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Organic Ion Transporters and Statin Drug Interactions

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Abstract
Purpose of Review Statin drug-drug interactions (DDIs) are both troublesome to patients as well as costly to medical resources. The ability to predict and avoid these events could lead to improved outcomes as well as patient satisfaction. This review will explore efforts to better understand and predict these interactions specifically related to one drug transport system, the organic anion-transporting polypeptides (OATPs) specifically OATP1B1 and OATP1B3.
Recent Findings Since the publication of the discovery of OATPs, there have been various pharmacokinetic models that have been proposed to explain the variation in pharmacokinetic and clinical effects related to the OATPs. The effects in transport activity appear to be partially related to the individual polymorphisms studied. Drug-drug interactions can occur when other drugs compete for the metabolic site on the OATPs. Various medications are identified as substrates and/or inhibitors of the OATPs, thereby complicating the ability to fully predict the impact on levels and effects. All of the models reviewed claim successes but show limited clinical utility.

There are specific populations that have been identified, predominately various Asian descendants that require lower doses of statins to avoid adverse events. The concept of attributing these actions to the OATPs has been explored, but current models cannot accurately predict statin blood levels or elimination constants. The current research only points to the differences in the human genome and the single-nucleotide polymorphisms that exist between us.
Summary Based upon the currently available studies, there is beginning to be a glimmer in the understanding how different populations respond to statin transport and elimination. Additionally and unfortunately, there are other enzymes to be studied to better predict patient differences. Clearly, there has been much work completed, yet many more questions require answering to better understand these transport proteins.

Keywords Organic ion transporters · Pharmacokinetics · Statins

Introduction

Basic principles of pharmacokinetics help us understand the metabolic fate of statins. Pharmacokinetics measures the rate of absorption, distribution, metabolism, and excretion for these chemicals. Statins are ingested in their active hydroxylic acid form with the exception of simvastatin and pravastatin. They reach peak plasma concentration (T_{max}) in the range of about 4 h. When consumed with food, lovastatin is more efficiently absorbed. Rosuvastatin, pitavastatin, and simvastatin are not affected by food, whereas fluvastatin, pravastatin, and atorvastatin have a reduced absorption with food.

Basic Statin Metabolism

Statins undergo a complex metabolic fate, beginning with absorption, followed by first pass hepatic uptake, metabolism, and eventually elimination from the liver into either the

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systemic circulation or the biliary tract. P-glycoprotein (P-gp) efflux transporters generally reduce absorption into the portal circulation. Within the enterocyte, several members of the cytochrome P450 (CYP) family can metabolize some statins before eventual absorption into the portal circulation. Hepatic uptake is mediated by several membrane transporters, including organic anion-transporting polypeptide 1B1 (OATP1B1), which facilitates metabolism by additional CYP enzymes (phase I metabolism) and glucuronidation (phase II metabolism). Additional efflux transporters on the canalicular membranes of hepatocytes facilitate biliary excretion.

The solute carrier group (SLC) superfamily is encoded by 22 genes of the human SLC22A family. The human isoforms include OAT1-4 and 7 as well as URAT1. The metabolic sites for the organic anion transporter (OAT) family include the hepatocytes, proximal tubule of the kidney, the blood-brain barrier, other sites with in the brain, and many other critical locations. OATP1B1 is a 691-amino acid glycoprotein that contains 12 putative membrane-spanning domains and a large fifth extracellular loop. OATP1B1 AND OATP1B3 share 80% of the amino acid identity of each [1].

The general predicted OATP structure consists of proteins with 12 transmembrane domains [2•]. Drug transport, while not fully understood, appears to be by anion exchange which couples the cellular uptake of substrate with the efflux of various endogenous intracellular substances in addition to statins. These include repaglinide, valsartan, digoxin, and fexofenadine [3].

Low intracellular pH appears to stimulate substrate by various OATPs, also suggesting that intestinal OATP uptake could be altered if the pH was made more neutral. Therefore, changes in diet or ingestion of herbal supplements may affect drug transport via the organic ion transport proteins. Ginger, St. John's wort, liquorice, and grapefruit juice have been documented to affect cyclosporine levels via a potential p-glycoprotein or CYP3A4 interaction but OAT interactions cannot be ruled out [4].

