PharmaPendium®

Enabling comprehensive assessments of drug–drug interaction risks

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Here, Dr. Kevin Lustig, President and CEO of The Assay Depot, Inc., and Dr. Maria Thompson, Principal Consultant, look at the dynamics of drug metabolizing enzymes and transporters and ask how an understanding of this critical aspect of biology enables assessments of drug–drug interaction risks. In addition, they comment on PharmaPendium, which includes the DMPK solution with its DDI Risk Calculator, as an important tool in making these assessments successfully.

Abstract

Understanding the dynamics of drug metabolizing enzymes and transporters (METs) is critical to successful drug development. MET behavior can significantly impact drug safety. Many factors regulate enzymes and transporters, which in turn affect the pharmacokinetic properties of drugs and mediate drug interactions. Evaluation of drug interaction profiles required detailed in vitro and in vivo studies along with predictive modeling.

Thanks to its comprehensive data on METs, PharmaPendium offers a unique platform for modeling advanced drug interactions. This MET data and the ability to predict drug–drug interactions (DDIs) are incredibly valuable for optimized research workflows and accelerated drug development. They enable intelligent, in silico drug design and provide scientists with comprehensive knowledge about drug metabolism, significantly reducing the need for costly and time-consuming lab work and animal models and informing critical decisions on clinical trial design.

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Introduction

Every successful drug discovery and development effort needs to factor in drug efficacy and safety, both of which are intimately linked to drug metabolism. Knowledge and understanding of drug transport and metabolism are crucial during drug development to predict potential drug interactions and inter-individual variations. The U.S. Food and Drug Administration recommends that "pharmacokinetic interactions between an investigational new drug and other drugs should be defined during drug development, as part of an adequate assessment of the drug's safety and effectiveness."

Drug metabolism

Drug metabolism is an important aspect of clinical pharmacology and is the primary mechanism by which drugs are converted into their inactive metabolites. Equally important is the effect of metabolism on those drugs that are converted into pharmacologically active metabolites or in some cases, into reactive, toxic, and carcinogenic metabolites. Drug metabolizing enzymes are broadly categorized into two distinct classes: phase I or functionalizing enzymes and phase II or conjugating enzymes.

Cytochrome P450 (CYP) monooxygenases are the most important phase I enzyme class involved in drug metabolism. The subfamilies, CYP 1A2, 2C and 3A4 are together responsible for over half of the known drug metabolic reactions. Non-CYP enzymes may also mediate biotransformation. Phase II biotransformation of drugs involves conjugation or covalent addition of endogenous moieties to the drug, which converts a lipophilic substrate into a polar product.

Drug metabolizing enzymes are found in most body tissues with the highest levels in the liver, small and large intestines and some expression in the nasal mucosa and lung tissues. Notably, a single enzyme pathway can drive the metabolism of multiple drugs. Similarly, metabolism of one drug can involve multiple pathways acting in series or in parallel.

Drug transport

Membrane-bound carriers or transporters are the primary mediators of drug transport. They directly affect drug absorption, distribution, metabolism and excretion (ADME) for the majority of compounds. Though hundreds of membrane transporters have been identified, most of those associated with drug transport belong to the ATP-binding cassette (ABC) or solute carrier (SLC) superfamilies. Drug transporters are critical determinants of drug efficacy and toxicity. For instance, transporters in the gastrointestinal tract affect drug absorption by increasing uptake (uptake transporters) or limiting drug absorption (efflux transporters). The P-gp transporter in the blood–brain barrier prevents drugs from entering the central nervous system through efflux mechanisms.

Regulation of drug transport and metabolism

Drug transporters and metabolizing enzymes show significant differences based on sex, age, ethnicity, genetics (polymorphisms) and a variety of external factors, such as diet and lifestyle. It is important to understand these variations not only during drug development but also when designing individualized medicine strategies. The representative examples below demonstrate how these proteins are differentially regulated and affect the pharmacokinetic properties of drugs.

The metabolizing enzyme CYP3A4 shows higher activity in females than males. Hence, drugs that are metabolized by CYP3A4 will show higher clearance in females, and doses may have to be adjusted accordingly. Males have a higher activity of the enzyme CYP2D6, so they show higher clearance rates for drugs metabolized by this enzyme.

Most drug transporters, such as P-gp and MRP-1 follow a developmental pattern. The activity of transporters increases during the first few months after birth, reaching adult levels at 2 years of age. Similarly, most drug metabolizing enzymes are immature in neonates. For examples, levels of CYP enzymes at birth are only ~30% of normal adult levels and the different CYP enzyme families attain adult levels at different ages.

