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Drug Interactions with Tacrolimus

Teun van Gelder

Department of Internal Medicine, University Hospital Rotterdam – 'Dijkzigt', Rotterdam, The Netherlands

Contents

Abstract

Tacrolimus is a drug for which therapeutic drug monitoring is recommended. The existence of a wide variety of potential drug interactions further supports the current strategy of measuring whole blood tacrolimus concentrations in transplanted patients.

Cytochrome P450 (CYP)3A, the major phase I metabolising enzyme in humans, and the multi-drug efflux pump, P-glycoprotein, are present at high levels in the villus tip of enterocytes in the gastrointestinal tract. Oral bioavailability of tacrolimus can be increased by concomitant administration of inhibitors of either CYP3A or P-glycoprotein. CYP activity in the liver also influences tacrolimus concentrations. As a result, several drugs that are frequently being used in transplantation, such as corticosteroids and antifungal agents, will affect tacrolimus concentrations. Knowledge of such drug interactions is extremely important, as they may lead to clinically important under- or overexposure to tacrolimus, with acute rejection episodes or serious toxicity as a result.

Tacrolimus can no longer be called a 'new' immunosuppressive drug. It has been used in thousands of allograft recipients and has become the standard immunosuppressive drug in numerous transplant centres.[1] Because of its variable pharmacokinetics and narrow therapeutic index, monitoring drug concentrations is essential to avoid the risks of over- and under-immunosuppression. For routine clinical practice therapeutic drug monitoring of tacrolimus whole blood concentrations is recommended and target ranges have been defined.[2] Nevertheless, in everyday clinical practice and in the field of therapeutic drug monitoring we still do encounter new and sometimes life-threatening[3] interactions with this drug. As this may result in increased or decreased[4] drug concentra-

tions or in an altered pharmacodynamic effect of tacrolimus, these interactions may harm the patient and thus deserve further and continued attention.[5]

The mechanism of action of tacrolimus is similar to that of cyclosporin, involving the formation of complexes with immunophilins. Tacrolimus binds to FK 506 binding protein 12 (FKBP12) and cyclosporin binds to cyclophilin A. The immunophilin-drug complex interacts with calcineurin, leading to inhibition of early steps in T-cell activation. Other effects probably contribute to the overall pharmacodynamic effect of tacrolimus as well, but it is unclear to what extent.[6,7]

Increased tacrolimus toxicity is observed with increased tacrolimus concentrations. The most frequently observed adverse events associated with both oral and intravenous use of tacrolimus are tremor, headache, hypertension, nausea and renal dysfunction.[8] Hyperglycaemia also occurs and necessitates insulin therapy in some.[8]

1. Pharmacokinetics

Excellent reviews have been published on the pharmacokinetics of tacrolimus.[9,10] Oral bioavailability of tacrolimus is poor and ranges from 4 to 89% (mean of around 25%).[10] The pharmacokinetics of tacrolimus shows considerable interindividual variation, for which most clinicians use therapeutic drug monitoring, aiming at specific target levels depending on the clinical situation. Food appears to have a significant effect on the rate and extent of absorption.[11] However, in renal transplant recipients a significant food effect was not discernible.[12] Whole blood tacrolimus concentrations are approximately 20 times higher than the corresponding plasma concentrations owing to extensive binding of tacrolimus to erythrocytes. Therefore whole blood is the preferred medium for pharmacokinetic monitoring. Tacrolimus is eliminated by metabolism and the metabolites are subsequently excreted in the bile. Metabolism occurs in the liver, through the cytochrome P450 (CYP) 3A4 enzyme, but also in the intestinal mucosa. The volume of distribution of tacrolimus in blood is approximately 50L, indicating extensive distribution of tacrolimus outside the blood compartment. The mean terminal elimination half life of tacrolimus has been reported to be approximately 10 to 20 hours. It is, however, important to note that this half life is based on patient data, and obtained with abbreviated sampling schedules. In pharmacokinetic studies in healthy volunteers 'true' half lives of 34 to 38 hours have been determined.[13] For children these data may be slightly different.[14,15] The vast majority of tacrolimus and its metabolites are excreted in bile. Less than 1% of an intravenous dose of tacrolimus is excreted unchanged in urine. Renal insufficiency therefore does not influence tacrolimus clearance.

