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Clinical Pharmacology: Concise Drug Reviews

Concise Review: Clinical Relevance of Drug–Drug and Herb–Drug Interactions Mediated by the ABC Transporter ABCB1 (MDR1, P-glycoprotein)

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Key Words. P-glycoprotein • Drug interaction • Complementary and alternative medicine • CAM • Pharmacokinetics Pharmacodynamics

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Identify important sources of variability in drug exposure caused by drug interactions mediated by P-glycoprotein.
2. Describe how unwanted drug–drug interactions may lead to unexpected serious toxicity or undertreatment.
3. Prevent these interactions by individualizing pharmacotherapy; this means selecting noninteracting drugs or adapting the dose of (the) interacting drug(s).

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ABSTRACT

The importance of P-glycoprotein (P-gp) in drug–drug interactions is increasingly being identified. P-gp has been reported to affect the pharmacokinetics of numerous structurally and pharmacologically diverse substrate drugs. Furthermore, genetic variability in the multidrug resistance 1 gene influences absorption and tissue distribution of drugs transported. Inhibition or induction of P-gp by coadministered drugs or food as well as herbal constituents may result in pharmacokinetic interactions leading to unexpected toxicities or undertreatment. On the other hand, modulation of P-gp expression and/or activity may be a useful strategy to improve the pharmacological profile of anticancer P-gp substrate drugs.

In recent years, the use of complementary and alternative medicine (CAM), like herbs, food, and vitamins, by cancer patients has increased significantly. CAM use substantially increases the risk for interactions with anticancer drugs, especially because of the narrow therapeutic window of these compounds. However, for most CAMs, it is unknown whether they affect metabolizing enzymes and/or drug transporter activity. Clinically relevant interactions are reported between St John's wort or grapefruit juice and anticancer as well as nonanticancer drugs. CAM–drug interactions could explain, at least in part, the large interindividual variation in efficacy and toxicity associated with drug therapy in both cancer and noncancer patients.

The study of drug–drug, food–drug, and herb–drug

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interactions and of genetic factors affecting pharmacokinetics and pharmacodynamics is expected to improve drug safety and will enable individualized drug therapy.
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Disclosure of potential conflicts of interest is found at the end of this article.

Introduction

In patients, drug–drug interactions can result in unexpected life-threatening and even lethal toxicities. Up to 10% of all admissions in general hospitals are caused by improper use of drugs and combinations of drugs, resulting in potentially severe drug–drug interactions [1, 2]. Adverse drug reactions can especially be severe when these interactions involve cytotoxic anticancer agents [3, 4]. Anticancer drugs are dosed close to the maximum-tolerated dose, and factors affecting the pharmacokinetics may therefore greatly increase the likelihood of development of life-threatening toxicities.

Thus far drug–drug interactions have been thought to result from inhibition of drug metabolism, inhibition of renal drug excretion, displacement out of the protein binding, or pharmaceutical interactions. However, interference at the level of ATP binding cassette (ABC) and other transporters is increasingly being identified as the mechanism behind clinically important drug–drug interactions. Drug–drug and herb–drug interactions at the level of ABCB1 (multidrug resistance 1 [MDR1], P-glycoprotein [P-gp]) is the subject of this paper.

Milestones, Position in ABC Transporter Family, Main Molecular Mechanism

P-gp was first identified by Juliano and Ling in 1976 as a surface glycoprotein in Chinese hamster ovary cells expressing the MDR phenotype [5]. Cloning of the encoding gene and structure analysis of the protein revealed that P-gp is a 160-kDa ATP-dependent efflux transporter, belonging to the ABC transporter superfamily [6, 7].

Tissue Distribution and Physiological Function

The anatomical localization of P-gp in various tumors (where it confers the MDR phenotype) and at the apical/luminal membrane of polarized cells in several normal human tissues with excretory (liver, kidney, adrenal gland) and barrier (intestine, blood–brain barrier, placenta, blood–testis and blood–ovarian barriers) functions [8–11] suggests for P-gp a physiological role in detoxification and protection of the body against toxic xenobiotics and metabolites by secreting these compounds into bile, urine, and the intestinal lumen and by preventing their accumulation in the brain, testis, and fetus (Fig. 1) [12].

Impact of Genetic Polymorphism in the *ABCB1* Gene on Function

Currently, at least 105 variants in the *ABCB1* gene have been identified, with significant differences in their frequencies among different ethnic groups. The majority of these single nucleotide polymorphisms (SNPs) involve intronic or noncoding regions, thus not affecting the P-gp amino acid sequence. However, several variants in the *ABCB1* coding regions result in amino acid change and potentially affect P-gp expression and activity. Hoffmeyer et al. [13] reported an association among a SNP in exon 26 (C3435T) of *ABCB1*, reduction in duodenal P-gp levels, and higher peak plasma concentrations of the P-gp substrate digoxin in healthy volunteers. Confirming and contradicting studies have subsequently been published about the influence of SNPs in *ABCB1* on disposition of digoxin and also on other P-gp substrate drugs (such as fexofenadine, tacrolimus, irinotecan, SN-38, paclitaxel, and cyclosporin A) and on P-gp expression and activity (see reviews [14–21]). Moreover, genetic variation in *ABCB1*, by potentially altering the physiologic protective role of P-gp, has recently been assessed in the etiology of several human pathophysiological conditions. An increasing number of studies have associated certain SNPs in *ABCB1* with susceptibility to diseases such as pharmacoresistant epilepsy, Parkinson's disease, inflammatory bowel diseases (ulcerative colitis and Crohn's disease), colorectal cancer, and renal carcinoma [22–27].

