Comparison of the static *in vivo* approach to a physiologically based pharmacokinetic approach for metabolic drug–drug interactions prediction

Background: The *in vivo* mechanistic static model (IMSM) and the physiologically based pharmacokinetic (PBPK) model are two approaches used to predict the magnitude of drug–drug interactions (DDIs). The aim of this study was to evaluate the performance of IMSM and to compare IMSM with the PBPK approach implemented in Simcyp. **Methods:** The predictive performances of IMSM were evaluated on a panel of 628 DDIs. Subsequently, the IMSM and PBPK approaches were compared on a set of 104 DDIs. **Results:** The IMSM yielded 85% of predictions within 1.5-fold of the observed value on the 628 DDIs panel. The predictive performances of IMSM were better than those of the PBPK approach (median fold error 1 vs 0.86 on 104 studies; $p = 0.02$). **Conclusion:** The IMSM approach is an alternative tool for metabolic DDIs prediction.

First draft submitted: 20th November 2015; Accepted for publication: 2nd February 2016; Published online: 4 April 2016

Keywords: cytochromes • drug–drug interaction • evaluation • mechanistic model • prediction

Pharmacokinetic drug–drug interactions (DDIs) are an important issue because they may alter the efficacy and the safety of many drugs. Among the mechanisms leading to clinically relevant DDIs, interactions on conjugation enzymes (e.g., glucuronidation [1]) are quite scarce, while metabolic interactions on cytochrome P450 (CYP) enzymes are very frequently involved. To cite just one example, the exposure to midazolam may vary 400-fold depending on whether it is associated with rifampicin (a potent inducer of CYP3A4) or itraconazole (a potent inhibitor of CYP3A4) [2]. Therefore, the health authorities require that the potential for DDIs of a drug candidate be evaluated before approval [3,4]. The magnitude of an interaction is usually expressed as the ratio of the victim drug AUC given in combination with an interacting drug (i.e., inducer or inhibitor) to the victim drug AUC given alone. Quantitative prediction of the magnitude of a DDI is useful to

identify the clinical interaction studies to be performed in drug development, and the dosing adaptation to be made in the context of drug prescription. Three main kinds of approaches for quantitative predictions of metabolic DDIs have been described. They will be presented here by historical order of appearance. The first approach rely on *in vitro* determination of the type of inhibition (competitive, noncompetitive or suicide), and measurements of the characteristics of substrates and inhibitors. Coupled with a mechanistic static interaction model (MSM), the predictive performances of this method were encouraging, approximately 80–85% of predicted exposures within twofold of *in vivo* value [5–8]. The second approach relies on the same *in vitro* data, plugged into a physiologically based pharmacokinetic (PBPK) model [9,10]. This approach, also called the mechanistic dynamic interaction model (MDM), demonstrated better predictive performances

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than the former [11]. The last approach rely on *in vivo* data only, coupled with a mechanistic static interaction model, and will be denoted *in vivo* mechanistic static model (IMSM). It was introduced by Ohno [12,13] and extended in several directions by our group [14–19]. It demonstrated good predictive performances on moderate size studies ($n = 50$ – 100) devoted to DDIs mediated by each of the main CYPs. However, to date, the IMSM approach has not been evaluated on a large panel of DDIs and has not been compared with a PBPK approach. The current study was undertaken to fill these gaps.

Methods

The prediction models

A rigorous and quite exhaustive derivation of the equations involved in the static *in vivo* approach for metabolic DDIs prediction has been presented by Hisaka *et al.* [20]. For clarity, the main equations and assumptions associated with the three approaches are summarized here. For simplicity, but without loss of generality, the victim drug is assumed to be eliminated by a single cytochrome in the liver, and also by other hepatic mechanisms (metabolism or biliary excretion), and possibly by renal route. Consideration of elimination by several CYPs would simply involve summation terms.

