A Molecular Weight-Based Quantitative Method for the Prediction of Exposure of P-glycoprotein or Non- P-Glycoprotein Substrates Following Drug-Drug Interaction Studies: Induction

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Article

A Molecular Weight-Based Quantitative Method for the Prediction of Exposure of P-glycoprotein or Non-P-Glycoprotein Substrates Following Drug-Drug Interaction Studies: Induction

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Abstract

These days, in-silico methods based on chemical descriptors (molecular weight (MW) and/or logarithmic partition coefficient (logP) for the prediction of exposure of drugs (AUC) following drug-drug interaction (DDI) are gaining momentum. The objective of this study was to develop a simple quantitative method to predict AUC of P-glycoproteins (P-gP) and non P-gp substrates following interaction with inducer(s). The AUC of a substrate following induction was predicted by using the MW ratio of two interacting drugs. The suitability of the proposed method was validated on 75 substrates or drugs (36 (non P-gp) and 39 (P-gp). Approximately, 76% and 54% predicted values had ≤50% or ≤30% prediction error, respectively. The average fold error (AFE) was 1.042. The predictive power of the proposed method for DDI following induction was found suitable and to a great extent an accurate approach when compared with the observed clinical data.

Keywords: chemical descriptors; drug-drug interaction; inducers; molecular weight; P-glycoproteins and non- P-glycoproteins

Introduction

Drug-drug interaction (DDI) can lead to with or without therapeutic benefit of a drug. DDI can alter the pharmacokinetics (PK) and/or pharmacodynamics (PD) of a drug [1]. In PK drug interactions, the concentrations of one or more drugs is generally altered by another drug. The change in PK of a drug concentrations may be due to the changes in absorption, distribution, metabolism, or elimination (ADME) [1]. The pharmacodynamic (PD) interaction can produce additive, synergistic, or antagonistic effects of a drug [1].

The knowledge of DDI is important to identify the impact of one drug on the efficacy or toxicity of another drug. Clinical DDI studies are regularly conducted to ensure that a patient or a patient population receives a right dose for therapeutic benefit or to avoid toxicity of a drug. Besides, conducting clinical DDI studies, several modeling methods (extrapolation from in-vitro data, static, expanded static, physiologically-based, and quantitative models) have also been developed to predict the exposure (area under the curve (AUC) and/or maximum plasma concentration (C_{max})) of a drug following DDI studies [2–10]. In these models, in-vitro data are regularly used as input parameters to develop the DDI models [3–5,9].

During drug discovery, the knowledge of physicochemical properties of molecules plays an important role in order to find suitable drug candidates which can provide therapeutic benefit and low toxicity of a drug [11]. The physicochemical properties of a molecule impact absorption, distribution, metabolism, and excretion (ADME) and toxicity of a drug [11]. The physicochemical properties of compounds are regularly used to predict or estimate PK or/and PD of drugs [12]. The major physicochemical properties which affect biological behavior of drugs are molecular weight

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(MW), ionization, solubility, lipophilicity (logP), hydrogen bonding, charge, and the total polar surface area (TPSA) [13].

MW plays a very important role in characterizing many physicochemical and biological characteristics of ADME, efficacy, and toxicity of a compound [11–13]. For example, MW and solubility of a drug affect absorption and bioavailability. Ionization of a drug at physiological pH provides information on its membrane permeability whereas, lipophilicity (logP) affects the distribution of a drug across tissues [13].

Considering that in-vivo DDI studies are intensive, time consuming, and costly, in recent years, in-silico methods have been developed for the prediction of DDI and are becoming popular [14–17]. Molecular representations such as chemical descriptors and molecular structure similarity information derived from fingerprint-based modeling have been proposed [17]. Chemical descriptors are quantitative measurements of structural, physical, or chemical properties of a compound. The widely used descriptors are the MW and log P [11–13].

The size of a molecule in terms of its MW is related to many physicochemical properties of a compound. Therefore, MW of a molecule dictates the ADME, efficacy, toxicity, and formulation of a drug. These days, MW is regularly used in computer-aided drug design (in-silico) in the early stages of drug development. The following is a brief description of the relationship between MW and many physicochemical, physiological, and pharmacological properties of a compound.

Cell Permeability: Cell permeability of a molecule is dependent on it's size or MW. Drugs with lower MW (less than 500 grams per mole) exhibit better absorption characteristics than drugs with high MW. This is because these small molecules can readily pass through lipid bi-layers of cell membranes. This passage is necessary for the drug to effectively reach to its target sites within the body. On the other hand, drugs with high MW may encounter difficulties in absorption and permeation through biological membranes [18–22].

