ELSEVIER

Drug–drug interactions affected by the transporter protein, P-glycoprotein (ABCB1, MDR1) II. Clinical aspects

Adorjan Aszalos

Laboratory of Cell Biology, 37 Convent Drive, Room 2108, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, United States

The simultaneous use of several drugs (polypharmacy) for the treatment of cancer, HIV, and other diseases and for multiple ailments of the elderly is a common practice in modern medicine. Co-administration of drugs may result in unwanted side effects. One reason for these side effects can be the altered function of transport proteins, especially of P-glycoprotein (Pgp), due to its simultaneous interaction with several drugs. We describe here some of the observed, unexpected side effects of polypharmacy in the clinic. We also describe intentional modulation of the function of Pgp that is introduced when facilitation of absorption of a drug through the intestines is needed and in cancer chemotherapy. In addition, we mention some methods of testing and ways by which doctors and patients can be alerted to potential side effects.

Introduction

Drug–drug interactions can be characterized as either intentional or unintentional drug–drug interactions. Both forms exist in clinical practice and we list several examples below. Assessing possible unintentional drug–drug interactions in whole animals and humans is complicated due to the fact that many transporters (ABC type cassette pumps, efflux pumps) function in animals and humans and drugs could be modulators of several of them. Each of these efflux pumps has its own well-designated biological functions and a summary of them is given by Schinkel [1]. There is a multiplicity of efflux pumps in human organs. For example, the GI tract prevents substrates from entering through the intestines by B1, C2, and G2 transporters and from the blood circulation by the C1 transporter. At the blood–brain barrier (BBB) the following transporters prevent drugs from entering the CNS: B1, C1, C2, C4, C5, and G2. The liver effluxes drugs and metabolites into the blood circulation by the C1, C3, C4, C5, and C6 efflux pumps, and into the GI tract by the B1, B4, B11, C2, and G2 efflux pumps. The placenta is protected from drugs and other molecules by the B1, C2, and G2 efflux pumps and molecules are transferred to the fetus by the C1 and C3 transporters. The kidney pumps out parent drugs and their metabolites into the urine by B1, C2, C4, and G2 transporters and into the blood circulation by the C1 transporter. At the blood–testis barrier, the B1 and the C1 transporters operate.

Because of the multiplicity of transporters at many organ locations, one can assess possible drug–drug interactions with individual transporters, if suitable *in vitro* or *in vivo* models exist. Such models are described in this paper. In the clinic, however, it is difficult to assess drug–drug interactions when some unexpected side effects occur during polypharmacy of patients. Nevertheless, it is possible in some cases to characterize drug–drug interactions solely at the Pgp level, as detailed below. Generally, the influence of a simultaneously introduced drug on pharmacology and toxicology of the first drug in whole animals or humans can indicate potential problems.

Drug–drug interactions resulting in side effects, as observed in the clinic

Several examples of drug–drug interactions observed in clinics, and attributed to modulation of Pgp, are found in the literature. These examples may alert clinicians to the possibility of causing toxic side effects if they intend to introduce polypharmacy.

In patients with soft tissue sarcoma expressing high levels of Pgp, intravenous cyclosporine (median dose 19.5 μg/(kg/day)) was

Corresponding author: Aszalos, A. (aszalosa@mail.nih.gov)

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2007.07.021

administered to suppress Pgp function in the tumor. As cancer chemotherapy, VP16/Ifos and VAC cycles were alternated (etoposide: 150 mg/m^2, ifosfamide: 3000 mg/m^2; days 1 and 2, vincristine: 0.05 mg/kg, dactinomycin: 15 μg, and cyclophosphamide: 300 mg/m^2; days 1–5). Introduction of cyclosporine significantly elevated the systemic toxicity of the VAC but not the VP16/Ifos arm. Drugs in the VAC arm are known to be modulators of Pgp and cyclosporine is a substrate of Pgp. It was concluded that a possible elevation of serum concentration of drugs caused the unwanted high toxicity, due to the Pgp-modulating effect of cyclosporine [2].

It was reported that co-administration of the antifungal agent itraconazole and digoxin increases the serum concentration of digoxin and decreases renal digoxin clearance. Because itraconazole is a modulator of the function of Pgp, drug–drug interactions at the Pgp level were thought to be the reason for this finding [3].