The fraction of elimination clearance (CL) due to cytochrome metabolism is denoted as CR (contribution ratio), defined as:

$$CR = \frac{(CL/F) - (CL_{-CYP}/F_{-CYP})}{(CL/F)}$$

where CL_{-CYP} and F_{-CYP} are the clearance and the bioavailability of the victim drug when the cytochrome activity is suppressed, for example, by mutation on both CYP alleles or complete inhibition by an inhibitor. CR may be calculated after intravenous or oral administration, and the corresponding values may differ. Note that CR is defined with respect to total clearance, not hepatic clearance.

A general equation to calculate the AUC ratio in case of metabolism inhibition, irrespective of administration route, is [21]:

$$\frac{AUC^*}{AUC} = \frac{CL/F}{CL^*/F^*} = \frac{F^*}{F} \cdot \frac{1}{\frac{CR}{1+B} + (1-CR)}$$

$$\text{where } B = \frac{I_{h,u}}{K_i}$$

is used for competitive or noncompetitive inhibition, and

$$B = \frac{k_{inact} I_{h,u}}{K_{deg} (I_{h,u} + K_i)}$$

is used for mechanism-based inhibition.

$I_{h,u}$ is the intracellular unbound concentration of the

inhibitor in the liver, K_i is an inhibition constant, k_{inact} and k_{deg} are rate constants and K_i is the concentration of inhibitor when the rate constant of inactivation reaches half k_{inact} . The superscript * denotes a parameter value when the victim and inhibitor drugs are combined. The assumptions on which these equations rely are the following:

- The metabolic pathway follows a Michaelis–Menten (MM)-type kinetics.
- The intracellular substrate concentration C_u is well below the Michaelis constant, K_m (in other words, CL is independent of substrate dose).
- The penetration of the substrate into liver cells is perfusion-limited (diffusion is rapid).
- Unbound concentrations of the substrate in liver cell water and plasma water are equal (no active transport, and bound drug does not cross membranes).
- $I_{h,u}$ is constant (approximately equal to the time-average concentration of unbound inhibitor).

Note that the AUC ratio is always lower after intravenous administration of the victim drug or the inhibitor than after oral administration, because CR and $I_{h,u}/K_i$ are lower. Hence, efforts to predict DDIs have been primarily devoted to oral administration.

In case of oral administration of the victim drug and the inhibitor:

$$\frac{AUC^*}{AUC} = \frac{fu \cdot CL_i / F_g}{fu^* \cdot CL_i^* / F_g^*} = \frac{F_g^*}{F_g} \cdot \frac{1}{\frac{CR}{1+B} + (1-CR)}$$

where CL_i is the hepatic intrinsic clearance of the victim drug, fu is the unbound drug fraction and F_g is the fraction of drug escaping from the intestine. Additional assumptions required by this equation are:

- Hepatic clearance is described by the well-stirred mode;
- Elimination clearance is equal to hepatic clearance: renal clearance is assumed to be null;
- The fraction of the substrate drug absorbed (F_a) is assumed to be constant (independent of the inhibitor);
- Substrate fu is assumed to be constant (no displacement by the inhibitor: $fu/fu^* = 1$);
- Substrate blood to plasma concentration ratio is assumed to be constant (independent of the inhibitor).

The *in vitro* approach, also known as mechanistic static model

The parameters B and CR are estimated from *in vitro* data. The value of CR is approximated by fm , the fraction of hepatic intrinsic clearance (not elimination clearance) due to the cytochrome pathway. When the renal clearance is not negligible and $F_g = F_g^*$, Hisaka [20] showed that the relationship between fm and CR is:

$$CR = \frac{fm}{1 + \frac{1}{fu \cdot CL_i \left(\frac{1}{CL_r} + \frac{1}{BPR \cdot Q_h} \right)}}$$

where CL_r is the renal clearance of the victim drug, Q_h is liver blood flow and BPR is the blood to plasma concentration ratio of the drug. When $CL_r = 0$, CR and fm are equal.

