REVIEW ARTICLE

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The Role of P-Glycoprotein and Organic Anion-Transporting Polypeptides in Drug Interactions

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Abstract

The use of polytherapy in clinical practice necessitates an appreciation and understanding of the potential for drug interactions. Recent publications provide insight into the role of the active transport systems P-glycoprotein (P-gp) and human organic anion-transporting polypeptides (OATPs) in drug interactions. Active drug transporters influence the bioavailability of a number of drugs by controlling their movement into, and out of, cells.

The active transport systems P-gp and OATP play an important role in drug elimination. The activity of these transport systems is controlled, in part, by genetic factors; however, drugs and foods also influence the activity of these systems. It appears that interference with P-gp or OATP, either as upregulation or inhibition, may affect plasma drug concentrations by altering intestinal absorption, proximal renal-tubular excretion or biliary excretion. Overall, the net bioavailability of a drug or substance is affected by the relative contributions of cellular efflux (P-gp) and influx (OATP) mechanisms and to what extent these systems are active during phases of uptake and absorption versus removal and excretion from the body.

Many of the drugs and foods that affect active drug transport activity are known to interact with the cytochrome P450 enzyme system; therefore, the net effect of concomitant drug administration is complex. One must now consider the impact of metabolism (CYP-mediated drug biotransformation), P-gp-mediated drug efflux and OATP-mediated uptake when making assessments of drug absorption and distribution.

It is widely accepted that the potential for drug interactions exists with polytherapy. Pharmacokinetic interactions – those that occur when the absorption, distribution, elimination or metabolism of one drug is altered by another – can influence plasma or tissue drug concentrations. It is well appreciated that some pharmacokinetic interactions are beneficial (i.e. they can help maintain drug levels within a desired range), whereas others may be harmful (i.e. they result in supratherapeutic or subtherapeutic drug concentrations). Although subtherapeutic drug concentrations may simply manifest as a failure to control or cure the condition for which the agent was prescribed, supratherapeutic concentrations of certain drugs may bring about serious or even fatal consequences. Pharmacodynamic interactions – those that occur when two or more drugs affect the activity of a common receptor or organ – may be beneficial or harmful, depending on the net effect. Therefore, the ability to predict drug interactions should help clinicians choose appropriate therapy to achieve desired outcomes.

The role of the cytochrome P450 (CYP) isoenzymes in drug metabolism and the pharmacokinetic drug interactions that result from inhibition or induction of this system are widely accepted.[1] Clinicians familiar with the roles of the various CYP enzymes in drug metabolism can predict the consequences of drug coadministration and explain patients' responses to medication regimens. Some interacting drug combinations are used to take advantage of drug interactions to enhance drug levels. Avoidance of other drug combinations can eliminate problems that may result from interference with drug metabolism.

However, it has become apparent that additional mechanisms play a role in many drug interactions that were formerly attributed to CYP isoenzymes. Recently, attention has been drawn to drug-drug and drug-food interactions involving transporter systems, such as P-glycoprotein (P-gp) and human organic anion-transporting polypeptides (OATPs).[2] Interactions caused by such drug transporters are being reported with increasing frequency and an understanding of the possible implications of these novel mechanisms should help guide therapy.

1. Cytochrome P450 Enzymes

Interference with normal drug metabolism is the most widely recognised drug interaction. Drugs that mainly rely on metabolism for excretion from the body are primarily water soluble and are excreted through the urine or bile. In some cases, metabolism is responsible for the transformation of a prodrug to an active metabolite. The enzymes most often responsible for drug metabolism are the CYP enzymes, which are located predominantly in the liver but also are found in the intestines, lungs and other organs. The family of CYP enzymes is responsible for the oxidative biotransformation of drugs.[3]

At least 30 different CYP enzymes have been identified.[3] Each enzyme – called an *isoenzyme* because each is derived from a different gene – is categorised by the letters CYP followed by an Arabic number, a letter and another Arabic number. When noted in uppercase, as in CYP3A4, the designation refers to the human gene and when noted in lower case, as in Cyp11A1, the designation refers to the rodent gene. CYP3A represents the most abundant enzyme group in humans. These isoenzymes account for approximately 30% of the CYP enzymes that are produced in the liver and are responsible for many clinically important drug interactions.[1] The subclass of isoenzymes named CYP3A4 is found extensively in the small intestine.[1,3] Notably, most drugs are metabolised by a small subset of CYP isoenzymes, including 3A4, 2D6, 1A2, 2C9, 2C10 and 2C19.[4]

