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Predicting Prospective Drug-Drug and Drug-Excipient Interactions using GastroPlusTM – A Mini Review

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Abstract

Physiologically based pharmacokinetic (PBPK) models plays a pivotal role in predicting drug-drug interactions (DDIs), for optimizing drug therapy and to ensure patient safety. PBPK modelling provide a mechanistic understanding of drug disposition in various physiological compartments. This mini-review emphasizes the importance of PBPK modelling, its application in DDI predictions and application of GastroPlusTM - an advanced simulation program in PBPK modeling for DDI. With the integration of physicochemical attributes and absorption, distribution, metabolism, excretion (ADME) data, GastroPlusTM enables prediction of dose optimization for special populations like paediatric, diseased individuals or organ impaired population. It is also useful to study the formulation related changes and for the assessment of potential DDIs in fixed dose combination products. In this mini-review, we cover different types of DDIs, steps to be followed for simulating DDI using GastroPlusTM and a few case studies. It is expected that this short review provides the reader with a brief overview on the building and application of PBPK models for DDI predictions.

Keywords: Pharmacokinetic; GastroPlusTM; Microsomal Cells; Hepatocytes; Recombinant Enzymes

Abbreviations: PBPK: Physiologically Based Pharmacokinetic; DDI: Drug-Drug Interactions; ADME: Absorption, Distribution, Metabolism, Excretion; TDI: Time-Dependent Inhibition; MBI: Mechanism-Based Inhibition; ARA: Acid Reducing Agents

Introduction

Predicting drug-drug interactions (DDIs) during the early stages of drug development is important. Majority of the drug-related adverse events are attributed to DDIs [1]. The physiologically based pharmacokinetic (PBPK) models are tools used to predict the DDI in vivo. They are usually combined with the in vitro drug interaction study data that are designed to determine the inhibition and induction potential of the drugs using human liver microsomal cells, hepatocytes and recombinant enzymes [2,3]. Leading regulatory agencies like the USFDA and the EMA have published detailed guidelines for the investigation of pharmacokinetic DDIs using in vivo and in vitro studies [4,5]. Drug interactions occur when two (or more) drugs interact with each other during absorption, distribution, metabolism and/or excretion phases. These interactions potentially lead to increase/decrease/no change in the pharmacological activity of one or more drugs involved in the interaction [6] (Lin. The "victim" drug is the one that undergoes a change in its pharmacokinetic and pharmacodynamics properties due to the influence of other drug(s). The "perpetrator" drug is the drug that causes the change in PK/PD of the victim drug [7,8]. Metabolic drug interactions are most complex form of the drug interactions that includes various metabolic enzymes like CYPs, UGTs and SULTs that are present in the liver and the intestines. The membrane transporters (influx and efflux) located in the liver, intestines, kidney and gall bladder may interact with the drugs that can lead to clinically relevant DDIs [6]. Estimating and interpreting the interaction between both the enzymes and transporters is considerably more challenging. The PBPK models are mathematical models built using customized equations or through commercially available

software (E.g.: GastroPlusTM, SimCypTM and PKSIMTM) that help in predicting the DDIs mechanistically. These models include drug specific inputs, protein abundance data (enzyme and transporters) and the data from in vitro drug interaction studies [9]. The application of PBPK modelling has grown over time and it is currently being employed to waive off clinical DDI studies (E.g: DDIs mediated by CYP enzymes) [10]. This reduces the development costs and also reduces unwarranted clinical investigations [11]. Although numerous commercial software is used in the pharmaceutical industry, in this review, we focus on the applications of GastroPlusTM software to build PBPK models for evaluating metabolic DDIs. This review briefly includes basic outline for PBPK modeling, types of interactions considered by the model and data required to perform the DDI studies in GastroPlusTM. We have also included a few case studies from the literature on the DDI models to provide the reader with an overview on this topic.