Recently the *ABCB1* SNP C3435T has been associated with the efficacy of antiemetic treatment with 5-hydroxytryptamine type 3 receptor antagonists (such as granisetron, ondansetron, tropisetron) in patients with cancer [28], whereas in patients affected by depression, the same polymorphism has been linked to the development of postural hypotension induced by the antidepressant nortriptyline [29].

MDR1 gene polymorphism has also been suggested to affect the therapy outcome of patients with several malignancies. Goreva et al. [30] reported an association between C3435T and G3677T SNPs in *ABCB1* and the risk for drug resistance in patients with lymphoproliferative diseases. A correlation between several commonly occurring *ABCB1* SNPs and overall survival and the risk for relapse has been reported in patients affected by acute myeloid leukemia

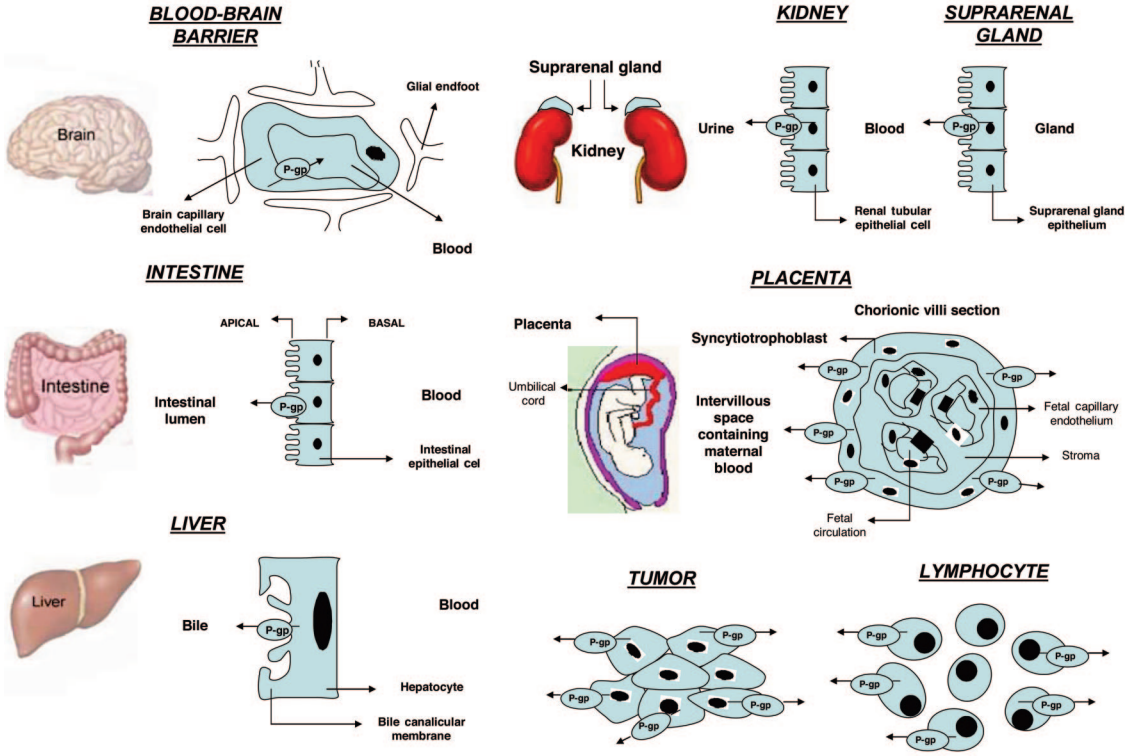

Figure 1. Schematic representations of the main sites of localization of P-glycoprotein in the body.

treated with etoposide, mitoxantrone, or daunorubicin (well-known P-gp substrates) [31]. Moreover, the *ABCB1* SNP C3435T has been suggested as a significant predictor of treatment outcome in children affected by acute lymphoblastic leukemia, although these findings have not been confirmed in adults [32, 33]. Another study showed a greater response to preoperative chemotherapy in breast cancer patients homozygous for the C3435T genotype [34], whereas conflicting results have been reported about the impact of genetic variation in the *MDR1* gene (in particular, G2677T/A) on the response to paclitaxel chemotherapy in patients with ovarian carcinoma [35].

Several factors may have contributed to the conflicting findings reported in the literature: demographic data from subjects selected for the various *MDR1* SNPs and the methods used to measure P-gp expression differ from one study to another (i.e., protein detection by Western blot versus immunohistochemistry, various antibodies used, etc.). Moreover, discrepancies may be related to the route of drug administration and extent of metabolism relative to P-gp–mediated transport. For instance, cyclosporine is a P-gp but also a cytochrome P450 3A4 enzyme (CYP3A4) substrate, therefore a potential P-gp effect may be hidden by CYP3A4 activity. In this regard, environmental factors, such as diet, that affect CYP enzyme activity could also influence transporter function. Differences in dietary constituents among different populations may have contributed to the conflicting results among studies. For example, one of the possible reasons hypothesized for the reported divergent effects of *MDR1* SNPs on fexofenadine disposition among whites living in the U.S. and in Germany was the difference in dietary salt intake between the two populations [14, 36, 37]. Furthermore, although well-known P-gp substrate drugs that are not metabolized to a relevant extent in humans (such as digoxin, fexofenadine, talinolol) have been used as probe drugs for P-gp function in humans, the involvement of other transporters and associated genetic variability could have influenced study results. Another possible reason for the contradictory reports associating *ABCB1* variants with variation in drug response is that most of the studies have not considered haplotypes, whereas several recent studies suggested that the primary determinant of functional differences in P-gp resides not in SNP differences but in *ABCB1* haplotypes [38]. Given the known interpopulation differences in drug response, it is especially important to consider variability among ethnic groups and to characterize variability in haplotype structure and linkage disequilibrium and recombination within and among ethnic populations.