The calculation of $I_{h,u}$ to be plugged in EQUATION 2 is a matter of debate. In the US FDA guidance [4], this value is calculated as follows:

$$I_{h,u} = fu_b \cdot \left[I_{max,b} + \frac{k_a \cdot F_a \cdot F_g \cdot D}{Q_h} \right]$$

where all parameters pertain to the inhibitor. Here, the assumptions are:

- The mechanism of inhibition has been correctly identified (mechanism-based or other);
- K_i is independent of the substrate;
- B and fm have the same value *in vitro* and *in vivo*;
- The inhibitor is not metabolized, or the metabolites have no impact on the interaction;
- Penetration of the inhibitor into liver cells is perfusion-limited (diffusion is rapid);
- Unbound concentration of the inhibitor in liver cell water and plasma water are equal (no active transport, and bound drug does not cross membranes). However, a partition coefficient $K_p = I_{h,u}/I_{p,u}$ may be used if this condition is not satisfied.

The *in vivo* approach, also known as *in vivo* mechanistic static model

This approach assumes that the AUC ratio for a DDI caused by a CYP inhibitor is as follows:

$$\frac{AUC^*}{AUC} = \frac{F_g^*}{F_g} \cdot \frac{1}{1 - CR \cdot IR}$$

where IR , the inhibition ratio, is a characteristic of the inhibitor for a given CYP. By comparison with EQUATION 2, EQUATION 6 implies:

$$IR = 1 - \frac{CL^*/F^*}{CL/F} = \frac{B}{1 + B}$$

Note that IR is defined with respect to the elimination clearance, not to hepatic clearance. Assuming that $F_g^*/F_g = 1$, both CR and IR are calculated from *in vivo* data. The CR parameter may be calculated as follows:

$$CR = \frac{(AUC^*/AUC) - 1}{(AUC^*/AUC) \cdot IR}$$

using the AUC ratio of the victim drug whose CR is to be calculated, obtained with an inhibitor whose IR is known. The calculation of IR is:

$$IR = \frac{(AUC^*/AUC) - 1}{(AUC^*/AUC) \cdot CR}$$

using the AUC ratio of a victim drug whose CR is known, obtained with an inhibitor whose IR is to be calculated.

The assumptions behind these equations are:

- IR is independent of the substrate. This has been thoroughly evaluated for CYP3A4 inhibitors [19];
- IR depends on the dose (actually the concentration) of the inhibitor, because in EQUATION 7, B depends on $I_{h,u}$;
- As stated above, $fu^*/fu = 1$ and $F_g^*/F_g = 1$. The validity of the first assumption is not an issue: if fu^*/fu is not equal to 1, the calculation from EQUATION 6 yields in fact $(fu^* \cdot AUC^*)/(fu \cdot AUC)$, that is, the ratio of unbound AUCs, which is actually the measure of interest for drug-dose adjustment. The second assumption may be an issue for CYP3A4 only, because the other CYPs have negligible activity in the gut, so F_g and F_g^* are close to one. With CYP3A4, as shown earlier by simulation [20] and by studying DDIs with the rather selective inhibitor grapefruit juice [19], the lack of consideration of the variation of F_g has been shown to have little impact on the predictive performances.

The PBPK approach, also designated as mechanistic dynamic model

$I_{h,u}$ is not treated as constant, that is, the inhibitor concentration versus time (t) profile $I_{h,u}(t)$ is properly taken into account. Depending on the complexity of the PBPK model, all other assumptions may be relaxed or not.

Although the methods have been presented here in the context of inhibition, description of interactions by induction is also possible with similar concepts [12,22]. In this case, the potency of the inducer is described by a parameter named inductive capacity (IC). These methods may be extended in several directions:

- In case of a DDI involving multiple CYPs, by 'summing' the contributions of each pathway using the respective CRs, IRs and ICs (or their equivalent) [16],
- In case of CYP polymorphism, by modifying the CRs by a factor characterizing the impact of the variant genotype relative to the wild genotype [15,16],
- In case of cirrhosis, mainly by reducing the CRs by a factor depending on the severity of the disease, according to the Child–Pugh score [23].

