Citation: CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 226; doi:10.1002/psp4.12164

LETTER TO THE EDITOR

Quantitative Prediction of Drug–Drug Interactions Involving Inhibitory Metabolites by Physiologically Based Pharmacokinetic Models: Is it Worth It?

M Tod[1,2]*, S Goutelle[1,3], L Bourguignon[1,3] and N Bleyzac[2,4]

To the Editor:

We read with interest the article of Templeton *et al.*[1] on the quantitative prediction of drug-drug interactions involving metabolites.

Physiologically based pharmacokinetic modeling of interactions involving inhibitory metabolites is certainly valuable to get a deep understanding of the interaction mechanisms, to forecast time-dependent interaction kinetics, and to predict the substrate concentration profile in all compartments.

However, such a precise assessment is rarely needed from a clinical perspective. Most often, the goal is simply to predict the increase in the victim drug area under the curve (AUC) at steady state caused by the exposure to the inhibitory entity (the drug parent and its metabolites), because this is sufficient to estimate the risks associated with drug-drug interactions, guide clinical decisions, and establish prescribing information. Due to its complexity, as acknowledged by Templeton *et al.*,[1] the physiologically based pharmacokinetic procedure requires extensive validation and is sensitive to many modeling and experimental assumptions. As a result, it is time-consuming and costly.

We advocate the *in vivo* mechanistic static model (IMSM) as a valuable alternative. IMSM is based on static (i.e., steady state) equations of physiologically based pharmacokinetic models. This approach relies only on two kinds of parameters: the fraction of oral drug clearance by each cytochrome P450 involved in the elimination of the substrate (analogous to fm), and the inhibition potency (analogous to I/Ki) of the interactor toward each cytochrome P450. With the IMSM method, both parameter values are estimated solely from *in vivo* data using the AUC ratios gained in clinical studies (one study per parameter to estimate). These parameters have been calculated by our group for a wide range of substrates and interactors (see www.ddi-predictor.org). The IMSM approach has been extensively validated (see ref. 2 and the references therein). Due to its principle, IMSM can readily accommodate drug-drug interactions involving multiple species (enantiomers, metabolites of the inhibitor), because the inhibition potency reflects the action of all molecular species at the site of interaction. A few examples are shown in **Table 1**.[1,3,4] Of note, the interactions with bupropion were published in 2016, but were predicted using the parameters published by our group in 2011.[5]

The main limitations of the IMSM approach in its current form are: (i) interactions involving transporters are not described; and (ii) linear kinetics of the substrate is required. On the other hand, the IMSM approach is (i) accurate, (ii) robust, provided the main cytochrome P450s involved in the substrate metabolism are known, and (iii) fast and easy to use.

1. Templeton, I.E. *et al.* Quantitative prediction of drug-drug interactions involving inhibitory metabolites in drug development: how can physiologically based pharmacokinetic modeling help? *CPT Pharmacometrics Syst. Pharmacol.* **5**, 505–515 (2016).
2. Tod, M. *et al.* Comparison of the static in vivo approach to a physiologically based pharmacokinetic approach for metabolic drug–drug interactions prediction. *Int. J. Pharmacokinet.* **1**, 25–34 (2016).
3. Gheldiu, A.M. *et al.* Assessment of a potential pharmacokinetic interaction between nebivolol and bupropion in healthy volunteers. *Pharmacology* **98**, 190–198 (2016).
4. Todor, I. *et al.* Evaluation of a potential metabolism-mediated drug-drug interaction between atomoxetine and bupropion in healthy volunteers. *J. Pharm. Pharm. Sci.* **19**, 198–207 (2016).
5. Tod, M., Goutelle, S., Clavel-Grabit, F., Nicolas, G. & Charpiat, B. Quantitative prediction of cytochrome P450 (CYP) 2D6-mediated drug interactions. *Clin. Pharmacokinet.* **50**, 519–530 (2011).

Table 1 Predictions of the *in vivo* mechanistic static model approach

Inhibitor	Substrate	Observed AUC ratio	IMSM-predicted AUC ratio[a]	Reference substrate[b]	Reference
Sertraline	Desipramine	1.54	1.55	Nortriptyline	1
Bupropion	Nevibolol	7.2	7.4	Desipramine	3
Bupropion	Atomoxetine	5.1	5.24	Desipramine	4
Amiodarone	Warfarin	1.5	1.65	Phenytoin	1

AUC, area under the curve; IMSM, *in vivo* mechanistic static model.
[a]Obtained from www.ddi-predictor.org.
[b]Substrate used to calculate inhibitor potency.

[1]Groupement Hospitalier Nord, Hospices Civils de Lyon, Lyon, France; [2]EMR3738, Université Claude Bernard Lyon 1, Lyon, France; [3]UMR5758, Université Claude Bernard Lyon 1, Lyon, France; [4]Institut d'Hémato-Oncologie Pédiatrique, Hospices Civils de Lyon, Lyon, France. *Correspondence: M Tod (Michel.tod@chu-lyon.fr)
Received 2 November 2016; accepted 6 December 2016; published online on 16 December 2016. doi:10.1002/psp4.12164