Additional studies involving larger samples sizes and stratification according to haplotype are required for a complete understanding of the contribution of genetic variability in *ABCB1* and related proteins to drug disposition,

therapeutic response, and toxicity [21, 39]. To reduce the risk of a spurious association between *MDR1* genotypes and in vivo phenotypes, demographic data of subjects selected for the various *MDR1* SNPs as well as sample size and environmental factors should also be considered carefully. Moreover, standardization of assays relating to P-gp protein and mRNA detection and quantification is desirable too [14].

Main Clinically Applied Substrate Classes

P-gp presents high transport capacity and broad substrate specificity: a wide number of clinically relevant drugs with structurally different features and belonging to different classes (e.g., several anticancer drugs, some HIV protease inhibitors [HPIs], H_2-receptor antagonists, antiarrhythmics—cardiac glycosides and calcium channel blockers—immunosuppressive agents, corticosteroids, antiemetic and antidiarrheal agents, analgesics, antibiotics, anthelmintics, antiepileptics, sedatives, antidepressants) can be transported by P-gp (for review, see [14, 40]); in general, they are hydrophobic and amphipathic molecules in nature, uncharged or basic, although zwitterionic and negatively charged compounds can also be transported.

Inhibitors (Competitive, Noncompetitive)

Some P-gp drug substrates are able to inhibit P-gp–mediated transport of other substrates. The discovery by Tsuruo and colleagues [41] that verapamil (weak P-gp substrate) could reverse P-gp–mediated MDR in leukemia cells was followed by the identification of several other P-gp inhibitors [42, 43] that can block P-gp activity by competition for drug-binding sites (competitive inhibitors) or by blockade of the ATP hydrolysis process (noncompetitive inhibitors). The first agents identified as P-gp inhibitors were drugs (e.g., verapamil and cyclosporin A) already used in the clinic that were themselves transported by P-gp (so-called first-generation inhibitors). Because of their low substrate selectivity and the concomitant inhibition of the drug-metabolizing CYP3A4, so-called second-generation (cyclosporin A analog PSC833) and third-generation (LY335979, VX710, GF120918, XR9576) P-gp inhibitors were developed. These and other selective P-gp inhibitors have been extensively tested preclinically and in patients to reverse MDR. Of interest is that GF120918 (elacridar), originally developed as a P-gp inhibitor, was also identified as an effective breast cancer resistance protein (BCRP; *ABCG2*) inhibitor [44].

Recently it has been reported that benzimidazole gastric H^+, K^+ -ATPase proton pump inhibitors (PPIs—omeprazole, pantoprazole, lansoprazole, and rabeprazole), which are used by up to 50% of patients with cancer, are effective inhibitors of P-gp in vitro [45], although their potency towards BCRP inhibition is even greater [46]. Drug interactions with benzimidazoles are increasingly reported [1, 2, 47–50]. However, it has been noted that the 50% inhibitory concentration (IC_{50}) values of PPIs in inhibiting P-gp observed in vitro are higher than their expected intraluminal (intestinal) and plasma concentrations obtained after oral dosing in humans, making a drug–drug interaction at these levels unlikely. Considering that PPIs have also been shown to be CYP3A4 and CYP2C19 substrates, and that they are able to inhibit BCRP activity, under certain circumstances, for instance in poor metabolizers of CYP2C19, plasma levels of omeprazole and pantoprazole would reach the range of reported IC_{50} values, thus making a clinical drug–drug interaction possible with coadministered substrate drugs for P-gp and/or BCRP [45].

In addition, several widely used drugs have been described to inhibit P-gp function, thus potentially leading to relevant drug–drug interactions. They include various antimicrobial agents (e.g., ceftriaxone, cefoperazone, clarithromycin, erythromycin, itraconazole, ketoconazole), Ca^{2+} antagonists (verapamil, diltiazem, quinidine, quinine, nifedipine, nicardipine), HPIs (ritonavir, indinavir, saquinavir, nelfinavir), and other compounds such as amiodarone, propranolol, dipyridamole, tacrolimus, hydrocortisone, progesterone, and tamoxifen, to name a few [51, 52].

Furthermore, many pure herbal constituents commonly used as complementary and alternative medicines (CAMs) by cancer patients and dietary phytochemicals have been reported to modulate P-gp expression and/or activity. Indeed, piperine [53], ginsenosides [54, 55], silymarin from milk thistle and other flavonoids [56], capsaicin [57], and resveratrol [57] were reported to inhibit P-gp activity in vitro, whereas curcumin [58, 59] and curcuminoids [60] and several catechins from green tea [61–63] were shown to reduce P-gp expression and activity in vitro. Importantly, some of these herbal constituents (such as piperine, silymarin) have been observed to interact with P-gp at dietary concentrations, thus making a drug–herbal interaction in vivo more likely [53, 56]. Similarly, constituents of grapefruit and orange juice were also found to block P-gp function and certain juice–drug interactions for commonly used drugs have been described too [64–70]. The modulation of P-gp as well as other transporters (i.e., organic anion transporting polypeptides [OATPs]) or drug-metabolizing enzymes (such as CYP3A4) may provide an explanation for many reported clinical herb/juice–drug interactions.

