Review

Ongoing Challenges in Drug Interaction Safety: from Exposure to Pharmacogenomics

Jane P. F. Bai*
Office of Clinical Pharmacology, Office of Translational Science, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, USA

Summary: The complex transporter-cytochrome P450 (CYP) enzyme interplay in the disposition of drugs makes it very challenging to address the safety of clinical drug interactions. Thus, two major subjects are discussed herein. First, the concept of an intravenous drug interaction study (where the perpetrator is administered intravenously or orally while the drug candidate administered intravenously) to facilitate prediction of maximal possible systemic exposure of a substrate drug when oral drug interactions occur is explored. If a substrate drug with oral bioavailability is equal to or less than 80%, an intravenous drug interaction study at low dose along with a few key oral drug interaction studies could be useful for achieving this objective with the aid of modeling and simulations. Along with the clinical safety of the drug, one could then attempt to predict the safety margin when the worst drug interactions occur. Secondly, the efficacy and safety disparity of clopidogrel, statins and irinotecan each among races and genetic variants are discussed to illustrate that pharmacogenetic knowledge is important for the interpretation and prediction of drug interaction-induced adverse events, whereas drug interaction-induced adverse events are equally informative for identifying genes-based mechanisms involved.

Keywords: drug interactions; transporters; intravenous drug interaction; maximum tolerable systemic exposure; modeling and simulation; pharmacogenomics; adverse events

Introduction

Drug interactions are an ever-evolving, challenging, and yet critical safety issue in disease management and treatment. Thirty years ago, to ensure the clinical safety of drugs, drug interactions involving CYP enzymes were the key issue to address. Scientific research efforts on P-glycoprotein and related drug interactions took the spotlight approximately fifteen years ago, and research efforts on transporters have since unveiled an ever-increasing list of transporters in the intestine, liver, kidney, blood-brain barrier and placenta. BCRP (breast cancer resistant protein), OATP1B1 (organic anion transporting-polypeptide), MRP2 (multidrug resistant protein 2), PEP1 and PEP2 (di/tri-peptide transporters), and OCT (organic cation transporters) each significantly influence the dispositions of different types of drugs.1-2 These transporters have overlapping substrate or inhibitor specificity. There is an extensive, inter-twined transporter/enzyme network with overlapping substrate and inhibitor specificities and this concerted network is very efficient in eliminating xenobiotics. The complex transporter-CYP enzyme interplay plays the key role in the disposition of drugs. As a result of this complex interplay and the lack of specific inhibitors for individual transporters and CYP enzymes, it is not only unlikely but also costly to sort out the specific CYP enzyme or transporter involved in the outcome of drug interaction between each and every pair of concomitantly used drugs.

During the development of a drug, it is unlikely to predict all clinically possible medications. Hence, it is important to assess maximum tolerable systemic exposure when drug interactions occur. Clinical manifestations of drug-induced adverse events are affected by systemic exposure (AUC and Cmax) of a drug and patient intrinsic factors. The intrinsic factors of a patient include age,
Drug Interaction Safety Issue

Drug interaction safety issue: maximum tolerable systemic exposure of a drug

The goal of drug interaction studies is to ensure the clinical safety of drugs. With tremendous effort made during drug development to proactively address the safety of clinical drug interactions, there have only been a few cases where serious or fatal adverse events from drug interactions occurred post approval. It is expected that gene polymorphisms of transporters affect clinical drug interaction outcomes of a drug. In light of ongoing drug interaction challenges, discussion hereafter is focused on 1) the concept of interaction study between an intravenous drug candidate and perpetrator co-administered intravenously or orally to facilitate estimation of maximum tolerable exposure of a substrate drug when drug interactions occur and 2) the need for integrating pharmacogenetics with drug interactions to ensure drug safety.

