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Emerging Significance of P-glycoprotein in Understanding Drug Disposition and Drug Interactions in Psychopharmacology

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ABSTRACT ~ P-glycoprotein (P-gp) is a member of the superfamily of energy-dependent efflux protein pumps involved in the transport of a wide variety of endogenous and exogenous substrates. The role of P-gp has been extensively studied in the development of multidrug resistance (MDR) in cancer cells during chemotherapy. However, recent data suggest that P-gp is also present in normal tissue, such as the gut, blood-brain barrier, lymphocytes, liver, kidney, and other organs, where it plays a role in the absorption, distribution, metabolism, and elimination of a multitude of drugs. Psychotropic drugs, as well as many other drugs, act as substrates, inhibitors, or inducers of P-gp function. While there is a growing interest in developing inhibitors of this transporter as an approach to increasing drug bioavailability, the utility of exploiting inducers of the protein is less clear. Changes in P-gp transport activity have recently been linked to clinically significant drug-drug and drug-herb interactions. Because of its wide tissue distribution and its effect on drug disposition, clinicians should recognize the potential impact of P-gp modulation on the therapeutic efficacy and adverse events of psychopharmacologic agents that are substrates for this transporter. More research is needed in the field of psychopharmacology to classify central nervous system-active P-gp substrates and to characterize the utility of modulating P-gp activity at the blood-brain barrier. *Psychopharmacology Bulletin*. 2002;36(1):67-81

Introduction

Recent clinical observations have identified a diverse array of new and complex drug-drug interactions, recognized as a result of significant loss in therapeutic effects and/or reduction in plasma concentrations. Because these

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interactions cannot be explained solely by alterations in the activity of drug-metabolizing enzymes such as the cytochrome P450 superfamily, investigations have focused on the involvement of carrier-mediated drug transport proteins. One such transporter, P-glycoprotein (P-gp), has been associated with multidrug resistance (MDR) in neoplastic cells. P-gp is thought to function as an energy-dependent efflux pump that decreases intracellular concentrations of many anticancer drugs and leads to the development of cross-resistance to cytotoxic chemotherapeutic agents. Inhibitors of P-gp have been used to increase intracellular concentrations of chemotherapeutic agents and therefore improve response in treating malignancies expressing these transport proteins.^{1,2} More recently, altered absorption, bioavailability, and trough plasma concentrations of P-gp substrates, including cyclosporin, indinavir, and digoxin have been reported in patients concomitantly administered modulators of P-gp such as quinidine and St. John's wort.³⁻⁶

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Complex drug-drug interactions may best be viewed through a conceptual model in which coadministration of two interacting drugs may lead to altered therapeutic and/or adverse effects in an individual patient at either the pharmacokinetic or pharmacodynamic level.⁷ Alterations in transport activity may lead to drug interactions at the pharmacokinetic level by changing drug absorption, availability for metabolism, or distribution. These alterations may result in changes in the dose-response relationship. Modulation of transport activity at the blood-brain barrier may affect the concentration-response relationship leading to changes in therapeutic and/or adverse responses without changing systemic plasma concentrations. The role of P-gp and other membrane transporters in complex drug interactions is becoming increasingly evident. This review will address the clinical importance of recognizing potential drug-drug interactions resulting from P-gp modulation with emphasis on interactions involving psychotropic drugs and/or drugs with central nervous system (CNS) side effects.

Adenosine Triphosphate-Binding Cassette Superfamily of Transport Proteins

Nomenclature

Transport proteins are classified as either uptake or export transporters and exhibit polarized flux into or out of cells, respectively. Uptake solute carrier (SLC) transport proteins are typically located on the basolateral membrane (eg, hepatocyte sinusoidal membrane) while export transport proteins are typically located on the apical membrane (eg, biliary canalicular membrane). These transport proteins are divided

into families, subfamilies, and individual members based on their amino acid sequence homology in a manner analogous to the nomenclature of the cytochrome P450 superfamily of drug-metabolizing enzymes. However, a systematic nomenclature for transport proteins is still being developed, has not been universally adopted, and is likely to change as new transport proteins are sequenced. Consequently, multiple common names are used for the same transporter.