Inducers

Clinical and preclinical findings reveal that the expression of P-gp (like some of the CYP isoenzymes) is inducible.

Expression levels of P-gp (as well as other transporters) and drug-metabolizing enzymes appear to be regulated by nuclear receptors like the pregnane X receptor (PXR), constitutive androstane receptor, and vitamin D binding receptor [71]. Some (active constituents of) herbs, like hyperforin from St John's wort (SJW), can activate one or more of these receptors, thereby increasing the expression of metabolizing enzymes and transporters [72, 73]. Several carotenoids and their metabolites (such as retinol and β-carotene) have been shown to activate the PXR in vitro [74]. Recent in vitro studies demonstrated that several drugs, including rifampicin, paclitaxel, and reserpine, can induce CYP3A4 and *MDR1* gene expression through a similar mechanism [75–77]. Other putative P-gp inducers are clotrimazole, phenobarbital, phenytoin, troglitazone, and the flavonoids kaempferol and quercetin [51]. However, thus far, only rifampin and SJW have been documented to significantly induce intestinal P-gp in humans: in duodenal biopsies performed in healthy volunteers after rifampin administration, P-gp was induced 3.5-fold [78]. Similarly, administration of SJW induced human intestinal P-gp 1.4 fold [79]. For the other inducers, only in vitro data are available, thus raising doubts whether results obtained in cell lines can be extrapolated to the human in vivo situation. Moreover, recent preclinical studies demonstrate a tissue specificity of P-gp induction with potential differences among species [80]. Therefore, although interactions between P-gp substrates and commonly used drugs/CAMs that are reported to induce P-gp expression in vitro have been described in the literature (see below), clearly, preclinical animal models that behave similarly to humans in terms of transporter and metabolism induction as well as further studies in humans are needed to evaluate their clinical relevance.

Pharmacological and Toxicological Functions

The pharmacological functions of P-gp have been extensively studied in in vitro and in vivo models: P-gp was first described as a plasma membrane protein that could cause MDR in tumor cells by actively extruding a wide range of structurally diverse compounds, thus contributing to the resistance against chemotherapy occurring in several cancers. In addition, the strategic physiological distribution of P-gp in organs that play key roles in processes of drug absorption, distribution, and elimination suggests that P-gp has a relevant impact on limiting cellular uptake of drugs out of the blood circulation into the brain, placenta, and testis and from the intestinal lumen into epithelial cells lining the gut. In addition, P-gp may also mediate excretion of drugs out of hepatocytes into the bile canaliculi and out of renal tubules into the urine.

The effect of P-gp on the pharmacokinetics of substrate drugs has been demonstrated in vivo using *mdr1a* and *mdr1a/1b* knockout mice. Mice lacking one or both *mdr* genes showed significant alterations in drug absorption, distribution, and elimination [81–84]: compared with wild-type *mdr1a*$^{(-/-)}$ and *mdr1a/1b*$^{(-/-)}$ mice displayed greater sensitivity to the centrally neurotoxic anthelmintic ivermectin and other known P-gp substrates like vinblastine, digoxin, and cyclosporin A. Compared with wild-type, *mdr1a*$^{(-/-)}$ and *mdr1a/1b*$^{(-/-)}$ mice also presented higher concentrations of drugs in many tissues (especially in the brain) and a slower rate of drug elimination. Other in vitro and in vivo studies documented the effect of P-gp expression on the apparent oral bioavailability of substrate drugs. Hunter et al. [85] reported the apical efflux of vinblastine across intestinal Caco-2 cell layers and the efflux was inhibited in the presence of the P-gp inhibitor verapamil and other P-gp modulators. In in vivo experiments, the apparent bioavailability of the P-gp substrate paclitaxel after oral administration was 11% in wild-type and 35% in *mdr1a*$^{(-/-)}$ mice [86]. Bardelmeijer et al. [87] reported an apparent bioavailability after oral administration of docetaxel, another P-gp substrate, of 3.6% in wild-type and 22.7% in *mdr1a/1b*$^{(-/-)}$ mice. In other studies, oral administration of the P-gp inhibitors valspodar (PSC 833) or cyclosporin A or elacridar (GF120918) followed by oral paclitaxel [88–90] or by oral docetaxel [87] resulted in significantly greater apparent oral bioavailability in wild-type mice compared with those treated without the P-gp inhibitor (Fig. 2A). These findings led to important potential clinical implications: drug–drug interactions between substrates and P-gp inhibitors can modify the drug's pharmacokinetics by increasing bioavailability and organ uptake, leading to more adverse drug reactions and toxicities. Possibly, coadministration of substrates for P-gp and P-gp–inducing agents may lead to a reduction in plasma drug levels and consequently undertreatment.

Furthermore, the localization of P-gp in the placenta has been shown to play a key role in preventing fetal exposure to various potentially harmful or therapeutic compounds. Inhibition of P-gp activity in the placenta can affect the distribution and consequently the fetal toxicity and/or efficacy of P-gp substrate drugs [91–94]. Drug–drug interactions should be considered very carefully in pregnant or lactating breast cancer patients who will be treated with anticancer drugs, substrates for P-gp, such as anthracyclines.

