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In silico methods for predicting drug–drug interactions with cytochrome P-450s, transporters and beyond☆

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ABSTRACT

Drug–drug interactions (DDIs) are associated with severe adverse effects that may lead to the patient requiring alternative therapeutics and could ultimately lead to drug withdrawal from the market if they are severe. To prevent the occurrence of DDI in the clinic, experimental systems to evaluate drug interaction have been integrated into the various stages of the drug discovery and development process. A large body of knowledge about DDI has also accumulated through these studies and pharmacovigillence systems. Much of this work to date has focused on the drug metabolizing enzymes such as cytochrome P-450s as well as drug transporters, ion channels and occasionally other proteins. This combined knowledge provides a foundation for a hypothesis-driven in silico approach, using either cheminformatics or physiologically based pharmacokinetics (PK) modeling methods to assess DDI potential. Here we review recent advances in these approaches with emphasis on hypothesis-driven mechanistic models for important protein targets involved in PK-based DDI. Recent efforts with other informatics approaches to detect DDI are highlighted. Besides DDI, we also briefly introduce drug interactions with other substances, such as Traditional Chinese Medicines to illustrate how in silico modeling can be useful in this domain. We also summarize valuable data sources and web-based tools that are available for DDI prediction. We finally explore the challenges we see faced by in silico approaches for predicting DDI and propose future directions to make these computational models more reliable, accurate, and publically accessible.

Contents

1. Introduction

When one drug causes changes in the pharmacological effects or clinical responses of another drug co-administered for co-morbidities,

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this phenomenon is termed a drug–drug interaction (DDI). In the majority of cases a DDI is an undesirable and yet avoidable event. Positive uses of DDIs do exist, for example so called 'boosters' which enhance the pharmacokinetics of drugs that are extensively metabolized by P450s [1–3], also prevention of peripheral metabolism of DOPA-decarboxylase inhibitors by co-administration of L-DOPA [4]. However we (as have others in past reviews of DDI) [5–7] have focused on the negative effects induced by DDIs in this review. DDIs frequently complicate pharmacotherapy and may lead to adverse outcomes in patients. Several groups have reported on estimates that DDI accounts for more than 30% of all drug adverse reactions [8–10]. Furthermore, a recent study on drugs withdrawn from the market showed that DDIs are one of the leading contributing causes to drug failure [11]. Along with an increasing frequency of polypharmacy we are currently experiencing [12], these factors make DDIs a developing risk to public health. Even the increasing use of therapeutic proteins (TP) requires assessment of TP-DDI [13]. There are mainly two types of DDI of concern namely, pharmacokinetic (PK) or pharmacodynamics (PD). PD-based DDI occurs when the pharmacological effects of a drug are altered (enhanced or diminished) by the other drug due to competition at its therapeutic targets or interfering with other cellular factors, such as related signaling pathways. PK-based DDI refers to drug interactions that influence the disposition of another drug in the body, e.g. its absorption, distribution, metabolism, and elimination (ADME), causing an altered plasma concentration of the first drug that may lead to detrimental consequences (such as toxicity). PK-based DDI is the major focus in this article.

Over the past 20 years in vitro approaches have been increasingly used in both academia and industry to predict DDI [14,15]. A large number of studies have been conducted to identify and eliminate compounds with DDI potential in the early stage of drug development (reviewed in [14,15]). Additionally, the regulatory agencies of the United States and European Union have both issued guidances to help companies evaluate DDI potential of a new chemical entity with known drugs [16–19]. Industry and academics have also written white papers for addressing DDI [20, 21]. This focus has significantly advanced our understanding of PK-based DDI at the molecular level, in particular about the involvement of drug metabolizing enzymes and transporters, resulting in a large amount of experimental data. Furthermore, postmarketing surveillance systems of drugs and de-identified electronic health records of patients are now more publically accessible and represent a rich and fairly reliable resource to identify clinically relevant DDI [22]. These databases specifically provide information about population-based responses to drug(s). Gathering the experimental and population-based information together creates an enormous amount of knowledge on DDI on many levels, e.g. in vitro, in vivo, and in populo. The knowledge pyramid of DDI (shown in Fig. 1A) indicates that the clinical relevance of DDI is improved as the data levels move upwards, however the difficulty in acquisition is dramatically increased as well. DDI may be uncovered in early drug development or later on during postmarketing surveillance. Ideally the earlier these DDIs are caught the better to address them. It is key to use multiple approaches to estimate the likelihood of DDI e.g. for just a chemical structure using its 2D sketch to provide an input for in silico approaches, or for synthetic compounds with little other activity data DDI can be assessed using in vitro approaches. These methods could be extended all the way to a FDA-approved drug that have been marketed for years but may be repurposed for a new indication, or coadministered with a new drug for which DDI is unknown.