At least five families of human hepatic basolateral uptake transporters have been identified thus far (Table 1): family 10 (sodium taurocholate cotransporting polypeptide), family 19 (reduced folate transporter; high-affinity thiamine transporter), family 21 (organic anion-transport polypeptide [OATP]), family 22 (organic cation transporter; organic anion transporter), and family 26 (diastrophic dysplasia sulfate transporter). Family 21 is one of the most studied to date, and its three major specific members are the SLC transport proteins SLC21A3 (OATP-A), SLC21A6 (OATP-C, OATP-2), and SLC21A8 (OATP-8).⁸

TABLE 1

Superfamily of Transmembrane Hepatic Transporter Proteins

UPTAKE SLC	EXPORT ABC
<u>Family 10 (NTCP)</u>	<u>Subfamily B (MDR)</u>
SLC10A1	ABCB1 (MDR1, P-gp)
<u>Family 19 (RFC, THTR)</u>	ABCB4 (MDR2,3)
SLC19A1	ABCB11 (BSEP)
SLC19A2	<u>Subfamily C (MRP/CFTR)</u>
SLC19A3	ABCC1 (MRP1, GS-X)
<u>Family 21 (OATP)</u>	ABCC2 (MRP2, cMOAT)
SLC21A3 (OATP-3)	ABCC3 (MRP3, MLP2)
SLC21A6 (OATP-C, OATP-2)	ABCC4 (MRP4)
SLC21A8 (OATP-8)	ABCC5 (MRP5)
<u>Family 22 (OCT, OAT)</u>	ABCC6 (MRP6)
SLC22A1	
SLC22A4	
SLC22A7	
<u>Family 26 (DTDST)</u>	
SLC26A2	
SLC26A3	
SLC26A4	
SLC26A6	

SLC=solute carrier; NTCP=sodium taurocholate cotransporting polypeptide; RFC=reduced folate transporter; THTR=high-affinity thiamine transporter; OATP=organic anion-transport polypeptide; OCT=organic cation transporter; OAT=organic anion-transporter; DTDST=diastrophic dysplasia sulfate transporter; ABC=adenosine triphosphate-binding cassette; MDR=multidrug-resistant; P-gp=P-glycoprotein; BSEP=bile-salt export pump; MRP=multidrug-resistant related protein; CFTR=cystic fibrosis transmembrane regulator protein; GS-X=glutathione conjugate export pump; cMOAT=canalicular multispecific organic anion transporter; MLP=MRP-like protein.

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The adenosine triphosphate (ATP)-binding cassette (ABC) superfamily of export transport proteins is found in humans and other mammals, as well as in other organisms.⁹ This superfamily contains subfamily B, often referred to as the multidrug-resistant subfamily, and subfamily C, also known as the multidrug-resistant related protein, cystic fibrosis transmembrane regulator protein subfamily. The multidrug transporter P-gp, a member of subfamily B, is the most extensively studied protein of the ABC superfamily of transporters.¹⁰

Detailed information on the sequence and evolving nomenclature of these transport proteins can be found on the Internet at www.expasy.ch/prosite/.

