DRUG INTERACTIONS IN CARDIAC TRANSPLANT PATIENTS - THERAPEUTIC STRATEGIES. EXPERIENCE OF TÎRGU-MUREŞ TRANSPLANT CENTRE

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Abstract: *The treatment of co-morbidities in the patients with heart transplant imposes restrictions or dose adjustment of calcineurin inhibitors, especially when taken with certain medications of CYP3A4-dependent metabolism. In case of administrating CYP3A4 inhibitors antibiotics (macrolides, fluoroquinolones) or inducers (rifampicine), blood concentrations should be monitored daily and made immediate adjustments in dosage. Hypertension and diabetes treatment should take into consideration the same principles. Administration of drugs with renal pharmacotoxicological tropism must consider their additive nephrotoxicity with immunosuppressive medication. The article presents the experience of cardiac transplantation centre of Tîrgu-Mureş on 35 transplanted patients during the period 1999-2011.*

Cuvinte cheie: *inhibitori de calcineurină, CYP3A4, interacţiuni ale medicamentelor, transplant cardiac*

Rezumat: *Tratamentul co-morbidităţilor la pacienţii cu transplant cardiac impune restricţii sau ajustări ale dozei de inhibitor de calcineurină, mai ales în cazul administrării unor medicamente cu metabolism CYP3A4-dependent. În cazul administrării unor antibiotice inhibitoare CYP3A4 (macrolide, fluorochinolone) sau inductoare (rifampicină) concentraţia sanguină trebuie monitorizată zilnic şi efectuate corecţii imediate ale dozei. Tratamentul hipertensiunii şi al diabetului trebuie să ţină cont de aceleaşi principii. Administrarea unor medicamente cu tropism farmacotoxicologic renal trebuie să ţină cont de nefrotoxicitatea aditivă a acestora cu medicaţia imunosupresivă. Este prezentată experienţa Centrului de transplant cardiac din Tîrgu-Mureş, pe 35 de transplantaţi, pe perioada 1999-2011.*

INTRODUCTION

Immunosuppressive medication in transplanted patients led to a revolution in therapy, both in terms of survival and in terms of life quality. Calcineurin inhibitors (cyclosporine, tacrolimus) have several pharmacological characteristics that make them ineffective for long-term therapy (in the absence of monitoring blood levels by pharmacokinetic criteria required by the clinical guidelines).(1,2)

These drugs present high-risk of CYP3A4 and CYP3A5 dependent interactions with direct and immediate consequences (over/underdosing); limited safety margin requires close pharmacokinetic and clinical monitoring to avoid dosage that may lead to subtherapeutic blood levels (associated with acute or chronic rejection) or excess toxic levels (risk of bacterial, viral or fungal infections); moreover, relative overdose caused by drug interactions in the metabolism may increase dose-dependent nephrotoxicity, alter glucose metabolism (with fostering iatrogenic diabetes) and increase blood pressure - associated co-morbidities, which require concomitant treatment and promote further deterioration of the renal function.

Biodegradation of cyclosporine occurs at hepatic level CYP3A4 isoform dependent (resulting a large number of inactive metabolites - over 30) by oxidation (aliphatic hydroxylation) and N-methylation. The same isozyme is involved in the metabolism of tacrolimus. Both substances are both substrate and inhibitor of this isoenzyme (3) and both inducers and inhibitors of CYP 3A4 are likely to significantly alter blood concentrations of cyclosporine.

The emergence of certain drug interactions, clinically relevant, both in terms of pharmacokinetic and pharmacodynamic is inherent in clinical practice and inevitable in particular clinical situations (often requiring hospitalization and therapy supervision by pharmacokinetic criteria, as long as the concomitant treatment is indispensable).

PURPOSE

Preventing, or taking effective corrective measures to avoid changing plasma levels of calcineurin inhibitors in terms of polypharmacy (inevitable phenomenon in transplant patients). Monitoring therapy involves empirical dose adjustments when plasma levels are outside the target range. This requires patient hospitalization, temporarily stopping the medication, reducing or increasing the dose and/or taking certain therapeutic decisions (corrective medication).

The assumed goal is to obtain a benefit/risk ratio as favourable as possible, consistent with the rules imposed by the clinical guidelines.

METHODS

Concomitant medication was analyzed in 35 patients undergoing heart transplantation at the Institute for Cardiovascular Diseases and Transplantation of Tîrgu-Mureş in the period 1999-2011. Drug interactions have been clinically interpreted and clinical signs of sub- or overdose were correlated with individual values of plasma cyclosporine and tacrolimus, respectively.

The reference values were those recommended by the clinical guidelines, using as a parameter the residual concentration C_0 (***through peak***, pre-dose concentration): 10-20 ng/ml during the first 3 months post-transplantation and 5-15 ng/ml for tacrolimus later and 250 -350 initially, then 100-200 ng/ml (6 months post-transplantation) for cyclosporine.(1)

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Any value for blood level was classified as drug interaction, after the exclusion of other possible causes (usual dose modifications, after chronic treatment and regular monitoring, altered elimination pathways-estimating creatinine clearance based on MDRD formula (4,5) due to nephrotoxicity, liver function) and administered medication was investigated.

