Research Article

Impact of Genetic Polymorphism on Drug-Drug Interactions Mediated by Cytochromes: A General Approach

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Abstract. Currently, quantitative prediction of the impact of genetic polymorphism and drug-drug interactions mediated by cytochromes, based on *in vivo* data, is made by two separate methods and restricted to a single cytochrome. We propose a unified approach for describing the combined impact of drug-drug interactions and genetic polymorphism on drug exposure. It relies on *in vivo* data and uses the following three characteristic parameters: one for the victim drug, one for the interacting drug, and another for the genotype. These parameters are known for a wide range of drugs and genotypes. The metrics of interest are the ratio of victim drug area under the curve (AUC) in patients with genetic variants taking both drugs, to the AUC in patients with either variant or wild-type genotype taking the victim drug alone. The approach was evaluated by external validation, comparing predicted and observed AUC ratios found in the literature. Data were found for 22 substrates, 30 interacting drugs, and 38 substrate-interacting drug couples. The mean prediction error of AUC ratios was 0.02, and the mean prediction absolute error was 0.38 and 1.34, respectively. The model may be used to predict the variations in exposure resulting from a number of drug-drug-genotype combinations. The proposed approach will help (1) to identify comedICATIONS and population at risk, (2) to adapt dosing regimens, and (3) to prioritize the clinical pharmacokinetic studies to be done.

KEY WORDS: cytochromes; drug interactions; genetic polymorphism; quantitative prediction.

Pharmacokinetic drug-drug interactions may increase or decrease drug exposure, thereby compromising their efficacy or safety. Predicting drug-drug interactions is considered as important by regulatory agencies and drug development organizations worldwide (1). In order to reduce the cost and duration of experimental studies, *in silico* modeling of drug interactions based on *in vitro* experiments has been advocated (1). Another approach for quantitative prediction, based on *in vivo* data, has been proposed and validated for CYP3A4 substrates by Ohno (2,3). This approach avoids a number of pitfalls associated with *in vitro*–*in vivo* extrapolation, such as complex enzyme kinetics, interference with metabolites or enantiomers, estimation of intracellular inhibitor concentration, etc. We extended Ohno's approach to CYP2D6, 2C9, and 2C19 substrates, demonstrating its wide applicability (4–7). Here, we

address the problem of predicting interactions mediated by multiple cytochromes between two drugs given by oral route, and its interplay with genetic polymorphism, which may alter the profile and severity of drug interactions. A number of case reports of fatal or near-fatal drug-drug interactions associated with cytochrome polymorphism point to the clinical relevance of this issue (e.g., 8–11). Physiologically-based pharmacokinetic approaches have been developed for the quantitative prediction of drug-drug interactions, and these models could be tailored for complex interactions (12–14). But to the best of our knowledge, there is no simple general theory or model for quantitative prediction of multiple interactions as a function of genotype.

In this article, we derive two equations that characterize the impact of genetics and multiple CYP enzymes on the magnitude of a drug interaction. The goals of our study were to assess the method by external validation against published AUC ratios of drug-drug interactions involving multiple enzymes, several drugs, and various genotypes and to deduce from the model some general rules regarding the interaction at risk as a function of genotype.

METHODS

Presentation of the Equations

To characterize such interactions, we define (1) AUC^{XM} as the AUC of the substrate in patients with genetically variant alleles; XM may refer to poor, intermediate, or ultra-

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metabolizers (PM, IM, or UM, respectively), (2) AUC^{XM*} as the AUC of the substrate when an inhibitor or an inducer is coadministered, (3) AUC^{EM} as the AUC of the drug administered alone at the same dose in patients with

wild-type genotype, by convention typically the extensive metabolizer (EM). Assuming that the interaction is mediated by two cytochromes, we calculate the following AUC ratios:

$$\frac{AUC^{XM*}}{AUC^{EM}} = \frac{CR_1 * FA_1 + CR_2 * FA_2 + (1 - CR_1 - CR_2)}{CR_1 * FA_1 * (1 + IX_1) + CR_2 * FA_2 * (1 + IX_2) + (1 - CR_1 - CR_2)} \quad (1)$$

$$\frac{AUC^{XM*}}{AUC^{EM}} = \frac{1}{CR_1 * FA_1 * (1 + IX_1) + CR_2 * FA_2 * (1 + IX_2) + (1 - CR_1 - CR_2)} \quad (2)$$

Where CR, the contribution ratio, is the fraction of drug's apparent clearance due to metabolism by a given CYP; FA, the fractional activity, is the fraction of activity of the CYP resulting from the impact of a genetic variation, relative to the activity of the reference genotype; IX is the potency of the inhibitor or the inducer. Each CR, and the sum of CRs, must be less than or equal to 1. The reference value of FA in EM individuals who are homozygote wild-type is equal to 1. FA is <1 in IMs and PMs and >1 in UMs. If the interacting drug is an inhibitor, IX is negative and ranges from 0 (no inhibition) to -1 (complete inhibition). If the interacting drug is an inducer, IX is positive and ranges from 0 (no induction) to infinity. IX was previously denoted as IR for inhibitors and IC for inducers in former publications (2–7), but a modification was required to afford a greater level of generality of the approach. These formulas may easily be extended to the case of more than two cytochromes. The model allows the prediction of the mean DDI effect of genomic and CYP enzyme metabolism data arising from various drug combinations used in patients with various genotypes.