Structure and Function

P-gp, which plays an important role in normal xenobiotic absorption and elimination, is a 170-kDa transmembrane protein that is encoded by the human gene *MDR-1*. P-gp has a 1280 amino acid sequence with two homologous halves each containing a hydrophobic area with six transmembrane domain (TMD) regions involved in drug transport and a nucleotide ATP-binding domain (NBD) site.^{11,12} Interaction of the two TMD halves is necessary, and a flexible linker region is sufficient, for proper interaction of the two ATP-binding sites. Both NBD sites are essential for proper P-gp function and both are capable of hydrolyzing ATP, though not simultaneously. Drug binding and ATP hydrolysis are intimately coupled.¹³

P-gp expresses both basal and drug-stimulated ATPase activity. Endogenous substrates (ie, lipids and hydrophobic peptides) are thought to be responsible for its basal activity, while xenobiotic substrates contribute to its drug-stimulated ATPase activity. The drug-stimulated ATPase activity is thought to be sensitive to drug interactions.^{14,15} Compounds that interact with P-gp are organized into three different classes based on the effect of their interaction. Class I includes drugs that stimulate ATPase activity at low concentrations but inhibit activity at high concentrations (eg, verapamil, vinblastine, and paclitaxel). Class II includes drugs that cause a dose-dependent increase in ATP hydrolysis without inhibition (eg, diltiazem, bisantrene, and valinomycin). Finally, class III includes drugs that inhibit both basal and verapamil-stimulated ATPase activity (eg, cyclosporin A, rapamycin, and gramicidin D). Moreover, all three classes of drugs exhibit varying degrees of affinity for both stimulatory and inhibitory sites, suggesting that interaction between overlapping catalytic and inhibitory sites may modulate P-gp ATPase activity.¹⁶

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Three models of P-gp-mediated transport have been proposed to explain the role of P-gp in regulating cellular concentrations of ingested drugs and xenobiotics. These models are the altered partitioning model, in which overexpression of P-gp alters partitioning and decreases intracellular drug concentration; the flip phase model, in which the substrate is carried from the inner half to the outer half of the cell membrane; and the vacuum cleaner model, in which P-gp directly interacts with substrates within the lipid bilayer and transports them to the extracellular space.¹⁷ The net results of P-gp activity are, thus, increased drug efflux and decreased drug influx. Additionally, there is evidence that phosphorylation may play a role in drug transport specificity.

P-gp recognizes and transports a broad range of substrates including human immunodeficiency virus (HIV) protease inhibitors (indinavir), chemotherapeutic agents (paclitaxel, vinblastine, etoposide, daunorubicin), antibiotics (erythromycin), steroids (dexamethasone), antiarrhythmics (verapamil, quinidine), antidepressants (amitriptyline, nortriptyline), antihistamines (fexofenadine), analgesics (morphine), and many other compounds (Tables 2 and 3).^{11,18} In addition, P-gp was shown to play a role in placenta permeability, resistance to immunosuppressant therapy, increased first-pass effect of cyclosporin A, and restriction of drug transport across the blood-brain barrier.

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Role of P-glycoprotein in Psychotropic Drug Disposition

The blood-brain barrier is a physical barrier formed by the endothelial cells lining the brain capillaries. It plays an important role in protecting the brain from toxic substances and maintaining a constant internal environment necessary for neuronal activity. Drug characteristics that facilitate crossing of the blood-brain barrier include lipophilicity, degree of ionization, molecular weight, protein and tissue binding, and affinity for specific transport carriers. Many hydrophobic drugs (eg, loperamide, vincristine, etoposide, and domperidone) that would not be expected to cross the blood-brain barrier show variable brain penetration.^{19,20} This observation is significant because these compounds have now been reported to be P-gp substrates.^{21,22} The high concentration of P-gp on the apical membrane of endothelial cells is consistent with the belief that it plays a protective role in the brain by either increasing efflux or limiting influx of P-gp substrates.^{23,24}

Several studies looking at CNS concentrations of P-gp substrates in knockout versus wild-type mice have shown that elimination of P-gp activity at the blood-brain barrier results in increased brain concentrations, as well as increased potential for neurotoxicity, of some P-gp substrates (digoxin, cyclosporin, vinblastine, ivermectin, colchicine).²⁵⁻²⁹

Furthermore, induction of P-gp expression by the administration of dexamethasone³⁰ or morphine³¹ has shown decreased CNS availability and adverse effects from P-gp substrates. These data contribute to the mounting evidence that P-gp may play a role in limiting substrate access to the CNS.