RESULTS

Antiinfectious treatment. Because of immunosuppression, virtually all patients experienced episodes of infections (bacterial, fungal, viral).

In all patients, antibioprofilaxy was performed with co-trimoxazole for the prevention of *Pneumocystis carinii* infection. Although the manufacturer recommends caution in the chronic renal patients (interstitial nephropathy, crystalluria), the risk of plasma level modification is low; close monitoring is required only in case of a creatinine clearance below 30 ml/min/1.73 m^2. Also, for the prophylaxis or treatment of *Cytomegalovirus* infection, ganciclovir or valganciclovir were administered.

Induced immunosuppression frequently determines bacterial infections that should be treated promptly. Macrolides (especially erythromycin and clarithromycin), with marked inhibitory effect on CYP3A4 isoform should be avoided, as it determines significant increase of plasma levels of cyclosporine and tacrolimus.

Azithromycin does not inhibit CYP3A4; among macrolide, it is the antibiotic of choice. However, the first-line treatment should be represented by betalactamine, in the lack of drug sensitivity, despite an additive nephrotoxicity. If antibiogram recommends it (or the presumed susceptibility of Gram-negative infection), imipenem + cilostatine or meropenem are administered (nephrotoxicity or interference with CYP3A4-dependent metabolism is minimal).

Enzymatic inductors (rifampin used for tuberculosis reactivation after immunosuppression) can lead to cyclosporine dose reassessing (increasing the dose) and to a very careful clinical supervision. In one of our patients treated with immunosuppressive therapy, reactivate tuberculosis led to the need for rifampicin, a very potent inducer of CYP3A4. The evolution was unfavourable (tuberculosis, immunosuppression, drug interactions), and despite the careful monitoring, the patient died. Serious infections with methicillin-resistant Staphylococcus aureus (MRSA) requires the use of glycopeptides – in case of vancomycin nephrotoxic antibiotic, the daily determination of serum immunosuppressant is absolutely necessary, as well as the determination of creatinine clearance.

Immunosuppressive medication frequently promotes fungal infections to be treated compulsorily. Concomitant treatment with cyclosporine and azole antifungals (with significant inhibition of CYP3A4 capacity at usual doses) determines marked increase in plasma levels of immunosuppressant; it requires dosage adjustment in clinical practice using C_0 value. In case of fungal infection, all heart transplanted patients were hospitalized and treated with voriconazole (or fluconazole, ketoconazole, itraconazole) to determine the daily value of C_0 for cyclosporin or tacrolimus and where appropriate, an immediate dosage adjustment based on actual data obtained.

Corrective measures in cancineurine inhibitors association with anti-infective drugs are summarized in table no. 1.

Table no. 1. Drug interactions with antiinfectious agents

Suspected drug	Mechanism of interaction	Consequences	Corrective action / comments
ANTIBACTERIAL			
Aminoglycosides	additive nephrotoxicity	• decrease of renal elimination of immunosuppressant with increased immunosuppression	• Avoiding association; • Reserved for serious infections with multidrug-resistant bacteria (compulsory antibiogram test); • Use only after estimating glomerular filtration rate; • Daily plasma levels monitoring; dose adjustment for both drugs
β-lactamine (penicilline, cephalosporine)	additive nephrotoxicity		• Short-term treatment; • Monitoring of renal function; • Routine monitoring of serum
Imipenem + cilostatine Meropenem	-	-	• rarely of clinical significance
Co-trimoxazole	-	-	• Routine monitoring of serum; • *Pneumocistis carinii* infection prophylaxis • Reducing the dose of chemotherapy when GFR <30 ml/min/1.73 m^2
Glicopeptids	additive nephrotoxicity (vancomicine, unlikely after teicoplanin)	• toxic risk	• Administration only in case of absolute need; • Short-term treatment; • Use only after estimating glomerular filtration rate; • Monitoring plasma
Quinolone	CYP3A4 Inhibitory activity	• rarely of clinical significance	• Routine monitoring of serum
Macrolide	CYP3A4 Inhibitory activity (except azithromycin)	• Increased plasma levels of immunosuppressant	• Avoiding association; • Daily monitoring plasma levels
Rifampicine	CYP3A4 inductor	• marked decrease in plasma levels of immunosuppressant	• Administration only in case of absolute need; • Daily monitoring plasma levels • Increasing the dose of immunosuppressive
ANTIFUNGAL AGENTS			
Nystatine	-	-	• Not necessary (lack of oral absorption of Nystatin)
Azole antifungals (imidazoles, triazoles)	Marked inhibition of CYP3A4	• Increased plasma levels of immunosuppressant	• Short-term treatment; • Daily monitoring plasma levels • Adjusting immunosuppression (halving)
ANTIVIRAL AGENTS			
Ganciclovir, valganciclovir	-	-	• Prophylaxis of cytomegalovirus infection; • Routine monitoring of serum

Antihypertensive treatment and dyslipidemia. Hypertension and dyslipidemia are common and frequent adverse reactions of the immunosuppressive medication.

