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Drug-Drug Interactions Mediated by P-Glycoprotein – An Overview

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ABSTRACT

Drug-drug interactions lead to lethal toxicities. Currently P-glycoprotein also plays significant role in drug-drug interactions. It is an efflux membrane transporter widely distributed throughout the body and is responsible for limiting the cellular uptake and the distribution of xenobiotics and toxic substance. The pharmacokinetics of a drug may be altered when co-administered with compounds which inhibit or induce P-glycoprotein pump which can affect pharmacodynamic and pharmacokinetic action of drugs. The present review summarizes various drug-drug interactions mediated by P-glycoprotein transporter.

Keywords: P-glycoprotein, drug efflux, drug interaction

INTRODUCTION

Transporter mediated drug-drug interactions are being reported with increasing frequency [1]. The efflux transporter P-glycoprotein (P-gp) has received the most attention with regard to its role in restricting drug absorption and distribution and as a potential source for variability in drug pharmacokinetics and pharmacodynamics [2]. This transporter plays an important role in protecting sensitive tissues from toxic xenobiotics and can also interfere with the delivery of clinically used drugs.

P-gp belongs to the ATP-Binding Cassette (ABC) transporter family also known as MDR1 or ABCB1. It is expressed in various body tissues, such as liver, kidney, intestine, testis, and brain [3]. After drug administration, inhibition of P-gp by the drug can result in increased absorption of any co-administered drug that is P-gp substrate. Therefore, P-gp related interactions have critical clinical role and it is important to understand which drugs are substrates, inhibitors, or inducers of P-gp to minimize or avoid unwanted interactions [1].

P-gp is highly expressed in cancer cells, leading to efflux of anticancer agents from cells leading to drug resistance. Moreover, the resistance to Central Nervous System (CNS) drugs, such as antidepressants and antiepileptic or anti-HIV medicine, also lead to P-gp over expression [3]. P-gp is one of the most recognized transport proteins that exhibit genetic polymorphism that might affect the outcome of drug therapy. Over 50 polymorphisms (single nucleotide polymorphisms and insertions/deletions) in the ABCB1 gene are known, and some of them appear to change the mRNA expression, protein expression and function of P-gp [4].

Co-administration of drugs that interact with P-gp as substrates, inhibitors or inducers can result in adverse drug-drug interactions. Induction or inhibition of these proteins also leads to drug interactions. Inhibition of this efflux transporter could increase the bioavailability of drugs. P-gp induction can, on the other hand, accelerate efflux transport and reduce the bioavailability of drugs [5]. List of drugs that interact with P-gp inhibitors and inducers are given in Table 1.

Drugs that are transported by P-gp are also metabolized by cytochrome P450 (CYP) isoform 3A4 (e.g., cyclosporine, antiepileptic drugs, antidepressant, fluoroquinolones, quinidine and ranitidine), which can confound interpretation of interactions [6]. P-gp may restrict the uptake of several antidepressants into the brain, thus limiting the distribution of these drugs into the brain and high rate of treatment failure [7].

P-gp regulates the absorption and elimination of psychotropic drugs. Therefore, psychotropic drugs that are P-gp substrates may cause a drug interaction when P-gp inhibitors and inducers are co-administered, or when psychotropic drugs or other medicines those are P-gp substrates are added to a prescription [8]. This paper reviews some of the

commonly used medicinal drugs which taken part in interaction of the drugs which is mediated by P-gp.

Table 1: Drug-drug interactions mediated by P-glycoprotein (MDR1)