Centrally acting drugs need to achieve adequate brain concentrations to exert their therapeutic effects. An *in vitro* study assessing the affinity of conventional and atypical antipsychotics for P-gp demonstrated that quetiapine and risperidone had a higher affinity (V_{\max}/K_m ratios of 1.7 and 1.4, respectively) whereas haloperidol and clozapine had the lowest affinity (V_{\max}/K_m ratio of 0.3 for both drugs).³² In another *in vitro* study,³³ loperamide, domperidone, and ondansetron were shown to be

TABLE 2

P-glycoprotein Substrates of Clinical Relevance

SUBSTRATES	EVIDENCE
<i>Animal in vivo and in vitro</i>	
Amitriptyline	In vivo mouse
Nortriptyline	In vivo mouse
Risperidone	In vivo mouse
Olanzapine	In vivo mouse
Methadone	In vivo mouse
Morphine	In vivo mouse, in vivo rat, BBCEC
Fentanyl	In vivo mouse, BBMEC
Phenytoin	In vivo mouse, LLC-PK1
Itraconazole	In vivo mouse, in vivo rat, BBEC
Loperamide	In vivo mouse, LLC-PK1
Fexofenadine	In vivo mouse, LLC-PK1, MDCK
Dexamethasone	In vivo mouse, in vivo, rat, LLC-PK1
Indinavir	In vivo mouse
Digoxin	In vivo mouse, in vivo rat, MDCK
Domperidone	In vivo mouse, LLC-PK1
Ondansetron	In vivo mouse, LLC-PK1
<i>Human in vitro</i>	
Quetiapine	P-gp membranes
Risperidone	P-gp membranes
Olanzapine	P-gp membranes
Chlorpromazine	P-gp membranes
<i>Human in vivo</i>	
Loperamide	Hvol
Fexofenadine	Hvol
Digoxin	Hvol

BBCEC=bovine brain capillary endothelial cells; BBMEC=bovine brain microvessel endothelial cells; BBEC=bovine brain endothelial cells; LLC-PK1=porcine kidney proximal tubule cells; MDCK=Madin-Darby canine kidney cell line; P-gp=P-glycoprotein; Hvol=healthy volunteers.

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good P-gp substrates, demonstrating transport in the apical direction (32%, 28%, and 40% efflux, respectively). Haloperidol, flunitrazepam, and clozapine did not exhibit detectable transport or were very poorly transported, whereas phenytoin was slightly transported (8%) by P-gp in the apical direction. In addition, brain penetration of loperamide and ondansetron in knockout mice was increased 7- and 4-fold, respectively, over wild-type mice. Finally, administration of loperamide at doses ranging from 5 to 160 mg/kg to wild-type and knockout mice resulted in a marked difference in the behavior of mice at all doses up to 80 mg/kg. Wild-type mice merely demonstrated piloerection, whereas knockout mice demonstrated central opiate-like effects including pronounced excitement characterized by compulsive circling movements interrupted by periods of immobility, a crouched appearance, and an erect tail on an arched back. These toxicities in the knockout mice were even observed at the lowest dose tested (5mg/kg) in this study.³³

Recently, amitriptyline and its metabolites were shown to achieve significantly higher plasma concentrations ($P < .05$) as well as increased brain penetration in knockout mice compared to wild-type mice.³⁴ Cerebrum:spleen ratio and encephalon:spleen ratio were two to four times higher ($P < .05$) in knockout than in wild-type mice. The plasma concentrations of fluoxetine and its metabolite, however, did not differ