The drug mibefradil, a calcium channel blocker, had to be withdrawn from the market because of observed severe side effects associated with its use. It was observed in clinical trials that mibefradil, administered concomitantly with digoxin, caused a significant increase of the C_{max} and area under the curve (AUC) of digoxin in patients. It could be concluded that interactions at the level of Pgp resulted in these increases, since interaction due to metabolic interference is unlikely, because digoxin is not metabolized significantly [4].

In a case of liver transplantation, a woman was treated with tacrolimus, an immune suppressor, and with mibefradil. Both of these drugs are metabolized by cytochrome P450, and are also modulators of Pgp. Four days after administration of these drugs, the woman developed confusion and other side effects. It was concluded that tacrolimus metabolism was reduced by mibefradil, its blood concentration became elevated, and it passed through the BBB by overwhelming Pgps at the barrier. This caused toxicity in the CNS compartment, leading to mental confusion [5].

In testing the importance of Pgp at the BBB, the antidiarrheal drug, loperamide was administered to healthy volunteers with or without quinidine, which is also a substrate of Pgp [6]. Loperamide, used alone (16 mg), does not produce an opiate-like effect in the CNS, despite being a potent opiate. It produces no associated respiratory depression. However, administered together with quinidine (600 mg), a Pgp modulator, loperamide did cause respiratory depression. Administered together, the plasma concentration of loperamide did not change significantly. It is possible therefore, that suppression of Pgp activity at the BBB by quinidine allowed the entry of loperamide into the CNS and caused opiate-induced respiratory depression. Loperamide should, therefore, not be administered along with any drugs that modulate Pgp.

Drug–drug interactions were also observed by Merry *et al.* [7] between the protease inhibitors saquinavir and ritonavir in patients. An average increase of 33 fold in C_{max} and 58 fold in AUC was measured in HIV-infected patients. The average C_{max} increased from 146 to 4795 ng/ml and the average AUC increased from 470 to 27,458 ng h/ml in patients. Both protease inhibitors are substrates of Pgp.

A number of other examples of drug–drug interactions based on certain or most likely Pgp-based activity are found in the literature and are listed in Table 1.

TABLE 1

Drug–drug interactions resulting in changes in pharmacokinetic parameters

First drug	Second drug	AUC ratio[a]	C_{max} ratio[a]	Reference
Erythromycin	Digoxin	–	2.04	Maxwell [30]
	Fexofenadine	2.9	1.82	Davit *et al.* [31]
	Saquinavir	1.9	2.06	Grub *et al.* [32]
	Talinolol	1.34	–	Schwarz [33]
Ketaconazole	Fexofenadine	2.64	2.34	Davit *et al.* [31]
	Saquinavir	1.9	2.71	Grub *et al.* [32]

[a] Ratios in C_{max} and AUC: first drug + second drug/first drug.

Drug–drug interactions in absorption

Many orally introduced drugs are not absorbed through the intestine. One reason for this is that Pgp is expressed at the brush-border of membranes of intestinal epithelial cells, and does not allow drugs that are substrates of Pgp to enter the circulation. Therefore, some unexpected drug–drug interactions, as well as intentional drug–drug interactions, may occur by blocking the function of Pgp at the intestinal epithelial cells.

Interaction between rifampin and digoxin was observed by Greiner [8] in the clinic. They found that the AUC of oral digoxin was significantly lower if rifampin (600 mg/day) was also co-administered. However, if digoxin was administered intravenously, that decrease was negligible. Clearance and half-life of digoxin remained about the same with or without rifampin. It was concluded that increased intestinal expression of Pgp (3.5-fold in the presence of rifampin) was the reason for the observed decrease in the AUC and, therefore, less digoxin was absorbed through the gut. It is known that rifampin, as well as St John's Wort extract, increases Pgp expression in cells. This is a clear demonstration of drug–drug interactions due to induction of Pgp by a drug.

An unexpected drug–drug interaction was observed in humans when rhabdomyolysis was diagnosed in a patient treated with esomeprazole (a proton pump inhibitor), atorvastatin, and clarithromycin (an antibiotic). The observed side effect was thought to occur due to inhibition of the function of Pgp by esomeprazole and probably also by clarithromycin [9].

Intentional drug–drug interactions at the intestinal Pgp level were observed with the combination of paclitaxel and cyclosporine. In a clinical study [10], a patient received the usual dose of paclitaxel (60 mg/m^2) with or without cyclosporine (15 mg/kg). The bioavailability of paclitaxel increased with cyclosporine from about 5 to 50%. It was concluded that cyclosporine suppressed the efflux function of Pgp in the intestine and allowed paclitaxel to be absorbed. It should be noted that inhibition of the metabolizing enzyme CYP3A4 by cyclosporine may have contributed to this observed result.