Regulation of OATPs

The general regulation of the organic transport proteins appears to be multifactorial.

Hepatic OATP1B1 and OATP1B3 may be controlled by the liver-enriched hepatocyte nuclear factor 1a (HNF1α). Both transcription (e.g., the synthesis of RNA from DNA) and translation (synthesis of a protein from an mRNA) may be involved in regulating OATP activity. With respect to drug development, the complexity of OATP regulation requires in vitro measurements of more than one OATP substrate and metabolite [5]. Table 1 displays the pertinent transporter with respect to statin metabolism. Figure 1 and Table 2 display other transporter enzymes involved in statin transport and metabolism. Of importance, OATP is not the only transporter or enzyme involved in statin metabolism. Table 2 and Fig. 1 show the full gamut of transporters with respect to the individual medications.

Table 1 Organic Ion transporters involved in statin metabolism [2•, 3]

Transporter (gene)	Substrate	Inhibitor	Where located
OAT1B1 aka OATP-C or OATP2 (SLCO1B1)	Statins and other drugs	Cyclosporine, rifampicin, and some protease inhibitors	Hepatocytes (sinusoidal)
OAT1B3 aka OATP-8 (SLCO1B3)	Statins and other drugs	Same as above	Hepatocytes (sinusoidal)
OATP1A2 aka OATP-A (SLCO1A2)	Statins and other drugs	Rifampicin and some protease inhibitors	Brain capillaries, endothelia, cholangiocytes, distal nephron

Current Research Models

A separate conundrum in studying drug interactions is the lack of a good in vitro model.

Laboratory mice may express threefold activity of OAT1B3 compared to humans [7••]. Additionally, multiple pharmacokinetic analyses have shown that plasma concentrations of statins are often different when comparing predicted to observe [6]. Given that OATP2B1 and the OATP1B subfamily transporters are of particular importance for hepatic statin drug disposition, this article will focus predominantly on those two entities.

The OATP inhibitors are often at the same time inhibitors or inducers of CYP enzymes and other transporters. This makes the isolation of the OATP actions difficult. Efforts have been concentrated on better understanding of the interactions of various statins and other medications that affect the organic ion transport system.

Gemfibrozil and gemfibrozil-glucuronide are known inhibitors of OATP1B1 and OATP2B. Co-administration of gemfibrozil with substrate drugs of OATP1B1 and OATP2B1 can change hepatic clearance and are also specific to OATP2B1, result in alterations of intestinal drug absorption. Since the withdrawal of cerivastatin, it has also been known that gemfibrozil and gemfibrozil-glucuronide inhibit CYP2C8 and CYP2C9. This combination has been shown clinically to result in decreased metabolism and/or reduction of hepatic uptake ultimately resulting in renal failure.

Rifampin is transported by OATP1B1 and OATP1B3. Additionally, rifampin induces metabolic enzymes and transporters via binding to the pregnane-x-receptor (PXR), which