TABLE 3

P-glycoprotein Inhibitors and Inducers of Clinical Relevance

<u>INHIBITORS</u>	<u>INDUCERS</u>
Amiodarone	Cyclosporine
Atorvastatin	Dexamethasone
Bepidil	Morphine
Chlorpromazine	Nicardipine
Diltiazem	Nifedipine
Dipyridamole	Phenobarbital
Erythromycin	Phenothiazine
Felodipine	Rifampin
Fluphenazine*	St. John's Wort
Ketoconazole*	Verapamil
Nicardipine	Yohimbine
Propranolol*	
Quinidine*	
Ritonavir*	
Tamoxifen	
Valspodar (PSC 833)	
Verapamil*	
Vitamin E (Aquasol)	

*Combined P-glycoprotein and cytochrome P450 3A4 inhibitors

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between knockout and wild-type mice, and there were no differences in brain penetration of these substances.

Data from these animal studies lend further support for a protective role of P-gp at the blood-brain barrier and provide evidence that modulation of P-gp activity plays an important role in the disposition of concomitantly administered P-gp substrates.

Evidence That P-glycoprotein Contributes to Clinically Significant Drug Interactions

It is well recognized that coadministration of cytochrome P450 inhibitors or inducers with CYP substrates may lead to clinically significant drug-drug interactions. Likewise, there is emerging evidence to suggest that clinically significant drug interactions may occur when P-gp inhibitors or inducers are coadministered with P-gp substrates.⁶ Moreover, some interactions that were previously shown to be a result of inhibition of cytochrome P450 3A4 (CYP 3A4) are now shown to result from P-gp inhibition or a combination of P-gp and CYP 3A4 modulation.³⁵⁻³⁷

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Inhibition of P-glycoprotein

Coadministration of a P-gp substrate with a P-gp inhibitor may increase substrate concentrations in the CNS by inhibiting blood-brain barrier efflux and/or increase systemic bioavailability following oral administration of the substrate by inhibiting P-gp-mediated efflux back into the gastrointestinal tract. Additionally, inhibition of P-gp at the hepatic-canalicular interface may decrease elimination of potentially pharmacologically active metabolites, and inhibition at the renal tubular level could inhibit excretion of renally cleared drugs. The clinical result of these inhibitory effects would be that coadministration of even an otherwise non-CNS active substrate could lead to increased CNS concentrations, and consequently, significant CNS side effects.

In a study of eight healthy volunteers who were given 16 mg of loperamide orally with either 600 mg of quinidine (a P-gp inhibitor) or placebo, a significant decrease in ventilatory response (25% of baseline CO₂ response slope, $P < .001$) to increasing CO₂ concentrations was observed when loperamide was given with quinidine as compared to placebo (Table 4).³⁸ Additionally, inhibition of P-gp by quinidine led to significant increases in the plasma area under the curve (AUC) for both loperamide (99.55±20.31 versus 247.00±45.25 ng/[mL·hr]; $P < .005$) and its metabolite (149.15±39.30 versus 289.55±49.39 ng/[mL·hr]; $P < .02$) compared to placebo. Although coadministration of quinidine eventually led to increased systemic plasma concentrations of lop-

eramide and its metabolite, the CNS effect began prior to these changes. Moreover, the CNS effect dissipated while systemic plasma concentrations were still elevated. Evidence from this study, coupled