Derivation of the Equations

The metabolic clearance of the victim drug is assumed to be close to total clearance. Metabolism is assumed to occur for a small part in the gut wall (with gastrointestinal availability F_g) and for the main part in the liver (with hepatic availability F_h). Metabolism occurs by two cytochromes denoted 1 and 2, and possibly by other pathways. Then, under the well-stirred clearance model, the oral clearance is as follows:

$$CL_{oral} = CL / (F_g \cdot F_h) = fu \cdot CL_i / F_g \quad (3)$$

Where fu is the unbound fraction of drug in the blood, and CL_i is the intrinsic clearance in the liver. If the cytochromes are altered, either by genetic variation or drug-drug interaction, the oral clearance of the victim drug becomes (XM may be PM, IM, or UM, and * denotes

coadministration with an interacting drug):

$$CL_{oral}^{XM*} = fu \cdot CL_i^{XM*} / F_g^{XM*} \quad (4)$$

The ratio of victim drug AUC coadministered with an interacting drug in a CYP-variant individual to that of victim drug given alone in a wild-type individual is therefore:

$$\frac{AUC^{XM*}}{AUC^{EM}} = \frac{CL_{oral}^{EM}}{CL_{oral}^{XM*}} \cdot \frac{F_g^{XM*}}{F_g^{EM}} \cdot \frac{CL_i^{EM}}{CL_i^{XM*}} \quad (5)$$

As shown by Hisaka (15), the improvement of predictive performance obtained by considering the ratio F_g^*/F_g is small, provided that F_g is less than 0.6, and that the inhibition of intestinal and hepatic cytochromes are at least moderately correlated ($r=0.6$). Hence, we made a simplifying assertion that this ratio is close to 1 and remove it from the equation. The external validation shows that this assumption is a reasonable simplification.

Assuming minimal or no interdependence between the metabolic pathways, the intrinsic clearance in an EM individual may be decomposed as the sum of three terms:

$$CL_i^{EM} = CR_1^{EM} \cdot CL_i^{EM} + CR_2^{EM} \cdot CL_i^{EM} + (1 - CR_1^{EM} - CR_2^{EM}) \cdot CL_i^{EM} \quad (6)$$

The intrinsic clearance of the victim drug administered alone in a CYP-variant individual is as follows:

$$CL_i^{XM} = CR_1^{EM} \cdot FA_1 \cdot CL_i^{EM} + CR_2^{EM} \cdot FA_2 \cdot CL_i^{EM} + (1 - CR_1^{EM} - CR_2^{EM}) \cdot CL_i^{EM} \quad (7)$$

Where FA is a positive number, lower than 1 in IMs and PMs, greater than 1 in UMs. FA is assumed to be the same for all substrates of a given CYP. FA characterizes the CYP activity of

a given genotype and depends only on the allele combination. Each allele is assumed to contribute to the overall CYP activity, independent of the other alleles. Therefore, if there are m categories of alleles and n_i alleles in each category,

$$FA = \frac{1}{2} \sum_{i=1}^m n_i \cdot FAA_i \quad (8)$$

Where FAA_i is the fraction of activity of the variant CYP allele relative to the wild-type CYP allele.

The intrinsic clearance of the victim drug coadministered with an interacting drug in a CYP-variant individual is as follows:

$$\begin{aligned} CL_i^{XM*} = & CR_1^{EM} \cdot FA_1 \cdot (1 + IX_1) \cdot CL_i^{EM} \\ & + CR_2^{EM} \cdot FA_2 \cdot (1 + IX_2) \cdot CL_i^{EM} \\ & + (1 - CR_1^{EM} - CR_2^{EM}) \cdot CL_i^{EM} \end{aligned} \quad (9)$$

Where IX is the potency of the interacting drug. IX is negative for an inhibitor and varies between zero (no inhibition) to -1 (complete inhibition). IX is positive for an inducer, with no upper limit. These equations assume linear kinetics, i.e., the concentration of victim drug is low compared with its K_m for each cytochrome, and its clearance is independent of dose and time. Inhibition may occur by competitive, noncompetitive, or mechanism-based inhibition, as discussed by Ohno (2).

The ratio of AUC^{XM*} to AUC^{XM} is as follows:

$$\frac{AUC^{XM*}}{AUC^{XM}} = \frac{CL_i^{XM*}}{CL_i^{XM}} \quad (10)$$

Leading to Eq. 1 described above. The ratio of AUC^{XM*} to AUC^{EM} is as follows:

$$\frac{AUC^{XM*}}{AUC^{EM}} = \frac{CL_i^{EM}}{CL_i^{XM*}} = \frac{CR_1^{EM} + CR_2^{EM} + (1 - CR_1^{EM} - CR_2^{EM})}{CR_1^{EM} \cdot FA_1 \cdot (1 + IX_1) + CR_2^{EM} \cdot FA_2 \cdot (1 + IX_2) + (1 - CR_1^{EM} - CR_2^{EM})} \quad (11)$$

Which may be simplified to Eq. 2 presented above.