Building PBPK models in GastroPlusTM to predict DDIs

Model Development and Validation

The whole body PBPK model must be developed and verified for all the drugs involved in the study (perpetrator and the victim drugs) [12]. Briefly, the process of developing the model includes gathering drug inputs such as physicochemical, molecular, and biological properties and integrating them into the physiological model of an appropriate species which is available within GastroPlusTM platform. Pharmacokinetic characteristics such as clearance pathways and volume of distribution have to be part of the model development process [2,13]. Although, data generated in-house are preferred, in the absence of this, literature data can be utilized when available. The model validity is defined as the model's ability to accurately predict PK data obtained from various sources, via multiple dosing routes and across different doses. Plenty of guidance documents, white papers and peer-reviewed journal publications on the PBPK model development, validation and reporting format are available elsewhere [14,15]. The reader is encouraged to refer these literatures for deeper understanding on the topic [16-19]. The suggested literatures provide a detailed view of the model development process, do's and don'ts and the best PBPK modelling practices to be followed. The validated model is then employed to predict various metabolic DDIs for the given combination of drugs.

In vitro studies to assess DDI

The in vitro metabolic phenotyping performed during the initial stages of drug development is based on the mass balance studies; if an enzyme contributes to >25% to the drug elimination pathway, it is identified and characterized. When a significant portion of the drug is eliminated by a specific enzyme or pathway, this is considered as a major metabolic pathway [20,21]. Significant increase or decrease in the exposure of the victim drug is expected if the perpetrator drug acts on the major metabolic pathway. Perpetrator can be either an inhibitor or an inducer of the metabolic pathway. The inhibition can be either a reversible or a time-dependent inhibition (TDI). The TDI is a phenomenon in which the inhibition of an enzyme increases as the inhibitor is incubated with the enzyme for a longer period of time. It is also known as mechanism-based inhibition (MBI) [22]. If the inhibition potential is identified for a drug during the initial stages of development, a clinical study or a PBPK based assessment is performed to understand the complete risk of exposure. Typically, for induction, the extent of the enzyme induction is measured by mRNA levels based on its activation [20]. The induction potential is measured qualitatively based on the mRNA fold change for a particular enzyme in the presence of drug [21].

Types of DDI simulations

Static DDI simulations

During early stages of drug development, static DDI predictions are used to screen the DDI potential for an investigational drug in a quantitative manner. In static models, the victims and perpetrators models are constant and do not vary as a function of time [23]. Perpetrator concentrations at the site of metabolism are calculated using mean unbound systemic concentrations [23]. If the AUCR (Ratio of AUC in the presence and absence of perpetrator) outcome for static DDI is 0.8>AUCR<1.25, the application would need further investigation [24].

Dynamic DDI simulations

Dynamic DDI simulations are more advanced and are generally considered superior to the static DDI predictions. The dynamic DDIs measure both AUCR and CmaxR (Ratio of Cmax in the presence and absence of perpetrator). The concentrations of perpetrator are predicted at steady state condition using Km and Vmax (Vmax is the maximum reaction velocity at which enzyme become saturated with substrate and Km is substrate concentration at which half of the maximum velocity is achieved) values given in the model [25]. The perpetrator steady state concentration at the metabolism site are used for the calculations. This is considered as a more realistic method and is widely accepted by the regulatory agencies across the world [23]. The input parameters required for predicting DDI in GastroPlusTM simulation software (Simulations Inc, USA) for the substrate ("Victim") and the "perpetrator" (inhibitors and inducer) are given in Table 1. The required parameters for the DDI simulations have been taken from the GastroPlusTM Version 9.8.3 by Simulations Plus, Lancaster, California, USA. Fm- fraction of the drug metabolized by the particular enzyme; fg-fraction of drug that escaped gut metabolism, Ki- inhibition constant; IC50 - half maximal inhibitory concentration; Kinact-maximal rate of drug inactivation; Kdeg - enzyme degradation constant (default value considered in the model for enzymes); EC50 - concentration causing half the maximal effect; Emax- maximum induction effect; TDI – Time dependent inhibition. Recent work by Zhang et al., and Buddha et al., summarize cases where GastroPlusTM has been

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used to predict DDIs across the pharmaceutical industry. Some of them will be discussed briefly here [26,27]. Along with the metabolic DDIs discussed above, absorption DDIs also play a role in altering drug exposure [28]. The pH dependent DDIs caused by the acid reducing agents (ARAs) alter the general absorption pattern of various drugs due to the alteration of the gastric pH (from 1.5 to 3 under fasting state to pH 4 to 5). This leads to reduced bioavailability of weakly basic drugs eventually leading to the reduced drug exposure [29, 30, 31]. These pH dependent DDIs can be identified during the initial stages of development using in vitro tools. Dodd et al have established an early risk identification strategy based on drug's physico-chemical properties like – solubility, pKa and log P. They also proposed the identification strategy for pH DDI using GastroPlusTM software [32].