TABLE 4

Clinically Relevant Drug-Drug Interactions Involving P-glycoprotein

Drug 1/Drug 2

N	SUBJECT TYPE	STUDY DESIGN	RESULTS	POSSIBLE MECHANISM
<i>LOP (16 mg)/QUI (600 mg)³⁸</i>				
8	Hvol	Randomized, double-blind, crossover	QUI decreased respiratory response to CO ₂ rebreathing; QUI decreased LOP plasma concentration.	QUI inhibition of P-gp increases LOP absorption and delivery to the brain.
<i>MOR (10 mg)/RIF (600 mg)⁴⁶</i>				
10	Hvol	Randomized, double-blind, placebo-controlled, crossover	RIF completely suppressed MOR-associated antinociception; RIF decreased AUC of MOR by 27% and of MOR-6-GLU by 19%.	Long-term administration of MOR may increase P-gp expression in the CNS.
<i>DIG (0.5 mg)/SJW (900 mg)⁵</i>				
25	Hvol	Single-blind, placebo-controlled, parallel	SJW decreased DIG AUC by 25% and DIG C _{max} by 26%.	SJW induces P-gp.
<i>DIG (0.5 mg)/SJW (900 mg)⁵¹</i>				
8	Hvol	Single-blind, crossover	SJW decreased DIG AUC by 18%; SJW increased duodenal P-gp 1.4-fold and CYP 3A4 1.5-fold; SJW increased hepatic CYP 3A4 1.4-fold.	SJW induces intestinal P-gp and CYP 3A4, as well as hepatic CYP 3A4.
<i>FEX (60 mg)/SJW (900 mg)⁵²</i>				
10	Hvol	Open-label	Single-dose SJW increased C _{max} , but repetitive dosing had no effects on FEX disposition.	Single dose SJW may inhibit P-gp.
<i>CyA FEX (MDZ-PO/MDZ-IV)/SJW (900 mg)³</i>				
10	Hvol	Open-label	SJW significantly reduced FEX and MDZ-PO AUC; MDZ-IV AUC also was decreased.	SJW simultaneously induces P-gp and CYP 3A4 to a similar extent.

LOP=loperamide; QUI=quinidine; Hvol=healthy volunteers; P-gp=P-glycoprotein; MOR=morphine; RIF=Rifampin; AUC=area under the curve; MOR-6-GLU=morphine-6-glucuronide; CNS=central nervous system; DIG=digoxin; SJW=St. John's wort; FEX=fexofenadine; CyA=cyclosporin A; MDZ-PO=oral midazolam; MDZ-IV=intravenous midazolam.

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with preclinical data,³³ suggests that quinidine interacted both at the pharmacokinetic and pharmacodynamic level by inhibiting P-gp-mediated CNS efflux as well as systemic elimination of loperamide. The opioid-like effect observed in this study illustrates the clinically significant impact a P-gp inhibitor can have on drug disposition, in this case leading not only to increased adverse CNS events, but possibly also to an increased potential for abuse.

Inhibition of P-gp is now recognized as the mechanism for previously observed pharmacokinetic drug-drug interactions with the P-gp substrate digoxin. Although it was originally hypothesized to be an interaction at the level of plasma protein binding, the mechanism is now recognized to be quinidine inhibition of P-gp mediated digoxin elimination, which may possibly explain adverse CNS events such as confusion, depression, and delirium.^{39,40} Coadministration of quinidine increased serum concentrations of digoxin by 2- to 3-fold (0.45–1.1 versus 0.7–1.8 ng/mL) and significantly decreased its renal clearance (1.64 ± 0.60 versus 1.09 ± 0.24 ml/[min·kg]; $P < .05$).⁴¹ These results indicate that quinidine modulation of P-gp in the kidneys and intestinal tract affect both absorption and elimination. In another study, the AUC of digoxin was increased by 76% and its renal clearance decreased by 62% (both $P = .0001$) when coadministered with valsopodar, a second-generation P-gp inhibitor.⁴² Clarithromycin was similarly shown to increase serum concentration and decrease renal clearance of orally-administered digoxin through inhibition of P-gp.⁴³ Taken together, and assuming that renal clearance of digoxin did not change, these clinical studies suggest that P-gp inhibitors can modulate uptake and/or efflux activity to reduce the clearance of digoxin, possibly leading to increased CNS distribution and risk of adverse CNS events.