Smoking increases the activity of CYP1A2, which means increased clearance of caffeine and theophylline.

Polymorphisms in transporters and enzymes can affect drug distribution and elimination. For example, CYP2D6 activity increases when multiple gene copies arise. A wide variety of drug toxicities and/or efficacies can be affected by variations in the CYP2D6 status, such as tamoxifen. CYP2D6 status can dictate which patient groups respond optimally to tamoxifen.

It is important to take into account all the above-mentioned variations, not only in clinical practice but also during drug discovery and development. During clinical management of patients, these physiological and pharmacological factors will drive decisions such as drug dosage and co-administration of drugs to exploit drug interactions favorably for the patient, and to predict and mitigate the risk of any adverse events caused by unfavorable drug–drug interactions.

PharmaPendium's DMPK Solution, which includes a powerful drug–drug interaction risk calculator, provides access to preclinical and clinical data on drug metabolizing enzymes and transporters, in addition to in-depth pharmacokinetic parameters on all approved drugs. This helps scientists to make informed decisions in drug candidate assessment and to identify drug–drug interactions.

The ability to quickly search a single comprehensive source of data stretching back to 1938 is invaluable. Identifying information salient to a compound of interest can dramatically impact the time and cost of drug development, enabling researchers to deliver higher quality compounds to the clinic in a reduced time.

Drug interactions

Drug interactions occur when one drug affects the pharmacokinetics of other drugs and/or metabolites. They can lead to unexpected accumulations of a drug, even to toxic levels, and adversely impact the efficacy of a drug. Two factors that can produce drug interactions are modulation of absorption/distribution and metabolism driven by the combined activity of drug transporters and metabolizing enzymes.

Drug absorption and distribution

Inhibition of transporters can affect drug absorption and/or distribution to different sites. For example, the transporter P-gp, through efflux mechanisms, reduces drug distribution across the blood-brain barrier. Similarly, the transporter OATP monitors or limits drug distribution to the liver. The clinical implications for drug administration are that concomitant use of other drugs that activate or inhibit these transporters may affect distribution of the first drug. A frequently cited example is that of quinidine, an inhibitor of P-gp. When quinidine is co-administered with loperamide, the former inhibits P-gp and allows higher concentrations of loperamide to cross the blood–brain barrier, which can lead to dangerous neurotoxicity, including respiratory depression.

DDIs and drug metabolism

Drugs can interact by induction or inhibition of metabolizing enzymes. The most prominent enzyme thus regulated and involved in drug interactions is the CYP group. Enzyme inhibition leads to decreased drug metabolism, which in turn increases the drug levels in the body. Identifying the type of inhibition may help counter it during clinical drug administration.

A more complex phenomenon that can lead to drug interactions is enzyme induction. This entails increased transcription and synthesis of enzyme proteins, resulting in augmented catalytic activity. Enzyme induction often leads to enhanced clearance of drugs, resulting in reduced activity. In some rare cases, induction is associated with increased production of the active metabolite(s) of the drug.

A clinically relevant example is the induction of CYP2E1, which increases metabolism of acetaminophen to produce a hepatotoxic metabolite. A key difference between enzyme inhibition and induction is that inhibition may be seen following even one dose of the drug whereas induction typically requires chronic drug administration. This must be considered when designing different approaches for acute and chronic drug therapies.

Interactions between metabolizing enzymes and transporters

Since most drugs are substrates, inhibitors or inducers of both metabolizing enzymes and transporters, metabolism may affect transport and vice versa when enzymes and transporters are in close physical proximity. For example, both P-gp and CYP3A4 are expressed in intestinal enterocytes, and both these proteins have common substrates. This proximity can limit drug bioavailability either by intestinal first-pass metabolism of the drug via CYP3A4 or by P-gp-mediated efflux of the drug. These interactions have important clinical implications when co-administering different drugs with variable effects on transporters and metabolizing enzymes.

PharmaPendium is a unique data solution that can serve as a major resource for modeling drug interactions resulting from the effects of drug metabolizing enzymes and transporters. It is a rich source of information for researchers and clinicians, providing data on phase I and phase II metabolizing enzymes, transporters and dynamic pharmacokinetic parameters. This repository offers detailed data on interactions between drugs, enzymes and transporters including the role of the drug as a substrate, inducer or inhibitor. The DMPK solution provides comparative data on drug–drug interactions not widely available in the scientific literature. In addition, the DDI Risk Calculator identifies drug–drug interaction risks in a manner compliant with the 2012 FDA Guidance for Industry Drug Interaction Studies. Helping to identify potential interactions for multiple drugs simultaneously means a full risk profile against marketed drugs can be created.