The MSM approach has been compared with the MDM approach in a number of papers [11,24,25]. As a result, although the MSM approach works quite good, the MDM approach is generally considered to perform better. This is why we considered MDM as the gold standard, and chose to compare IMSM to MDM.

Evaluation of the IMSM predictions

The IMSM approach is currently implemented in the website www.ddi-predictor.org. The website returns predicted AUC ratios for DDIs (171 substrates, 94 inhibitors and 21 inducers) mediated by CYPs 1A2, 2D6, 2C9, 2C19 and 3A4 [14–19], allowing $171 \times (94 + 21) = 19,665$ DDIs to be predicted. Multiple interactions between two drugs, involving several CYPs or simultaneous inhibition and induction, are also accommodated. These drug interactions may also be predicted according to the genotype of the patient, in case of polymorphic CYPs (i.e., 2D6, 2C9 and 2C19) [15,17,18], and in case of cirrhosis, according to Child–Pugh severity score [23]. The website includes a database for validation purpose: predictions for a large number of substrates–interactor pairs may be compared with published data. For this article, all the published AUC ratios of the DDI database were extracted, and compared with the predicted AUC ratios, obtained by the full equation implemented in the website [16]:

$$\frac{AUC^*}{AUC} = \frac{1}{\sum_i CR_i (1 + IX_i) + (1 - \sum_i CR_i)}$$

where the summation is over all the CYPs known to be involved in the metabolism of the drug, and IX is the potency of the inhibitor or the inducer. If the interacting drug is an inhibitor for the i -th CYP, then $IX = IR$ and its value is negative. If the interacting drug is an inducer for the i -th CYP, then $IX = IC$ and its value is positive.

To allow comparison with previous publications, the same metrics of performances were used. The bias was assessed by the mean fold prediction error of the AUC ratio:

$$MFE = 10^{\frac{1}{n} \sum \left| \log_{10} \left(\frac{R_{pred}}{R_{obs}} \right) \right|}$$

where n is the number of studies and R_{pred} , R_{obs} are the predicted and observed AUC ratios, respectively.

The imprecision was assessed by the root mean-squared error:

$$RMSE = \sqrt{\frac{1}{n} \sum (R_{pred} - R_{obs})^2}$$

The proportions of predictions within twofold and 1.5-fold of the observed AUC ratio were computed.

More robust metrics of performances were also calculated: the median (MDFE) and the interquartile range (IQFE) of fold errors. The standard errors of the mean fold error and MDFE were computed by bootstrap (100 replications). The MDFEs were compared by the Wilcoxon signed-rank test.

Comparison of the IMSM & MDM predictions

Two large datasets dealing with the evaluation of the MDM approach implemented in the Simcyp Population-Based ADME Simulator (Simcyp Ltd., Sheffield, UK) have been published previously [11,25]. We extracted the observed and predicted AUC ratios from these two publications. The corresponding predictions provided by the IMSM approach were calculated using EQUATION 9 implemented in www.ddi-predictor.org. The average fold error (AFE), root mean square error, MDFE and IQFE were computed for each method.

Results

Evaluation of the IMSM predictions

The analysis of the database of published interactions in [ddi-predictor](http://ddi-predictor.org) website retrieved 628 predictions of metabolic interactions. These predictions covered 142 substrates combined with at least one of 95 interactors (18 inducers, 77 inhibitors). The plot of the predicted versus observed AUC ratios for the 628 predictions is shown in **Figure 1A**. There were 30 values (4.8%) outside the 50–200% interval around the observed value. There was no clear explanation for these discrepancies. The distribution of fold errors is shown in **Figure 1B**. The predictive performances of the MDM and IMSM approaches are presented in **Table 1**. In this table, the performances reported for the MDM approach were taken from the original publications [11,24,25], and were computed on a set of studies different from ours. Hence the results are not directly comparable. The MDFE and IQFE of IMSM were 1 and 0.27, respectively.