Drug–Drug Interactions

In the literature several drug–drug interactions mediated by P-gp transporters have been described (Table 1). In general, the involvement of P-gp in drug–drug interactions is diffi-

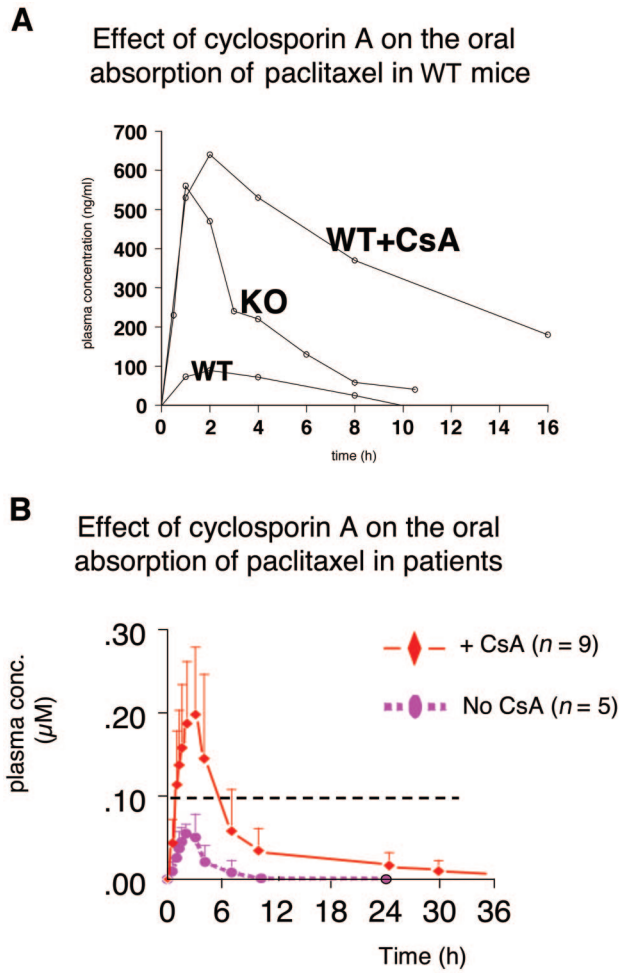

Figure 2. Effect of cyclosporin A on the oral absorption of paclitaxel. **(A):** Coadministration of oral paclitaxel and cyclosporin A (CsA) in wild-type (WT) mice resulted in a significantly greater area under the curve (AUC) of paclitaxel in plasma. The effect was even greater than the AUC of paclitaxel when given to P-glycoprotein–deficient *mdr1a/b* knockout (KO) mice. The results indicate that P-glycoprotein effectively prevents oral uptake of paclitaxel from the gut. CsA may also have inhibited cytochrome P450 3A4 enzyme (CYP3A4) to explain the additional difference in the AUC compared with the experiment in KO mice. From Sparreboom A, van Asperen J, Mayer U et al. Limited oral bioavailability and active epithelial excretion of paclitaxel (Taxol) caused by P-glycoprotein in the intestine. Proc Natl Acad Sci U S A 1997;94:2031–2035, with permission. **(B):** Coadministration of oral paclitaxel and CsA in patients with advanced cancer resulted in a significantly greater AUC of paclitaxel in plasma. These results are the clinical proof of the concept that inhibition of P-glycoprotein (and possibly also CYP3A4 in the gut epithelium) results in a significantly greater uptake of paclitaxel from the gut leading to a significantly greater systemic exposure to paclitaxel. Reprinted from Meerum Terwogt JM, Beijnen JH, ten Bokkel Huinink WW et al. Co-administration of oral cyclosporin enables oral therapy with paclitaxel. Lancet 1998;352:285, with permission from Elsevier.

cult to prove in humans because, as a result of the overlapping substrate specificity of inhibitors and inducers between CYP3A4 and P-gp, many drug interactions may involve both CYP3A4 enzymes and P-gp [95]. Moreover, P-gp and CYP3A4 may be functionally linked, and several potential mechanisms whereby the functions of P-gp and CYP3A4 could be complementary have been proposed [96]. Furthermore, drug–drug interactions may involve additional ABC transporters as well.

Clinical **drug–drug** interactions were reported in the literature between digoxin (a good P-gp substrate) and other drugs, such as quinidine [97–99], verapamil [100–102], talinolol [103], clarithromycin [104], itraconazole [105], erythromycin [106], and propafenone [101, 107, 108].

Other clinically relevant drug interactions described in the literature involve the antimicrobial drug rifampicin. Rifampicin is a well-known inducer of intestinal CYP3A4. However, recent findings indicate that it can also induce P-gp expression. In a clinical study, the oral bioavailability of digoxin in eight healthy volunteers was decreased by 30% during rifampicin therapy. Intestinal biopsies obtained from the same patients before and after administration of rifampicin showed a significant increase in intestinal P-gp expression after administration of the antimicrobial drug, which correlated inversely with the oral area under the concentration–time curve (AUC) of digoxin. In addition, pretreatment with rifampicin had little effect on the renal clearance of digoxin. These results suggest that the digoxin–rifampicin interaction mainly occurs at the intestinal level and that chronic exposure to rifampicin can result in P-gp induction [78]. Similar interactions with rifampicin have been reported for talinolol [109], fexofenadine [110], and cyclosporin A [111].