The importance of drug transport and metabolism

A critical element of drug discovery and development involves determining the exact role of transport and metabolism and its impact on the pharmacokinetic parameters of the drug candidate. An inadequate focus on this aspect during drug development can lead to late-stage failures or even withdrawals from the market. In depth interaction studies during new drug development determine whether potential drug interactions might require dose adjustments of the new drug or other drugs concurrently administered. It is also necessary to determine if additional therapeutic monitoring is required or if some drug combinations would be entirely contraindicated. The three major interactions that need to be examined for new drugs are:

1. **Metabolism-based drug interactions**: It is necessary to determine if the new drug is a substrate of an enzyme that can be modulated by other drugs during co-administration and whether the new drug is likely to affect the metabolism of other drugs already in use.
2. **Transporter-based drug interactions:** Similarly, it needs to be determined whether transporters can affect the absorption and disposition of the new drug and whether the new drug affects transporters to modulate the absorption and disposition of other drugs.
3. **Multiple drug–drug interactions:** These complex interactions involve multiple metabolizing enzymes and transporters being modulated in different ways by co-administration of different drug combinations.

Detailed and comprehensive experiments involving in vitro and in vivo interaction studies are currently used for such analyses. Early in the process of drug development, a compound's interaction profile is evaluated in vitro by determining whether the drug is a potential substrate, inducer or inhibitor of enzymes and transporters. To study drug metabolism, candidate compounds are analyzed by exposing them to cellular extracts expressing drug metabolizing enzymes, such as microsomes, hepatocytes and liver slices. In addition to cell extracts, studies also use recombinant enzymes to determine the metabolic profiles of drugs. It is important to assess the pathways affected and the potential of the drug candidates to induce or inhibit enzymes. Drug transporters are similarly studied using a variety of in vitro assays and screens. Population pharmacokinetics is considered a useful adjuvant to in vitro screens.

For the in vivo aspect, researchers have traditionally resorted to the use of specialized animal models. Candidate molecules are administered at high doses to animals to determine basic ADME. Animal models that are traditionally used to study metabolizing enzymes and transporters include native, knockout, humanized, chimeric and disease mouse models, in addition to rats, rabbits, dogs and monkeys (Salyers and Xu 2012). However, direct application of these data to humans can be tricky owing to the significant differences in the expression, specificity and activity of these metabolizing enzymes among species (Guengerich 1997).

Potential drug–drug interactions are examined using rats or rhesus and cynomolgus monkey models for induction-based interactions and mice, rats and monkeys for inhibition-based interactions. Transporters are studied during drug development for potential drug interactions using in vivo mouse, rat, rabbit or dog models (Salyers and Xu 2012).

Accurate analyses of drug metabolism and transport for novel drug candidates and elucidation of potential drug–drug interactions require a combination of in vitro assays and

in vivo models. In silico modeling can be used to predict effects on drug transport and metabolism and in turn, on drug–drug interactions. Mechanistic static models like PharmaPendium's DDI Risk Calculator or the physiologically based pharmacokinetic (PBPK) models provide comprehensive information about drug interactions. Such studies can help predict clinical consequences of drug–drug interactions and design strategies during the early phases of drug development. However, even modeling approaches require accurate datasets covering expression profiles of these proteins.

To this end, PharmaPendium's DPMK solution provides a resource to obtain reliable data on drug interactions and prioritize the safest, most promising candidates for further drug development. Using the case of quinidine, loperamide and the P-gp transporter cited as an example above, with just a few keystrokes, we could find a list of carefully curated data relating to the effect of P-gp on drug transport. This represents a wealth of information for the drug development scientist, enabling an understanding of all that has already been done and providing a platform for the rational, intelligent design of future experiments. PharmaPendium offers risk assessments for drug development projects in areas such as drug interaction-induced toxicity. Additionally, this solution sheds light on past regulatory issues, providing an opportunity to avoid pitfalls and streamline the regulatory submission process. The wealth of detailed, filterable data can guide drug development decisions, avoiding costly late-stage drug failures. This means delivery benefits to the pharmaceutical industry, both in terms of dollars saved and in enabling redirection of finite resources to pursue other more viable compounds.

References

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PharmaPendium®

PharmaPendium informs critical drug development decisions on safety and efficacy, risk assessments and mitigation and study designs with fully searchable FDA and EMA drug approval documents and FAERS data, a drug-drug interaction risk calculator and comparative safety, pharmacokinetic, efficacy, and metabolizing enzyme and transporter data.

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