Over the past 15 years numerous reviews by several groups [23–26] have described computational modeling and how such in silico methods can be used for ADME/Tox predictions. These methods have played an important role in various stages of drug discovery and development [27–36]. In silico models have been constructed to predict DDI and assist in decision-making since it is not feasible to test all possible combinations of drug interactions experimentally. In addition some methods are ideally suited to working with molecules as they are designed. Three groups of in silico approaches have emerged as useful techniques to assess risk of interactions, and they can be applied at different points of the life cycle of a molecule to predict unfavorable DDI (Fig. 1B). With an increasing knowledge of multiple mechanisms behind DDI, mechanistic models for drug interaction potential evaluation can be constructed. Hypothesis-driven in silico approaches assess DDI potential of compounds or drugs through their interaction profile with important proteins that participate in the DDI, such as cytochrome P450 enzymes [21] and transporters (e.g. P-glycoprotein). The second group of mechanistic models is built by physiologically based PK (PBPK) modeling that extrapolates in vitro PK data of drugs to in vivo risk of DDI. This method uses a mathematical estimation of how the plasma concentration–time course of a drug is altered by another drug. The increasing availability of clinical information about drug effects from drug spontaneous reporting systems and electronic health records has promoted the development of the third group of approaches to the problem of DDI. This is termed 'informatics-driven' methods, which make it possible to identify DDI with high clinical relevance. Both PK- and PD-based DDI can be discovered through this latter approach. We shall briefly review the multiple computational methods and their applications in detecting DDI between existing drugs and novel ones. We shall also explore multiple factors that may complicate in silico predictions of DDI and discuss the potential risk of drug interaction with other substances, such as Traditional Chinese Medicines and nanoparticles.

2. In silico modeling to predict DDI

Traditionally healthcare professionals in the US rely on the package insert while in Europe the Summary of Product Characteristics (SPC) is useful to alert them about the occurrence of DDIs. However the package insert, SPC or electronic database containing this information clearly is not an exhaustive list of all the potential DDIs. The number of possible drug combinations with the several thousands of approved drugs is enormous along with the number of DDIs. Therefore it is important to prioritize a list of potential DDIs and opt for focused testing in vitro then in vivo or even clinical studies on them. Repositories of preliminary knowledge about DDI are therefore available from preclinical studies, pharmacological studies on drug PK, clinical trials and pharmacovigilance programs. Such databases are a prerequisite for the development of in silico modeling methods. While in the past such DDI data was limited, collation of the individual publications and package inserts brings us to the point where some DDIs are known for most new drugs as well as many that did not make it to the market. Computational methods represent techniques to recognize, predict and explain DDI in a high-throughput fashion and further refine testing. These approaches can also allow the design of candidate compounds with improved PK properties [37]. When closely integrated with laboratory experiments, in silico modeling may represent an efficient method to predict a DDI and understand the molecular basis of it [38].

2.1. Hypothesis-driven in silico approaches

A number of key components of ADME processes, such as drug metabolizing enzymes and transporters, have been widely characterized and modeled over the past twenty years. Many clinically relevant PK-based drug interactions have been attributed to modulation of functions of these proteins including CYP3A4, P-glycoprotein (P-gp), and organic anion transporting polypeptide 1B (OATP1B), etc. (Table 1). With the development of high-throughput screening, a large volume of data is now aggregated about pharmacological activities of drugs against these targets and (for some) three-dimensional (3D) structural information is available [39]. This provides an experimental basis for computational modeling interactions between drug(s) and targets. Hypothesis-driven in silico models seek to predict at the specific protein level and understand the underlying mechanisms for previously recognized DDIs. Protein-specific mechanistic models can provide qualitative estimation

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