

Title: Biomarker-based quantitative risk assessment for CYP3A induction DDI in early clinical development

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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 DDI 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 will describe a Bayesian model relating the fold-increase in CMR to percent decrease in total exposure of the orally administered CYP3A substrate midazolam and demonstrate its application in context of a proposed classification of CYP3A inducers to guide DDI risk assessment.

Methods:

We have collated literature data on six prototypic CYP3A inducers including in-house data on compounds in clinical development. Based on these data we fit a model of the form $Y = A\{1 - \exp(-Bx^\gamma)\} + \epsilon$, where Y is the percent decrease in midazolam AUC and x is the log fold-increase in CMR. 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. The model was fit using Markov Chain Monte Carlo methods implemented in WinBUGS [1] and facilitated by using the R2WinBUGS [2] package in R.

The availability of clinical biomarker and DDI data on in-house drug development candidates permitted model validation via a posterior predictive check of its performance in estimating effects of new molecular entities on midazolam pharmacokinetics from effects on CMR.

A case study describing application of this model to predicting the effects of an investigational drug candidate 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. [3]

The model-based predictions of effects on oral midazolam exposure when viewed in context of a proposed classification of CYP3A inducers permitted early forecasting of DDI risk and associated therapeutic index. . The application of a Bayesian approach to the modeling permitted forecasting of the probability of observing clinically meaningful levels of CYP3A induction ($\geq 60\%$ decrease in midazolam exposure).

Results:

Posterior predictive checks and cross-validation demonstrate that the model fits the CMR-midazolam data well and gives good predictive performance. Posterior mean, median and 90% credible intervals for the model parameters are given below:

Parameter	Mean	Median	90% Credible Interval
A	93%	95%	(77% , 99%)
B	2.3	1.9	(1.5 , 4.0)
Gamma	1.3	1.3	(0.7 , 2.2)

Combining Bayesian dose-response modeling for effect of compound A on fold-change CMR with the predictive model above, we obtain the following predictions of effects of compound A on midazolam AUC and probability of having effects larger than St. John's Wort (~60% decrease) and less than pioglitazone (~30% decrease)

Dose	Predicted % ↓ in MDZ AUC	Probability of	
		≤ 30% ↓ MDZ AUC	≥ 60% ↓ MDZ AUC
2 mg	19%	76%	<1%
6 mg	51%	5%	19%
15 mg	74%	<1%	99%
25 mg	81%	<1%	>99%

Conclusions:

This communication describes a Bayesian approach to bridging some key gaps in the current status of clinical pharmacologic approaches to DDI risk assessment for CYP3A inducers, via application of contemporary model-based knowledge management approaches. 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 clinical pharmacokinetic DDI studies until after demonstration of proof-of-concept and definition of the likely clinical dose range.

References:

- [1] Lunn, D.J., Thomas, A., Best, N., and Spiegelhalter, D. (2000) WinBUGS -- a Bayesian modelling framework: concepts, structure, and extensibility. *Statistics and Computing*, **10**:325--337.
- [2] Sturtz, S., Ligges, U., and Gelman, A. (2005) [R2WinBUGS: a package for running WinBUGS from R. *Journal of Statistical Software*, **12**\(3\).](#)
- [3] Venkatakrishnan K, French JL, Okusanya O, Manganello J, Dvorak RV, Russell T, Benincosa LJ: Autoinduction via CYP3A induction in a multiple dose toleration study: Illustration of DDI risk assessment in early clinical development. Poster presentation at the 108th Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, March 21-24, 2007 held at Anaheim, CA