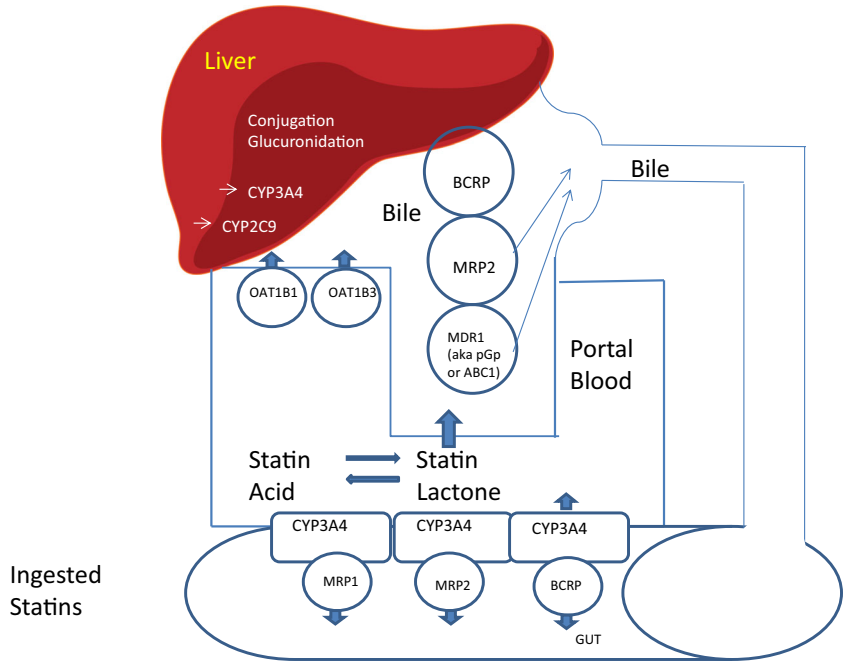

Fig. 1 Metabolic fate(s) of ingested statins

can activate CYP3A4. Statins such as atorvastatin and simvastatin when co-administered with rifampin can result in decreased concentrations of the acid metabolite and a decrease in the area under the curve. Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin with rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

Table 2 Transporters and enzymes affecting statins [6]

Statin	Transporters and enzymes affecting metabolism
Simvastatin lovastatin	CYP3A4 (intestinal and hepatic) OAT1B1 p-glycoprotein MDR1 BCRP
Atorvastatin	BCRP (intestinal) CYP3A4 (intestinal and hepatic) OAT1B1 and OAT2B1 p-glycoprotein
Rosuvastatin	BCRP (intestinal) CYP2C9 (minor) OAT1B1 andOAT1B3 NTCP OAT2B1
Pravastatin	BCRP (intestinal) OAT1B1 and OAT1B3 OAT2B1
Fluvastatin	BCRP (intestinal) OATP1B1 OAT1B3 OAT2B1 CYP2C9 CYP3A4
Pitavastatin	BCRP (intestinal) MDR1 OAT1B1 andOAT1B3 OATP2B1 CYP2C9 (minor)

BCRP breast cancer resistant protein, *CYP* cytochrome P450, *MDR1* multidrug resistant protein, *OAT* organic anion transporters, *OATP* organic anion-transporting polypeptides

Finally, most are aware of the effect of cyclosporine on statins. Cyclosporine is both an inhibitor of OATP2B1 and OATP1B1 as well as a substrate for CYP3A4. This dual effect can result in either inhibition or increased exposure with CYP3A4 substrates. The third possible explanation is an increase in hepatocellular accumulation. Cyclosporine also interacts with intestinal ABCB1 or ABCC2. Drugs co-administered with cyclosporine can show enhanced intestinal absorption and enhanced clinical effect [6].

Like other enzyme systems, single-nucleotide polymorphisms (SNPs) can result in altered and unpredicted metabolism of many medications. Tirona and colleagues demonstrated these SNPs in a hetergenous population of African- and European-Americans. Human liver cells were used in an RNA extraction procedure to produce OAT clones for testing. These unrelated subjects were found to have 14 non-synonymous polymorphisms in OATP-C. While statins were not studied, there was markedly reduced uptake in estrone sulfate and estradiol glucuronide in several of the OATP variant patients. The authors noted that as more medications are identified as OATP-C substrates, human differences in genetic heterogeneity in OATP-C drug disposition will become more apparent. OATP-C effect uptake of drugs compared to other OATPs should also be explored. A full study on all OATP

polymorphisms must be conducted. This would also need to include the regulatory control mechanisms involved in the transcriptional activation of OATP-C [8].

In a small Japanese study, pravastatin was used as a probe drug, and the results showed reduced renal and non-renal clearance. In a group of 120 healthy individuals, there were five non-synonymous variants and one non-synonymous variant observed in the OATP-C and OAT3 genes, respectively. The OATP-C variants were associated with differences in the disposition kinetics of pravastatin. Identified polymorphisms in the OAT3 gene did not appear to be associated with changes in renal and tubular secretory clearance. The results that showed a different haplotype in the Japanese resulted in a significantly higher serum concentration after a 10-mg dose of pravastatin. Larger gene pool studies may further clarify the results noted in this article [9].