Drugs that act as substrates, inhibitors or inducers of CYP enzymes have been the focus of many traditional drug-drug interaction investigations. Numerous drug-drug interactions are mediated by CYP isoenzymes by means of enzyme inhibition or induction.[1,4] Enzyme inhibition may occur through competitive, noncompetitive or uncompetitive mechanisms. Competitive inhibition occurs when two substances compete for the catalytic site of the enzyme. Noncompetitive inhibition occurs when two substances bind to separate domains of the enzyme (e.g. the substrate binds to the catalytic site and the inhibitor binds to a different site that alters the substrate binding/catalytic site). Uncompetitive inhibition results when an inhibitor specifically binds to an enzyme-substrate complex. This circum-

stance is not often encountered in clinical situations because enzyme saturation is not attained for most pharmacological agents. Ketoconazole and erythromycin are two common examples of CYP inhibitors.[1] Terfenadine, a second-generation antihistamine, is a substrate of CYP and is primarily metabolised by CYP3A4.[5] Consequently, coadministration of ketoconazole or erythromycin with terfenadine is well documented to increase plasma concentrations of the antihistamine because of the dependence of terfenadine on CYP-induced metabolism.[6,7] In the case of the interaction of terfenadine with ketoconazole or erythromycin, QT prolongation and torsades de pointes have been reported secondary to increased terfenadine plasma concentrations.[8] Because of this clinically significant and potentially life-threatening interaction, terfenadine has been removed from the US market.

Another type of drug interaction is induction, whereby a drug stimulates excess production of a CYP isoenzyme.[1] The result is increased metabolism of a second agent (substrate), which leads to decreased plasma concentrations and possibly reduced efficacy. Antibacterials (acting as the inducer) and oral contraceptives (acting as the substrate) were believed to interact in this manner. However, although some antibacterials can reduce the plasma estradiol concentration in some patients,[9] the total increase in unwanted pregnancy might not be significant compared with baseline oral contraceptive failure rates. The most striking example is seen in the combination of rifampicin and oral contraceptives, which can lower estradiol concentrations to potentially subtherapeutic levels, raising the risk of unwanted pregnancy.[10-13] Many antiepileptic medications also significantly reduce the serum concentration of oral contraceptives and these drug interactions may result in contraceptive failure.[14,15]

Although CYP-mediated drug interactions have received much attention, research conducted during the past decade suggests that other mechanisms may be responsible for changes in the absorption, distribution or excretion profile of a drug. Altered drug disposition through mechanisms independent of the CYP pathway has been explored for drugs that undergo minimal hepatic metabolism. Fexofenadine, the active metabolite of terfenadine, is an antihistamine that is minimally (≤5%) metabolised by the liver or intestine.[16] Fexofenadine plasma concentrations were significantly increased after coadministration of ketoconazole or macrolide antimicrobials.[17] Because fexofenadine does not undergo significant hepatic metabolism, these data suggest that a non-CYP-mediated pathway altered the disposition of the antihistamine.

Drug interactions are not limited to changes in biotransformation. The bioavailability of some agents may be affected by coadministration of drugs or substances that influence absorption through active transport mechanisms. As we learn more about these systems, it becomes evident that metabolism and transport systems can differentially affect both the absorption and tissue distribution of pharmacological agents. The remainder of this article reviews what is currently known about the most recognised active transport systems – P-gp and OATP – and their affect on drug bioavailability.

2. Drug-Transporting Proteins

It has become increasingly evident that drug interactions can occur when active drug-transport systems (pumps) are inhibited or induced, which alters the overall absorption, distribution and excretion of pharmaceutical compounds. Two active transport pumps – P-gp and OATP – are transmembrane proteins found in many tissues throughout the body.[2,18] Many drugs and foods affect the activity of active drug transport systems. Interestingly, many of these drugs and foods also affect CYP3A4 isoenzymes.[19,20] In certain instances, metabolic conversion is known to play a primary role in reducing the bioavailability of a compound. However, in instances where drug metabolism is not extensive, as in the case of fexofenadine, it is reasonable to consider transport proteins as the primary forces that affect the absorption and excretion kinetics of these compounds.[21] The relative contribution of these systems can have important implications on the bioavailability and, ultimately, the efficacy and safety of pharmaceutical compounds. For instance, it has been established that active transport pathways such as OATP and P-gp alter the plasma levels of drugs such as terfenadine and its metabolite fexofenadine and these pathways were probably, in part at least, responsible for the cardiotoxic plasma concentrations of terfenadine that led to its withdraw-

al.[22] Further studies on metabolism- and transport-mediated drug interactions will be helpful in guiding drug discovery programmes[23,24] and may aid in the physician's ability to increase the effectiveness of drug therapy.