Drug interaction safety issue: maximum tolerable systemic exposure of a drug

The critical drug interaction questions one should ask when dealing with a new molecular entity are 1) what its maximum systemic exposure is when drug interactions occur, and 2) whether such a maximum systemic exposure results in severe adverse events. Let’s examine how drug exposure is affected by drug interaction based on basic pharmacokinetics. Oral bioavailability (F) is determined by the fraction dose absorbed and first-pass effect; that is \( F = 100\% \times F_{ab} \times F_{gut} \times F_{hepatic} \) (Fab, fraction dose absorbed; Fgut, fraction dose available after gut wall first-pass metabolism; Fhepatic, fraction dose available after hepatic first pass metabolism). Oral drug interaction affects absorption, first-pass effect and total clearance whereas intravenous drug interaction only affects total clearance, as evidenced by equations (1) and (2).

\[
\text{AUC (iv)} = \frac{\text{Dose}}{\text{CL}_{\text{total}}} \quad \text{Eq. (1)}
\]

\[
\text{AUC (oral)} = F \times \left( \frac{\text{Dose}}{\text{CL}_{\text{total}}} \right) \quad \text{Eq. (2)}
\]

Since AUC(iv) is larger than AUC(oral) at the same dose if F is less than 1 (i.e. first-pass effect exists), it is intravenous drug interaction, not oral drug interaction, that reflects maximum exposure of a drug, which may occur, when concomitant medication extensively inhibits its elimination and consequently leads to clinical manifestation of severe or fatal adverse events. To cost-effectively estimate the intrinsic clearance (CLintrinsic) of a drug with or without inhibitors for future modeling and simulation to predict the worst drug interactions, an intravenous drug interaction study is indispensable, using an intravenous victim drug along with a perpetrator given orally or intraveously.

Statins are good examples of what oral exposure of a drug would be when first pass metabolism and systemic clearance are extensively inhibited by inhibitors. Drug interactions involving statins have been extensively studied ever since severe and fatal rhabdomyolysis were reported due to cerivastatin and gemfibrozil co-administration. Inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase, statins effectively treat atherosclerosis by lowering cholesterol. In general, statins are substrates of several CYP enzymes (including CYP3A4, CYP2C8, CYP2C19, and CYP2C9) and multiple transporters (including OATP1B1, BCRP, and MDR1). Involvement of individual CYP enzymes or transporters in their dispositions varies from statin to statin. Maximum fold-increase caused by drug interactions at AUC of atorvastain, cerivastatin, pravastatin, rosuvastatin, and pitavastatin each is greater than the calculated 100/F ratio (Table 1), indicating that drug interactions actually affect both total systemic clearance and first pass metabolism. The inhibitors in Table 1 inhibit multiple processes involved in the disposition of individual statins. Cyclosporine apparently inhibits both
CYP3A4 and OATP1B1 for cerivastatin and atorvastatin, and inhibit OATP1B1 to a major extent for pravastatin, fluvastatin, and pitavastatin. The inhibition of CYP3A4 for lovastatin and simvastatin, inhibits OATP1B1 for pravastatin and pitavastatin, inhibits CYP2C8, 3A4 and OATP1B1 for cerivastatin, and inhibits CYP2C9 and OATP1B1 for rosuvastatin. Based on the results in Table 1 the maximum fold-increase in AUC resulting from drug interactions exceeds those predicted by the ratio of 100/bioavailability. It is a general misconception that fold-change in oral exposure caused by drug interactions is at most equivalent to the 100/bioavailability ratio. As a matter of fact, CLtotal could decrease as well, leading to greater exposure than what is predicted by the ratio of 100/bioavailability. Understanding the maximum tolerable exposure (AUC, Cmax) of each statin, which could possibly occur due to drug interactions, is vital in assessing clinical safety.

**Use of intravenous drug interactions to predict maximum exposure and safety:** Clinical applications of a drug in treating various diseases often take place over time after approval for treating one or two specific indications. It may not be possible to foresee all possible clinical medications for a drug candidate during its development, or predict possible exposure when drug interactions occur. Therefore, it is important to assess maximum tolerable systemic exposure. Rather than searching for specific inhibitors for each and every transporter or enzyme involved in the disposition of a drug, it is most cost-effective to conduct an intravenous drug interaction study to help assess maximum tolerable exposure and clinical safety of a drug, if clinically feasible. Intravenous drug interaction studies could be conducted using intravenous victim drug plus a perpetrator a administered intravenously or orally. Usually, thorough QT study required for a new molecular entity is conducted at a supra-therapeutic oral dose for an orally administered drug, from which the bioavailable dose is likely much higher than the intravenous low dose proposed here. So the safety observed during a thorough QT study could support an intravenous drug interaction study. Bypassing the intestinal and hepatic elimination, intravenous exposure is expected to be higher than oral exposure for a drug with substantial first-pass elimination. Therefore, intravenous drug interaction studies should be considered to understand maximum tolerable exposure. Intravenous drug interaction studies need to consider whether intravenous Cmax of a victim drug resulting from drug interaction is clinically tolerable. Therefore, an intravenous dose lower than its target dose could be a sensible alternative.