Clinical Issues

With respect to statins, other population differences are noted. Pharmacokinetic data have shown that Asians taking statins have higher serum levels of these drugs than Caucasians. The FDA has issued caution when treating Chinese patients with simvastatin doses exceeding 20 mg/day when administered with niacin. This followed the observation in the Heart Protection Study 2 of increased risk of myopathy in those taking simvastatin 40 mg administered with niacin-containing products (> 1 g/day). Current rosuvastatin labeling notes higher blood levels in patients of Asian heritage (Filipino, Chinese, Japanese, Korean, Vietnamese, or Asian-Indian). A 5-mg rosuvastatin initiation dose may be appropriate for this group. Pitavastatin was approved based on a largely research in Japanese patients. Differences in Japanese and Caucasian pharmacokinetics with pitavastatin are still under investigation. No specific recommendations appear in the pitavastatin labeling. Atorvastatin and fluvastatin offer no current special population warning for Asian groups. Labeling in Asian countries differs from the higher doses used in the USA. Initiation of therapy with low doses of all statins in Asian and Asian-American patients remains the most prudent approach [10].

The aforementioned ethnic differences may likely be attributed to differences in OATP1B1 pharmacokinetics. Li and colleagues developed an experimental model that measured both unbound drug fraction in liver, permeability between liver compartments, and permeability limited distribution to selected tissues [11, 12]. An older model examined described SLCO1B1 and ABCG2 genotyped pharmacokinetic time course data atorvastatin, pitavastatin, pravastatin, repaglinide, and rosuvastatin in Caucasian and Asian populations [13]. The authors suggest that their model may accurately predict rosuvastatin pharmokinetic values by controlling for allele frequencies with respect to Caucasian, Chinese, and Korean groups and low-dose statin administration. The major limitation of this study was the inclusion of only one SLCO1B1 allele. The study result also suggested that there were unpredictable differences in biliary secretion of rosuvastatin noted in different ethnic groups and leading to different statin exposure levels. The study suggested development of techniques that can simultaneously sequence genes of other enzymes as well as organic transporters to better predict clinical outcomes [12].

Currently, the focus is to develop better models to predict transporter-related drug interactions. Yee and colleagues have conducted in vitro studies suggesting the fatty acid decarboxylates tetradecanedioate (TDA) and hexadecanedioate (HDA) that are substrates of OATP1B1 as well as OAT1 and OAT3 may useful in the future to predict SNPs and DDIs [14••].

Other pharmacokinetic modeling is currently proposed to model physiologic pharmacokinetic parameters (PBPK). A model taking into account at least nine different pharmacokinetic parameters has been proposed by Yoshikado and colleagues and may hold promise but needs more clinical validation [15].

The varying sites of drug metabolism can interfere with pharmacokinetic predictions as well. Other factors such as unbound drug concentrations in the blood and the liver, transport across the hepatic sinusoidal membranes, rate of hepatic metabolism, and/or excretion into bile make predictions difficult. To solve this, Patilea-Vrana and colleagues have proposed and extended clearance model (ECM). Drugs entering the liver that are metabolized or excreted into the bile faster than the drug can exit the sinusoidal membrane; the loss of the drug from the systemic circulation will be determined only by sinusoidal uptake. The proposed ECM may predict in the future whether transporters or metabolic enzymes or both can be better explored and utilized to predict the metabolism of drugs and the impact of DDIs within patients with SNPs. In vitro and potentially in vivo trials are needed to test the model and validate its predictability. The model is entirely theoretical and cannot be utilized clinically without better and replicable methods of determining sinusoidal influx (CL_{sin}) and efflux clearances (CL_{sef}), canalicular efflux (biliary) clearance (CL_{cef}), metabolic clearance (CL_{met}), hepatic blood flow, (Q_h), and fraction unbound of the drug in the blood/plasma (f_{up}) [16].

The larger question is the overall clinical significance of the OATP drug interactions. In a study of 278 patients with familial hypercholesterolemia (FH), Khine and colleagues have reviewed the incidence of myopathy by drug and other characteristics. Simvastatin was the most common statin and most associated with muscle symptoms. Rosuvastatin and

pravastatin were the most tolerated in FH. Genotyping was done in this population, and it was concluded that OATP1B1 genotypes were not associated with statin muscle symptoms. The authors concluded that age, not genotype, was the strongest risk factor for statin-associated muscle pain [17].

Summary

There is a lot of current effort being placed on better understanding DDIs due to the organic ion and other transporters. As noted, the largest effort consists of finding mediated substances or pharmacokinetic models that will better predict these interactions. There is a need for continued model development, in vitro testing as well as human research to better predict, understand, and avoid these interactions.

Compliance with Ethical Standards

Conflict of Interest Kenneth Kellick declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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