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Short communication

Drug-drug interactions of tacrolimus

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SUMMARY

Introduction: Tacrolimus, potent immunosupressive drug, has large inter- and intra-individual pharmacokinetic variability.
The aim: The aim of this current topic is to describe the importance of tacrolimus drug-drug interactions.
Pharmacokinetic interactions between tacrolimus and other drugs: Concerning the fact that it is also a medicine with the narrow therapeutic range, its interactions with other drugs mediated by both P-glycoprotein and CYP3A enzymes are potentially very important.
Conclusion: Interactions between tacrolimus and other drugs leading to overexposure to tacrolimus is connected with significant toxicity, while the subtherapeutic blood concentrations increase the probability of transplanted organ rejection.

Keywords: tacrolimus, P-glycoprotein, CYP3A enzymes, drug-drug interactions

INTRODUCTION

Tacrolimus is a macrolide immunosuppressant that is used to prevent organ rejection in patients with liver, kidney or heart grafts. It is a lipophilic drug with a narrow therapeutic window. Due to its physicochemical characteristics it is a subject of intensive metabolism and has highly variable absorbtion and, as a result of that, its main characteristics are variable pharmacokinetics [1-4]. However, due to its potency, tacrolimus is widely used to prevent allograft rejection in the patients with transplanted organs or tissues [5]. Due to all these facts, tacrolimus is the most common research drug subject in the transplantation area.

THE AIM

The aim of this current topic is to describe the importance of tacrolimus drug-drug interactions, as well as to present short review of such interactions.

PHARMACOKINETIC INTERACTIONS BETWEEN TACROLIMUS AND OTHER DRUGS

Tacrolimus absorption from the human gastrointestinal tract shows great variability. In some patients it is rapidly absorbed after oral administration (maximal blood concentration can be achieved in approximately 1 to 2 hours), while in others absorption time can be slower or even delayed.

The bioavailability of tacrolimus is low (about 20%) due to its extensive presystemic metabolism, but may vary between 4 to 93% [6, 7]. It is a substrate of P-glycoprotein

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efflux pump, which is one of the drug transporters that determine a range of its uptake and efflux [8-11].

P-glycoprotein functions as a transmembrane efflux pump, pumping substrates from the intracellular to extracellular space. This pump is presented in the intestinal epithelium, renal tubules epithelium, hepatocytes, blood-brain-barrier and placenta [12]. Therefore, tacrolimus bioavailability is largely determined by its pumping back into the intestinal lumen mediated by this efflux transporter. P-glycoprotein inductors and inhibitors interact with tacrolimus through this pump (Table 1) [11, 13]. Some drugs, substrate of P-glycoprotein, may occupy active places of this pump, which may lead to higher tacrolimus absorption and bioavailability [9, 11]. On the other hand, the inhibition or induction of P-glycoprotin may produce the increased or decreased tacrolimus blood concentration, respectively.

Tacrolimus is metabolized in the liver by cytohrome P450 (CYP) [7]. It is a substrate of both CYP3A4 and CYP3A5 enzymes. Gene polymorphisms of both CYP3A4 and CYP3A5 enzymes are significant factor which contributes to its highly variable bioavailability [14-18]. Therefore, tacrolimus large inter- and intra-individual pharmacokinetic variability could be at least partially explained by the genetic polymorphism of CYP3A genes.

Drug interactions with tacrolimus mediated by CYP3A enzymes, affecting its concentrations in blood are presented in Table 2 [19-24]. CYP3A enzyme system inhibitors may lead to the increased tacrolimus blood concentrations, while its inducers may reduce them. Substrates of CYP3A enzyme system probably occupy them leading to increased tacrolimus blood concentrations. Overexposure to aforementioned substrates can results in significant tacrolimus toxicity, while the subtherapeutic blood concentrations probably lead to the increased probability of organ rejection [22, 25, 26].

Table 1. Drugs that interact with tacrolimus through P-glycoprotein efflux pump

P-glycoprotein		
Inhibitors	Inducers	Substrates
azithromycin	avasimibe	azithromycin
amiodarone	ambrisentan	actinomycin
conivaptan	dabigatran	vinblastine
verapamil	everolimus	vincristine
diltiazem	imatinib	dexamethasone
dronedarone	carbamazepine	digoxin
erythromycin	ranolazine	doxorubicin
indinavir	ritonavir	etoposide
itraconazole	rifampin	colchicine
captopril	rifampicin	cortisol
carvedilol	sirolimus	lovastatin
quinidine	talinolol	paclitaxel
ketoconazole	tipranavir	terfenadine
clarithromycin	topotecan	fexofenadine
conivaptan	phenytoin	
lopinavir		
ranolazine		
ritonavir		
felodipine		
cyclosporine		