2.1 P-Glycoprotein

P-gp is a large cell-membrane protein (approximately 170 kD)[2,25] that is responsible for the transport of many substrates, including drugs.[26-28] It is further classified as a member of the adenosine triphosphate (ATP)-binding cassette superfamily of transport proteins (ABC transporters).[29] In humans, this transmembrane glycoprotein is encoded by the *ABCB1* gene – also previously known as the multidrug resistance gene (*MDR1*), which was originally discovered in drug-resistant neoplastic cells.[30,31] The human *MDR1*-encoded P-gp is a large, phosphorylated, glycosylated protein that is 1280 amino acids in length and molecularly organised as homologous halves of 610 amino acids that are joined by a flexible connecting region of 60 amino acids.[28] Each half of the P-gp monomer contains a hydrophobic domain comprising transmembrane-spanning segments and a hydrophilic domain containing a nucleotide-binding site. The nucleotide-binding sites can bind ATP and its analogues; both sites are important because inactivation of either site prevents substrate-stimulated ATPase activity. Hydrolysis of ATP, with its associated liberation of energy, is critical for the function of P-gp.

Although P-gp expression was originally discovered in tumour cells, it also occurs in many healthy, normal tissues.[32] For example, P-gp is found in high levels in the luminal membranes of renal proximal tubules, the surface cells of the medulla and cortex of the adrenal gland, the biliary canalicular membrane of hepatocytes, the apical surface of mucosal cells in the small and large intestines, the ductules of the pancreas and the astrocyte foot processes of the blood-brain barrier.[2,28,31,32] Accordingly, the presence of P-gp in these tissues suggests that the transmembrane protein likely facilitates excretion of substances into urine and bile and into the intestinal lumen (i.e. reduced absorption) and prevents excess accumulation in the brain.[28]

In addition to its role in healthy human tissues, P-gp is recognised to operate as an efflux pump that exports drugs from cells (figure 1).[26-28,33] In general, P-gp is an energy-dependent pump with broad substrate specificity that expels primarily large cationic or neutral hydrophobic drugs from cells.[26,31] As such, it can play an important role in determining the plasma concentration of a drug, especially when liver metabolism is minimal. Examples of drugs that act as substrates of P-gp are presented in table I.[33]

For drugs that are substrates of P-gp, the net effect is that the drug is pumped back into the intestinal lumen, which results in lower plasma concentrations. The possible cooperative role of P-gp and CYP has been examined in the case of first-pass extraction of substances in the intestinal lumen.[34] Mechanistically, substances internalised into cells are acted upon by CYP to a certain degree. The amount of drug that may initially escape biotransformation is pumped back out into the intestinal lumen where it may once again be absorbed, leading to another chance for an encounter with the cellular CYP. Cooperatively, this cyclic mechanism is an effective means of reducing the amount of xenobiotic that reaches the bloodstream. Recent research using human intestinal mucosa has confirmed the colocalisation of P-gp and CYP3A4 protein in enterocytes, including high P-gp content on the apical surface. Moreover, intestinal concentrations of the two target compounds were substantially higher than in paired liver specimens from the same donor.[35] These findings support the notion that both CYP biotransformation and active efflux via P-gp in the gut play a significant role in reducing oral drug bioavailability.

Strategies to inhibit P-gp function are under investigation in several areas, including antiretroviral

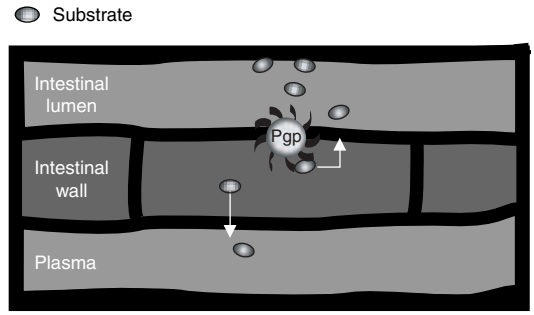

Fig. 1. Normal activity of the P-glycoprotein (P-gp) efflux mechanism in the gastrointestinal tract.

Table I. Representative substrates of the P-glycoprotein transporter family[2,33]

Drug class	Specific agent(s)
Antihistamines	Astemizole, fexofenadine, terfenadine
Cardiac glycosides	Digoxin
Chemotherapy agents	Dactinomycin, daunorubicin, doxorubicin, etoposide, mitomycin, paclitaxel, teniposide, vinblastine, vincristine
Cytotoxic agents	Colchicine, emetine, ethidium bromide, mitoxantrone, puromycin, trimetrexate
HIV protease inhibitors	Indinavir, nelfinavir, ritonavir, saquinavir
Immunosuppressant agents	Ciclosporin
Miscellaneous	Ivermectin, loperamide
Steroids	Aldosterone, hydrocortisone, dexamethasone, estrogen, progesterone

therapy and oncology, for the purpose of increasing concentrations of pharmacologic agents in target tissues and thereby improving drug effectiveness.[31] In numerous tumour types, including chronic myelogenous leukaemia[36] and non-small-cell lung cancer,[37] resistance to chemotherapeutic agents has been correlated with increased P-gp expression. Similarly, increased P-gp expression also known to reduce the bioavailability of certain antiretroviral agents and some compounds, such as nelfinavir, appear to directly inhibit P-gp activity.[38]