2. Drug Interactions

Drug interactions and other factors affecting the pharmacokinetics of tacrolimus may occur at the level of absorption, distribution, metabolism and excretion of tacrolimus. Also tacrolimus may affect the pharmacokinetics of other drugs. In this review an overview will be given of potentially important clinical interactions that may alter exposure to tacrolimus. Certainly not all drug interactions are pharmacokinetic in nature; for example, neurotoxicity of drugs such as ganciclovir may be aggravated if combined with tacrolimus. Similarly, a potential for renal function disturbances is present if tacrolimus is combined with nephrotoxic compounds such as nonsteroidal anti-inflammatory drugs,[16] antibiotics[17] and chemotherapeutic agents.[9] Co-administration of tacrolimus and ACE inhibitors may also lead to increased nephrotoxicity, especially in situations of impaired renal blood flow. Such more pharmacodynamic interactions are difficult to prove, as measurements of concentrations of either the parent drug or its metabolites may not be conclusive. If combined use of any of these agents with tacrolimus can not be avoided both clinical and laboratory parameters should be carefully monitored.

2.1 Absorption

Absorption of tacrolimus may be influenced by alterations in gastrointestinal motility. Under normal circumstances the drug is absorbed rapidly, reaching peak concentrations on average approxi-

mately 1 to 2 hours after oral administration in most patients. The rate and the extent of tacrolimus absorption decreases in the presence of food, with high fat meals producing the greatest effect.[18] Fleckenstein et al.[19] reported that combining tacrolimus with ursodeoxycholic acid did significantly affect the tacrolimus levels in liver transplant patients.

Irrespective of the organ transplanted, the absorption and bioavailability after oral administration appear to show high inter-patient variability. Based on the low blood clearance of tacrolimus it can be predicted that the low bioavailability of tacrolimus is either due to gut metabolism or to poor oral absorption of the drug.[10] Magnesium oxide and aluminium hydroxide appear to decrease tacrolimus absorption, either through binding of the drug or through pH mediated degradation. The latter process may also be responsible for the decreased bioavailability observed if tacrolimus is combined with sodium bicarbonate. Although theoretically this interaction may be much less apparent by separation of these agents and tacrolimus by a couple of hours, for the sake of compliance it is recommended to avoid using magnesium oxide, aluminium hydroxide and sodium bicarbonate if possible.

Intestinal phase I metabolism and active extrusion of absorbed drug have recently been recognised as major determinants of oral bioavailability.[20] For tacrolimus CYP3A, the major phase I metabolising enzyme in humans, and the multidrug efflux pump, P-glycoprotein,[21] are present at high levels in the villus tip of enterocytes in the gastrointestinal tract.[20] Oral bioavailability of tacrolimus can be increased by concomitant administration of inhibitors of either CYP3A or P-glycoprotein. The drugs interfering with CYP3A will be discussed in tsection 2.3. Many of these drugs are also a substrate and/or inhibitor of P-glycoprotein.[20] It is possible that the variability in the extent of tacrolimus absorption is at least partly caused by genetic polymorphism of either CYP3A4 or P-glycoprotein. For cyclosporin, a drug with a similar high interindividual variability in oral bioavailability, and also a substrate for CYP3A4 and P-glycoprotein, this was recently studied.[22] Von Ahsen et al.[22] were not able to demonstrate that genetic polymorphisms for CYP3A4 or P-glycoprotein were associated with the amount of cyclosporin needed to maintain certain cyclosporin trough concentrations.

2.2 Distribution

Tacrolimus is distributed extensively in the body, as reflected by the large volume of distribution. Within the circulation the drug is strongly bound to erythrocytes, in plasma it is strongly protein bound.[23,24] The pharmacologically active component is considered to be the 'unbound fraction' in plasma water. This unbound fraction can vary considerably without affecting the total blood concentrations.

2.3 Metabolism

Metabolism of tacrolimus largely occurs through the CYP3A4 enzyme system. The main metabolic pathways are hydroxylation and demethylation, and the predominant metabolite is 13-*O*-demethyl-tacrolimus.[25] Some metabolites may have biological activity.[25,26] Co-administration of drugs that inhibit or induce CYP3A4 may increase or decrease tacrolimus metabolism.[27,28] The list of drugs interacting at the level of the CYP450 enzyme system is long (table I). For most drugs formal studies demonstrating an interaction with tacrolimus have not been performed, and only rarely have healthy volunteer studies proven the extent of such interactions.[29] Recommendations are usually based upon clinical cases, animal experiments or are merely extrapolations of experience with cyclosporin. For example the use of hypericum (St John's wort), known to induce the CYP system, has caused acute rejection in a heart transplant recipient treated with cyclosporin,[30] and is therefore relatively contraindicated in combination with any drug that is metabolised through the CYP3A4 system. Several of the HIV protease inhibitors are known to inhibit the CYP3A4 enzyme system. For both cyclosporin[31] and tacrolimus[32,33] severe toxicity has been described due