Data for External Validation

A bibliographic search on MEDLINE from January 1966 to December 2012 was carried out to identify available datasets of drug-drug interactions in humans with CYP2D6, 2C9, or 2C19 polymorphisms. Keywords used were “pharmacogenetics,” “genotype,” “cytochrome P450,” “pharmacokinetics,” “drug interaction,” “metabolic ratio,” “polymorphism,” “allele,” and “metabolism.” No language restrictions were applied. In MEDLINE, we used a species filter to limit the search to “human.” Major reviews on pharmacogenetics and drug-metabolizing enzymes were also systematically searched in MEDLINE. Cross-references and quoted papers were checked in order to update the primary reference list.

The parameters (CRs, FAs, and IXs) were mainly taken from previous publications (2–7). These values had been validated by external validation. Additional values were calculated using references described in Tables I and II, by solving Eqs. 1 or 2 for either CR, FA, or IX knowing all other parameters.

The AUC ratios, used for estimation or validation, were calculated using the median AUCs as a point estimate. When medians were not available, mean AUCs were used. Neither the interindividual variability of the AUC ratios nor the precision of AUC ratio point estimate, which are often not reported and not computable with the reported data, were taken into account.

Evaluation Criteria

The AUC ratios predicted by Eqs. 1 and 2 were compared with the observed values found in the literature.

The validation consisted of visual examination of the plot of predicted *versus* observed AUC ratios. Predicted values in the range 50–200% of the observed ratio were considered acceptable. The bias of AUC ratio prediction was evaluated in terms of the mean prediction error, which is the predicted value minus the observed value. The imprecision of the prediction was assessed in terms of the mean absolute prediction error.

RESULTS

The primary goal of the analysis was to evaluate the above equations by external validation. The available data, found by a search of the literature, are summarized in Tables I, II, III, and IV. Data were gathered for 22 substrates, 30 interacting drugs, and 38 substrate-interacting drug couples. Due to the multiple genotypes studied, 80 AUC^{XM*}/AUC^{XM} ratios and 72 AUC^{XM*}/AUC^{EM} ratios were available for the external validation.

The relationship between the predicted and observed AUC^{XM*}/AUC^{XM} ratios is plotted in Fig. 1, based on the data of Table IV. The mean prediction error was 0.02 and the mean absolute prediction error was 0.38. A single point, corresponding to the voriconazole–ritonavir interaction, was outside the acceptable prediction range. The interaction was overestimated fourfold (observed ratio = 0.04, predicted ratio = 0.16). Considering the known properties of voriconazole (64,65), this overestimation is probably due to nonlinear kinetics of voriconazole in the usual dosing range.

The relationship between the predicted and observed AUC^{XM*}/AUC^{EM} ratios is plotted in Fig. 2, based on the data of Table IV. The mean prediction error was 0.02 and the mean absolute prediction error was 1.24. Five points were outside the acceptable prediction range; four of which were

Table I. Contribution Ratio (CR) of the Victim Drugs for Each Pathway

Victim drug	Pathway #1	CR ₁	Pathway #2	CR ₂	Reference
Amitriptyline	2D6	0.53	2C19	0.28	(5,6)
Aripiprazole	2D6	0.34	3A4	0.41	(5,16)
Diazepam	2C19	0.64 ^a	3A4	0.10	(17–20)
Flecainide RS, R, S	2D6	0.12	–	–	(5)
Flurbiprofen	2C9	0.93	–	–	(7)
Gliclazide	2C9	0.24	2C19	0.76	(6,7)
Haloperidol	2D6	0.50	3A4	0.30	(21,22)
Lansoprazole S	2C19	0.86	3A4	0.14	(6)
Losartan	2C9	0.40	–	–	(7)
Metoprolol	2D6	0.75	3A4	0.22	(5)
Metoprolol R	2D6	0.80	3A4	0.20	(5)
Metoprolol S	2D6	0.71	3A4	0.25	(5)
Mirtazepine	2D6	0.17	3A4	0.83	(23)
Moclobemide	2C19	0.71	–	–	(6)
Omeprazole	2C19	0.84	3A4	0.16	(6)
Oxycodone	2D6	0.20	3A4	0.54	(24,25)
Quetiapine	2D6	0.15	3A4	0.85	(26)
Rabeprazole	2C19	0.72	–	–	(6)
Risperidone	2D6	0.75	3A4	0.25	(5)
Voriconazole	2C19	0.68	3A4	0.31	(6)

^a Mean of three estimates based on ref (17–19)

borderline. The ratio for the omeprazole–clopidogrel interaction in CYP2C19*2*2 patients was overestimated 2.95-fold (observed ratio = 2.08, predicted ratio = 6.13).

The impact of the genotype on the magnitude of drug-drug interactions is illustrated by Fig. 3 for the metoprolol–terbinafine and metoprolol–itraconazole interactions.