Absorption of cyclosporine, the immune suppressor drug, also could be increased if the efflux system is inhibited by a water-soluble vitamin E derivative (2.6 IU/kg), as was shown in 10 healthy volunteers [11]. A significant increase in the AUC of cyclosporine (3908 ± 2601 ng h/ml versus 6296 ± 5102 ng h/ml) could be measured with the co-administration of the vitamin E preparation. These results in humans were corroborated by Tu *et al.* [12], who showed that the soluble vitamin E preparation enhances

permeability of amperenavir, a protease inhibitor, through a polarized Pgp-expressing Caco-2 cell monolayer.

Some excipients in pharmacological preparations can modulate the function of Pgp and facilitate the absorption of drugs. This was shown to be the case for saquinavir, a protease inhibitor. More of the orally administered drug was absorbed and its bioavailability was increased in healthy volunteers when cremophor was used as solubilizing agent. Cremophor El dose dependently increased C_{max} and AUC of saquinavir without changing the terminal half-life and the time to reach C_{max} [13].

Drug–drug interactions to facilitate cancer chemotherapy

One reason for producing intentional drug–drug interactions is to suppress the function of Pgp in tumor cells. Along with an anti-cancer drug, a modulator of Pgp is administered. Tumor cells express Pgp and other transporters [14] such as MRP1 and ABCG2 when they are under stress, for example, by an insult from a cytotoxic anti-cancer drug. The expression of Pgp in such cells involves a complicated cell-signaling mechanism, which is outside the scope of this review. One should consult the literature for more information on this subject [15]. Many modulators of Pgp have been tried in preclinical and clinical trials since the early 1990s. The first generation of Pgp modulators, which included quinidine, cyclosporine, quinine, and verapamil, reached phase III studies and limited clinical use. Unfortunately, they all were found to cause cancer chemotherapeutic drugs to become more toxic, or were ineffective at the applied dose. Their ineffectiveness may have resulted from the mandated dose reduction of the applied anti-cancer drug. That is, it had been estimated that a lower dose of the anti-cancer drug was necessary when Pgp modulators were used, because at a lower dose, one can reach the therapeutic concentration in tumor cells equal to that when the higher dose is applied without the Pgp modulator. It was estimated by the U.S. Food and Drug Administration that only about one-third of the anti-cancer drug was necessary with the Pgp modulator to achieve equivalent drug concentrations in Pgp-expressing cancer cells as when used without the Pgp modulator at full dose. IND and NDA protocols initially submitted to the FDA followed this guidance. Other problems may have arisen from testing Pgp modulators in different populations during IND studies, then using the modulators after NDA approval in other populations in the clinic.

A second generation of Pgp modulators, such as valspodar (PSC833) and biricodar (VX-710) were tested in clinics. Valspodar has been perhaps the most studied Pgp modulator in clinics, since it is devoid of the immunomodulating activity that was an additional disadvantage of using cyclosporine (A). A phase II trial with valspodar in patients with refractory acute leukemia yielded 32% complete remission [16]. Valspodar was given as a continuous infusion of 10 ng/(kg/day) on days 1–5, with the anti-cancer drugs mitoxantrone, etoposide, and cytorabine. A problem identified with this Pgp modulator was the observed decrease in clearance of etoposide and its extended half-life compared with its use in the same protocol without valspodar. It is possible that this Pgp modulator also inhibited the bile acid transporter in the canalicular membrane and could have affected the secretion of the anti-cancer drug, or its metabolite, causing the observed toxicity. Another relatively successful recent application of valspodar was in patients with acute myeloid leukemia [17]. However, this Pgp modulator was discontinued by the Novartis Company because of frequently observed unwanted pharmacological side effects.