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Induction of P-glycoprotein

Chronic coadministration of a P-gp inducer along with P-gp substrates may reduce substrate concentrations in the CNS by increasing blood-brain barrier efflux and/or reduce systemic bioavailability following oral administration of the substrate by increasing P-gp-mediated efflux into the gastrointestinal tract. These interactions could significantly reduce the CNS efficacy and/or toxicity of medications that may depend, in part or in whole, on P-gp-mediated transport. Opiate analgesics, fexofenadine, digoxin, HIV protease inhibitors (indinavir), and possibly tricyclic antidepressants (amitriptyline, nortriptyline) are examples of potentially affected substrates (Table 4).

Substrate cross-specificity for CYP 3A4 and P-gp is well recognized; moreover, this cross-specificity may extend to inducers of CYP 3A4 and

of P-gp.³⁵ Rifampin, St. John's wort, and phenothiazines are inducers of both CYP 3A4 and P-gp.^{5,44,45} Chronic administration of rifampicin (600 mg per day for 10 days) in a randomized, double-blind, placebo-controlled crossover study in 10 healthy volunteers showed complete suppression of morphine-associated antinociception. The AUC and maximum serum concentrations of morphine were significantly reduced during coadministration of rifampin compared to placebo ($-27.7 \pm 19.3\%$ and $-40.7 \pm 27.1\%$, respectively; $P .01$). In addition, there were significant reductions in plasma AUC for both morphine-3-glucuronide ($P .01$) and morphine-6-glucuronide ($P .05$).⁴⁶ These results, together with animal data,³¹ suggest that potential upregulation of P-gp expression may play a role in the development of tolerance to morphine-associated analgesia after prolonged use.

Digoxin, a P-gp substrate with CNS events at high plasma concentrations, can be used as a marker substrate for P-gp activity.⁴⁷⁻⁵⁰ Changes in P-gp activity as reflected by digoxin disposition may give insight into potential P-gp-mediated drug interactions. For example, chronic administration of rifampin (600 mg/day for 10 days) in eight healthy subjects resulted in a significant decrease in digoxin AUC_(0-144h) (54.8 ± 11.6 versus 38.2 ± 12.4 ng/[mL·h]; $P < .05$) and C_{max} by 58% (5.4 ± 1.9 versus 2.6 ± 0.7 ng/mL; $P < .05$) compared to baseline.⁴⁴

Interactions with the herbal St. John's wort, purportedly through induction of P-gp, have been reported (Table 4). In a study of healthy volunteers who received digoxin for 5 days and then were given placebo or St. John's wort for 10 additional days, concentrations on day 5 were compared with those on days 6 and 15 (1st and 10th days of comedication).⁵ Following chronic (10 days) dosing of St. John's wort, there was a 25% decrease in digoxin AUC_(0-24h) (17.2 ± 4.0 versus 12.9 ± 2.3 [mcg·h]/L; $P = .0035$), a 26% reduction in C_{max} (1.9 ± 0.5 versus 1.4 ± 0.4 mcg/L; $P = .0095$); and a 33% reduction in digoxin trough concentrations ($P = .0023$). However, there was no significant difference in AUC_(0-24h) after the first dose of St. John's wort at day 6 for St. John's wort and placebo (17.7 ± 3.0 and 18.1 ± 2.9 [mcg·h]/L, respectively) or in C_{max} (2.1 ± 0.5 and 1.9 ± 0.5 mcg/L, respectively; $P = .057$). These observations suggest induction of P-gp activity following chronic, but not acute, dosing of St. John's wort.