Table II. Inhibition or Induction Potency of Interacting Drugs with Respect to Each CYP

Interacting drug	Pathway #1	IX ₁	Pathway #2	IX ₂	References
Amiodarone 1,200 mg/day	2D6	–0.60	3A4	–0.42	(27,28)
Cimetidine 1,600 mg/day	2D6	–0.20	3A4	–0.44	(2,4)
Clarithromycin 800 mg/day	3A4	–0.50	2C19	–0.88	(2,29)
Clopidogrel 75 mg/day	2C19	–0.28	–	–	(6)
Diltiazem 200 mg/day	3A4	–0.80	–	–	(2)
Diphenhydramine 150 mg/day	2D6	–0.62	–	–	(4)
Dronedarone 1,600 mg/day	2D6	–0.50	–	–	(4)
Dronedarone 800 mg/day	2D6	–0.26	–	–	(4)
Erythromycin 1.5 g/day	3A4	–0.82	–	–	(2)
Fluconazole 200 mg	2C9	–0.56	–	–	(7)
Fluconazole 400 mg	2C9	–0.65	–	–	(7)
Fluconazole 400 mg/day	2C19	–0.78	3A4	–0.79	(7)
Fluoxetine 20–60 mg/day	2D6	–0.93	3A4	–0.28	(4,30)
Fluoxetine 20 mg/day	2D6	–0.93	2C19	–0.44	(4,6)
Fluvoxamine 50 mg/day	2C19	–0.98	3A4	–0.30	(2,6)
Itraconazole 100–200 mg/day	3A4	–0.95	–	–	(2)
Ketoconazole 200–400 mg	3A4	–0.95	–	–	(2)
St. John Wort 900 mg/day	2C19	0.71	3A4	1.20	(3,31)
Moclobemide 300 mg	2C19	–0.62	–	–	(6)
Omeprazole 40 mg/day	2C19	–0.43	–	–	(6)
Paroxetine 20 mg/day	2D6	–1.00	–	–	(4)
Phenytoin 300 mg/day	2C9	–0.68	–	–	(7)
Phenytoin 300 mg/day	2C19	1.06	3A4	4.70	(3,32)
Quinidine 100–200 mg/day	2D6	–1.00	–	–	(4)
Rifampicin 600 mg/day	2C9	1.22	2C19	4.20	(33)
Rifampicin 600 mg/day	2C19	4.20	3A4	7.70	(3,33)
Ritonavir 600 mg/day 2 days	3A4	–0.95	–	–	(34)
Ritonavir 800 mg/day	2C19	8.17	3A4	–0.96	(35,36)
Voriconazole 800 mg/day	2C19	–0.64	3A4	–0.98	(2,6)

Table III. Estimates of the Fractional Activities of Various *CYP2D6*, *CYP2C9*, and *CYP2C19* Allele Combinations (References 5–7)

CYP2D6		CYP2C9		CYP2C19	
Genotype	FA	Genotype	FA	Genotype	FA
*1–2*3–8	0.47	*1*2	0.82	*1*2	0.30
*3–8*3–8	0.01	*2*2	0.70	*2*2	0.005
*1–2*10	0.54	*1*3	0.56	*1*17	1.59
*10*10	0.10	*3*3	0.13	*2*17	0.80
*1×3	1.67	*2*3	0.39	*17*17	2.03

Metoprolol is metabolized by cytochromes 2D6 and 3A4, but only CYP2D6 is polymorphic. Terbinafine and itraconazole are strong inhibitors of CYP2D6 and 3A4, respectively. In a patient under treatment by metoprolol, the introduction of terbinafine increases metoprolol exposure by a factor of 1.02 in PMs to 4.2 in UMs, as shown by the AUC^{XM*}/AUC^{XM} ratios. The order of variation is the opposite when itraconazole is added to metoprolol treatment; metoprolol exposure is increased by a factor of 8.9 in PMs to 1.2 in UMs. Hence, the profile of interactions changes with CYP2D6 genotype; interactions at risk are metoprolol–terbinafine in UMs and metoprolol–itraconazole in PMs. Compared to metoprolol exposure afforded in an EM patient treated by metoprolol alone, the association metoprolol–terbinafine yields a 2.8 (UM) to 3.8-fold (PM) higher exposure, as shown by the AUC^{XM*}/AUC^{EM} ratios. With itraconazole, the corresponding figures are 0.8 (UM) to 33-fold (PM).

DISCUSSION

In this study, a unified approach for describing the combined impact of drug-drug interactions and genetic polymorphism on drug exposure was proposed and evaluated by external validation for a wide range of substrates, interacting drugs, and genotypes. In the previous publications on this approach, the interaction was assumed to involve a single cytochrome (2–4,7); the impact of cytochrome polymorphism was not considered in the context of drug-drug interaction (5), or it was restricted to a single cytochrome, and only inhibition was considered (7). By contrast, the present model solves three problems which were unresolved in context of this approach, namely (1) interactions on multiple pathways, (2) simultaneous genetic variations in multiple pathways, as well as (3) mixed interactions such as simultaneous induction and inhibition, which may occur with ritonavir or phenytoin for example.

Two metrics were used to characterize these interactions. The ratio AUC^{XM*}/AUC^{XM} is useful for adapting the dose of the substrate in a patient in whom the treatment was well equilibrated, but an interacting drug is added to the current treatment. On the other hand, the ratio AUC^{XM*}/AUC^{EM} is useful for adapting the initial dose of the substrate to be given to a patient whose genotype is known. Estimating the dose to be given is very simple in most cases.

$$\text{Adjusted dose} = (\text{Current or usual dose})/(\text{AUC ratio}) \quad (12)$$

For prodrugs (such as codeine, clopidogrel, and losartan), the formula becomes:

$$\text{Adjusted dose} = (\text{Current or usual dose}) * (\text{AUC ratio}) \quad (13)$$

However, the decision to adjust the dose depends obviously on additional considerations, such as the therapeutic index of the victim drug (the dose will be adjusted only if the variation of AUC is considered clinically important), and/or the victim drug cannot be replaced by another suitable treatment.