A more recently introduced Pgp modulator, elacridar (GF 120918), has shown superior characteristics; noninterference with doxorubicin pharmacokinetics and excellent blocking of Pgp activity in mice. For this reason, clinical trials were initiated. Elacridar was administered *per os* in increasing doses, days 1–5, and doxorubicin up to 75 mg/m^2 was given at day 3. The pharmacokinetic and hematologic toxicity of doxorubicin was not altered in most patients. Three patients out of 47 showed some doxorubicin-related side effects that were attributed to CYP-450-related demethylation [18]. A third generation of Pgp modulators, such as zosuquidar, is presently being evaluated in acute myeloid leukemia patients [19]. In a phase I clinical trial, the pharmacokinetics of doxorubicin were studied in patients with advanced malignancies co-administered with this Pgp modulator. Zosuquidar was administered intravenously over 48 hours with increasing doses up to 640 mg/m^2 and doxorubicin at 75 mg/m^2. At doses above 500 mg/m^2 of zosuquidar, some elevation of the AUC (up to 25%) and some decrease in clearance time (up to 22%) were observed. Elevated leukopenia and thrombocytopenia were also observed, but these side effects were not significant.

One can see from these few examples that some success has been achieved, mostly with the newer Pgp modulators. (See other examples in Table 2.) Further clinical trials will determine the usefulness of Pgp modulators in cancer chemotherapy.

One interesting application of a Pgp modulator in clinical use was when the uptake of Tc-99m sestamibi, a contrast agent, into Pgp-expressing tumor cells could be enhanced with a Pgp modulator. Sestamibi is also a substrate of Pgp. Its uptake into the

TABLE 2

Some clinical observations concerning the use of Pgp modulators in cancer chemotherapy

Anti-cancer drug	Pgp modulator	Pharmacological effect	Outcome	Reference
Etoposide	Valspodar, i.v.	Elevated AUC	Increased toxicity	Filipits *et al.* [34]
Doxorubicin	Valspodar	Elevated AUC	Increased toxicity	Broxterman *et al.* [35]
Paclitaxel	VX-710, i.v.	Elevated AUC	Increased toxicity	Roelofsen *et al.* [36]
Doxorubicin	VX-710, i.v.	No change	No change	Vanhoefer *et al.* [37]
Doxorubicin	Elacridar, p.o.	Infrequent elevation of AUC	Mostly no change	Leith [38]
Paclitaxel	Laniquidar, p.o.	No change	No change	Drach *et al.* [39]

tumor cells could be enhanced in patients with metastatic renal carcinoma by co-administration of valspodar [20], allowing direct visualization of Pgp inhibition *in vivo*.

Another possible way to avoid toxic side effects with Pgp modulators is by using multiple modulators simultaneously, at sub-pharmacological doses. This possibility was pointed out by Ross *et al.* [21]. They investigated the use of a combination of cyclosporine and the solubilizing agent cremophor. They found, in patients with acute myeloid leukemia, that the two Pgp modulators act synergistically. The reduced dose of each modulator induced lower inherent toxicities than when each of these agents was used singly at the higher pharmacological dose in patients. The synergistic activity is the result of the different modes of action of these two modulators on Pgp.

Patient, doctor, and USFDA alerts for possible drug–drug interactions

There are certain, established ways to alert physicians, patients, and the USFDA concerning potential toxic drug–drug interactions. It should be noted however, that some of the alerts and ways of reporting do not differentiate between interactions that are metabolic, Pgp-related, or a combination of the two [22].

Drug inserts

Prescription drugs come with ''inserts'' that indicate possible side effects if certain other drugs are also taken by the patient. An example of inserts is the one supplied with DETROL (Tolterodine), an antimuscarinic agent used to treat an overactive bladder. The drug insert indicates that the patient should consult a doctor if any of the following medications are also taken: clarithromycin, cyclosporine, erythromycin, ketaconazole, itraconazole, miconazole, and vinblastin. These drugs are substrates of Pgp and therefore drug–drug interactions are possible at the Pgp level.

An FDA warning was also posted for Kaletra (lopinavir/ritonavir). Co-administration with ketaconazole, itraconazole, and voriconazole may cause, among other side effects, visual disturbances. All these co-administered drugs are substrates of Pgp. The protease inhibitors, which are also Pgp substrates, may enter through the BBB when co-administered with other Pgp-modifying drugs and may cause unwanted side effects.

MEDWACH

When an unwanted drug–drug interaction is observed in the clinic, the case is reported to the USFDA via the MEDWACH system. For example, one such case was reported when a liver transplant patient treated with the immunosuppressive agent, tacrolimus, also received diltiazem up to 200 mg/ml blood level. The combination of the two drugs resulted in neurotoxicity. It was surmised that the combination of the two drugs caused a synergistic opening of the BBB, resulting in the toxic effect.