P-glycoprotein inhibitors			
Sr.No	Drug	Inhibitor	Toxicity
1.	Digoxin	Quinidine	Quinidine inhibit P-gp efflux, increase digoxin bioavailability due to decreased renal clearance of digoxin [9]
2.	Digoxin	Atorvastatin	Atorvastatin inhibit P-gp efflux, increase digoxin bioavailability due to decreased renal clearance of digoxin [10]
3.	Digoxin	Verapamil	Verapamil inhibit P-gp efflux, increase digoxin bioavailability due to decreased renal tubular elimination of digoxin [11,12]
4.	Digoxin	Talinolol	Talinolol inhibit P-gp efflux, increase digoxin bioavailability and renal clearance of digoxin remained unchanged [13]
5.	Digoxin	Clarithromycin	Increase digoxin bioavailability by inhibiting P-gp mediated tubular secretion of digoxin [14]
6.	Digoxin	Itraconazole	Itraconazole Inhibit P-gp efflux, increase digoxin bioavailability due to decreased renal clearance of digoxin [15]
7.	Digoxin	Ritonavir	Ritonavir inhibit P-gp efflux, increase digoxin bioavailability by decreased renal clearance of digoxin [16]
8.	Digoxin	Omeprazole	Omeprazole inhibit P-gp efflux, increase digoxin bioavailability [17]
9.	Digoxin	Cremophor EL	Cremophor EL inhibit P-gp efflux, increase digoxin bioavailability [18]
10.	Paclitaxel	Cyclosporin	Cyclosporin inhibit P-gp efflux, increase paclitaxel bioavailability by decreased renal clearance of paclitaxel lead to toxicity [19]
11.	Paclitaxel	Elacridar	Elacridar inhibit P-gp efflux, increase paclitaxel bioavailability and lead to toxicity [20]
12.	Paclitaxel	Valspodar	Valspodar inhibit P-gp efflux, increase paclitaxel bioavailability and lead to toxicity [20]
13.	Docetaxel	Cyclosporine	Cyclosporine inhibit P-gp efflux, increase docetaxel bioavailability [21,22]
14.	Saquinavir	Ritonavir	Ritonavir inhibit P-gp efflux, increase saquinavir bioavailability and lead to toxicity [20]
15.	Topotecan	Elacridar	Elacridar inhibit P-gp efflux, increase topotecan bioavailability and lead to toxicity [20]
16.	Tacrolimus	Ketoconazole	Increase tacrolimus bioavailability by inhibiting P-gp efflux [23]
17.	Tacrolimus	Clotrimazole	Clotrimazole inhibit P-gp efflux, increase Tacrolimus bioavailability [24]
18.	Talinolol	Erythromycin	Increase talinolol bioavailability due to increased intestinal net absorption by inhibiting P-gp efflux by erythromycin [25]

19.	Talinolol	D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS)	TPGS inhibit P-gp efflux, increase talinolol bioavailability [26]
20.	Daunorubicin	Polysorbate 80	Polysorbate 80 inhibit P-gp efflux and increase daunorubicin intracellular levels in cell cultures [20]
21.	Saquinavir	Cremophor EL	Cremophor EL increase saquinavir bioavailability by inhibiting P-gp activity [27]
22.	Loperamide	Quinidine	Quinidine inhibit P-gp efflux, increase loperamide entry in CNS causing Respiratory depression [28]
23.	Sulfonylurea	Clarithromycin, Verapamil	Inhibition of P-gp efflux, elevated risk of hypoglycemia due to increased bioavailability of sulfonylurea [29]
24.	Repaglinide	Atazanavir	Atazanavir inhibit P-gp efflux, increase repaglinide bioavailability and decreased renal clearance of repaglinide [30]
25.	Dabigatran	Ketoconazole, amiodarone, verapamil,ticagrelor and clarithromycin	Inhibit P-gp drug efflux, increase dabigatran bioavailability and increased risk of severe haemorrhage [31]
26.	Methotrexate	Omeprazole/ pantoprazole	Inhibit P-gp efflux, increase AUC and decrease renal clearance [20]
27.	Sorafenib	Verapamil	Verapamil inhibit P-gp efflux, increase sorafenib bioavailability by decrease renal clearance [32]
28.	Erlotinib	Amiodarone	Amiodarone inhibit P-gp efflux, increase erlotinib bioavailability [33]
29.	Fexofenadine	Lopinavir/ ritonavir	Lopinavir/ ritonavir inhibit P-gp efflux, increase fexofenadine bioavailability [34]

P-glycoprotein inducers

Sr.No	Drug	Inducer	Toxicity
1.	Digoxin	Rifampin	Rifampin induce P-gp efflux, decrease digoxin bioavailability due to increased renal clearance [35]
2.	Talinolol	Rifampin	Rifampin induce P-gp efflux, decrease talinolol bioavailability [36]
3.	Tacrolimus	Rifampin	Rifampin induce P-gp efflux, decrease tacrolimus bioavailability by increasing renal clearance of tacrolimus [37]
4.	Sulfonylurea	Rifampicin	Rifampicin induce P-gp efflux, decrease sulfonylurea bioavailability which lead to therapeutic efficacy [29]
5.	Dabigatran etexilate	Rifampicin	Rifampicin induce P-gp efflux, decrease dabigatran etexilate bioavailability [38]
6.	Fexofenadine	Carbamazepine	Carbamazepine induce P-gp efflux, decrease fexofenadine bioavailability [39]
7.	Non-vitamin K antagonist oral anticoagulants (NOACs) like Dabigatran, rivaroxaban, apixaban, edoxaban	Carbamazepine, levetiracetam, Phenobarbital, phenytoin and valproic acid	Induce P-gp efflux thus decrease the effect of non-vitamin K antagonist oral anticoagulants (NOACs) [40]