As illustrated by the metoprolol examples (Fig. 3), the interplay between drug-drug interactions and genetic polymorphism depends on the pathway impacted by the interacting drug, but also on the reference exposure considered. If the reference is to a specific individual patient, then the reference exposure is AUC^{XM} . If the reference is the homozygous wild-type population, then the reference exposure is AUC^{EM} . When the reference is the patient, the basic principle is that the higher the contribution of a CYP in the elimination of a drug, the stronger the interaction may be. Hence, an UM for CYP2D6 taking a drug metabolized by several CYPs including 2D6 is prone to stronger interactions by CYP2D6 inhibitors than patients carrying one of the other CYP2D6 genotypes, e.g., EMs, IMs, or PMs, but to weaker interactions with drugs interacting with the remaining CYPs. Conversely, a PM for CYP2D6 taking a drug metabolized by several CYPs including 2D6 is prone to weaker interactions by CYP2D6 inhibitors than EMs, IMs, or PMs, but to stronger interactions with drugs interacting with the remaining CYPs. When the reference is the homozygous wild-type population, it is useful to consider the relationship $AUC^{XM*}/AUC^{EM} = (AUC^{XM*}/AUC^{XM}) \times (AUC^{XM}/AUC^{EM})$. It shows that the AUC ratio is the product of two terms; the first describing the impact of the interaction in the variant individual, the second the impact of the genetic variation on the exposure to the victim drug. This second term may be greater or lower than one, thereby enhancing or reducing the impact of the interaction.

This work illustrates that the profile of interactions at risk for a given substrate depend on the genotype of the major cytochrome involved in its metabolism. The risk is especially high for substrates of two CYPs where the main cytochrome changes according to the genotype. Such drugs include amitriptyline, diazepam, glimepiride, haloperidol, metoprolol, and voriconazole.

To date, the CRs have been estimated for 21, 40, 26, and 25 drugs metabolized by CYP3A4, CYP2D6, CYP2C9, and

Table IV. Data Used in the External Validation

Victim drug	Inhibitor or inducer	Pathway	Genotype	AUC ^{XM*} / AUC ^{XM} observed	AUC ^{XM*} / AUC ^{XM} predicted	AUC ^{XM*} / AUC ^{EM} observed	AUC ^{XM*} / AUC ^{EM} predicted	Ref
Amitriptyline	Fluoxetine 20 mg/day	2D6	EM	2	2.57	–	–	(37)
Aripiprazole	Itraconazole 100 mg/day	2D6	*1*1	1.28	1.63	1.28	1.63	(38)
			*1*10	1.39	1.86	1.7	2.20	
			*1*5	1.72	1.91	1.81	2.32	
			*10*10	1.89	2.28	2.66	3.28	
			*2*10	1.54	1.86	1.87	2.20	
Aripiprazole	Paroxetine 20 mg/day	2D6	EM	2.4	1.52	2.4	1.52	(39)
			IM	1.3	1.24	2.93	1.52	
Aripiprazole	Fluvoxamine 50 mg/day	2D6	EM	1.63	1.14	1.63	1.14	(39)
			IM	1.65	1.18	2.71	1.44	
Diazepam	Diltiazem 200 mg/day	2C19	EM 30% IM 70%	1.24	1.13	1.24	1.64	(40)
			PM	1.25	1.28	1.79	3.53	
Diazepam	Fluconazole 400 mg/day	2C19	EM 2/3 IM 1/3	2.5	2.37	–	–	(41)
Diazepam	Voriconazole 800 mg/day	2C19	EM 2/3 IM 1/3	2.2	2.03	–	–	(41)
Flecainide	Paroxetine 20 mg/day	2D6	*1*1	1.28	1.14	1.28	1.14	(42)
			*1*10	1.16	1.07	1.36	1.14	
			*10*10	1.01	1.00	1.21	1.14	
Flecainide R	Quinidine 200 mg/day	2D6	EM	1.18	1.14	1.18	1.14	(43)
			PM	0.79	1.00	2.38	1.14	
Flecainide S	Quinidine 200 mg/day	2D6	EM	1.07	1.14	1.07	1.14	(43)
			PM	0.68	1.00	2.05	1.14	
Flurbiprofen	Fluconazole 200 mg	2C9	*1*1	2.02	2.09	2.02	2.09	(44)
			*1*3	1.79	1.97	3.12	3.34	
			*3*3	1.4	1.55	4.71	8.12	
Flurbiprofen	Fluconazole 400 mg	2C9	*1*1	3.02	2.53	3.02	2.53	(44)
			*1*3	2.47	2.34	4.32	3.96	
			*3*3	1.22	1.70	4.1	8.90	
Gliclazide	Rifampicin 600 mg/day	2C9,2C19	EM	0.29	0.22	–	–	(45)
Haloperidol	Itraconazole 200 mg/day	2D6	*1*1	1.55	1.40	1.55	1.40	(21)
			*10*10	1.65	2.08	5.43	3.77	
Lansoprazole S	Fluvoxamine 50 mg/day	2C19	*1*1	14	8.68	14	8.68	(46)
			*1*2 ou 3	6.2	3.86	11.4	9.69	
			*2*2 ou 3	2	2.27	14.9	10.03	
Losartan	Phenytoin 300 mg/day	2C9	*1*1	1.41	1.37	1.41	1.37	(47)
			*1*2	0.7	1.32	2.12	1.42	
Metoprolol	Diphenhydramine 150 mg/day	2D6	EM	1.61	1.87	1.61	1.87	(48)
			PM	1.1	1.02	4.63	3.95	
Metoprolol	Dronedaron 800 mg/day	2D6	EM	1.24	1.24	1.24	1.24	(49)
			PM	1	1.01	2.95	3.91	
Metoprolol	Dronedaron 1,600 mg/day	2D6	EM	1.6	1.60	1.6	1.60	(49)
			PM	1	1.01	2.96	3.94	
Metoprolol	Amiodaron 1,200 mg/day	2D6	EM with 20% UM	2.33	2.25	2.33	2.25	(50)
			IM	1.61	2.11	2.54	3.50	
Metoprolol R	Diphenhydramine 150 mg/day	2D6	EM	1.92	1.98	1.92	1.98	(51)
			PM	1	1.02	4.66	4.93	
Metoprolol S	Diphenhydramine 150 mg/day	2D6	EM	1.64	1.79	1.64	1.79	(51)
			PM	1	1.02	2.82	3.42	
Mirtazapine	Cimetidine 1,600 mg/day	2D6	EM	1.54	1.66	–	–	(52)
Moclobemide	Omeprazole 40 mg/day	2C19	EM	2.2	1.44	2.2	1.44	(53)
			PM	0.8	1.01	2.6	3.42	
Omeprazole	Clopidogrel 75 mg/day	2C19	*1*1	1.28	1.31	1.28	1.31	(54)
			*2*2	1.02	1.01	2.08	6.13	
Omeprazole	Fluvoxamine 50 mg/day	2C19	EM	5.6	7.76	5.6	7.76	(55)
			IM	2.38	3.52	7	8.54	
			PM	1.15	1.46	11.5	8.92	
Omeprazole	Moclobemide 300 mg	2C19	EM	2.07	2.07	2.07	2.07	(56)
			PM	1.17	1.02	6.65	6.19	
Omeprazole	Clarithromycin 800 mg/day	2C19	*1*1	2.12	2.07	2.12	2.07	(29)
			IM *1*2 or *1*3	2.11	2.18	5.49	5.29	
			PM *2*3	2.34	2.51	34.1	15.31	

