Current Topics in Pharmacology
Vol. 24, 2020

Short Communication

Regression-based model for the evaluation of CYP2D6-mediated drug-drug interactions

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ABSTRACT

We aimed to construct a linear regression-based model between area-under-curve (AUCr) and the therapeutic range-to-inhibition constant ratio (TR-to-K_i). As result, a linear log-log regression model, between the averaged AUCr, calculated as the mean from the values of different drug-drug interactions (DDIs) between several victim-drugs with the same inhibitor ($AUCr_{avg}$), and the mean TR-to-Ki ratio (TR_m-to-K_i), calculated as the mean value between the maximum and minimum TR of the inhibitor divided by its K_i, obtained the best correlation ($r^2 = 0.72$; $p = 0.0116$). Accordingly, a drug-drug interaction involving reversible inhibitory drugs of CYP2D6 could be managed by adjusting dose of victim and/or inhibitory drug to the magnitude of the desired change, by applying data of TR and K_i of inhibitor to the equation of regression line presented here.

KEYWORDS: area-under-curve, inhibition constant, CYP2D6, drug-drug interactions, therapeutic range.

INTRODUCTION

Drug-drug interactions (DDIs) are changes in a drug's effects due to the recent or concurrent use of one or more drugs that may become critical to a patient's health. In particular, those cytochrome P450 (CYP)-mediated DDIs' can lead to serious adverse drug reactions (ADR) and constitute one of the main concerns in clinical pharmacology [1]. However, these clinically relevant DDIs are generally preventable, and their identification, quantification and management should be considered as a main objective in the safe practice of pharmacotherapy.

The Food and Drug Administration, based on the equation for basic models of reversible inhibition of CYP enzymes other than CYP3A ($R1 = 1 + [I]_{max}/ K_i$; Eq. 1), where R1 is the predicted ratio of the victim drug's area-under-curve (AUCr) in the presence and absence of an inhibitor, $[I]_{max}$ is the maximal unbound plasma concentration of the inhibitor, and K_i is the unbound inhibition constant (determined *in vitro*), recommends conducting clinical studies of a given DDI when AUCr at steady-state (SS) of a probe drug (e.g. dextromethorphan), whose clearance is determined by metabolism through the P450 enzyme, is >1.1 [2].

The successful correlation of *in vitro* to *in vivo* data is dependent on the inhibitory concentration ([I]) used (e.g., $[I]_{avg}$ average plasma concentration, $[I]_{max}$ maximal unbound plasma concentration, $[I]_h$ maximal hepatic concentration). In this sense, today, it remains controversial which of the previously described [I] values or, conversely, another new value of [I] (e.g. average value of the therapeutic range (TR)) should be applied to Eq. 1 to improve prediction models used in clinical practice.

Thus, we propose the use of TR data, since they refer both to the dosage range and to the plasma

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concentration at which the desired therapeutic effect is obtained, and due to its easy accessibility (we know that in clinical pharmacology obtaining plasma concentration is only possible in a small number of drugs with low therapeutic index, e.g., digoxin, immunosuppressants), instead of $[I]_{max}$ in Eq. 1.

On the other hand, depending on the mode of interaction between CYP enzyme and the inhibitor, reversible CYP inhibition, that occur in an inhibitor dose (concentration)-dependent manner in the clinical setting, may be further described as competitive [3]. When this competitive inhibition occurs, the IC50, a parameter used for K_i-calculation by means of the Cheng-Prusoff equation [4], rises and, thus, the degree of inhibition reduces along with the increase in the concentration of the victim-drug [5].

Because of this, our objective has been to correlate the variations in interaction intensity (AUCr) with those of TR, for a set of known inhibitors of the CYP2D6, with the aim to clinically evaluate CYP2D6-mediated DDIs.