Comparison of the IMSM & MDM predictions

To afford a better, unbiased comparison between the IMSM and MDM approaches, a dataset allowing a

direct comparison was built, starting from Einolf's dataset [11], which originally contained 100 interaction studies. Among these, one study with mephentoin was discarded because the dose of fluvoxamine was lower than that computed in our IMSM approach. One midazolam–itraconazole study was discarded because itraconazole was stopped 4 days before midazolam administration. Fifteen other studies were discarded because they involved a single dose of an inhibitor known to have a long half-life, leading to some degree of accumulation upon repeated dosing, which can affect the IR value (IR is greater after repeated dosing than after single dose in this case). Since the IRs were calculated after repeated administration, these data were not suitable for the comparison. The remaining studies were merged with the data reported by Guest [25] for interactions between benzodiazepines and azole antifungal agents (seven studies), and recent data from the literature, allowing to add fourteen studies. Finally, 104 studies could be included in the direct comparison (Supplementary Table 1). These 104 studies involved 21 substrates and 18 inhibitors. The predictive performances of the MDM and IMSM approaches are compared in Table 2 and in Figures 2 & 3.

The MDfE (0.86 ± 0.036) was significantly different from unity for the MDM approach ($p < 0.01$), but not for the IMSM approach (1 ± 0.024). The MDfE of IMSM and MDM were significantly different ($p = 0.02$ by the Wilcoxon signed-rank test).

Discussion

In this study, two kinds of results are presented. First, the largest evaluation reported so far of the IMSM for quantitative prediction of CYP-mediated DDIs is presented. Second, this approach is compared with the MDM for quantitative prediction of the AUC ratio of DDIs in a subset of data.

Regarding the first evaluation, carried out on 628 studies, the performance metrics show that the IMSM approach works very well, at least on these examples. Arguably, the database of DDI-predictor website contains only the CYP substrate drugs and interactors that are deemed to accommodate to this approach. The IMSM approach works correctly if cytochromes are the main interaction mechanism, and the kinetics of the substrate is (at least approximately) linear. When the main mechanism of interaction is different, for example, competition on a transporter, the current IMSM approach is likely to fail. Strong interactions of this type have been described for a limited number of drugs such as statins or glinides when coadministered with cyclosporin [26,27]. Other examples of interactions with a complex mechanism

that were successfully described by a PBPK model are repaglinide–gemfibrozil [28], repaglinide–rifampicin [29], interactions with amiodarone and its active metabolite [30], and midazolam–AZD2327 [31]. Apart from this issue, the IMSM approach is robust, in the sense that it is not fooled by erroneous *in vitro* data (which are not used) or by complexities such as metabolites with inhibiting properties. There are examples of important discrepancies between *in vitro* and *in vivo* data on drug interactions. Diclofenac has been presented as a substrate metabolized primarily by CYP2C9, based on *in vitro* data. Yet, *in vivo*, mutations on CYP2C9 that are known to impair this enzyme do not increase the exposure to diclofenac, showing that CYP2C9 is a minor pathway for diclofenac elimination [32]. Montelukast has been presented as a strong inhibitor of CYP2C8 *in vitro* that should

Figure 1. Evaluation of the *in vivo* mechanistic static model approach based on 628 published interaction studies. (A) Predicted versus observed AUC ratios. The line is the $y = x$ line. The dashed lines represent the 50–200% interval. Values above $x = 1$ represent drug–drug interactions (DDIs) by inhibition. Values below $x = 1$ represents DDIs by induction. (B) Histogram of the fold errors (= predicted/observed AUC ratio). The vertical line at $x = 1$ represents the ideal value (no prediction bias).