Table IV. (continued)

Victim drug	Inhibitor or inducer	Pathway	Genotype	AUC^{XM*}/AUC^{XM} observed	AUC^{XM*}/AUC^{XM} predicted	AUC^{XM*}/AUC^{EM} observed	AUC^{XM*}/AUC^{EM} predicted	Ref
Omeprazole	Ketoconazole 200 mg	2C19	EM	1.36	1.12	1.36	1.12	(57)
Omeprazole	St John Wort 900 mg/day	2C19	PM	1.99	2.64	9.2	15.65	
Oxycodone	Quinidine 100 mg	2D6	*1*1	0.56	0.56	0.56	0.56	(31)
			UM	1.4	1.42	1.04	1.25	(24)
			EM	1.25	1.25	1.25	1.25	
			PM	1.66	1.00	1.6	1.25	
Oxycodone	Ketoconazole 400 mg	2D6	UM	1.05	1.93	0.84	1.81	(24)
			EM	1.9	2.05	1.9	2.05	
			PM	2.4	2.32	2.32	2.58	
Quietapine	Fluoxetine 60 mg/day	2D6	EM	1.12	1.61	–	–	(58)
Rabeprazole	Fluvoxamine 50 mg/day	2C19	*1*1	2.83	3.40	2.83	3.40	(59)
			*1*2	2.56	1.74	2.31	3.52	
			*2*2	0.93	1.01	3.36	3.57	
Risperidone	Fluoxetine 20 mg/day	2D6	EM	4.7	4.30	–	–	(60)
Voriconazole	Ritonavir 600 mg/day 2 days	2C19	*1*1	1.54	1.42	1.54	1.42	(61)
			*1*2	1.95	2.28	2.67	4.36	
			*2*2	9.06	10.12	26.4	30.96	
Voriconazole	Erythromycin 1.5 g/day	2C19	*1*1	1.39	1.34	1.39	1.34	(62)
			*1*2	1.58	1.94	2.2	3.71	
			*2*2	1.52	2.90	6.1	7.47	
Voriconazole	Rifampicin 600 mg/day	2C19	EM	0.04	0.16	–	–	(63)
			*1*2	0.62	0.53	1.68	1.28	

CYP2C19, respectively. The IXs have been calculated for 24, 11, 24, and 12 moderate to strong inhibitors or inducers of CYP3A4, CYP2D6, CYP2C9, and CYP2C19, respectively. The FAs have been determined for 5 or 6 groups of genotypes of CYP2D6, CYP2C9, and CYP2C19 (5–7). Hence, many more quantitative predictions for various combinations may be propagated using this modeling approach, in contrast to the smaller number of exemplar published studies (approximately 80), found for external validation.