MATERIALS AND METHODS

To choose between multiple possible correlations, we previously carried out a theoretical approach based on the fact that Eq. 1 is fulfilled at all points of the regression line and, on the other hand, that between one point (point [1]) and the next (point [1']) of the regression-line, there is a change of AUCr and $[I]_{max}$ values, whose difference we want to correlate. Thus:

for point [1] we will have $\frac{AUC}{AUC_i} = 1 + \frac{[I]_{max}}{K_i}$;

and for point [1´] $\frac{AUC´}{AUC_i} = 1 + \frac{[I]´_{max}}{K_i}$

The difference between them being equal to $\frac{AUC´}{AUC_i} - \frac{AUC}{AUC_i} = \frac{[I]´_{max}}{K_i} - \frac{[I]_{max}}{K_i}$ and, therefore, $\frac{\Delta AUC}{AUC_i} = \frac{\Delta[I]_{max}}{K_i}$. For a $\Delta \approx 0$, we can write $\frac{dAUC}{AUC_i} = \frac{d[I]_{max}}{K_i}$ and integrating (taking into account that K_i represents an [I]), we will have: $Ln\frac{AUC}{AUC_i} = Ln\frac{[I]_{max}}{K_i}$ (for a slope equal to 1 and Y-intercept equal to zero).

Finally replacing [I] max with TR we will have:

$$Ln\ AUC_r = Ln\frac{TR}{K_i}, \text{ Eq.2}$$

According to Eq. 2, we only analysed a log-log linear-regression model constructed on the basis of two main variables: the average of AUCr of the victim-drugs ($AUDr_{avg}$) and the mean of the TR value-to-K_i ratio (TR_m-to-K_i) of the inhibitors.

For this, we assumed the following criteria and conditions: dose proportionality between the dose to achieve the maximum and the average concentrations of inhibitors at SS ($[I]_{max}$ and $[I]_{avg}$, respectively); and, thus, since TR refers to either the dosage or the SS-plasma concentration interval at which the desired therapeutic effect is obtained ($[I]_{avg}$), TR can be used as a proxy of the [I]max.

Inclusion criteria: CYP2D6-mediated DDIs with available clinical data of AUCr, obtained from the literature, and victim-drugs metabolized exclusively or mostly by CYP2D6. Exclusion criteria: DDIs

Table 1. Values of inhibition constant (K_i, in μM) and mean therapeutic range (TR_m, in μM), calculated as the mean value between the maximum and minimum therapeutic range, of the inhibitors.

Inhibitor	**K_i**	**TR_m**
Amiodarone	11.8 *	3
Amitriptyline	30	0.43
Chlorpromazine	4.8	0.28
Cimetidine	7.7 *	6.44
Citalopram	24	0.32
Diltiazem	150	0.42
Diphenhydramine	10	0.25
Fluoxetine	0.54	0.24
Fluvoxamine	0.83 *	0.39
Hydroxychloroquine	66	0.89
Labetalol	7	1.1
Mexiletine	30	7.54
Propafenone	0.03 *	4.99
Quinidine	0.02 *	9.26
Sertraline	0.47 *	0.38
Verapamil	16	0.33

K_i and AUCr data from Ito *et al*. [6] except *K_i from Van den Brink *et al*. [9].

Table 2. Cytochrome P450 2D6-mediated drug-drug interactions (DDI) studied: values of the area-under-curve ratio (AUCr) of the victim-drugs; and values of the two correlated variables: Ln $AUCr_{avg}$ = the neperian logarithm of the averaged AUCr of several victim-drugs with the same inhibitory drug (see second column), and Ln (TR_m-to-K_i)= neperian logarithm of the mean therapeutic range of inhibitor-to-inhibition constant ratio.

Drug-Drug Interaction		***Ln TR_m-to-K_i***	***Ln $AUCr_{avg}$***
Inhibitor	***Victim Drug (AUCr)***		
Amiodarone	FLC (1.37)	-1.4	0.31
Amitriptyline	ATN (1.24), MTP (1.44)	-4.2	0.29
Chlorpromazine	PRPr (1.69)	-2.8	0.52
Cimetidine	ATN (1.07), MTP (1.61), PRPr (1.91; 1.94; 1.47)	-0.18	0.47
Citalopram	DSP (1.47), IMP (1.15), LVM (0.74)	-4.3	0.11
Diltiazem	ATN (1.07), MTP (1.33), PRPr (1.48; 1.33)	-5.87	0.26
Diphenhydramine	MTP (1.61)	-3.66	0.48
Fluoxetine	CRV (1.77), DSP (4.80; 7.43; 5.31), IMP (3.33), PRPh 1.50), RTV (1.19), TLT (4.84)	-0.81	1.33
Fluvoxamine	DSP (1.14), IMP (3.63)	-0.75	0.87
Hydroxychloroq.	MTP (1.65)	-4.3	0.50
Labetalol	DSP (2.27), IMP (1.53)	-1.84	0.64
Mexiletine	MTP (1.82)	-1.38	0.60
Propafenone	PRPr (2.13)	5.11	0.76
Quinidine	DSP (7.5), ENC (3.18; 11.4), IMP (1.54), MTP (3.24), MXL (1.32), PRP (2.7)	6.14	1.48
Sertraline	DSP (1.2; 1.37; 1.74; 1.54; 2.29), IMP (1.68)	-0.22	0.49
Verapamil	MTP (1.33), PRPr (1.42)	-3.88	0.32