Interference with the normal transport function of P-gp may lead to clinically significant increases or decreases in serum drug concentrations. Drug interactions may occur if P-gp activity is induced or inhibited by a second drug (figure 2).[33] A list of agents known to alter P-gp activity can be found in table II;[33] ketoconazole, erythromycin, verapamil and ciclosporin are well known drugs that inhibit P-gp function.[2] Concomitant administration of a P-gp inhibitor (e.g. ketoconazole) with a P-gp substrate (e.g. fexofenadine) would be expected to lead to abnormally increased plasma concentrations of the substrate. Concurrent administration of a P-gp inducer (e.g. rifampicin) with a P-gp substrate (e.g. digoxin, fexofenadine) would be expected to reduce the bioavailability of the substrate through diminished intestinal absorption, increased renal or biliary clearance or a combination of these factors.[33] Interference with P-gp may be concentration-dependent and it is important to compare drug concentrations used in experimental *in vivo* and *in vitro* models with typical therapeutic concentrations following standard administration in patients. Additionally, some substances act as both inhibitors and inducers of P-gp. One example is hypericum (St. John's wort), which initially inhibits P-gp and increases substrate drug concentrations (e.g. fexofenadine) but subsequently enhances production of P-gp and thereby augments clearance of the substrate.[39]

In addition to the potential for either supra- or sub-therapeutic bioavailability stemming from drug-induced changes in P-gp activity, the genetic heterogeneity of P-gp expression further complicates the clinical picture when agents acting on or through P-gp are administered. A study by Kim et al.[40] identified substantial genetic heterogeneity of P-gp among European American and African American subjects. The investigators reported that the one allele with enhanced activity was found in approximately 40% of European American subjects but occurred in <20% of African American subjects. This finding suggests increased P-gp activity in certain populations, which might lead to excess efflux activity of P-gp substrate drugs.[40] A host of single-nucleotide polymorphisms (SNPs) in *MDR1* have been identified in various racial and ethnic populations and are associated with altered drug concentrations in, and susceptibility to, certain disease states,[41,42] though discordant findings on the consequences of specific SNPs have been reported.[42] The prevalence of linkages between *MDR1* SNPs may explain the discrepancies in reports on the influence of individual variations; haplotype identification may be critical to assessing the functional consequences of *MDR1* polymorphisms on P-gp activity

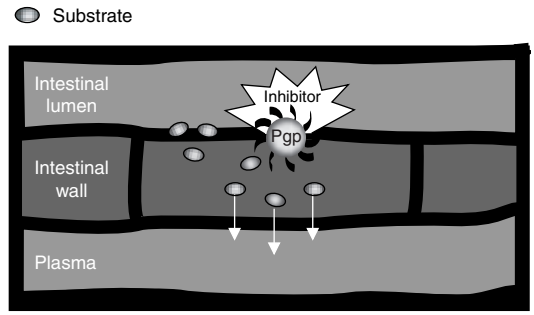

Fig. 2. Effect of inhibition on the P-glycoprotein (P-gp) efflux mechanism.

Table II. Selected inhibitors and inducers of P-glycoprotein (P-gp) function[2,33]

P-gp inhibitors		P-gp inducers
Amiodarone	Mefloquine	Clotrimazole
Bepridil	Mepacrine	Galanin
Cefoperazone	Nicardipine	Hypericum (St John's wort)[a]
Ceftriaxone	Nifedipine	Isosafrole
Clarithromycin	Progesterone	Kaempferol
Ciclosporin	Propranolol	Midazolam[b]
Diltiazem	Quinidine	Nifedipine
Dipyridamole	Quinine	Phenobarbital (phenobarbitone)
Erythromycin	Tacrolimus	Phenytoin
Fluphenazine	Tamoxifen	Quercetin
Hydrocortisone	Trifluoperazine	Reserpine[b]
Itraconazole	Valinomycin	Rifampicin
Ketoconazole	Verapamil	Troglitazone

a This agent causes initial inhibition and subsequent induction of P-gp.

b This agent can act as a P-gp inhibitor or inducer, depending on the concentration.

and, ultimately, disease susceptibility and drug disposition.[43]