Having been studied extensively as a victim drug with regard to its drug interactions with potent inhibitors, midazolam, metabolized to 1-hydroxymidazolam by CYP3A4 with a Km of 2.4 μM (~782 ng/ml), is used herein as an example of how an intravenous drug interaction study at a low dose along with the results of other pharmacokinetic studies may be used to predict oral drug interaction outcomes. The study by Tsunoda et al. reported that exposure of intravenous midazolam 2 mg increased ~5 fold when co-administered with oral ketoconazole 200 mg, and consequently its intravenous clearance decreased by 4.7 fold. Based on reports that oral bioavailability of midazolam averaged 30%, a crude non-compartmental estimation predicts an average AUC of 813 ng·h/ml for oral midazolam 6 mg when co-administered with oral ketoconazole 200 mg, under the assumptions that ketoconazole causes a complete inhibition of the oral first pass effect of midazolam and similar reductions in CLoral and CLiv occur for midazolam. Though only a crude estimation, estimated AUC is interestingly not far off from the observed data of 738 ng·h/ml. The reasons for such close prediction are 1) intravenous and oral doses only differed by 3 fold and 2) orally bioavailable dose could be 1.8 mg (dose multiplied by bioavailability, 6 mg × 0.3), close to the intravenous 2 mg dose. Another example is the study by Olkkola et al. showing that oral itraconazole 200 mg increased the exposure of intravenous midazolam 0.05 mg/kg (3.5 mg for a body weight of 70 kg) by 3.2 fold. Itraconazole appeared not as potent as ketoconazole, which is in agreement with their reported Ki of 15 nM and <10 nM. A rough non-compartmental estimation predicted that a 474 ng·h/ml for AUC of oral midazolam 7.5 mg in the presence of oral itraconazole 200 mg, which is much higher than the observed value of 267 ng·h/ml. The orally bioavailable dose could be 2.25 mg assuming an oral bioavailability of 30% and could only be ~25% lower than the intravenous dose of 3.5 mg. However, this estimation is off, indicative of the need for sophisticated modeling and simulation for better prediction.

With the first-pass elimination as the key determinant,
Drug Interaction Safety Issue

Fig. 1. Decision tree for including intravenous drug interaction studies

an oral bioavailability of 80% or less as the cut-off point is suggested herein for reference with regard to choice of oral drug interaction studies versus intravenous plus oral drug interaction studies (Fig. 1). The rationale of using 80% as the cut-off is that intravenous exposure is only 1.25 fold higher than oral exposure at the same dose for a drug with an oral bioavailability of 80% and that exposure increase would only be 1.25 fold (100/80) if oral first pass metabolism is completely inhibited and change in total clearance is not considered. To predict maximum likely drug interaction-caused systemic exposure for a substrate drug with oral bioavailability higher than 80%, key oral drug interactions suffice. When oral bioavailability is greater than 80%, the apparent CLintrinsic estimated from an oral study is considered acceptable and close to the CLintrinsic estimated from an intravenous study. For drugs without substantial first-pass effect, oral drug interaction studies may be appropriate; otherwise both oral and intravenous drug interaction studies would be useful to provide relevant information to assess clinical safety outcomes of drug interactions, if intravenous drug interaction studies are clinically feasible.

Comprehensive in-vitro studies would first be needed to delineate the mechanistic pathways of first-pass elimination and systemic clearance. Afterwards, an intravenous study would help to determine CLtotal, for used to estimate intrinsic clearance, CLintrinsic, with or without a perpetrator based on in-vitro Km and Vmax of a drug, Ki of a perpetrator, and estimated Qh (hepatic blood flow). For a specific disposition pathway, estimation of CLintrinsic may be performed using the following equations.