ATN = Atenolol; CRV = carvedilol; DSP = desipramine; ENC = encainide; FLC = flecainide; IMP = imipramine; LVM = levomepromazine; MTP = metoprolol; MXL = mexiletine; PRPh = perphenazin; PRP = propafenone; PRPr = propranolol; RTV = Ritonavir; TLT = tolterodine.

whose inhibitor was time-dependent, the AUCr was < 1.1 or TR data was not available.

Then, we collected data on *in vivo* AUCr and *in vitro* Ki, from 58 DDI studies involving CYP2D6 based on the dextromethorphan O-oxidation methodology, obtained from the literature review (data from Ito *et al*.) [6]. We also gathered bibliographic data on the TR for the 19 inhibitors involved in such DDIs (data from Regenthal *et al*.) [7]. After excluding, according to exclusion criteria, the DDIs corresponding to omeprazole (n = 3), because it is not an inhibitor of CYP2D6 (AUCR<1.1), paroxetine (n = 7) because it is a time-dependent inhibitor of CYP2D6 [8], and DDIs corresponding to ritonavir (n = 1) because the value of its therapeutic range was not available, the final sample to study was composed of 47 DDIs and 16 reversible inhibitors. These data are summarized in Table 1.

Finally, the correlation strength of the linear regression models was assessed by Pearson's correlation coefficient.

RESULTS

As results, data were fitted to a linear log-log regression model, which obtained the best correlation between the following two variables: the AUCr of the victim-drug, calculated as the mean from the values of different DDIs between several victim-drugs with the same inhibitor ($AUCr_{avg}$), and the mean therapeutic range of inhibitor-to-inhibition constant ratio of the inhibitor (TR_m-to-K_i), calculated as the mean value between

the maximum and minimum therapeutic range of the inhibitor divided by its inhibition constant (TR_m/K_i). Data are summarized in Table 2.

The equation for the linear regression obtained was: Ln AUCr avg = 0.08 Ln (TR_m-to-/Ki) + 0.71; Eq. 2, (r^2 = 0.72; standard error = 0.069, CI 95%: from 0.60 to 0.84, P = 0.0116), where the slope measures the proportionality between two variables, Ln $AUCr_{avg}$ and Ln (TR_m-to-/K_i). The plot of this regression line is illustrated in Figure 1.

DISCUSSION

Due to the increase of the adverse events caused by the DDIs, the development and the application of new methods for the detection of them, constitutes one of the most important roles of the clinical pharmacologist.

This model shows good predictive results for a panel of 47 DDIs and 16 CYP2D6 inhibitors, constituting a valuable, quick, simple and extensible regression-based method for the prediction of the intensity and clinical relevance of metabolic-based DDIs mediated by CYP2D6 and their management in clinical practice, by using TR data of the inhibitors.

According to the results, the simple knowledge of K_i and TR of the inhibitor would be sufficient to determine the intensity and clinical relevance of a DDI. In this sense, if K_i exceeds the maximal value of TR, then that drug is unlikely to inhibit the activity of that enzyme, and vice versa. The DDI management options would include adjusting dose of victim and/or inhibitor by applying data of TR and K_i of inhibitor, from literature, to the equation of regression line presented here.