The clinical significance of the described interactions is very important. For example, interactions between tacrolimus and proton pump inhibitors (omeprazole and lansoprazole) are of clinical importance. Proton pump inhibitors are metabolized by cytochrome P450 enzymes, most prominently CYP3A4 and CYP2C19 and they are also substrats of P-glycoprotein [27, 28]. Since tacrolimus and proton pump inhibitors share the affinity

Table 2. Drugs that interact with tacrolimus through CYP3A enzymes

CYP3A				
Inhibitors		Substrates		Inducers
bromocriptine	macrolides	alprazolam	lidocaine	aluminium hydroxide
verapamil	methylprednisolone	alfentanil	lovastatin	dexamethasone
voriconazole	metoclopramide	amiodarone	loratadine	ethosuximide
glibenclamide	metronidazole	amlodipine	nevirapine	isoniazid
grapefruit	midazolam	atorvastatin	nicardipine	carbamazepine
dalfopristin	midecamycin	warfarin	nifedipine	magnesium oxide
danazol	miconazole	venlafaxine	omeprazole	methylprednisolone
delavirdine	nelfinavir	vinblastine	paclitaxel	nevirapine
diltiazem	nefazodone	dabigatran	progesterone	orlistat
erythromycin	nicardipine	dantrolene	propafenone	prednisone
etinilestradiol	prednisolone	dapsone	sertraline	rifabutin
zafirlukast	prednisone	diazepam	simvastatin	rifampicin
indinavir	progesterone	disopyramide	tamoxifen	sirolimus
itraconazole	ritonavir	enalapril	testosterone	sodium bicarbonate
quinupristin	saquinavir	estradiol	triazolam	sulfapyridine
ketoconazole	troleandomycin	estrogen	felodipine	phenylbutazone
clarithromycin	fluvoxamine	etoposide	flutamide	phenytoin
clotrimazole	fluconazole	zolpidem	chlorpromazine	phenobarbital
cortisol	fluoxetine	quinidine	cyclophosphamide	
lansoprazole	chloramphenicol	clonazepam	cilostazol	
levofloxacin	cyclosporine	cocaine	cisapride	
lopinavir	cimetidine	cortisol		

for CYP3A4 enzymes and compete each other for these enzymes as well as for P-glycoprotein, drug interactions should be anticipated when these drugs are administrated simultaneously. Therefore, combining these drugs leads to increased tacrolimus blood concentrations, since, as it was mentioned, omeprazole and lansoprazole are inhibitors and/or substrates of CYP3A4 enzymes and P-glycoprotein efflux pump [27-30].

On the other hand, calcium channel blockers (diltiazem, nifedipine, amlodipine) are potent inhibitors and/or substrates of CYP3A4 and CYP3A5 enzymes, as well as of P-glycoprotein transporter, and they can rapidly increase tacrolimus blood concentrations [31]. Since calcium channel blockers decrease the clearance of tacrolimus by partial competative inhibiton of metabolic pathway, it leads to a significantly elevated tacrolimus blood concentrations [32, 33].

CONCLUSION

Tacrolimus drug-drug interactions mediated by both P-glycoprotein and CYP3A enzymes are potentially very important, concerning the narrow therapeutic range of this immunosuppressant and variable pharmacokinetics. Therefore, relativelly small alterations in tacrolimus bioavailability and its metabolism, as a whole, may lead to the significant increase or decrease of its blood level. Interactions with other drugs leading to overexposure of tacrolimus is connected with significant toxicity, while the subtherapeutic blood concentrations lead to the increased probability of transplanted organ rejection.

Understanding the fundamental principles of tacrolimus drug-drug interactions could contribute to better transplant patients pharmacotherapy, especially concerning the fact that it is a long-term and expensive treatment associated with transplant rejection risk.

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Interakcije takrolimusa sa drugim lekovima

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KRATAK SADRŽAJ

Uvod: Takrolimus, potentni imunosupresivni lek, ima veliku inter i intra-individualnu farmakokinetsku varijabilnost.
Cilj: Cilj ove aktuelne teme jeste da opiše značajne interakcije takrolimusa sa drugim lekovima.
Farmakokinetske interakcije između takrolimusa i drugih lekova: S obzirom na činjenicu da je ovo lek sa malom terapijskom širinom, interakcije takrolimusa sa drugim lekovima preko P-glikoproteina i CYP3A enzima su potencijalno veoma značajne.
Zaključak: Interakcije takrolimusa sa određenim lekovima vode ili ka preteranom izlaganju takrolimusu što je povezano sa značajnom toksičnošću, ili ka koncentracijama leka u krvi ispod minimalnih željenih što može dovesti do odbacivanja transplantiranog organa.

Ključne reči: takrolimus, P-glikoprotein, CYP3A enzimi, interakcije lekova

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