Another example of an unexpected side effect occurred in a female patient with head cancer and was reported to the USFDA. The patient's cancer chemotherapy included doxorubicin, decarbazine, and dexamethasone, and, in addition, she received lorazepam, diltiazem, enarapil, and ondansetron. During the fifth cycle of the therapy, she developed somnolence, hallucination, and ataxia. Since among the administered drugs, doxorubicin, diltiazem, dexamethazone, and ondansetron are Pgp modulators, the side effects related to the CNS indicated synergistic drug penetration through the BBB. This conclusion was strengthened by the fact that the liver and renal functions of the patient did not change and were normal during these toxic episodes. Normal renal function indicates normal clearance of the applied drugs. Also, normal liver function indicates unchanged metabolism of the applied drugs. Together, these facts indicate normal pharmacokinetics and pharmacodynamics of all the drugs used in this treatment schedule. Therefore, the observed side effects could have occurred only by opening the BBB (US/Dist. Rep.#1426509).

Web sites for consultation

There are several web sites for checking drug–drug interactions that are available to practically anyone. One example of these is the site operated by Caremark (http://www.caremark.com/wps/portal). Their homepage contains a link to a drug interaction ''tool''. One can enter the name of a drug and the system will search for interacting drugs. The Ohio Department of Aging recognizes the possibility of drug–drug and drug–food interactions mostly for elderly patients taking several prescription drugs. Its website, http://ohioline.osu.edu/ss-fact/0129.html, offers possibilities and consequences for drug–drug interactions.

For physicians, a useful tool is the Drug Interaction Checker website, http://medscape.com/druginfo/druginteracheker?srt=google. One can enter the name of the drug, its regimen, and other co-administered drugs intended to be used for a patient. The system can advise of possible side effects.

Experimental steps to assess the ability of a new candidate drug to influence the function of Pgp and potentially cause drug–drug interactions

It is possible to use the following experiments for the characterization of a new candidate drug with respect to its ability to modify the function of Pgp. These experiments may be included in IND and NDA submissions to the USFDA and could also be used for probing drug–drug interactions.

(1) *In vitro* test with Pgp-expressing cultured cells using flow cytometry (see Part I). More than one drug can be tested simultaneously by this method [23,24].
(2) Test with polarized cells, assessing directional transport of the drug candidate (alone or in combination with other drugs). This assay can provide information about whether a drug can enter systemic circulation if administered orally. If the ratio of diffusion basal to apical/apical to basal is smaller than 3 and this number is very similar with cells expressing or not expressing Pgp, the candidate drug can proceed to further development for oral administration [25].
(3) Assay the candidate drug in inside-out membrane vesicles of the intended drug target (if such vesicles are available). In case the drug candidate shows the ability to modify the function of Pgp, test increasing doses of the drug [26].
(4) Test drugs which may be used in combination with the new candidate drug for possible synergistic effects with known Pgp-modifying drugs. Use the above three methods for this purpose.
(5) Correlate animal model (mouse Pgp – mdr1a, mdr1b) results with results of *in vitro* methods using human Pgp (as listed 1–

4, above) in relation to the potential of the new candidate drug for its ability to modify the function of Pgp and penetration into the CNS.

(6) Determine the pharmacokinetics and pharmacodynamics of the new candidate drug and of its metabolites with potentially co-administered other drug(s) in animal models and correlate those with the *in vitro* models. For prediction of correlation of *in vitro* and *in vivo* methods for drug–drug interactions, Ueda *et al.* [27] advanced calculations based on measurements in both systems. He was able to conclude that interactions associated with membrane transport *in vivo* can be estimated from *in vitro* experiments (see also Schinkel *et al.* [28] and Adachi *et al.* [29]).

Naturally, if the first two test results are negative even at doses higher than the intended pharmacological efficacious dose, no more tests would be necessary.

Summary

Drug–drug interactions at the Pgp level sometimes result in unexpected side effects in the clinic. Several examples of such side effects are listed in this paper. They manifest themselves as changes in pharmacokinetics, systemic toxicity, neurotoxicity, and alteration of a drug's absorption in the intestines. In connection with these observations, we point out that sometimes it is difficult to relate these side effects to interference with Pgp because of the multiplicity of transporters operating at each organ level and some drugs may be substrates of several transporters.

Intentional drug–drug interactions at the Pgp level are introduced in the clinic to facilitate drug absorption through the intestine and to deliver cancer chemotherapeutic agents into Pgp-expressing cancer cells. Clinical experiences with Pgp modulators in cancer chemotherapy are listed for the first, second, and third generations of these modulators.