In fact, consistent with the correlated data and since the TR of an inhibitor refers both to the dosage range and to the plasma concentration at which the desired therapeutic effect is obtained, we can manage a DDI by dose adjustments of the CYP2D6 inhibitor, within the normal TR, in proportion to the magnitude of the desired change in the exposition to victim drug (AUCr), or directly by dose adjustments of victim drug aimed to avoid the appearance of ADRs. Also, it would be useful to assign the probability that a particular drug causes a clinically relevant interaction, once the main routes of elimination of the interacting drugs and the potential factors that influence them have been previously identified.

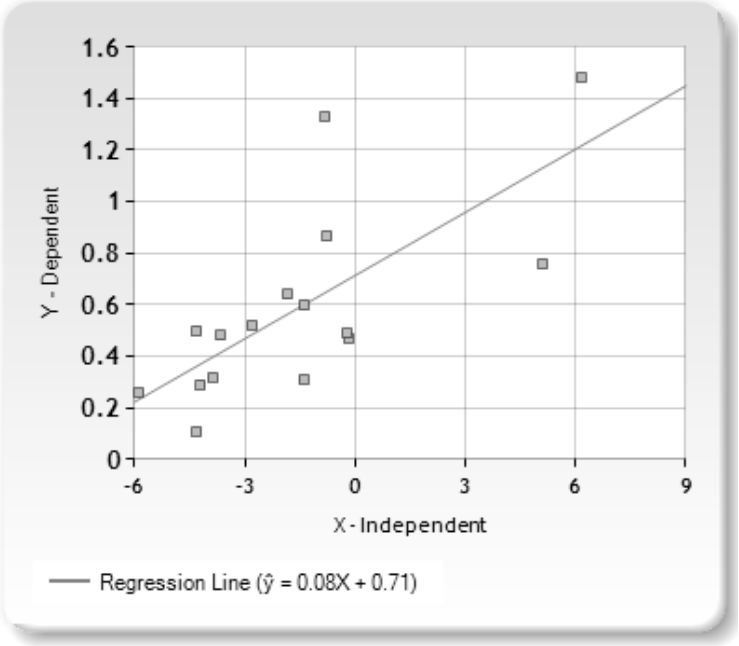

Figure 1. Plot of regression line between the neperian logarithm of the mean of the therapeutic range-to-inhibition constant ratio of the inhibitory drug (Ln TR_m-to-K_i; X-independent variable) and the neperian logarithm of the average of the of area under the plasma concentration-time curve ratio of the victim-drugs (Ln AUCr avg; Y-dependient variable).

Therefore, the present study constitutes a valid instrument for the management of the analysed CYP2D6-based DDIs, as well as an approach to make extrapolations in the case of DDIs for which no studies have been conducted, and for the new interactions that arise when new drugs are incorporated into pharmacological therapy, for which plasma concentration of inhibitors are not available for the prediction and management of a CYP2D6-mediated DDI. This would be much more important in the case of the victim-drugs with a narrow margin of safety and for planning dosage regimens with a better benefit/risk ratio without increasing time and/or cost.

However, it is important to appreciate that the present analysis is empirical, and must be regarded as an initial step in the prediction of CYP2D6-based DDIs and further research will be needed to demonstrate its clinical applicability.

Finally, as weaknesses of the present study, it should be noted that factors such as the role of hepatic uptake transporters, the existence of more than one elimination pathway/metabolic pathway, the influence of multisite kinetics for CYP2D6, chirality of victim-drugs and inhibitors, and nonlinear kinetics of substrates were not taken into account to achieve these results. These must be considered alongside the TR-to-Ki ratio to improve the prediction of CYP-mediated DDIs. In fact, the coefficient of determination (R = 0.52), which explains the percentage of the total variation observed in the dependent variable, indicates that the regression line obtained can explain 52% of the total variation observed, while that most of the remaining 48% should be looked for by other factors.

CONCLUSIONS

A drug-drug interaction involving reversible inhibitory drugs of CYP2D6 could be managed by adjusting dose of victim and/or inhibitory drug, according to the magnitude of the desired change, by applying data of therapeutic range and inhibition constant of inhibitor from literature to the equation of regression line presented here.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT TO PUBLISH

Not applicable.

FUNDING

The authors received no specific funding for this work.

AUTHORS' CONTRIBUTIONS

All authors participated in the research design, data analysis and the writing of the manuscript. All authors approve the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

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