fit to the study-level data using non- and weakly-informative prior distributions
- The model was fit using MCMC methods implemented in WinBUGS and facilitated by using the R2WinBUGS package in R.
- Five Markov chains of 100,000 samples following a burn-in of 50,000 iterations. Inference was based on a 1/50th thinned sample.

Likelihood

$$z_{ij} = \theta_i + \eta_j + \varepsilon_{ij}$$

$$\eta_j \sim N(0, \omega^2)$$

$$\varepsilon_{ij} \sim N(0, \sigma_z^2 / n_{ij})$$

$$y_{ik} \mid \theta_i = \overbrace{A\left\{1 - \exp\left(-B\theta_i^{\gamma}\right)\right\}}^{\mu_{y_{ik}}} + \delta_{ik} \qquad y_{ik} \in (0,100)$$

$$\delta_{ik} \sim N\left(0, \sigma_y^2 \left(1 - \mu_{y_{ik}}/100\right)^2 / n_{ik}\right)$$

i denotes drug/dose
j denote study (CMR)
k denote study (MDZ)

Priors

$$\theta_i \sim N(1.0, 10000)\,, i = 1, \ldots, 12$$

$$A \sim U(0,100)$$

$$B \sim Gamma(4,4)$$

$$\gamma \sim U(0,5)$$

$$\sigma_y \sim U(10,200)$$

$$\sigma_z^{-2}\,, \omega^{-2} \sim Gamma(0.01, 0.01)$$

Model assessment

• Competing models were assessed using DIC

• Final model was evaluated using cross-validation and posterior predictive checks

Application

Predict the effects of Compound X on % ↓ in MDZ AUC from modeling of CMR data collected in a multiple dose toleration study

The dose-response relationship for fold-change in CMR was analyzed using the following Bayesian sigmoid Emax model

$$\log(fold-change) = E_0 + \frac{E_{max} \times dose^h}{ED_{50}^h + dose^h} + \varepsilon, \quad \varepsilon \sim N(0, \sigma^2)$$

Non-informative prior distributions were used for Emax, ED50 and σ^2. Moderately informative priors were used for E0 (based on historical placebo data) and *h*. The prior for *h* was centered at 1.4 and placed 95% of the distribution between 0.5 and 5.0.

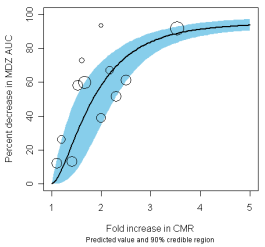
Integration of predictions from the dose-response model into the relationship described by the Bayesian meta-analytic model permitted prediction of the effects of Compound X on MDZ AUC.

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 (% ↓ in MDZ AUC ≥ 60%) to represent CYP3A induction of potential clinical relevance (≥ mean SJW effect)
- Pr (% ↓ in MDZ AUC ≤ 30) to represent CYP3A induction unlikely to be clinically relevant (comparable to or less than pioglitazone's effect)

RESULTS

Posterior summary of model relating CMR to effects on MDZ AUC

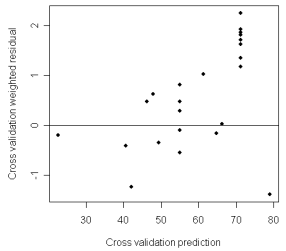


	Mean	SD	90% CI
A	96.1	2.54	(91.6, 99.7)
B	1.77	0.35	(1.23, 2.38)
γ	1.85	0.64	(1.05, 3.11)
σ_y	142	21.0	(110, 179)
σ_z	0.40	0.31	(0.09, 1.06)
ω	0.37	0.09	(0.22, 0.53)

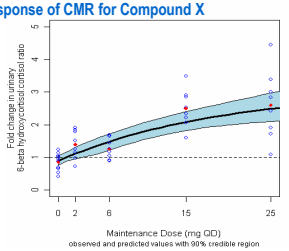
Model evaluation

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

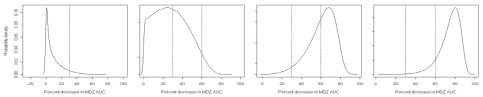
Both approaches demonstrate the model fits reasonably well, particularly for the NMEs. There is some indication that Rifampin is an outlier in this model (cluster with positive residuals).



Dose response of CMR for Compound X

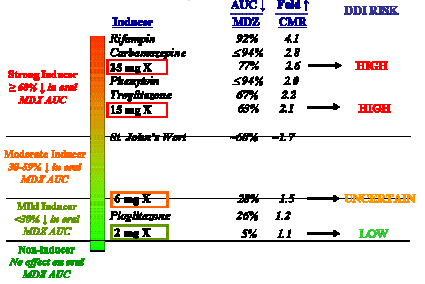


Predicted effects of Compound X on MDZ AUC



Dose	Fold-C_{eff}	Predicted % ↓ jn MDZ AUC (90% CI)	Pr (≤ 30% ↓)	Pr (≥ 60% ↓)
2 mg	0.5	5.31 (0.03 , 32.09)	0.94	~0
6 mg	1	27.6 (2.9 , 58.8)	0.55	0.04
15 mg	2	63.3 (34.7 , 79.7)	0.03	0.59
25 mg	3	76.7 (54.6 , 88.0)	~0	0.91

DDI risk assessment: Positioning Compound X on the spectrum of CYP3A inducers



SUMMARY AND CONCLUSIONS

• We have proposed a model-based approach to bridging a key gap to DDI risk assessment for CYP3A inducers in early clinical development This approach is based on a Bayesian meta-analysis of summary-level data for 12 prototypic CYP3A inducers

• Integration of the dose-response relationship for effect on CMR with this meta-analytic model permitted prediction of the effects of Compound X on MDZ AUC

•15 mg QD of Drug X (~2 × Ceff) was predicted to be a strong CYP3A inducer, indicating a low TI for DDI, resulting in termination from development

• The Bayesian methods employed here appropriately propagate uncertainty through the prediction of effects on MDZ AUC