LogP: LogP predicts how well a drug can penetrate through cell membranes. A high logP value indicates that a molecule is more soluble in lipids (lipophilic) and a low logP value indicates that a molecule is more soluble in water (hydrophilic). Higher logP values lead to poor solubility. A general trend is that as MW increases logP also increases, but this is not a strict rule. A logP value between 2 and 5 is desirable for optimal absorption and distribution [12,18–22].

Solubility: Solubility of a drug is very important in determining the bioavailability of a drug. Higher solubility is desirable for effective absorption and distribution in the body. Drugs with lower MW are generally more soluble in water. The correlation between MW and solubility is very important since water solubility is directly linked to a drug's ability to be absorbed into the systemic circulation. Furthermore, in drug development, through MW analysis one can predict and enhance the solubility of a compound [12,18–22].

Metabolism and excretion: Metabolism and excretion are highly influenced by the MW of a compound. Molecules with high MW are generally more susceptible to enzymatic degradation because such molecules have more chemical groups that can be modified by metabolic enzymes. Such high MW compounds are readily metabolized in water soluble products and are excreted quickly. Drugs metabolized by CYP3A4 appear to have larger MW and those metabolized by CYP2D6 have lower MW. Drugs metabolized by CYP2C8 appear to be most hydrophilic with the smallest logP and the largest polar surface areas [23].

The MW of a compound also plays an important role in the excretion of a molecule through kidneys. Molecules with a MW below 300-500 g/mol are more readily excreted (unchanged or in metabolites) by the kidneys because smaller molecules can more easily pass through the glomerular filtration. On the other hand, compounds with higher MW may not be excreted unchanged and are required to be transformed into small and water soluble metabolite(s) to be excreted by the kidneys [24].

Many drugs and their metabolites are also excreted in the bile. Drugs are transferred from plasma into the bile through hepatocytes. This transport takes place through active secretory

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transport system. Drugs with a MW of >300 g/mol and with both polar and lipophilic groups are generally excreted in bile [25,26].

Target binding: Target binding is related to a drug's action, where the molecular structure of the drug interacts or binds with a specific biological target. The MW of a compound plays a very important role in this target binding process. Compounds with high MW have more potential sites for target binding than compounds with lower MW [11,24].

From the aforementioned relationship between MW and physicochemical, physiological, and pharmacological properties of a compound, it is obvious that the pharmacokinetics, efficacy, safety, and toxicity of a molecule is related to it's MW. Change(s) in the MW of a compound may alter the physicochemical properties of a compound and in turn may impact the PK characteristics (mainly C_{max} andAUCs) of drugs. If one hypothesizes that using the MW of two interacting drugs in terms of MW ratio then one may be able to predict the C_{max} and/or AUCs of a drug following DDI studies. Therefore, the objective of this study was to develop a simple quantitative method to predict the AUC of drugs using the MW ratio of two interacting drugs in subjects following DDI studies (materials and methods). This study describes the effect of drug inducers on the AUC of substrates which are either P-glycoproteins (P-gp) or non-P-glycoproteins.

Results

The results of the study are summarized in Table 1. The observed and predicted values of AUC for individual drugs are shown in supplementary Tables S1 and S2.

The impact of several inducers were evaluated on 36 (non P-gp) and 39 (P-gp) substrates (drugs). The total number of substrates or drugs evaluated was 75 and the total number of observations (data points) were 109. Out of 109 observations, 96 (88.1%), 83 (76.1%), and 58 (53.2%) observations were within 0.5-2-fold, 0.5-1.5-fold, and 0.7-1.3-fold prediction error, respectively (Table 1). The AFE was 1.042 (Table 1). Overall, the predictive power of the proposed methods for P-gp and non P-gp substrates following induction was quite good.

Table 1. Summary of the results of drug-drug interaction studies.