In the context of drug development, we advocate a three-step approach for predicting drug-drug interactions. The first step is *in silico* modeling of drug interactions based on *in vitro* experiments. If a new drug is predicted to produce significant interactions, then confirmatory clinical studies should be carried out, as a second step. One study would be devoted to the estimation of CR by the pharmacogenetic method if the major cytochrome involved is polymorphic (5), or by the interaction method with a strong inhibitor if the major cytochrome is

Fig. 1. Predicted versus observed area under the curve (AUC) ratios of victim drug AUC in patients with genetic variants taking both drugs, to the AUC in patients with variant genotype taking the victim drug alone (external validation). The middle line is the identity line ($y = x$). The upper and lower lines represent $y = 2x$ and $y = 0.5x$, respectively

Fig. 2. Predicted versus observed area under the curve (AUC) ratios of victim drug AUC in patients with genetic variants taking both drugs to the AUC in patients with wild-type genotype taking the victim drug alone (external validation). The middle line is the identity line ($y = x$). The upper and lower lines represent $y = 2x$ and $y = 0.5x$, respectively

Fig. 3. Predicted AUC ratio of first and second kind for the metoprolol-terbinafine and metoprolol-itraconazole interactions, according to the CYP2D6 phenotype of the patient

CYP3A4 (2). The other studies would be drug-drug interaction studies aimed at estimating the IX of the new drug for each cytochrome suggested by *in vitro* experiments. In the third step, our model (Eqs. 1 and 2) would be used to predict the AUC ratios for all interactions and genotypes, using the reported CRs, IXs, and FAs.

A number of limits of this kind of approach have been described earlier (2–5). Briefly, the effect of inhibitors and inducers depend on their concentration, hence on their dosing rate. The impact of rare variants, as well as more than three copies of an allele, could not be assessed, due to the paucity of data. The impact of cytochrome polymorphism may depend on ethnicity, but this effect is not accounted for in the present model. The interpretation of an AUC ratio may be difficult when the drug has enantiomers and/or active metabolites because its pharmacological profile may vary in case of drug-drug interaction or cytochrome polymorphism. Several specific limits of the approach described here need to be pointed out, in addition to those discussed earlier. First, the contribution ratios are related to the relative abundance of the cytochromes in the intestine and the liver. When these relative abundance varies, as may occur in children less than 2 years or in adults with severe liver impairment, then the contribution ratios are expected to differ, and the present approach could not be used without modification. Second, this approach is not suitable for drug-drug interactions involving mechanisms not mediated by cytochromes. Especially, interactions involving influx or efflux transporters may not be predicted correctly, as interactions with statins (66). In the same way, the different cytochromes are assumed to work independently, so that the clearance terms are additive; more complex interactions, such as synergy, are not accounted for in the present approach. Third, the method is currently restricted to two-drug interactions. The important topic of multiple-drug interactions, which arises, e.g., with antiretroviral treatment, is not adequately covered. Fourth, cytochrome genomic variations may alter the exposure to interacting drugs, thereby modifying their inhibition or induction potency. In particular, the interacting drug concentration may be increased in slow metabolizers (if its dose has not been adjusted), thereby increasing the IX absolute value

of the interacting drug, leading to a higher than expected AUC ratio of the victim drug. This phenomenon is not accounted for in the present form of the model, but its impact is probably limited, as demonstrated by the good predictive performances of the method in the external validation. Fifth, there is no accounting for the impact of CYP3A5 polymorphism. This is not a limitation of the model, which could easily be extended in this respect. The limitation lies in the available data. Currently, it is not possible to estimate the parameters required by the model (the CRs, IXs, and FAs) for CYP3A5 substrates and interacting drugs due to the paucity of data.

Sixth, it must be recalled that the effect of the inhibitors and inducers, characterized by the IX value in our model, depends on their time-averaged unbound concentration in plasma, and thereby on their dosing rate. As demonstrated in the appendix, the value of IX is related to the dose of interacting drug by the following equation, assuming linear kinetics of the interacting drug:

$$IX = \frac{IX_{\max} \cdot \text{Dose}}{D_{50} + \text{Dose}} \quad (14)$$

Where Dose is the dose (in case of a single dose) or the dosing rate (in case of multiple doses) of the interacting drug, D_{50} is the dose or dosing rate resulting in a value of $IX_{\max}/2$, and $IX_{\max}$ is the value of IX for a very high dose of interacting drug. $IX_{\max}$ is equal to -1 for an inhibitor, and greater than zero for an inducer. For an inhibitor, D_{50} may be calculated if IX is known for a single-dose level. For an inducer, D_{50} and $IX_{\max}$ may be calculated if IX is known for two-dose levels. Hence, the AUC ratios for the victim drug may be calculated for different dose levels of interacting drugs.

Finally, this approach is aimed at predicting the mean exposure resulting from a drug-drug interaction for patients having a specific genotype. The exposure in a given individual may differ from the predicted value. This is because (1) all the parameters involved in the model (the CRs, IXs, and FAs) may vary between individuals around the typical values reported here, and (2) other sources of variation, such as food effect, disease, ethnicity, etc. may also play a role. Hence, the model predicts the mean change in exposure for various substrates given the CYP and genomic information as a specific case, but the model is not designed to predict the change in exposure for each individual patient.

A website (<http://www.ddi-predictor.org>) is dedicated to quantitative prediction of drug-drug interactions as a function of patient's genotype, based on the principles described in this article.