CONCLUSION

P-gp is an efflux transporter pump present in many organs and plays an important role in drug transport. Expression of P-gp can have important effects on drug action. The importance of P-gp transporters in drug-drug interactions is increasingly being identified. The main causes of interactions are changes in the pharmacokinetics of drugs. Altered expression of this efflux pump can lead to lower therapeutic efficacy or greater toxicity. Knowledge of these potential drug interactions can help to ensure the provision of safety and effective treatment.
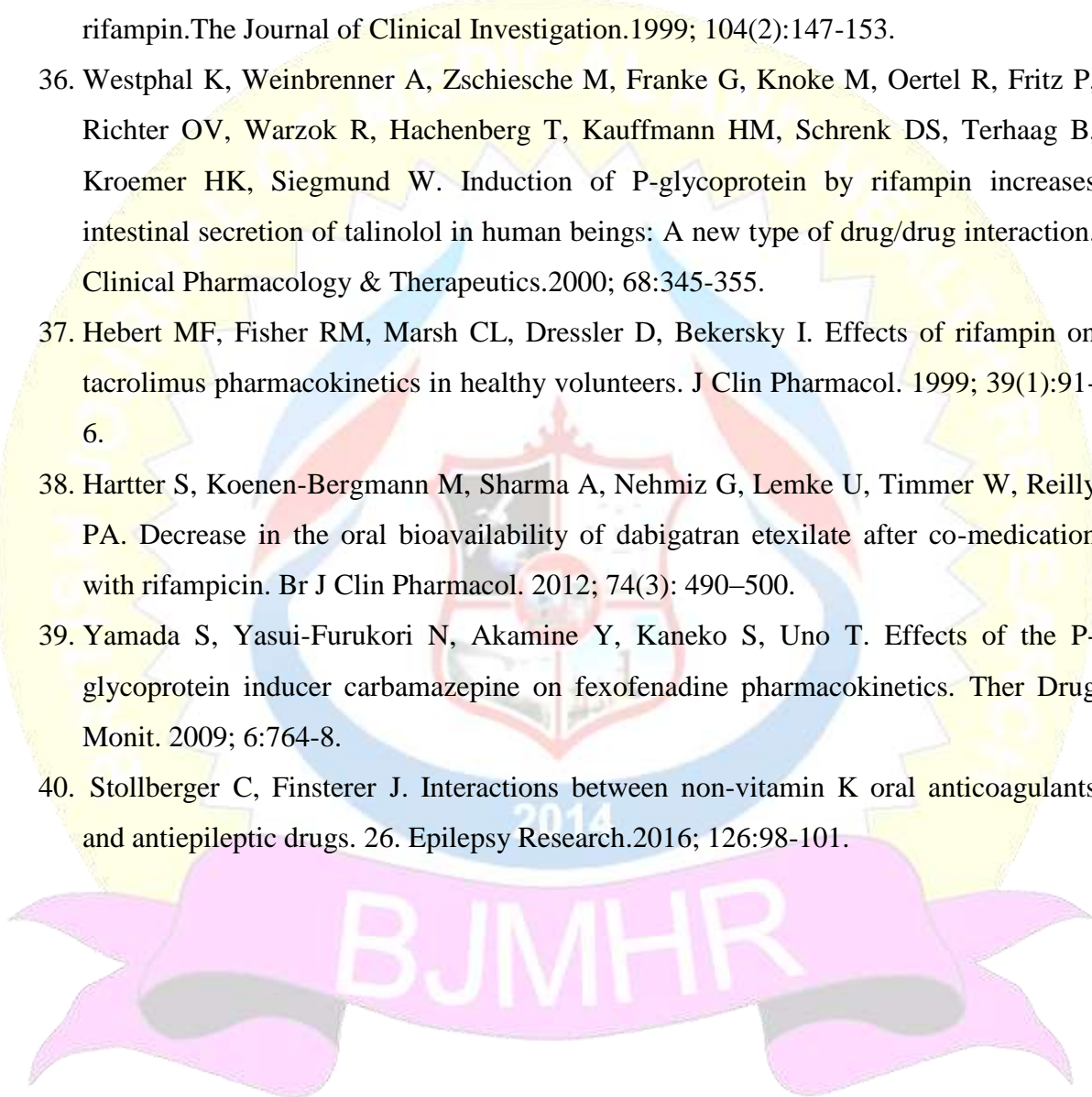
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