Fold-error	0.5-2	0.5-1.5	0.7-1.3	>2	<0.5	AFE
Number of drugs evaluated = 75 (without overlapping), total number of observations = 109						
Within fold-error (Non-P-gp & P-gp)	96 (88.1%)	83 (76.1%)	58 (53.2%)	10 (9.2%)	3 (2.8%)	1.042
Non-P-gp (n = 42)	39 (92.9%)	33 (78.6%)	24 (57.1%)	2 (4.8%)	1 (2.4%)	1.053
P-gp (n =67)	57 (85.1%)	50 (74.6%)	34 (50.7%)	8 (11.9%)	2 (3.0)	1.035
Not metabolized (n =15)	14 (93.3%)	13 (86.7%)	7 (46.7%)	0 (0%)	1 (6.7%)	0.843
Metabolized in the liver (n = 11)	10 (90.9%)	10 (90.9%)	7 (63.6%)	1 (9.1%)	0 (0%)	1.066
Metabolized in the gut and the liver (n =41)	33 (80.5%)	27 (65.9%)	20 (48.8%)	7 (17.1%)	1 (2.4%)	1.205

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There were 36 non P-gp substrates with 42 observations. Out of 42 observations, 39 (92.9%), 33 (78.6%), and 24 (57.1%) observations were within 0.5-2-fold, 0.5-1.5-fold, and 0.7-1.3-fold prediction error, respectively. The AFE was 1.053 (Table 1).

There were 39 P-gp substrates with 67 observations. Out of 67 observations, 57 (85.1%), 50 (74.6%), and 34 (50.7%) observations were within 0.5-2-fold, 0.5-1.5-fold, and 0.7-1.3-fold prediction error, respectively. The AFE was 1.035 (Table 1).

The results of the Pg-p substrates were divided into the following three categories. The results are summarized in Table 1.

- Drugs not metabolized by CYP-450 system (n =15); 93.3%, 86.7%, and 46.7% observations were within 0.5-2-fold, 0.5-1.5-fold, and 0.7-1.3-fold prediction error, respectively. The AFE was 0.843.
- Drugs metabolized in the liver by CYP-450 system (n = 11); 90.9% observations were within 0.5-2-fold and 0.5-1.5-fold, prediction error (63.6% within 0.7-1.3-fold prediction error). The AFE was 1.066.
- Drugs metabolized in the gut and the liver by CYP-450 system (n =41); 80.5%, 65.9%, and 48.8% observations were within 0.5-2-fold, 0.5-1.5-fold, and 0.7-1.3-fold prediction error, respectively. The AFE was 1.205.

Overall, the predictive performance of the proposed methods for the prediction of AUC for P-gp and non P-gp substrates following DDI studies was quite accurate (88% observations within 0.5-2-fold prediction error).

Discussion and Conclusions

In-silico methods for the prediction of DDI are gaining momentum because these methods are cost-effective and are efficient screening tool for DDI studies [11,12]. Chemical descriptors provide descriptions of a molecule's physical or chemical characteristics [12,13]. The two most widely used chemical descriptors are MW and logP [11–13]. In this study, MW was used for the prediction of DDI because sometimes logP of a molecule can be negative and sometimes there are lack of experimental values for logP. Furthermore, the predicted logP values may not be accurate.

The basic concept of the proposed method is the application of the ratio of MW of two interacting drugs. The MW ratio appears to serve as an empirical composite descriptor correlating with interaction magnitude for these inducers and the substrates. This may be the reason that the prediction of exposure of drugs following DDI based on the MW of two interacting drugs was found to be a simple and suitable approach. Although, the correlation between the ratios of MW and the ratios of placebo/interaction AUC values (data from clinical trials) following DDI studies was not strong ($r^2 = 0.45$) yet, the overall result of the predicted AUCs from the proposed method was quite accurate (88% observations within 0.5-2-fold prediction error). Furthermore, fairly accurate prediction of AUC of drugs following DDI studies also may be because many physiological and pharmacological properties are related to the MW of a drug.

Although, the liver is the major site of drug metabolism, gut also plays an important role in the metabolism of many drugs [27]. CYP3A represents approximately 80% of all CYPs expressed in the gut [27]. Many drugs such as midazolam, cyclosporine, alfentanil, tacrolimus, verapamil, nifedipine, and felodipine etc are significantly metabolized in the gut as well as in the liver [28]. This observation led to some adjustment in the method (method II versus method 1) and helped in a great deal to improve the predictive power of the proposed method for those drugs which are metabolized both in the liver and the gut.

P-gp also known as multidrug resistance protein 1 is an efflux transporter and has impact on the ADME of many drugs [29]. The expression of CYP3A and P-gp is regulated by pregnane X receptor (PXR) [29]. Co-administration of a drug as an inducer or inhibitor can reduce or increase the systemic exposure of a P-gp substrate drugs, respectively. Commonly used P-gp substrates in clinical DDI studies are digoxin, fexofenadine, dabigatran etexilate and talinolol [29]. It should be noted that the aforementioned four drugs are not metabolized in the liver or the gut.