Table 1: Model inputs for substrate and perpetrators (both inhibitor and inducer) used in GastroPlusTM for static and Dynamic simulation.

Type of DDI	Substrate	Inhibitor	Inducer
Static DDI simulations	Fm and fg	Ki or IC50	EC50 and Emax
		K_{inact} (TDI)	-
		K_{deg} (TDI)	K_{deg} (TDI)
		Inhibitor concentrations at the site of inhibition	Inducer concentrations at the site of induction
Dynamic DDI simulations	Km and Vmax for enzymes and transporters	Ki or IC50	EC50 and Emax
		K_{inact} (TDI)	-
		K_{deg} (TDI)	$K d_{eg}$ (TDI)
		Inhibitor concentrations are calculated using the PBPK model	Induction concentrations are calculated using the PBPK model

Case Studies

Perrier predicted the DDI impact on Ziritaxestat using GastroPlusTM. Ziritaxestat is a substrate of CYP3A4 and Pgp. It also has weak inhibitory action on CYP3A4. Mechanistic PBPK model was developed and validated using rifampicin, itraconazole, pravastatin and rosuvastatin clinical DDI data sets. The verified model was used prospectively to predict DDI with voriconazole (multiple dosing) and midazolam. It was predicted that these two inhibitors increase the AUC by 15 folds and 2.7 folds respectively. For Efavirenz (inducer) 3-fold decrease of AUC was predicted [33]. In a work published by Wang et al., dynamic methods to predict the potential DDI between Dabigatron Etexilate (anticoagulant) and Ticagrelor (anti-platelet) is reported. This combination is mostly prescribed together. It was predicted that the Dabigatran Cmax and AUC were increased 8.7% and 7.1%. It was concluded that even under steady state, Ticagrelor doesn't have significant metabolic DDI with Dabigatron [34]. Kollipara et al., utilized PBPK modelling in GastroPlusTM to perform prospective dynamic DDI simulations for Encorafenib, a drug that is cleared 83% by CYP3A4, 16% by CYP2C19 and substrate of Pgp. The victim model was developed and validated by performing retrospective clinical DDI studies with Posaconazole and Diltiazem. The outcome suggested that CYP3A4 mediated DDIs are more prominent than CYP2C19 mediated DDIs. Strong inhibition gave DDI ratio of 4.5 and strong induction resulted in DDI ratio of 0.3. Additionally, the exposure of Encorafenib was predicted in hepatic and renal impaired populations using GastroPlusTM [35,36]. In yet another study, Durk et al., studied the indirect effect of excipient (β-cyclodextrin) on the DDI of Itraconazole and Fenebrutinib. The Denebrutinib formulation had β- cyclodextrin as an excipient that forms a complex with the drug and delays the rate and extent of its absorption. This effect was studied in canine dog model. This effect was also confirmed by performing DDI by reducing the apparent permeability of Fenebrutinib. This study provided a new dimension for the application of GastroPlusTM in understanding the indirect interaction of formulation factors on the absorption DDIs.

Conclusion

Drug-drug interaction studies are important to assess the impact of drug co-administration on the PK/PD performance. The DDI evaluation provides a prospective understanding on the risk associated with the in vivo performance of a new drug candidate. Commercially available software can be used to predict potential DDI risk. Two types of models – static and dynamic models can be used for assessing DDI. The metabolic DDI risk assessment using commercial software involves developing PBPK models for the victim and the perpetrator drugs using physico-chemical, pharmacokinetic and in vitro data. The absorption DDI involves alteration of the GI conditions due to the action of one drug leading to change in the absorption pharmacokinetics of the other drug. While most of the published literature focuses on assessing the prospective DDIs due to one or more drugs, some of the recent work have demonstrated its utility in predicting drug-excipient interactions as well. With ever increasing computational capabilities and advancement in the commercially available software, prospective DDI predictions are set to be more accurate in future. More importantly, utilization of these

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tools to predict drug-excipient interactions in vivo holds a lot of promise, especially in an era where companies are looking to re-formulate the products as a part of life-cycle management or due to regulatory recommendations. Such prospective predictions can potentially be utilized to waive off clinical studies, thus saving resources and time to the companies.

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