Interactions mediated by P-gp that may have clinically relevant consequences have also been reported for some **excipients** used in pharmaceutical formulations. In in vitro experiments, polysorbate 80 was able to inhibit P-gp activity and to increase daunorubicin intracellular levels in cell cultures [112]. Polyoxyl castor oil and polysorbate 80 (substances used in drug formulations to dissolve some lipophylic and/or poorly soluble drugs, especially paclitaxel and docetaxel) were reported to increase the oral absorption of saquinavir and digoxin, respectively, through interaction with P-gp activity [113, 114].

In addition, **food and dietary constituents,** such as grapefruit, orange, apple, and pummelo juice, are also possible P-gp modulators. The in vivo effect of fruit juices, and in particular, grapefruit juice, on drug transport is still controversial, because some authors have predicted or reported greater whereas others have predicted or reported lower amounts of coadministered drugs reaching the systemic circulation. Indeed, several authors reported that flavonoids and furanocoumarins of grapefruit juice were able to inhibit

Table 1. Clinically relevant drug-drug interactions involving MDR1

Drug	Inhibitor/inducer	Measured effect/toxicity	Putative mechanism	References
Digoxin	Quinidine	Greater plasma levels, lower renal clearance	Inhibition of MDR1	[97–99]
Digoxin	Verapamil	Greater plasma levels, lower renal clearance	Inhibition of MDR1	[100–102]
Digoxin	Talinolol	Greater plasma levels and AUC, lower renal clearance	Inhibition of MDR1	[103]
Digoxin	Clarithromycin	Greater plasma levels, lower renal clearance	Inhibition of MDR1	[104]
Digoxin	Erythromycin	Greater plasma levels, lower renal clearance	Inhibition of MDR1	[106, 177]
Digoxin	Itraconazole	Greater plasma levels, lower renal clearance	Inhibition of MDR1	[105, 178]
Digoxin	Ritonavir	Greater plasma AUC and terminal half-life and toxicity of digoxin	Inhibition of MDR1	[179, 180]
Paclitaxel	Cyclosporin A	Greater apparent bioavailability	Inhibition of MDR1, CYP3A4	[157, 192]
Paclitaxel	Elacridar (GF120918)[a]	Greater bioavailability	Inhibition of MDR1, CYP3A4	[181]
Paclitaxel	Valspodar (PSC-833)[a]	Greater plasma AUC	Inhibition of MDR1	[151]
Docetaxel	Cyclosporin A	Greater bioavailability	Inhibition of MDR1, CYP3A4	[158]
Saquinavir	Ritonavir	Greater apparent oral bioavailability	Inhibition of MDR1, CYP3A4	[182, 183]
Tacrolimus	Verapamil	Greater plasma levels and toxicity of tacrolimus	Inhibition of MDR1, CYP3A4	[184]
Talinolol	Erythromycin	Greater AUC	Inhibition of MDR1	[185]
Cyclosporin A	Erythromycin	Greater plasma AUC and peak plasma concentrations	Inhibition of MDR1, CYP3A4	[186, 187]
Loperamide	Quinidine	Greater CNS adverse effects	Inhibition of MDR1	[175]
Digoxin	Rifampin	Lower plasma levels and AUC	Induction of MDR1, CYP3A4	[78]
Talinolol	Rifampin	Lower AUC	Induction of MDR1	[109]
Tacrolimus	Rifampin	Lower apparent oral bioavailability, lower total clearance	Induction of MDR1, CYP3A4	[188]
Cyclosporin A	Rifampin	Lower oral bioavailability	Induction of MDR1, CYP3A4	[111]
Digoxin	St John's wort	Lower AUC and peak plasma concentrations	Induction of MDR1	[79, 189]
Cyclosporin A	St John's wort	Lower plasma levels	Induction of MDR1	[121, 122]
Indinavir	St John's wort	Lower plasma levels	Induction of MDR1, CYP3A4	[123]
Tacrolimus	St John's wort	Lower plasma levels	Induction of MDR1, CYP3A4	[190]
Topotecan	Elacridar (GF120918)	Greater apparent oral availability	Inhibition of BCRP, MDR1	[159]
Methotrexate	Omeprazole/ pantoprazole	Greater AUC, lower clearance	Inhibition of BCRP, MDR1	[191]

[a]Experimental compound.
Abbreviations: AUC, area under the concentration–time curve; CNS, central nervous system; CYP3A4, cytochrome P450 3A4 enzyme; MDR, multidrug resistance

P-gp and CYP3A4 activity, thus influencing accumulation and efflux of anticancer drugs (well-known P-gp substrates) in P-gp–overexpressing cell lines [66, 70, 115–117]. In contrast, the apparent bioavailability after oral administration and the plasma concentrations of etoposide were significantly lower in subjects taking grapefruit juice [118]. Similar results were reported in healthy volunteers taking grapefruit juice and the nonmetabolized and P-gp–transported drug talinolol [119], whereas in rats, administration of grapefruit juice resulted in higher plasma concentrations and lower apparent oral clearance of talinolol [115]. The reasons for these discrepancies are still unknown: differences in the concentrations of drug-interacting compounds in the juices (such as fouranocoumarins and flavonoids) have been proposed to contribute to the discrepancies in the results [120], as well as the modulation of other transporters (such as OATPs, multidrug resistance–associated proteins [MRPs]) and metabolizing enzymes by grapefruit juice constituents and other environmental factors (i.e., dietary constituents). All these findings make it difficult to predict whether a grapefruit juice–drug interaction will occur and the magnitude of such interaction. Therefore, patients should be cautious with the consumption of grapefruit juice when treated with narrow-therapeutic-index drugs (especially with drugs whose absorption has been reported to be affected by P-gp, MRPs, OATPs).