CLintrinsic = \( \frac{V_{\text{max}}}{K_m + C_{\text{substrate}}} \)

Since there are no specific inhibitors for any transporter or drug-metabolizing enzyme and the disposition of a drug usually involves multiple processes, the apparent total CLintrinsic is most likely the sum of multiple contributing processes.

Total CLintrinsic = \( \sum CL_{\text{int}}(i) \)

Where n represents the number of key parallel pathways involved in the disposition of a drug.

Total CLintrinsic can be approximated using various assumptions considering the fact that individual parallel contributing processes may not be accurately singled out for calculation. Certainly, sequential pathways involved in the disposition of a drug may be affected by the same inhibitors. For example, cyclosporine is the inhibitor of both OATP1B1-mediated hepatic uptake and subsequent CYP enzyme-mediated metabolisms involved in the disposition of statins. Net CL due to sequential pathways may be estimated and modeled as well; for example, CLtotal = CIi · CLj if there are only 2 pathways, I and J, sequentially involved in the disposition of a drug.

These parameters may then be used along with additional selective oral drug interaction studies for modeling and simulation to estimate the maximum likely exposure of a drug when co-administered with a strong inhibitor which comprehensively and simultaneously inhibits multiple mechanisms involved in the disposition. To facilitate understanding of the proposed approach, simple model diagrams are shown in Figures 2A and 2B. As shown in Figure 2A, an intravenous drug interaction model is first established to obtain micro-rate-constants, phar-
Fig. 2. A: intravenous model to obtain microconstants; B: oral model

macokinetic parameters and intrinsic clearance based on a study where the victim drug is given intravenously while the perpetrator is given intravenously or orally. *In-vitro* metabolism and oral pharmacokinetic single and multiple dose studies may be used to design an oral drug interaction model, as shown in Figure 2B, by expanding the intravenous model to include first pass metabolism in the liver and gut. Again, the perpetrator is given orally or intravenously for the oral model. From modeling the results of oral studies at high doses and an intravenous study at low dose, of the victim drug, one could refine the oral model. At a low dose, the serum levels of a victim drug may be below $K_m$ (Michaelis Menten constant) for an enzyme or transporter, its fold-increase in exposure due to drug interaction is expected to be high and useful for estimating *in-vivo* $K_m$ and CLintrinsic. All *in-vitro* and *in-vivo* results are used to simulate and estimate the exposure of a victim drug under the worst scenario (Fig. 3). Excises of simulation have been applied to predict outcomes of drug interactions. One such example is a published stochastic prediction of the pharmacokinetics of midazolam following co-administration of ketoconazole.

Once the maximum exposure of an orally victim is estimated for the worst scenario of co-administering with a strong inhibitor, lower exposure that may occur from drug interactions do not need to be measured by pairwise drug interaction studies one by one for each possible medication. Based on the safety observed in clinical phases I, II, and III studies, along with pharmacological mechanisms of the drug candidate, it is possible to estimate maximum possible tolerable exposure. Such estimation and understanding help waive drug interaction studies that only result in lower exposure compared to the worst scenario.

With regard to inhibitors for such studies, cyclosporine and gemfibrozil may be considered since both inhibit CYP enzymes as well as multiple transporters. Multiple inhibitions provide the much needed increase in exposure for further simulation to predict maximum possible exposure of a drug that may occur. Certainly, concomitant use of cyclosporine or gemfibrozil, may not be foreseeable with a drug under development; nonetheless these strong inhibitors are good candidates for considera-
tion when conducting intravenous or oral drug interaction studies at low dose of the victim drug. If inclusion of these two drugs in drug interaction studies is not clinically feasible, alternative strong inhibitors may be used. Research efforts to explore such approach to predicting maximal possible exposure and safety of a victim drug help the pharmaceutical industry to cost-effectively develop better and safer drugs without exhaustive drug interaction studies. Modeling and simulation is used for simulating clinical trials and drug interactions and offer means to reduce unnecessary studies. Application of modeling and simulation technology to facilitate meaningful drug interaction studies has achieved some success.11)

One may question the usefulness of intravenous drug interaction studies for understanding the local gastrointestinal (GI) toxicity of an oral drug. GI toxicity is detected early from oral dose finding studies, and need not be delayed until intravenous or oral drug interaction studies. Intravenous formulation feasibility is obvious. If a drug is stable enough for sterile powder formulations but not in aqueous solution for a short-term storage plus shipping prior to the clinical intravenous drug interaction trial, intravenous preparations may still be feasible by formulation designs for on-site reconstitutions.