2.2 Organic Anion-Transporting Polypeptides

Compared with P-gp, less is known about OATP structure and function. Nevertheless, OATPs, classified in the group of solute carrier family proteins, are a class of transmembrane proteins that are involved in the transport of endogenous substances, such as bile acids.[2] Additionally, this class of proteins is gaining recognition for their role in drug absorption and excretion.[18,44] One must now consider the impact of metabolism (CYP-mediated drug biotransformation), P-gp-mediated drug efflux and OATP-mediated uptake when making assessments of drug absorption and distribution. The first human OATP to be identified shares approximately 67% amino acid sequence homology with the previously identified rodent liver protein.[45] Since that time, genomic and functional analyses have identified numerous isoforms of OATPs from different tissues (table III), and work continues on elucidating their normal cellular function and the role each may have in drug interactions.[2,18,46] Although less is known about OATPs in humans, the distribution of OATPs in rats suggests that they are widespread. Similar to P-gp, OATPs are expressed in human intestine, liver, kidney and brain tissues.[47-49] Unlike P-gp, OATP-mediated transport does not require hydrolysis of ATP.[2] OATPs typically pump drugs from areas of high concentration to areas of low concentration and facilitate drug transport through ionic bonding to substrate drugs (anionic drugs).[2] A number of genetic polymorphisms in human OATPs have been uncovered that may have clinical relevance for patients undergoing digoxin therapy and in the treatment of certain cancers.[49]

In contrast to the actions of P-gp, OATPs function primarily as drug-uptake pumps transporting drugs into cells (figure 3).[33] Interference with OATP through induction or inhibition of the transporter system may alter the disposition of a drug. Many endogenous substances and a wide variety of drug classes are substrates of OATP.[2] Furthermore, many agents that affect P-gp function also affect OATP activity. Ketoconazole, erythromycin and various fruit juices containing bioflavonoids or bergamottin (e.g. grapefruit, orange and apple) are now known to be inhibitors of OATP.[50] Table IV lists several substrates and inhibitors of OATP.[2] Taking into consideration the tissue and cellular localisation of OATPs and the overall direction of solute movement from intake through excretion, the net effect of OATP inhibition on an OATP substrate can be a net increase or decrease in plasma concentrations. For instance, in the case of inhibiting enterocyte OATPs, initial absorption would be diminished, leading to a lowered plasma concentration of substrate. However, inhibition may result in an increased plasma concentration, for instance in the case of inhibition

occurring on the basolateral surface of hepatocytes (figure 4).

Overall, the net bioavailability of a drug or substance is affected by the relative contributions of cellular efflux (P-gp) and influx (OATP) mechanisms and to what extent these systems are active during phases of uptake and absorption versus removal and excretion from the body.

3. Clinical Implications of Transporter-Mediated Drug Interactions

Many drug interactions are the consequences of inhibition or induction of CYP enzymes. However, recent evidence from *in vitro* and *in vivo* studies suggests that P-gp- and OATP-mediated drug interactions are clinically important. Drugs that alter the activity of drug transporters are known to affect the bioavailability of concomitantly administered drugs.[2,4,27] Recognition of drug transporter-mediated drug reactions that produce negative clinical outcomes (i.e. decreased tolerability or effectiveness) should help guide pharmacotherapy and improve patient care. Ultimately, awareness of concomitant medications and foods that precipitate these reactions is the responsibility of the treating physician. Clinically relevant effects of interference with the P-gp and OATP transport systems on drug disposition for several therapeutic classes are discussed herein.

3.1 Antiretroviral Therapy

The role of P-gp transporter systems in drug disposition has been studied extensively in patients with HIV infection. Current evidence suggests that all protease inhibitors used to treat HIV infection are transported by P-gp, which leads to active expulsion of these drugs from cells.[51-53] Saquinavir, ritonavir, nelfinavir and indinavir have all been shown to interact with P-gp and *MDR1*, thus limiting the cellular permeability of each agent.[52-54] Kim et al.[55] demonstrated that the *in vitro* interaction of protease inhibitors and P-gp was responsible for reduced CNS penetration of antiretroviral agents. Decreased oral bioavailability of the protease inhibitors has been explained based on P-gp-mediated efflux from the intestinal mucosa.[56] It has been hypothesised that P-gp may be responsible for subtherapeutic intracellular concentrations of the protease inhibitors in CD4 T lymphocytes and monocytes.[53,54,57] Expression of P-gp in the placenta also appears to limit penetration of protease inhibitors into the fetus, which possibly increases the risk for infection in the newborn.[54]

When expression of P-gp is high, antiretroviral efficacy may be reduced by limited absorption of the protease inhibitors from the small intestine, large intestine and key target cells or tissues. Current research suggests that the administration of drugs

Table III. List of some human organic anion-transporting polypeptides (OATPs), gene symbols and tissue distribution[49]

Common name of transporter	Gene family name	Tissue distribution
OATP-A	*SLC21A3*	Brain
OATP-C	*SLC21A6*	Liver
OATP-8	*SLC21A8*	Liver
OATP-B	*SLC21A9*	Kidney, liver, brain, small intestine
OATP-F	*SLC21A14*	Brain
OATP-D	*SLC21A11*	Ubiquitous
OATP-E	*SLC21A12*	Ubiquitous