Table 1. Predictive performances of the mechanistic dynamic model (published data) and <i>in vivo</i> mechanistic static model approaches.					
	Number and percentage of predictions within twofold of observed AUC ratio	Number and percentage of predictions within 1.5-fold of observed AUC ratio	MFE	RMSE	Ref.
IMSM (n = 628)	598 (95%)	534 (85%)	1.22	5.65 1.48*	Own data
MDM (n = 100)	75 (75%)	Not reported	1.67	4.34	[11]
MDM (n = 59) for DDIs with observed R > 2	38 (64%)	Not reported	1.91	5.55	[11]
MDM (n = 35)	25 (71%)	15 (43%)	1.68	3.81	[25]
MDM (n = 48)*	43 (90%)	Not reported	1.47	3.03	[24]
*Performance with three values excluded: melatonin–fluvoxamine, ramelteon–fluvoxamine × 2. *The victim drug was midazolam in all 48 cases. DDI: Drug–drug interaction; IMSM: <i>In vivo</i> mechanistic static model; MDM: Mechanistic dynamic model; MFE: Mean fold error; R: AUC ratio; RMSE: Root mean square error. The set of studies are different.					

be relevant *in vivo*, even after accounting for its high protein binding. Yet, it has shown no inhibiting properties *in vivo* [33]. Paroxetine is known to be an inhibitor of CYP2D6. Yet, the predicted AUC ratios from *in vitro* data are largely underpredicted if microsomal binding and mechanism-based inhibition are not taken into account [34]. Examples of inhibitors with stronger inhibiting properties *in vivo* than *in vitro* due to metabolites are bupropion toward CYP2D6 [35] and gemfibrozil toward CYP2C8 [36]. In these situations, the IMSM approach works better because it relies only on *in vivo* data to establish the CRs and IRs, and it requires only minimal assumptions about the mechanism of the interaction (the type of inhibition is not a strong determinant).

The choice of the performance metrics merits discussion. Classification of an AUC ratio prediction as ‘good’ when it falls within 1.5- or 2-fold around the observed value may be considered as very indulgent. This criterion has been used traditionally to evaluate PBPK models, especially in the context of interspecies scaling. But the criterion for bioequivalence is much more stringent (1.25-fold) and is used as an initial cut-off value to decide if a potential DDI deserves a clinical trial [4]. On the other hand, it may be a nonsense to desire a high accuracy of any prediction method of the mean AUC ratios. Indeed, the between-study variability of the AUC ratio for a given substrate–inhibitor pair is very large. For example, eight studies reported the interaction between midazolam and ketoconazole

Table 2. Predictive performances of the mechanistic dynamic model and <i>in vivo</i> mechanistic static model approaches on the same dataset.				
	Number and percentage of predictions within twofold of observed AUC ratio	Number and percentage of predictions within 1.5-fold of observed AUC ratio	MFE (SE)/MDFE (SE)	RMSE/IQFE
All DDIs (n = 104)				
IMSM	90 (87%)	70 (67%)	1.27 (0.034)/1 (0.024)	1.75/0.40
MDM	82 (79%)*	51 (49%)*	1.62 (0.092)/0.86 (0.036)	3.40/0.52 3.02 [§] / 0.52
DDIs with observed AUC ratio >2 (n = 59)				
IMSM			1.30/1	2.28/0.48
MDM			1.85/0.71	4.35/0.44 3.83 [§] /0.44
*Comparison with MSM: p = 0.14 (chi-square test). *Comparison with MSM: p = 0.008 (chi-square test). [§] Excluding one value (the midazolam–verapamil interaction). DDI: Drug–drug interaction; IMSM: <i>In vivo</i> mechanistic static model; IQFE: Interquartile fold error; MDFE: Median fold error; MDM: Mechanistic dynamic model; MFE: Mean fold error; RMSE: Root mean square error; SE: Standard error.				

(summarized in [25]). The AUC ratio ranged from 5 to 16. Even after accounting for the differences in ketoconazole dose (200 or 400 mg) or interval between midazolam and ketoconazole intake, the variability of the AUC ratio between studies remains large. The typical standard deviation of an AUC ratio of 1, 10 or 20 was estimated to 1, 3.16 or 4.5, respectively, in our former study [19].