Integration of drug interactions and pharmacogenetics

Genetic mutations that cause functional loss or reduced activity of an enzyme or transporter involved in the disposition of a drug lead to similar clinical consequences as drug interactions. The difference is that drug interactions affect those who have functional activity of an enzyme or transporter while genetic mutation affects only those who carry a mutant allele with reduced or no functional activity. Drug interactions and pharmacogenetics offer each other valuable information for improving the safety of drugs. Efforts on drug interactions and pharmacogenomics have been made to ensure the efficacy and safety of drugs. As a result, numerous drug labels have been updated with genomic biomarkers and the list of drug/genomic biomarker pairs includes warfarin/CYP2C9, carbamazepine/HLA-B*1502, abacavir/HLA-B-5701, panitumumab/Kras mutation, irinotecan/UGT1A1 variants, erlotinib/EGFR expression, cetuximab/EGFR expression, rasburicase/G6PD deficiency, trastuzumab/Her2/neu over expression, clopidogrel/CYP2C19 variants, and many others. Below are some examples to illustrate the continuing challenges of drug safety, from the perspective of drug interactions and pharmacogenetics.

Relation between drug interactions of clopidogrel and CYP2C19 polymorphisms: Clopidogrel, an antithrombotic drug, is a prodrug and needs CYP2C19 for its conversion to an active metabolite (R13094). Other enzymes including CYP3A4, 2B6, and 2C9 have also been implicated in its activation, but so far CYP2C19 stands out as the one with the most clinical evidence. The active metabolite targets P2Y12, a G protein-coupled receptor, thereby interfering platelet activation. At the time of clopidogrel approval in 1997, it
was not known what enzyme was involved its activation to a relatively short lived active metabolite which is difficult to isolate and identify.

Clinical variability in patient response to clopidogrel and clinical cases of treatment failure in preventing acute coronary syndromes prompted several clinical studies.[15–17] In May, 2009, the clopidogrel label was updated with pharmacogenetic information including the frequencies of non-functional alleles of CYP2C19 in Whites, Blacks, and Chinese. The impact of non-functional alleles of CYP2C19 on clopidogrel activation and the reported clinical association between CYP2C19 genotypes and clinical response to clopidogrel. Non-functional alleles of CYP2C19 are more common in Asians than Whites, indicative of the need for racially specific clinical dosing to adequately treat diseases in different races. A relevant statement has been added to the updated label of clopidogrel to reflect this need.

Drugs that inhibit CYP2C19 may cause reduced or complete loss of CYP2C19 activity and similar clinical consequences as CYP2C19 mutant alleles. Proton pump inhibitors (PPIs) including omeprazole, lansoprazole, esomeprazole, rabeprazole and pantoprazole are often co-administered with clopidogrel to prevent GI bleeding. These PPIs are substrates and inhibitors of CYP2C19 and CYP3A4, with differential interactions and potencies. PPIs thus potentially reduce or block clopidogrel activation through inhibition of 2C19 and CYP3A4. The statement, “Co-administration of Plavix with omeprazole, a proton pump inhibitor that is an inhibitor of CYP2C19, reduces the pharmacological activity of Plavix if given concomitantly or if given 12 hours apart” has been added to the May–2009 updated label of clopidogrel.

Is there a class effect with regard to interactions between PPIs and clopidogrel. The results of clinical studies investigating drug interactions between PPIs and clopidogrel are controversial. As pointed out by Last et al., there are numerous weaknesses in the study designs of these studies, including small study populations, ill-defined doses of PPI used in retrospective analysis, short duration of studies, use of surrogate laboratory biomarkers, confounding factors including the presence of diabetes mellitus and renal impairment that independently cause reduced platelet response.[18] Nonetheless, Norgard et al. conclude that concomitant use of PPIs with clopidogrel increases the risk of cardiovascular events except pantoprazole.[19] Whether there is a class effect of PPIs on the pharmacological activity of clopidogrel is being investigated.