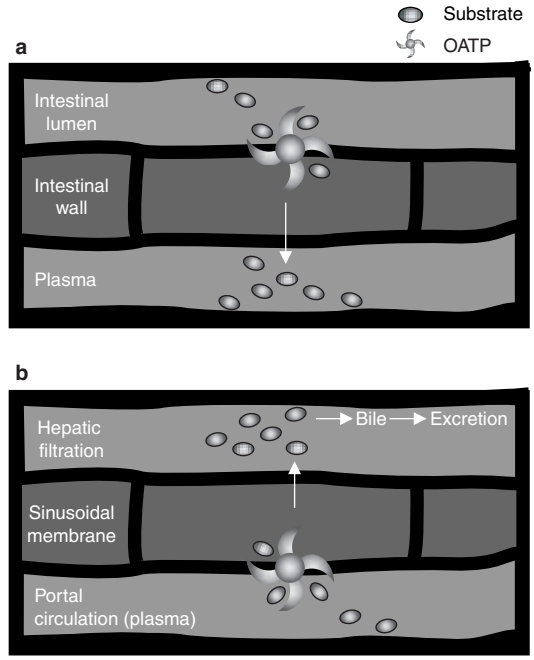

Fig. 3. Normal activity of the organic anion-transporting polypeptide (OATP) influx mechanism in the (**a**) gastrointestinal tract and (**b**) liver.

Table IV. Selected substrates and inhibitors of organic anion-transporting polypeptide (OATP) function[2,50]

OATP substrates	OATP inhibitors
Digoxin	Bioflavonoids, apple juice,
Enalapril	grapefruit juice, orange juice
Fexofenadine	Erythromycin
Hydrocortisone	Ketoconazole
Pravastatin, lovastatin	
Ritonavir, nelfinavir, saquinavir	

that block P-gp function may improve treatment outcomes in patients infected with HIV who are treated with protease inhibitors.[54] However, further data are needed to support this contention. Interestingly, a developing line of research suggests that *increased* P-gp activity in CD4+ T cells may inhibit viral replication.[58]

One interesting approach to the inhibition of P-gp has been low-dose administration of one protease inhibitor to optimise the overall bioavailability of a second protease inhibitor.[59] It may be beneficial to administer protease inhibitors concomitantly with agents directed to specifically reduce P-gp activity, but large controlled clinical trials are required for confirmation. Collectively, the data suggest that the efficacy of antiretroviral therapy may be compromised when other drugs that modulate P-gp function are given concurrently (table II).[2,33]

3.2 Haematology/Oncology

The clinical significance of drug-transporting proteins has been studied extensively in the fields of haematology and oncology. It is well known that P-gp is widely prevalent in clinical tumours; P-gp overexpression has been demonstrated during diagnosis and relapse.[60] Furthermore, P-gp expression may be induced after chemotherapy and lead to cellular resistance.[61] Administration of P-gp inhibitors to increase cellular concentrations of anticancer therapy is a relatively new approach to managing various types of neoplasms. Favorable results (i.e. increased survival) with P-gp inhibitors have been reported in the treatment of metastatic breast cancer and acute myeloid leukaemia.[62,63]

Many potential inhibitors of P-gp and *MDR1* have been tested in patients with cancer as part of the chemotherapy regimen. These include calcium channel antagonists, calmodulin antagonists (e.g. trifluoperazine), cyclic peptides and steroids.[60] Many of these first-generation, P-gp-modulating agents have intrinsic immunosuppressive properties or an unacceptable toxicity profile because they are administered in high doses. Second-generation agents (e.g. dexverapamil and PSC 833), which are more potent and less toxic, were subsequently developed.[60] Recently, third-generation P-gp modulators that are considered to be more selective (i.e. P-gp-specific inhibitors) have been developed. A preliminary phase I study reported that the combination of paclitaxel and biricodar (VX-710, a third-generation inhibitor of P-gp expression) was safe and reduced the systemic clearance of paclitaxel.[64] Although biricodar optimised the pharmacokinetic disposition of paclitaxel, it is unknown whether this combination permits full chemosensitisation. In the case of chemotherapy, identification of a potent, specific and safe P-gp inhibitor may reduce multidrug resistance and enhance the bioavailability of the chemotherapeutic P-gp substrate. Additionally, it may lead to increased drug concentrations in tumour tissue and to improved outcomes.