Furthermore, many other **dietary food and pure herbal constituents** (see above) commonly used as CAMs directly inhibit CYP and P-gp activity in vitro, and some of them (like piperine and silymarin) were shown to act as P-gp inhibitors at dietary concentrations. P-gp expression is clearly induced by the over-the-counter antidepressant herbal SJW, and clinically relevant drug–drug interactions have been reported between SJW and a wide range of drugs. Chronic administration of SJW together with cyclosporin A has been associated with a significant reduction in cyclosporin plasma levels and a higher risk for acute organ rejection in transplanted patients [121, 122]. In healthy volunteers, administration of SJW together with the HPI indinavir produced an approximately 57% lower plasma AUC of indinavir [123]. Coadministration of SJW with digoxin produced an 18% lower plasma AUC of digoxin and a 40% higher expression level of intestinal P-gp [79]. Other clinical studies confirmed that coadministration of SJW significantly reduced plasma concentrations of drugs like oral contraceptives, tacrolimus, warfarin, verapamil, fexofenadine, and some others, leading to important clinical implications, that is undertreatment and failure of therapies. Similarly, in rats and in cancer patients, the plasma concentrations of SN-38 (the active metabolite of irinotecan) were significantly lower and hematological and gastrointestinal toxicities were less when SJW was coadministered [124, 125]. Furthermore, in healthy volunteers, administration of SJW together with the protein tyrosine kinase inhibitor imatinib resulted in a significantly greater oral clearance and lower AUC, maximum concentration, and half-life of imatinib [126, 127]. Induction of CYP3A4 and enhanced P-gp expression have been suggested to be responsible for these interactions (for review, see [128–135]).

However, for most CAMs, it is unknown whether they affect metabolizing enzymes and/or drug transporters, potentially leading to unwanted pharmacokinetic interactions with drug therapy. Altered expression or activity of several drug transporters and drug-metabolizing enzymes can lead to lower therapeutic efficacy or greater toxicity.

The risk for interactions is significantly high in cancer patients, considering that several anticancer drugs (such as vincristine, vinblastine, vinorelbine, irinotecan, etoposide, docetaxel, and paclitaxel) are P-gp and/or CYP3A4 substrates, as well as certain supportive care agents concomitantly and commonly used by cancer patients, such as ondansetron, fentanyl, morphine, loperamide, and domperidone [83, 136–138]. Clearly, the risk for interaction is further increased by the intake of CAMs, products that are frequently used by people affected by cancer.

Possible Clinical Benefit of Drug–Drug Interactions

On the other hand, the study of drug–drug interactions with P-gp modulators is an interesting research field, because P-gp was discovered and described for its ability to confer the MDR phenotype to cancer cells. The modulation of P-gp activity was at first seen as a useful strategy for increasing the penetration and retention of anticancer drugs in resistant tumor cells, thus overcoming the intrinsic or acquired resistance against chemotherapy occurring in several cancers. Since the mid-1980s, various clinical trials with anticancer drugs in combination with P-gp modulators (calcium channel blockers—nifedipine or verapamil—or cyclosporin A) have been performed [139–141]. Unfortunately, with only few exceptions [142–146], these studies did not show any survival benefit for the combination of an anticancer drug plus a P-gp inhibitor [147–151]. In addition, because the P-gp inhibitors used in those trials presented overlap in substrate specificity with CYP3A4 inhibitors, pharmacokinetic interactions occurred, resulting in greater toxicity. To date, some clinical trials using second- and third-generation P-gp inhibitors with the aim of reversing MDR in tumor cells have been performed and others are still ongoing [152–154]. In a recent pilot phase II

trial, the combination of valspodar (PSC 833, a second-generation P-gp inhibitor) plus paclitaxel (administered i.v. at a reduced dose because of the expected pharmacokinetic interaction [155]) in patients with metastatic breast cancer showed acceptable toxicity but the activity was not significantly increased compared with single-agent paclitaxel [156]. Additional trials will further explore the feasibility and efficacy of this strategy.