Relation between transporter-mediated drug interactions and gene polymorphism: Membrane transporters are polymorphic and contribute to variability in the pharmacokinetics and clinical response of drugs. Loss or decrease in functions of membrane transporters due to gene mutation may contribute to local accumulation in an organ of a parent drug or its metabolites, resulting in differential clinical manifestation of adverse events. Reports suggest association of transporter polymorphisms with drug-induced adverse events. Below are examples of the relation between gene polymorphisms of transporters and drug-induced adverse events. Challenges facing the regulatory agencies in providing the public and prescribers with adequate guidance are discussed.

Relation between drug interactions of statins and SLCO1B1 polymorphisms: OATP1B1 is reported to be involved in the hepatic uptake of statins. Once taken up into hepatocytes, statins are eliminated by CYP enzymes-mediated metabolism or by transporter-mediated biliary secretion. The gene encoding OATP1B1 is SLCO1B1. A genome-wide association study on 85 patients identified strong association between rs4363657 single-nucleotide polymorphism (SNP) and myopathy.[19] The rs4363657 SNP is non-coding and in nearly complete linkage disequilibrium with nonsynonymous rs4149056 SNP. Thus, the rs4149056 C allele was identified as the suspect SNP.[20] Further analysis on this nonsynonymous SNP confirmed its association with the risk of myopathy, and the result was replicated using the candidate gene approach in a much larger study with a total of 20,356 British subjects.[19] An independent study on 509 patients by a different group of investigators also confirmed statistical association between this SNP and statin-induced adverse events.[21] In agreement, these clinical studies identified SLCO1B1 variants as a risk factor for statin-induced adverse events. There have been no studies on other ethnic groups such as Asians to define whether SLCO1B1 variants constitute a risk factor for statin-induced myopathy in this ethnic group.

There are case reports of developing rhabdomyolysis due to concomitant use of simvastatin and cyclosporine,[22–24] suggesting that drug interactions may cause rhabdomyolysis. Gemfibrozil has been reported to reduce hepatic uptake of statins via OATP1B1 and consequently increase systemic exposure.[1,25] In the approved label of pravastatin, there is a statement on the risk of coadministration with cyclosporine. For the approved label of simvastatin, there is also a statement on the risk of myopathy when co-administered with cyclosporine or gemfibrozil (both are OATP1B1 inhibitors). There is no information on labels of statins relating the relation between SLCO1B1 genotypes and risk of myopathy. These labels should be updated once evidence-based reviews render a statistically meaningful association between SLCO1B1 genotype and statin-induced rhabdomyolysis or myopathy.

Relation between drug interactions of irinotecan and polymorphisms of UGT1A1 and SLCO1B1 genes: Irinotecan is clinically used in combination with 5-FU and oxaliplatin for treating colorectal, ovarian,
stomach and lung cancers. Severe diarrhea is a gastrointestinal adverse condition reportedly caused by the active metabolites (SN-38) and inactive metabolite (SN-38-glucuronide) of irinotecan. Conjugation of SN-38 with glucuronic acid involves the enzyme, UDP-glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1), encoded by the UGT1A1 gene. Based on the results from 821 patients treated with irinotecan, hematological toxicity in patients carrying a UGT1A1*28 allele seemed dose related.26 The approved label of irinotecan recommends dose reduction when grade 3 or 4 diarrhea, neutropenia or other hematologic toxicity occurs, and consideration of reduction in the starting dose by at least one level for patients known to be homozygous for the UGT1A1*28 allele. Recent studies indicate that, in addition to UGT1A1*28, UGT1A1*6 also shows significant association with severe irinotecan treatment-related toxicity in Asians. Some studies even suggest that *6 allele is more relevant than UGT1A1*28 in Asians.27–30 The impact of this allele on the toxicity of irinotecan is worthy of further investigation.