Regarding the second evaluation (the comparison with the MDM approach), the IMSM provided performances similar if not better than those of the PBPK approach. This result raises questions about the position of the PBPK approach as the gold standard for predicting DDIs, if the goal is mainly to estimate the AUC ratio. Of course, the IMSM approach is limited to this aspect, whereas the PBPK approach yields more information, such as the concentration profile of the victim drug in blood and tissues. Depending on the goal of the analysis, prediction of the AUC ratio may be sufficient or not. In the context of drug prescription (by a physician) or prescription analysis (by a pharmacist), the AUC ratio is enough to take decisions such as adapting the dose or choosing another drug with less interaction potential. In the context of a clinical trial, the AUC ratio may also be enough to decide which comedications are allowed or not during the trial. In the context of drug development of a new chemical entity, the AUC ratio may also be enough to decide which DDI studies have to be undertaken (see below). The PBPK approach is valuable when the mechanism of interaction is not restricted to the CYPs, or when there are several active metabolites of interest, or when assessment of the interaction into a certain tissue (e.g., brain) is essential for drug action or toxicity. To facilitate the modeling of active transport processes, an approach based on tissue-specific mRNA expression data has been described and is currently available in the PBPK software PKSim [37]. Another advantage of the PBPK approach is that the distribution of the AUC ratio may be obtained by population simulation, although the results of this kind of simulation must be regarded with caution because it is correct only if the statistical model is correct. The issue is how to account properly for the correlations between the physiological or pharmacokinetic parameters of the PBPK model. Ignoring the correlations may lead to overestimate interindividual variability.

The PBPK approach is able to cope with a wide range of conditions regarding the prediction of DDIs. Factors of variability such as CYP polymorphisms and cirrhosis may also be incorporated in the IMSM approach [15,16,23]. In the DDI-predictor website, both are accommodated. Quantitative prediction of DDIs in neonates can be done by incorporating the

maturation functions of the CYPs [38] into the model. Currently, this possibility has not been implemented in the IMSM approach because there is a paucity of published data to evaluate the model.

The reasons for the quite disappointing performances of the PBPK approach needs discussion. On the one hand, the PBPK approach relies on a strong

Figure 2. Comparison of the mechanistic dynamic model and *in vivo* mechanistic static model approaches on 104 interaction studies. (A) Predicted versus observed AUC ratio with MDM. **(B)** Predicted versus observed AUC ratio with IMSM. **(C)** MDM-predicted versus IMSM-predicted AUC ratio. The line is the $y = x$ line. IMSM: *in vivo* mechanistic static model; MDM: Mechanistic dynamic model.

Figure 3. Histogram of the fold errors (= predicted/observed AUC ratio) for the comparison of mechanistic dynamic model and *in vivo* mechanistic static model approaches on 104 studies.

The vertical line at $x = 1$ represents the ideal value (no prediction bias).

IMSM: *in vivo* mechanistic static model;

MDM: Mechanistic dynamic model.

scientific background because it combines physiology, pharmacokinetics and mathematics in a comprehensive way. As such, it is a powerful framework, expected to yield accurate predictions. On the other hand, obviously, the success of the PBPK approach depends heavily on the correct specification of most parts of the model. If important pharmacokinetic processes are not taken into account in the model (such as active transport), or some parameters that are erroneous (such as a K_i), the predictions may be inaccurate. Hence it may be argued that the performances of the PBPK approach might have been better if the model had been refined for each example considered. The issue of poor prediction with the PBPK approach is not new. Prediction of the PK of a single drug (i.e., not in the context of DDI) from *in vitro* data with a PBPK model was shown to be inaccurate in many instances [39–41]. The problem is usually solved either by fitting the PBPK model to the clinical data to estimate some parameters [42] or by incorporating scaling factors from animal experiments into the model [39,40]. Although these approaches work quite well: first, they introduce an empirical adjustment, which is in contradiction with the philosophy of the PBPK model; second, they question the ability of the PBPK approach to make quantitative predictions solely from *in vitro* data.