3.3 Use of Antihistamines

It is now recognised that the disposition of some antihistamines is affected by drug-transporting proteins. This observation is most apparent with fexofenadine, an antihistamine that is minimally metabolised.[17]

Ketoconazole and erythromycin have been reported to increase the plasma concentrations and bioavailability of fexofenadine.[17] Following administration of fexofenadine 120mg twice daily (twice the recommended dosage) with erythromycin 500mg every 8 hours, the steady-state area under the plasma concentration-time curve (AUC) of fexofenadine increased by 109%.[17] Similarly, increased absorption of fexofenadine (164%) was found after concomitant administration with ketoconazole 400 mg/day.[17] Further evaluation of these data *in vitro*, in situ and in animal models has provided evidence that ketoconazole and erythromycin enhance the absorption of fexofenadine through a net inhibition of P-gp.[17]

St. John's wort, a herbal antidepressant, also appears to affect the bioavailability of fexofenadine

by interfering with P-gp activity. In a clinical study, a significant (50%) reduction in the bioavailability of fexofenadine was observed in healthy subjects after the administration of St. John's wort 900 mg/day for 12 days.[65] A second study reported that peak fexofenadine concentrations were increased by 58% after a single 900mg dose of St. John's wort, caused by an initial acute inhibition of P-gp followed by induction of P-gp, thereby augmenting the clearance of fexofenadine.[66] Rifampicin and troglitazone are two other examples of drugs that affect the bioavailability of fexofenadine by interfering with P-gp activity. It has been reported that the clearance of fexofenadine was increased when it was coadministered with rifampicin.[67] Similarly, coadministration of troglitazone and fexofenadine yielded a 40% reduction in fexofenadine bioavailability.[68] These interactions are likely related to P-gp induction.

Certain fruit juices can act as inhibitors of OATP, having the opposite effect (compared with ketoconazole and erythromycin) on the disposition of fexofenadine. It was noted recently that the administration of eight ounces of grapefruit juice three times a day for 2 days followed by oral fexofenadine resulted in a significant reduction in maximum concentration (C_{max}) of fexofenadine and AUC values (30%).[69] The reduced bioavailability of fexofenadine following grapefruit juice consumption appears to be caused by a net inhibition of OATP by citrus bioflavonoids or bergamottin. Similar findings suggest that other fruit juices (e.g. orange and apple) can decrease the overall absorption of fexofenadine, which is exemplified by a 70–75% reduction in fexofenadine bioavailability when administered following consumption of 1200mL grapefruit, apple or orange juice compared with a similar volume of water.[70] The effect was dose dependent; 25% grapefruit juice yielded a lesser reduction in bioavailability than full-strength grapefruit juice. It has been shown in rats that Oatp3 is capable of fexofenadine uptake. Although the relevant human OATP has not yet been definitively identified, these data support the role of OATP for the intestinal uptake of fexofenadine in humans.[70] Administration of fexofenadine 180mg as a single dose after 7 days of a high-salt diet (400 mEq/day) reduced the bioavailability of fexofenadine by 40% compared with administration after 7 days of a low-salt diet (10 mEq/day), which is consistent with an intestinal absorptive environment containing highly charged molecules that may limit the activity of OATP.[71]

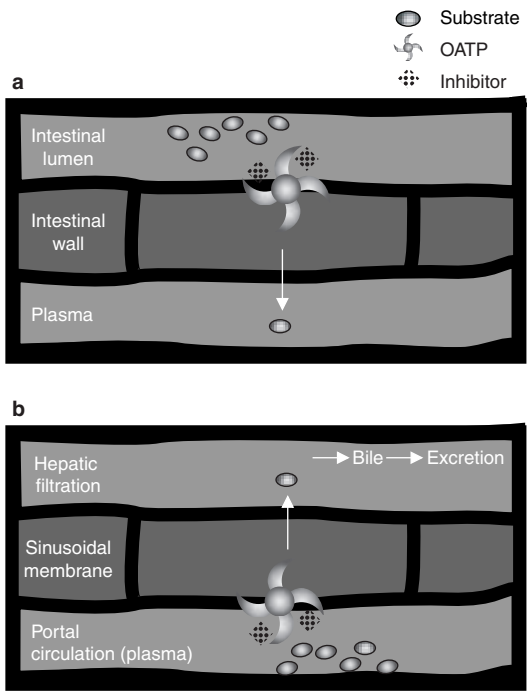

Fig. 4. Effect of inhibition on the organic anion-transporting polypeptide (OATP) influx mechanism in the (**a**) gastrointestinal tract and (**b**) liver.