Indicating potential side effects due to drug–drug interactions with co-administered additional drugs, systems such as drug-label inserts, MEDWACH reporting to the USFDA, websites for drug–drug interactions, and *a priori* test methods for the assessment of potential drug–drug interactions for candidate drugs were discussed, with examples provided.

Acknowledgements

The author appreciates the encouragement and hospitality of Dr Michael Gottesman, chief of the Laboratory of Cell Biology, and the editorial assistance of Mr George Leiman.

References

1 Schinkel, A.H. (2003) Mammalian drug efflux transporters of the ATP binding cassette (ABC) family: an overview. *Adv. Drug Deliv. Rev.* 55, 3–29

2 Theis, J.G.W. (1998) Increased systemic toxicity of sarcoma chemotherapy due to combination with the P-glycoprotein inhibitor cyclosporine. *Int. J. Clin. Pharmacol. Ther.* 36, 61–64

3 Alderman, C.P. and Allcroft, P.D. (1998) Digoxin–itaconazole interaction: possible mechanism. *Ann. Pharmacother.* 31, 438–440

4 Spieman, M. (1995) The interaction of the calcium antagonist RO40-5967 with digoxin. *Br. J. Clin. Pharmacol.* 39, 491–496

5 Krahenbuhl, S. *et al.* (1998) Serious interaction between mibefradil and tacrolimus. *Transplantation* 66, 1113–1115

6 Sadaque, A.J.M. *et al.* (2000) Increased drug delivery to the brain by P-glycoprotein inhibition. *Clin. Pharmacol. Ther.* 68, 231–237

7 Merry, C. *et al.* (1997) Saquinavir pharmacokinetics alone and in combination with ritonavir in HIV-infected patients. *AIDS* 11, F29–F33

8 Greiner, B. (1999) The role of intestinal P-glycoprotein in the interaction of digoxin and rifampin. *J. Clin. Invest.* 104, 147–153

9 Sipe, B.E. *et al.* (2003) Rhabdomyolysis causing av blockade due to possible atorvastatin, esomeprazole, and clarithromycin interaction. *Ann. Pharmacother.* 37, 808–811

10 Meervum-Terwgot, J.M. *et al.* (1999) Coadministration of cyclosporin A enables oral therapy with paclitaxel. *Clin. Cancer Res.* 5, 3379–3384

11 Chang, T. *et al.* (1996) The effect of water soluble vitamin E on cyclosporine pharmacokinetics in healthy volunteers. *Clin. Pharmacol. Ther.* 59, 297–303

12 Tu, L. *et al.* (1999) Vitamin E-TPGs increases absorption flux of an HIV protease inhibitor by enhancing its solubility and permeability. *Pharm. Res. (NY)* 16, 1812–1817

13 Martin-Facklam, M. *et al.* (2002) Dose dependent increase of saquinavir bioavailability by the pharmaceutic aid cremophor EL. *Br. J. Clin. Pharmacol.* 53, 576–581

14 Gottesman, M.M. *et al.* (2002) Multidrug resistance in cancer: role of ATP-dependent transporters. *Nat. Rev. Cancer* 2, 48–58

15 Pecorino, L. (2005) *The Molecular Biology of Cancer: Mechanisms, Targets and Therapeutics,* Oxford University Press

16 Advani, R. *et al.* (1999) Treatment of refractory and relapsed acute myelogenous leukemia with combination chemotherapy plus the multidrug resistance modulator PSC 833 (Valspodar). *Blood* 93, 787–795

17 Klonitz, J.E. *et al.* (2004) Dose escalation studies of cytarabin, daunorubicin, and etoposide with and without multidrug resistant modulation with PSC833 in untreated adults with acute myeloid leukemia younger than 60 years; final induction results of Cancer and Leukemia Group B Study 9621. *J. Clin. Oncol.* 22, 4290–4501

18 Planting, A.S.T. (1998) Phase I and pharmacokinetic (PK) studies targeting a 100 ng/ml plasma concentration of the potent multidrug resistance (MDR) modulator GF 120918 (GF) with doxorubicin (dox) in patients with advanced solid tumors. *Proc. Am. Coc. Clin. Oncol.* 17, 199a