In a second study, 0.5 mg of digoxin was given to eight healthy volunteers before and after 14 days of administration of St. John's wort. Gastrointestinal tissue, biopsied on day 15, demonstrated induction of both intestinal P-gp (1.37 ± 0.31 -fold; $P = .025$) and intestinal CYP 3A4 (1.48 ± 0.17 -fold; $P = .012$) when normalized to villin concentrations. This induction correlated with an 18% decrease in oral bioavailability of

digoxin AUC_(0-7h). In addition, a significant ($P=.008$) increase in demethylation of erythromycin (1.44±0.28-fold), as measured by the erythromycin breath test, was observed on day 15, suggesting that St. John's wort also induced hepatic CYP 3A4.⁵¹

Preliminary data are available suggesting that St. John's wort induces P-gp-mediated elimination of the antihistamine fexofenadine (Table 4). In a study by Hamman et al,⁵² the effects of a single dose and 14 days of chronic administration of St. John's wort on the disposition of fexofenadine given as a single oral 60-mg dose were evaluated. Following a single 900-mg oral dose of St. John's wort, there was a significant ($P<.05$) increase in fexofenadine C_{max} compared with baseline (289±109 versus 183±47 ng/mL), possibly owing to acute inhibition of P-gp. Following multiple dosing of St. John's wort, the C_{max} of fexofenadine was lower (185±87 ng/mL) than seen with acute dosing, but no different than baseline.⁵² In a second study,³ the effects of chronic dosing of St. John's wort (900 mg daily for 10 days) on the disposition of fexofenadine (P-gp substrate), intravenous midazolam (hepatic CYP 3A4 substrate), oral midazolam (hepatic and gut CYP 3A4 substrate), and cyclosporin (combined P-gp, and hepatic and gut CYP 3A4 substrate) were evaluated. Administration of St. John's wort simultaneously induced P-gp and CYP 3A4 activities to a similar extent. This correlated with a significant ($P<.05$) decrease in bioavailability of the substrates when comparing the AUC before and after treatment with St. John's wort.³ These studies suggest that St. John's wort induces intestinal P-gp, intestinal CYP 3A4, and hepatic CYP 3A4 and provide further evidence for St. John's wort interactions with P-gp and CYP 3A4 substrates.

Another important class of drugs transported by P-gp is the protease inhibitor group used in treating HIV infection. Dementia seen in patients with autoimmune deficiency syndrome may occur as a result of viral penetration into the CNS, with the brain serving as a viral reservoir.⁴ Alterations in P-gp activity at the gastrointestinal tract and blood-brain barrier may contribute to the progression of autoimmune deficiency syndrome-related dementia by increased presystemic (first pass) elimination and decreased CNS penetration of protease inhibitors.

In a recent study,⁴ 14 days of St. John's wort (300 mg three times per day) significantly reduced both the AUC of indinavir (by 57%±19%) and trough concentrations (by 81%±16%) in eight healthy volunteers, consistent with marked CYP 3A4 induction. In fact, it is likely that the observed interaction is a result of the combined induction of P-gp and CYP 3A4 by St. John's wort. Many

HIV protease inhibitors have poor brain penetration, and all currently marketed agents are P-gp substrates.^{53,54} Moreover, there was a 37-fold increase in brain concentrations of nelfinavir when a potent P-gp inhibitor (LY-335979) was administered to mice.⁵⁵ These findings underline the potential of P-gp inhibitors to enhance CNS penetration of protease inhibitors in HIV therapy.

Conclusion

P-gp plays an important role in the efflux of various psychopharmacologic agents across cell membranes. Because of its wide tissue distribution and broad substrate specificity, P-gp is important in drug absorption, distribution, and elimination. Hence, modulation of P-gp activity by coadministration of inhibitors or inducers can lead to clinically significant drug-drug and drug-herb interactions. Coadministration of P-gp inhibitors, such as quinidine, may result in improved drug bioavailability, through an increase in intestinal absorption and/or a decrease in renal clearance and an increase in CNS penetration. Coadministration of P-gp inducers, such as St. John's wort, may result in clinically significant reductions in CNS and/or systemic drug concentrations. The potential contribution of P-gp modulation should be kept in mind when evaluating patients with drug-emergent cognitive or psychiatric symptoms. More data are needed to classify CNS-active P-gp substrates and to understand effectively the mechanisms and clinical relevance of P-gp-mediated CNS drug interactions. ❀

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