In addition to the UGT1A1 enzyme, a few publications suggest the involvement of transporters in the clinical manifestation of irinotecan treatment-related severe diarrhea. Referring to the literature,31–32 hepatic elimination of irinotecan and its metabolites through hepatic transporters is illustrated in Figure 4. Irinotecan is taken up via OATP1B1 into hepatocytes where it is metabolized to SN-38 by carboxylesterase 2 and then subsequently to SN-38-glucuronide by UGT1A1. Irinotecan is secreted into bile via p-glycoprotein while both metabolites via MRP2. Biliary secretion seems correlated with irinotecan-induced diarrhea, with SN-38 as the documented suspect.33 A few studies imply that transporter-mediated drug interactions contribute to irinotecan-treatment-related diarrhea. In a phase II study in 16 advanced colorectal cancer patients treated with cyclosporine and irinotecan, grade 3/4 diarrhea was observed in 13%,34 which is lower than the reported rate (~30%) without cyclosporine observed by other investigators.35 A study involving 82 patients showed that cyclosporine decreased the clearance of irinotecan by 39% and increased the AUC of SN-38 by 23%, compared to historical control subjects.36 Since cyclosporine is an inhibitor of OATP1B1 and MRP2,1,32 may reduce the hepatic uptake of irinotecan via OATP1B1 and reduce the biliary secretion of SN-38 and SN-38-glucuronide via MRP2. This explains why cyclosporine increases exposure of SN-38 but reduces the rate of irinotecan-induced grade 3 and 4 diarrhea. Though not scientifically sound, these cross-study drug interaction-related comparisons nonetheless provide useful information for understanding how drug interactions that may be related to the clinical toxicity of irinotecan. In a prospective study with 81 patients on irinotecan and cisplatin, the 521 C allele (rs4149056) was found associated with grade 4 neutropenia and Grade 3 diarrhea was associated with the 388GG genotype.37 Another two case reports each with one patient reported that SLCO1B1*15/*15 was associated with irinotecan-induced adverse events.38,39 All together, evidence is surfacing to support the notion that SLCO1B1 mutants with reduced functional activity of OATP1B1 are associated with irinotecan-induced adverse events including grade 4 leukopenia and grade 4 neutropenia. OATP1B1-mediated drug interactions seem to corroborate irinotecan treatment-related adverse events in SLCO1B1 mutants. Larger clinical studies are needed to provide statistically meaningful information to update

![Fig. 4. Transporters involved in eliminating irinotecan and its metabolites](image-url)
the label of irinotecan with regard to the impact of SLC01B on irinotecan toxicity.

**Clinical implications: drug interactions/pharmacogenetics:** Genetic mutation and drug interaction-mediated inhibition may cause similar loss or reduction in activity of an enzyme or transporter, providing mutually corroborating scientific evidence for the interpretation of clinical consequences. Therefore, clinical drug interaction results are useful for identifying possible risk for developing severe adverse events in patients who carry mutant alleles of transporters or enzymes with reduced activity or complete loss of activity and vice versa. Clearly scientific disciplines of drug interactions and pharmacogenetics share an unavoidable intimate partnership in unveiling and understanding drug-related adverse events. Mechanistic disposition of drugs provides a blueprint for understanding the genetic basis of drug-induced adverse events and projecting drug interaction-induced adverse effects. Ultimately, the clarification of gene polymorphism-dependent drug interaction outcomes will provide better patient care.

**Conclusion**

Integrating clinical drug interaction and pharmacogenetic studies are an integral part of drug development. For developing oral drugs with non-negligible first-pass elimination, an intravenous drug interaction study at a low dose along with a few key oral drug interaction studies should be explored, with the aid of modeling and simulation technologies, to project possible maximum tolerable exposure and safety margin of a victim drug when drug interactions occur. Such an approach may potentially reduce the number of clinical drug interaction studies on the clinical safety of a drug.

**Acknowledgement:** The authors thank Dr. Shiew Mei Huang for her comments on the manuscript.

**References**


20) Tirona, R.-G., Leake, B.-F., Merino, G. and Kim, R.-B.: Polymorphisms in OATP-C: identification of multiple allelic variants associated with altered transport activity among European-