19 Sandler, A. *et al.* (2004) A phase I trial of a potent P-glycoprotein inhibitor, zosuquidar trihydrochloride (LY335979) administered intravenously in combination with doxorubicin in patients with advanced malignancy. *Clin. Cancer Res.* 10, 3265–3272

20 Chen, C.C. (1997) Detection of in vivo Pglycoprotein inhibition by PSC833 using Tc-99m sestamibi. *Clin. Cancer Res.* 3, 545–552

21 Ross, D.D. *et al.* (1994) Synergistic reversal of multidrug-resistance phenotype in acute myeloid leukemia cells by cyclosporine A and cremophor EL. *Blood* 83, 1337–1347

22 Cummins, C.L. (2002) Unmasking the dynamic interplay between intestinal P-glycoprotein and CYP3A4. *J. Pharmacol. Exp. Ther.* 300, 1036–1045

23 Aszalos, A. and Weaver, J.L. (1998) Estimation of drug resistance by flow cytometry. *Method Mol. Biol.* 91, 117–122

24 Ibrahim, S. *et al.* (2000) Influence of beta-adrenergic antagonists, H1-receptor blockers, analgesies, diuretics and quinolon antibiotics on the cellular accumulation of the anticancer drug, daunorubicin: P-glycoprotein modulation. *Anticancer Res.* 21, 847–856

25 Hochman, J.H. *et al.* (2000) Influence of P-glycoprotein on the transport and metabolism of indinavir in Caco-2 cells expressing cytochrome P4503A4. *J. Pharmacol. Exp. Ther.* 292, 310–318

26 Kharash, E.D. *et al.* (2005) Evaluation of first pass cytochrome P4503A (CYP3A) and P-glycoprotein activities using alfentinil and fexofenadine in combination. *J. Clin. Pharmacol.* 45, 79–88

27 Ueda, K. *et al.* (2001) Inhibition of the biliary excretion of methotrexate by probenacid in rats: quantitative prediction of the interaction from in vitro data. *J. Pharmacol. Exp. Ther.* 297, 1036–1043

28 Schinkel, A. *et al.* (1994) Disruption of the mouse mdr1a P-glycoprotein gene leads to a deficiency in the blood–brain barrier and to increased sensitivity to drugs. *Cell* 7, 491–502

29 Adachi, *et al.* (2001) Comparative studies on in vitro methods for evaluating in vivo function of MDR1, P-glycoprotein. *Pharm. Res. (NY)* 18, 1660–1668

30 Maxwell, D.L. (1986) Digoxin toxicity due to interaction of digoxin with erythromycin. *Br. Med. J.* 298, 572

31 Davit, B. *et al.* (1999) FDA evaluation using in vitro metabolism to predict and interpret in vivo metabolic drug–drug interactions: impact on labeling. *J. Clin. Pharmacol.* 39, 899–910
32 Grub, S. *et al.* (2001) The interaction of saquinavir (soft gelatin capsule) with ketaconazole, erythromycin and rifampin: comparison of the effect in healthy volunteers and in HIV-infected patients. *Eur. J. Clin. Pharmacol.* 57, 115–121
33 Schwarz, U.I. (2000) P-glycoprotein inhibitor erythromycin increases oral bioavailability of talinolol in humans. *J. Clin. Pharmacol. Ther.* 38, 161–167
34 Filipits, M. *et al.* (1996) MRP and MDR1 gene expression in primary breast carcinoma. *Clin. Cancer Res.* 2, 1231–1237
35 Broxterman, H.J. *et al.* (1997) Theoretical and practical considerations for the measurement of P-glycoprotein function in acute myeloid leukemia. *Leukemia* 11, 1116–1118
36 Roelofsen, H. *et al.* (1997) Increased level of the multidrug resistance protein in lateral membranes of proliferating hepatocyte-derived cells. *Gastroenterology* 112, 511–521
37 Vanhoefer, U. *et al.* (1997) Comparative antitumor efficacy of doxetaxel and paclitaxel in nude mice bearing human tumor xenografts that overexpress the multidrug resistance protein (MDR). *Ann. Oncol.* 8, 1221–1228
38 Leith, C. (1997) Acute myeloid leukemia in the elderly: assessment of multidrug resistance (MDR1) and cytogenesis distinguishes biologic subgroups with remarkably distinct responses to standard chemotherapy. *Blood* 89, 3323–3329
39 Drach, D. *et al.* (1992) Subpopulations of normal peripheral blood and bone marrow cells express a functional multidrug resistant phenotype. *Blood* 80, 2729–2734