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Rifampin is the most potent P-gp inducer compared to phenytoin or carbamazepine [29]. Rifampin reduced P-gp substrate exposure by 20-67% whereas, phenytoin or carbamazepine reduced P-gp substrate exposure by 12-42% [29]. This indicates that rifampin is a much more stronger in its inductive characteristics than phenytoin or carbamazepine.

Rifampin is a strong inducer and induces enzymes both in the liver and the gut. Rifampin is widely used as an inducer for many substrates. In this study, in order to evaluate the predictive power of the proposed method, the induction of rifampin was evaluated on many substrates. There were 20 substrates (induced by rifampin) for non P-gp and out of which 19 (95%) substrates were within 0.5-2-fold and 0.5-1.5-fold prediction error. The AFE was 1.13. There were 40 substrates (induced by rifampin) for P-gp and out of which 29 (81%) and 26 (72%) substrates were within 0.5-2-fold and 0.5-1.5-fold prediction error, respectively. The AFE was 1.20. The results indicate that the predictive power of the proposed methods is quite accurate even when an inducer as complex as rifampin is used.

The analysis in this study indicated that if a P-gp or a non P-gp substrate is metabolized in the liver then method 1 is appropriate for the prediction of AUC following interaction with an inducer. On the other hand, if a P-gp or non P-gp substrate is metabolized both in the liver and the gut then method II is a suitable method.

Midazolam is a widely used probe substrate for the assessment of induction or inhibition characteristic of a drug. Midazolam is a P-gp substrate and is metabolized in the liver and the gut by CYP-450 system. Induction data for midazolam by different inducers (rifampin, carbamazepine, rifabutin, and St John's wort) from different studies were collected. Rifampin and carbamazepine (n = 9) decreased the AUC of midazolam by 73% to 96% (Table S2). Seven out of 9 observations were within 0.5-2-fold prediction error. On the other hand, reduction in the AUC of midazolam following a weak or moderate inducer like St John's wort (n =3) ranged from 20% to 51% (Table S2) indicating that rifampin is more potent inducer of midazolam than St John's wort. All 3 observations were within 0.5-2-fold prediction error. The induction capability of St John's wort is dependent on the duration of administration and dose. St John's wort may be a weak inducer of intestinal metabolism (S74, S75).

Overall, The proposed methods for the prediction of DDI following the administration of strong to moderate inducers provided reasonably accurate prediction. There were 75 drugs with 109 observations (data points) and 96 (88.1%) and 83 (76.1%) observations were within 0.5-2-fold and 0.5-1.5-fold prediction error, respectively (Table 1).

In this study, the application of the ratio of the MW of two interacting drugs to predict the AUC of drugs following induction was found to be a suitable and a reasonably accurate approach. The DDI mechanisms are diverse and complex. It is difficult to comprehend that for a complex mechanism like DDI a simple parameter like MW ratio will provide acceptable prediction (within 0.5-2 or 0.5-1.5-fold prediction error) of AUCs following DDI studies. This may be because many physiological and pharmacological properties are related to the MW of a drug as described previously (introduction section). The proposed method does not require extensive data such as in-vitro drug metabolism data, many physical or chemical parameters, and extensive physiological parameters. The analysis is quick and simple and does not require any special software yet, the predictive power of this approach to a great extent is quite accurate. This simple quantitative method can be helpful in designing clinical trial(s) to determine precise magnitude of DDI determination or in some cases in clinical settings. In a separate manuscript, I will show the application of this (MW ratio) approach for inhibitors in DDI studies.

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Materials and Methods

In this study, the inducers of cytochrome P-450 (CYP-450) system such as rifampin, carbamazepine, phenobarbital, phenytoin, enzalutamide, and rifabutin were used. Rifampin [30], carbamazepine [31], and phenobarbital [32] are inducers of CYP-450 system both in the liver and the gut. The effect of aforementioned inducers were evaluated on drugs:

- Metabolized by CYP-450 system in the liver as well as in the liver and the gut (non P-gp substrates).
- Transporter mediated (P-gp) drugs:
  not metabolized by CYP-450 system
  metabolized by CYP-450 system in the liver as well as in the liver and the gut.
- Since midazolam is a widely used probe to assess the induction or inhibition potential of many inducers or inhibitors, in this study, the impact of many inducers on the AUC of midazolam was also evaluated.