Rightfully choosing the antihypertensive drug should take into account, in addition to the clinical criteria, the metabolic pathway. Our experience recommends calcium blockers (dihydropyridines as substrates, but not CYP3A4 inhibitors, verapamil and diltiazem have inhibitory activity on CYP 3A4, which have to be taken into account). Other alternatives are converting enzyme inhibitors (additive nephrotoxicity), diuretics (serum ionogram must be monitored and thiazides are ineffective in renal impairment). To lower plasma cholesterol, a statin is preferable to not interfere with the metabolism of calcineurin inhibitors (fluvastatine) and has a low risk of myopathy.

Treatment of diabetes. Preexistent or *de novo* diabetes (induced by immunosuppressive drugs) needs treatment and may facilitate kidney disease development. Iatrogenic diabetes may be favoured by specific immunosuppressants association with methylprednisolone. In addition to the careful monitoring of blood glucose, in diabetes, sulfonylurea derivatives should be avoided (prone to drug interactions with ordinary OTC drugs, ambulatory issued such as NSAIDs) and to use biguanides or insulin treatment, the efficiency being monitored by blood glucose and glycosylated hemoglobin. The discontinuation of corticosteroids is recommended as soon as possible after transplantation. Ulcerogenic effect of corticosteroids will be avoided with H2-blocking agents which do not inhibit CYP3A4 (famotidine; ranitidine or cimetidine are excluded) or proton pump blockers lacking enzyme inhibitory activity, both CYP3A4 (not influence immunosuppressants) and the CYP2C19 (not to interfere with some cardiovascular drugs, particularly antiplatelet agents that block fibrinogen binding ADP-dependent to receptor GPIIb / IIIa).

DISCUSSIONS

Antiinfectious treatment. Antibioprofilaxy remains controversial, some authors do not recommend it only under special circumstances (high risk, age over 60 years, body mass index over 35).(6)Although theoretically, the risk of drug interactions of beta-lactams with immunosuppressants is lower than the macrolides (lack of enzyme inhibitor activity) (7), Shullo MA et al. *(2010)* describe elevated serum tacrolimus after ceftriaxone administration, but not after azithromycin.(8)

On the other hand, nephrotoxic antibiotics must be avoided and nephrotoxicity associated with aminoglycosides, vancomycin respectively (aminoglycoside-associated nephrotoxicity) can be quantified (increased serum creatinine more than 0.5 mg/dL on 2 consecutive days or more than 50% increase blood creatinine).(9,10)

As with our results, the literature shows that the reactivation of tuberculosis infection is a complication that can have dramatic effects on tacrolimus concentration caused by rifampicin, even under the concomitant treatment with other CYP3A4 inhibitors.(11) This effect is due to rifampicin action as a potent inducer of CYP3A4.(12)

Azole derivative antifungal therapy often imperatively requires reducing the immunosuppressive dosage and strict plasma monitoring daily (13-15), although the calcineurin inhibitors present antifungal activity of their own, but masked by immunosuppression.(16) The inhibitory effect on CYP3A4 is expressed not only at hepatic level, but also at intestine level, demonstrated by different experiences with voriconazole parenteral vs. orally.(13)

Antihypertensive treatment and dyslipidemia. Calcium blockers with different structure from dihydropyridines (verapamil, diltiazem) are potent inhibitors of CYP3A4 and may affect plasma concentrations of tacrolimus or cyclosporine (being indicated only under strict monitoring). 1,4-dihydropyridine derivatives do not have inhibitory activity, but are a CYP3A4 substrate and can be widely used. *Mangray M. (2011)* highlights the advantages of calcium blockers by inhibiting vasoconstriction induced by immunosuppressant drugs, underlying nephrotoxicity. ACE inhibitors, although do not pharmacokineticaly interact with immunosuppressants, can cause hyperkaliemia and decrease the glomerular filtration rate.(17)

For the treatment of dyslipidaemia in case of ineffectiveness of fluvastatine, atorvastaine (metabolized by CYP3A4, but also CYP2C9) may be a viable alternative despite the limited clinical experience.(18)

Future prospects of immunosuppressive therapy to avoid CYP3A4-dependent interactions are targeted treatments of patients, after determining the individual genetic polymorphism.(19)

CONCLUSIONS

Calcineurin inhibitors therapy in transplanted patients presents increased risk of drug interactions, especially CYP3A4-dependent. Iatrogeny treatment (infection, hypertension, diabetes, dyslipidemia) should take into account possible interactions. When these are unavoidable, the patient must be hospitalized and blood levels of immunosuppresant must be strictly daily determined and the dose adjusted accordingly.

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