Modulation of P-gp activity with selective inhibitors could also be a useful strategy to increase the oral bioavailability of P-gp substrate drugs, in particular, to develop oral formulations of anticancer drugs transported by P-gp. Several preclinical animal studies (see above) and clinical trials in humans have been performed to evaluate the feasibility and the safety of this approach (coadministration of a substrate drug and a P-gp inhibitor). In a clinical study, cyclosporin A, an effective P-gp blocker, followed by oral paclitaxel (a well-known P-gp substrate) resulted in an eightfold higher systemic exposure to paclitaxel (Fig. 2B) [157]. Cyclosporin A also effectively resulted in a greater oral bioavailability of docetaxel, 91% versus 8% [158]. Elacridar, an effective inhibitor of BCRP as well as of P-gp produced a greater oral bioavailability of topotecan, 97% versus 40% [159]. Further studies in patients with advanced solid tumors confirmed that this strategy for oral treatment is at least as effective and safe as standard i.v. administration of these drugs, and clinical trials with third-generation modulators of P-gp (e.g., biricodar, zosuquidar, and laniquidar) specifically developed for MDR reversal are ongoing. The results will give insight into the possible clinical feasibility of this strategy [159–163]. Indeed, an interesting clinical application of selective modulation of P-gp activity might lead to greater passage of certain drugs across the blood–brain barrier, which might profoundly extend the range of drugs available for treatment of brain disorders [164]. These include primary and metastatic tumors, microbial infections, HIV infections, mood disorders, and neurological treatment–resistant disease, for example, refractory epilepsy and schizophrenia. Furthermore, preclinical studies have shown that the brain penetration of anticancer drugs that are transported by P-gp, such as paclitaxel, docetaxel, and imatinib, can be improved by concomitant use of P-gp inhibitors, such as cyclosporin A, valspodar, elacridar, and zosuquidar [165–169]. A clinical study determining the brain penetration of paclitaxel in combination with elacridar in patients with primary brain tumors is ongoing and the preliminary results are reported to be promising [170]. Similarly, clinical trials are exploring the activity of imatinib (Gleevec®; Novartis Pharmaceuticals Corporation, East Hanover, NJ) against the central nervous system (CNS) tumor glioblastoma [171] based on promising preclinical results. Taking into account that imatinib is a good P-gp and BCRP substrate drug with a limited distribution to the brain [172, 173] and that preclinical studies reported that the combination of imatinib with an effective P-gp inhibitor resulted in greater CNS accumulation [168, 174], modulation of P-gp as well as BCRP activity can be a useful strategy to improve CNS penetration of imatinib [170, 174].

However, the safety of this approach should be explored carefully as modulation of P-gp in the blood–brain barrier may lead to greater CNS accumulation of unwanted potentially toxic xenobiotics and endogenous compounds. Preclinical studies in wild-type and *mdr1a/b* knockout mice demonstrated that *mdr1a/1b* knockout mice are fertile and viable, but they are more sensitive to a range of drugs and toxins [81, 83, 84]. Moreover, absence or inhibition of P-gp activity can alter the specific pharmacodynamic activity of some P-gp substrate drugs, leading to CNS toxicity and adverse drug effects. For instance, the safe clinical use of the antidiarrheal drug loperamide may also be critically dependent on the presence of P-gp in the blood–brain barrier. Loperamide is a potent opiate, which demonstrates nearly exclusively peripheral opiate-like effects on the gastrointestinal tract and no central effects because it is a P-gp substrate. Thus, normally it cannot accumulate in the CNS. In *mdr1a* knockout mice, however, loperamide showed pronounced opiate-like effects and sometimes lethal effects at doses that are safe in wild-type mice [83]. In humans, coadministration of loperamide with the P-gp inhibitor quinidine produced opiate-induced respiratory depression, a clear central opiate effect that is normally not seen in humans [175].

On the same line, blocking of placental P-gp in HIV-infected pregnant women might be used to enhance HPI levels in the unborn child shortly before and during the delivery, thereby reducing the risk for HIV infection of the fetus. However, the safety of this approach needs to be studied in greater detail. Indeed, preclinical data using *mdr1a/1b* knockout mice demonstrated significantly greater fetal penetration of the HPIs indinavir and saquinavir, but also of other drugs and toxic compounds, indicating that placental P-gp might have a protective role for the fetus [92, 176].

Summary, Conclusions, and Perspectives

The importance of ABC transporters in drug–drug interactions is increasingly being identified. P-gp is involved in the interactions between cyclosporin A or verapamil and oral digoxin. Azole antifungals, such as fluconazole and itraconazole, interact with P-gp, explaining drug interactions with digoxin and other drugs. Benzimidazoles are transported by and inhibit P-gp. P-gp regulates oral bioavailabil-

ity and tissue distribution of the immunosuppressant tacrolimus. P-gp mediates drug interactions between antiretroviral drugs and comedications. Also, genetic variability in the *MDR1* gene affects absorption and tissue distribution of P-gp substrate drugs.

Furthermore, CAM use, like herbs, food, and vitamins, by patients has increased significantly in recent years. Surveys have shown that the prevalence of CAM use among cancer patients receiving conventional therapy is 54%–77%, and that about 72% of patients do not inform their treating physician. CAM use significantly increases the risk for interactions with anticancer drugs, especially because of the small therapeutic range and steep dose–toxicity curve of these drugs. Clinically relevant problems are seen with SJW and grapefruit juice. SJW significantly decreases the plasma levels of SN-38, the active metabolite of irinotecan, and increases imatinib clearance. Grapefruit juice affects the oral bioavailability of etoposide. However, it is expected that CAM–drug interactions are responsible for more of the, so far unresolved, interindividual variation and clinical problems seen in cancer and noncancer patients.

The main causes of interactions are changes in the pharmacokinetics of drugs, although interactions at the pharmacodynamic level are also possible. Many drugs are cleared by biotransformation and subsequently transported by P-gp, BCRP, or other transporters. Altered expression or activity of these proteins can lead to lower therapeutic efficacy or greater toxicity.

Increased knowledge of drug–drug, food–drug, and herb–drug interactions and of genetic factors affecting pharmacokinetics and pharmacodynamics is expected to improve drug safety and will enable drug therapy tailored to the individual patients' needs.

Disclosure of Potential Conflicts of Interest

The authors indicate no potential conflicts of interest.

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