Table I. Drugs that may alter tacrolimus pharmacokinetics

Antibiotics[8,10,14,17]
Erythromycin (increase)
Clarithromycin (increase)
Rifampicin (rifampin) [decrease]
Antifungal agents[8,10,14,39]
Fluconazole (increase)
Ketoconazole (increase)
Itraconazole (increase)
Clotrimazole (increase)
Calcium channel antagonists[8,10,28]
Diltiazem (increase)
Verapamil (increase)
HIV protease inhibitors[31-34]
Nelfinavir (increase)
Ritonavir (increase)
Antiepileptic drugs[8,14]
Phenytoin (decrease)
Phenobarbital (phenobarbitone) [decrease]
Other drugs
Corticosteroids (increase)[28]
Danazol (increase)[14]
Cimetidine (increase)[10]
Omeprazole (increase)[28]
Grapefruit juice (increase)[35-37]

to combined treatment with such protease inhibitors.[34] Grapefruit juice contains naringenine and 6′,7′-dihydroxybergamottin, well known inhibitors of CYP3A4, resulting in increased tacrolimus concentrations.[35-37] Corticosteroids are also known to induce the CYP system, and the gradual decrease in corticosteroid dose that most patients have, may be responsible for the reduced oral clearance of tacrolimus over time that several investigators have observed.[12,38]

Antifungal agents, such as ketoconazole, are well known for their inhibitory effect on the CYP system,[39] and have even been used to reduce the dose of tacrolimus and thus save money. If possible, drugs interfering at the level of the CYP system should be avoided. If tacrolimus and either of these drugs are used concomitantly, close monitoring of tacrolimus concentrations should be performed.

Also, it should not be forgotten that tacrolimus may influence the plasma concentrations of coadministered drugs.[40] A clinically important example is the observation that significantly higher mycophenolic acid predose concentrations are found in patients treated with tacrolimus and mycophenolate mofetil compared with a control group of cyclosporin and mycophenolate mofetil treated patients.[41] On the basis of the raw data it is hard to decide whether it is tacrolimus that increases mycophenolic acid levels, as was initially suspected, or cyclosporin that decreases mycophenolic acid levels. After a cross-sectional study, Smak Gregoor et al.[42] studied the influence of cyclosporine on mycophenolic acid pharmacokinetics in a longitudinal fashion.[43] These studies clearly show that cyclosporin decreases mycophenolic acid predose levels, a finding that was confirmed in an experimental model.[44] An effect of cyclosporin on mycophenolic acid concentrations was recently also reported for a paediatric patient population, although in this study tacrolimus seemed to reduce the clearance of mycophenolic acid as well.[45] Mycophenolate mofetil does not significantly influence tacrolimus concentrations.[46]

Another important interaction is that between HMG-CoA reductase inhibitors or statins and cyclosporin or tacrolimus. Most statins are also substrates of the CYP3A4 isoenzyme. Coadministration with cyclosporin results in a strong increase of plasma concentrations of these statins.[47] For tacrolimus this effect is less pronounced.[48] Life-threatening cases of rhabdomyolysis have been reported as a result of these interactions. The hydrophilic pravastatin seems to be associated with a relatively low risk of rhabdomyolysis.[49] The risk of developing rhabdomyolysis in transplanted patients also seems to be lower with tacrolimus compared to cyclosporine based treatment.[45]

2.4 Excretion

The main excretion route for tacrolimus is through bile. Mild hepatic dysfunction was found not to influence tacrolimus pharmacokinetics significantly.[13] High tacrolimus concentrations

have, for example, been reported in allograft recipients with hepatitis C infection.[50] Patients with severe liver dysfunction accumulate tacrolimus metabolites that may interfere with immunoassays used for quantitating tacrolimus in whole blood.[2,14,51]

3. Conclusion

Therapeutic drug monitoring is recommended for tacrolimus. The existence of a wide variety of potential drug interactions further supports the current strategy of measuring whole blood tacrolimus concentrations in transplanted patients. CYP3A4 and P-glycoprotein are involved in the pharmacokinetic pathways of tacrolimus and drugs known to interact with these enzyme systems will influence tacrolimus concentrations. Pharmacodynamic interactions are more difficult to prove, as measurements of concentrations of either the parent drug or its metabolites may not be conclusive. Knowledge of such drug interactions is extremely important, as they may lead to clinically important under- or overexposure to tacrolimus, with acute rejection episodes or serious toxicity as a result.

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Correspondence and offprints: Dr *Teun van Gelder*, Department of Internal Medicine, University Hospital Rotterdam – 'Dijkzigt', Room D412, P.O. Box 2040, Rotterdam, 3000 CA, The Netherlands.
E-mail: vangelder@INW1.AZR.NL