Owing to its good predictive performances, we suggest that the IMSM approach could be used in the context of drug development during the Phase I

of clinical trials. Assume, for example, that *in vitro* studies have shown that the drug candidate is a substrate of CYP3A4 with a high f_m , and an inhibitor of CYP2D6 with low K_i . Then, two prototype clinical DDI studies have to be carried out: one with a strong inhibitor of CYP3A4 (e.g., ketoconazole) and another with a sensitive substrate of CYP2D6 (e.g., dextromethorphan). Since the IR_{3A4} of ketoconazole and the CR_{2D6} of dextromethorphan are already known from previous data, the CR_{3A4} and the IR_{2D6} of the drug candidate can be calculated after completion of these studies by using EQUATIONS 8 and 9. Thereafter, the AUC ratio of drug interactions with all potential CYP3A4 inhibitors and CYP2D6 substrates included in the DDI-predictor website may be obtained by using EQUATION 6. The computation procedure is very quick, easy and inexpensive. Then, depending on the intended use of the drug candidate and its safety margin, confirmatory studies with selected substrates or inhibitors could be undertaken. As a result, implementation of the IMSM approach could accelerate the assessment of the DDI profile of drug candidate during drug development.

Finally, in the context of drug prescription, the IMSM approach can be useful for anticipating DDIs. This may help to select a drug combination less at risk of strong interaction, or to adjust the dose of substrates with narrow safety margin. Many interactions predicted as strong (AUC ratio >5) have not been studied experimentally [12–14,17,18].

Conclusion

The *in vivo* approach coupled with a mechanistic static model (IMSM) has confirmed his good predictive performances on a large panel of 628 DDIs, with 85% of predictions within 1.5-fold of the observed value. This approach compared also favourably with the PBPK approach implemented in Simcyp, on a panel of 104 interaction studies. The IMSM approach is a valuable, inexpensive and simple alternative for the prediction of metabolic interactions mediated by cytochromes. It may be of interest for in both drug development and management of DDIs in clinical practice.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- The magnitude of a pharmacokinetic interaction is usually expressed as the ratio of the victim drug AUC given in combination with an interacting drug (i.e., inducer or inhibitor) to the victim drug AUC given alone.
- Quantitative prediction of the magnitude of a drug–drug interaction (DDI) is useful to identify the clinical interaction studies to be performed during drug development, and the dosing adaptation to be made in the context of drug prescription.
- The prediction models. Two approaches for quantitative prediction of DDIs mediated by inhibition or induction of cytochromes are the mechanistic dynamic interaction model (MDM) based on *in vitro* data plugged into a physiologically based pharmacokinetic model, and the mechanistic static interaction model based on *in vivo* data (IMSM).
- Evaluation of the IMSM predictions. The predictive performances of IMSM (implemented in www.ddi-predictor.org) were evaluated on a panel of 628 DDIs. The IMSM yielded 85% of predictions within 1.5-fold of the observed value. The IMSM approach works correctly if cytochromes are the main interaction mechanism, and the kinetics of the substrate is (at least approximately) linear.
- Comparison of the IMSM and MDM predictions. The predictive performances of IMSM and MDM (implemented in Simcyp software) were compared on a set of 104 DDIs. The predictive performances of IMSM were better than those of MDM: median fold error 1 versus 0.86 on 104 studies, $p = 0.02$, interquartile fold error 0.40 versus 0.52.
- The IMSM approach is a quick, inexpensive and simple alternative for the prediction of metabolic interactions mediated by cytochromes. It may be of interest for in both drug development and management of DDIs in clinical practice.
- The MDM approach remains the best approach for the prediction of DDIs involving transporters, provided that the PBPK model is correctly specified.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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