Although the clinical consequences of these food interactions with fexofenadine have not been fully explored, it is possible that reduced bioavailability of fexofenadine may compromise its efficacy. Interactions of fexofenadine resulting in a 40% reduction in bioavailability, such as the interaction of fexofenadine with magnesium- and aluminum-containing antacids consequent to an acid-base interaction (fexofenadine is an organic acid originally named terfenadine carboxylate), are noted in its product labelling as situations to avoid because of concerns that reduced drug bioavailability will compromise clinical efficacy.[16] A similar advisory is included in the fexofenadine 60mg/pseudoephedrine 120mg product insert to avoid concurrent use with food because a high-fat meal may decrease fexofenadine bioavailability with this combination by 42%.[16] These concerns about decreased bioavailability of

fexofenadine inducing suboptimal clinical efficacy are based on dose-ranging studies wherein fexofenadine 40mg twice daily was less clinically consistent in relieving symptoms of allergic rhinitis than fexofenadine 60mg twice daily.[72]

In contrast to fexofenadine, the bioavailability of desloratadine, a newer antihistamine, was unaltered following grapefruit juice consumption.[67] Additional data collected in healthy volunteers have demonstrated the absence of clinically important drug-drug or drug-food interactions with desloratadine and agents that inhibit or induce CYP or active transport systems. These included erythromycin,[73] ketoconazole,[74] azithromycin,[75] cimetidine,[76] fluoxetine[76] and grapefruit juice.[69] Accordingly, desloratadine did not appear to have a high probability of being affected by CYP-, P-gp- or OATP-mediated drug interactions.[69]

3.4 Other Therapeutic Areas

Clinically significant drug interactions involving drug-transport mechanisms in other areas of medicine have also been identified. Loperamide, a substrate for P-gp, has been found to produce respiratory depression in the presence of quinidine, a known P-gp inhibitor.[77] In a study of healthy volunteers, inhibition of P-gp-mediated efflux by quinidine 600mg led to increased loperamide plasma concentrations and, presumably, higher CNS penetration with resultant respiratory depression.[77] Notably, respiratory depression was not observed when loperamide was given alone. Although this particular interaction raises safety concerns, it further highlights the possibility of a novel approach that can be used to improve delivery of some drugs to the brain (e.g. antiretroviral agents).

Digoxin plasma concentrations have been noted to be dependent on P-gp-mediated apical transport in the renal epithelial cell membranes.[28] Inhibition of P-gp was deemed responsible for several interactions with digoxin, a P-gp substrate. The mechanism of the well-known interaction between digoxin and quinidine (i.e. increased digoxin concentrations and potential cardiotoxicity) has been attributed to P-gp inhibition.[78] Concomitant administration of digoxin and verapamil, a P-gp inhibitor, is also associated with increased digoxin plasma concentrations and the potential for digoxin intoxication.[79] The interaction of digoxin and verapamil is considered to result from decreased renal tubular secretion via blockage of P-gp. Treatment with ciclosporin also inhibits the P-gp-mediated transport of digoxin.[80] In studies of digoxin and carvedilol, transcellular transport of digoxin was increased in *MDR1*-expressing porcine kidney epithelial cells[81] while in a small patient study, concomitant carvedilol administration increased digoxin C_{max} and increased renal clearance.[82]

Recently, coadministration of digoxin and high-dose atorvastatin (80mg) was associated with elevated steady-state digoxin levels (20%) and increased bioavailability (15%).[83] Because renal clearance of digoxin was unaffected, the authors hypothesised that the increased digoxin concentrations stemmed from the inhibition of digoxin secretion into the intestinal lumen by atorvastatin. This was confirmed with the use of an *in vitro* model system. Further investigation corroborated that the inhibition of intestinal P-gp was the probable mechanism for some drug interactions with digoxin because the renal clearance of the drug was not altered.[84] In this study, rifampicin was shown to increase intestinal P-gp 3.5-fold, with a subsequent 30% reduction in digoxin bioavailability.[84]

4. Conclusions

Disposition of a drug (i.e. the amount found in plasma and tissues) depends on the net effects of metabolism and active transport. These parameters are influenced by the activity of the CYP enzyme system and active transport systems, respectively. Coadministration of drugs or foods, or both, that alter the function of these systems or are substrates of these systems can result in drug-drug and drug-food interactions. The role of P-gp and OATP in drug interactions has only been appreciated recently and much remains to be learned about these novel transporter proteins. It appears that interference with P-gp or OATP, either as upregulation or inhibition, may affect plasma drug concentrations by altering intestinal absorption, proximal renal-tubular excretion or biliary excretion.

Many drugs that influence transporter systems also interact with CYP isoenzymes. Therefore, it is possible that drug interactions that were previously attributed to CYP enzymes may be caused by inter-

ference with P-gp, OATP or both. P-gp, OATP and CYP enzymes may coexist within the same cells, such as intestinal endothelial cells, and further complicate the differentiation of their individual contributions to overall drug bioavailability. The net effect of inducers and inhibitors of P-gp, OATP and CYP can be difficult to predict. However, knowledge of suspected CYP, P-gp and OATP substrates, inducers and inhibitors should help clinicians ascertain the potential for drug-drug and drug-food interactions and choose safe and effective drug regimens.

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