The MW of drugs used in this analysis were obtained from Drug Bank [33].

2.1. Method I: Drugs Metabolized by Cytochrome P-450 System Only in the Liver (P-gp and Non P-gp Substrates)

The AUC of a drug or substrate with the co-administration of an inducer was predicted by using the ratio of MW of two interacting drugs (inducer and the substrate). Irrespective of the MW of the inducer or the substrate, the MW was used in a way that the ratio of MW remains ≥1. The rationale for using the MW ratio ≥1 is when there is an interaction between two drugs then the exposure of a substrate will be similar (minor or no effect) or lower following induction than the placebo. It should be recognized that the constraint (MW ≥1) is neither arbitrary nor lacks theoretical mathematical basis. The constraint is based on the direction of interaction and simple mathematics. The theoretical basis of using MW ratio ≥1 is that interaction will produce a change in concentrations (AUC) which will be ≥1 in both induction (AUC of placebo/AUC after induction) or inhibition (AUC after inhibition/AUC of placebo) scenarios (based on the observations of DDI clinical studies). The predictive performance of the proposed method is based on this simple mathematical approach (ratio of MW must be ≥1). It does not matter if the ratio ≥1 is obtained using MW of inducer/substrate or substrate/inducer. The following equation was used to predict AUC of a substrate following DDI.

Predicted AUC following induction = AUC of a substrate before induction/MW ratio (1)

Since, the inducers increase enzymatic activity resulting in decreased concentrations of the substrates hence, the division (MW ratio) in the method. If the prediction is for clearance (CL) of a substrate then multiplication rather than division should be used. Method 1 should only be used when drugs are metabolized by CYP-450 system (irrespective of isozyme(s) involved in the metabolism of a drug) in the liver and irrespective of P-gp or non P-gp substrates.

2.2. Method II: Drugs Metabolized by Cytochrome P-450 System Both in the Liver and the Gut (P-gp and Non Pg-p Substrates)

In a study, Richter et al [34] determined the CYP3A4-dependent catalytic activity in human small intestinal and liver homogenates. The amount of CYP3A4 in the liver and the intestine was 23.6 pmol/mg and 76 pmol/mg protein, respectively, indicating that the amount of CYP3A4 was 3.2-fold higher in the intestine than the liver. Adjusting for human liver (1.6 kg) and gut (1 kg) weights [35], the ratio of gut and liver weight is 0.625 and the total amount of CYP3A4 will be 2-fold (3.2 x 0.625) higher in the gut than the liver. Yang et al [36] reported that the intrinsic activity of gut and liver may be similar. Considering that the content of CYP3A4 in the intestine is 2-fold higher (after weight adjustment) than the liver and intrinsic activity of the intestine and liver are similar, the following method was developed for the prediction of AUC for drugs which are metabolized by CYP-450 system in the liver and the gut. Liver and gut were considered as two different compartments as such overall MW ratio.

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Ratio = (Ratio of the MW of interacting drugs for the liver) + ((Ratio of the MW of interacting drugs for the gut) x 2) (2)

In all cases, the MW ratios should be ≥1.

Predicted AUC following induction = AUC of a substrate before induction/ratio of MW (3)

Method II is only applicable for those inducers (such as rifampin or carbamazepine or phenobarbital) which induce the metabolism of drugs both in the liver and the gut of a drug. If an inducer (such as rifabutin) does not induce gut metabolism then the method should not be used. In this case method I should be used.

The predicted AUC values were compared (validated) with the observed AUC values. The observed AUC values were obtained from the clinical trials following DDI studies.

2.3. Statistical Analysis

Prediction fold-errors of 2 (0.5-2), 0.5-1.5 (a 50% prediction error on either side of 1), and 0.7-1.3 (a 30% prediction error on either side of 1) and average fold error (AFE) were used for the assessment of the predictive performance of the proposed methods [37,38].

The prediction fold-error was calculated as follows:

Prediction fold-error = (predicted PK parameter/observed PK parameter) (4)

Average fold error (AFE), which is log-transformed ($\log_{10}$) ratio of the predicted and observed AUC was calculated using equation 5.

$$AFE = 10^{\wedge\sum \log(AUCpredicted/AUCobserved)/n} \quad (5)$$

where, n is the number of observations.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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