CONCLUSIONS

The proposed approach for predicting quantitatively the combined impact of drug-drug interactions and genetic polymorphism on drug exposure was evaluated by external validation for a wide range of substrates, interacting drugs, and genotypes. The model may be used to predict the variations in exposure resulting from a number of drug-

drug–genotype combinations. This approach will help (1) to identify comedications and population at risk, (2) adapt dosing regimens, and (3) prioritize the clinical pharmacokinetic studies to be done.

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APPENDIX: DERIVATION OF EQ. 11

In vitro, according to Hisaka (67), in case of reversible inhibition of a cytochrome, the ratio of victim drug intrinsic clearances is related to the inhibitor concentration, I_u , and the inhibition constant K_i as follows:

$$\frac{CL_i^{XM}}{CL_i^{XM*}} = 1 + \frac{I_u}{K_i}$$

In case of mechanism-based inhibition, the ratio of intrinsic clearances depends on k_{inact} , k_{deg} , and K_I which are the maximum inactivation rate constant, degeneration constant, and inhibitor concentration when the rate constant of inactivation reaches half k_{inact} , respectively (68):

$$\frac{CL_i^{XM}}{CL_i^{XM*}} = 1 + \frac{k_{inact} \cdot I_u}{k_{deg} \cdot (I_u + K_i)}$$

In vivo, using the following assumptions: (1) the metabolic clearance of the victim drug is assumed to be close to total clearance, (2) metabolism is assumed to occur for a small part in the gut wall and for the main part in the liver, (3) hepatic clearance is related to intrinsic clearance by the well-stirred model, and (4) the kinetics of victim drug is linear, i.e., clearance is independent of time and dose, then the ratio of oral clearances is approximately equal to the ratio of intrinsic clearances. Replacing I_u by the time-averaged unbound concentration of interacting drug at the target site, $I_{u,av}$:

$$\frac{CL_{oral}^{XM}}{CL_{oral}^{XM*}} = 1 + \frac{I_{u,av}}{K_i} \quad \text{and}$$

$$\frac{CL_{oral}^{XM}}{CL_{oral}^{XM*}} = 1 + \frac{k_{inact} \cdot I_{u,av}}{k_{deg} \cdot (I_{u,av} + K_i)}$$

Defining the *in vivo* potency of an inhibitor as follows:

$$IX = -\left(1 - \frac{CL_{oral}^{XM*}}{CL_{oral}^{XM}}\right)$$

It comes

$$IX = -\left(1 - \frac{1}{1 + \frac{I_{u,av}}{K_i}}\right) = -\frac{I_{u,av}}{K_i + I_{u,av}}$$

For a reversible inhibitor, and

$$IX = -\frac{(k_{inact}/k_{deg}) \cdot I_{u,av}}{K_i + \left(1 + \frac{k_{inact}}{k_{deg}}\right) \cdot I_{u,av}}$$

For a mechanism-based inhibitor. Because k_{inact} is much greater than k_{deg} (69), we have $k_{inact}/k_{deg} \gg 1$. Therefore,

$$IX = -\frac{k_{inact} \cdot I_{u,av}}{K_i \cdot k_{deg} + k_{inact} \cdot I_{u,av}}$$

Assuming linear kinetics of the inhibitor, its concentration $I_{u,av}$ is proportional to its dose or dosing rate:

$$I_{u,av} = \alpha \cdot \text{Dose}$$

Hence,

$$IX = -\frac{\alpha \cdot \text{Dose}}{K_i + \alpha \cdot \text{Dose}} = -\frac{\text{Dose}}{(K_i/\alpha) + \text{Dose}} = -\frac{\text{Dose}}{D_{50} + \text{Dose}}$$

for a reversible inhibitor, and

$$IX = -\frac{k_{inact} \cdot \alpha \cdot \text{Dose}}{K_i \cdot k_{deg} + k_{inact} \cdot \alpha \cdot \text{Dose}} = -\frac{\text{Dose}}{\frac{K_i \cdot k_{deg}}{\alpha \cdot k_{inact}} + \text{Dose}} = -\frac{\text{Dose}}{D_{50} + \text{Dose}}$$

for a mechanism-based inhibitor. The final expression is the same for both types of inhibitor, but the expression of D_{50} is different.

Similarly, the inductive effect may be determined *in vitro* on hepatocyte cell cultures and modeled as (3) follows:

$$\frac{CL_i^{XM*}}{CL_i^{XM}} = 1 + \frac{E_{max} \cdot I_u}{I_{50} + I_u}$$

Where E_{max} is the maximal induction effect and I_{50} is the inducer unbound concentration resulting in a half maximal induction.

Defining the *in vivo* potency of an inducer as follows:

$$IX = \frac{CL_o^{XM*}}{CL_o^{XM}} - 1$$

We have, by combining the last two equations:

$$IX = \frac{IX_{\max} \cdot I_{u,av}}{I_{50} + I_{u,av}}$$

Where $E_{\max}$ has been replaced by $IX_{\max}$ for consistency. Using $I_{u,av} = \alpha \cdot Dose$, we find:

$$IX = \frac{IX_{\max} \cdot \alpha \cdot Dose}{I_{50} + \alpha \cdot Dose} = \frac{IX_{\max} \cdot Dose}{(I_{50}/\alpha) + Dose} = \frac{IX_{\max} \cdot Dose}{D_{50} + Dose}$$

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