Review Article

Understanding the factors influencing pharmacokinetics of tacrolimus

Sivakumar V.*, Rakshna M., Soorya M. S., Pranesh S.

Department of Pharmacy Practice, PSG College of Pharmacy, Coimbatore, Tamil Nadu, India

*Correspondence:
Dr. Sivakumar V.,
E-mail: sivakumar7868@psgpharma.ac.in

ABSTRACT

Tacrolimus, a potent calcineurin inhibitor integral to immunosuppressive regimens, exhibits complex pharmacokinetics influenced by diverse factors and understanding these factors is crucial for safety, efficacy and dose optimisation. Genetic variations, particularly in CYP3A enzyme systems and P- Glycoprotein, contribute significantly to inter-individual variability in tacrolimus metabolism. Polymorphisms in these systems alter drug bioavailability, impacting clinical outcomes. Ethnicity further compounds this variability, with distinct genetic profiles leading to differential drug responses. Notably, black patients, often characterized by CYP3A5 expressor status, may have higher drug clearance. Age-related changes in tacrolimus clearance highlights the discrepancies in elderly and paediatric populations. On the other hand, prediction of gender-specific differences is difficult due to lack of evidence. Body composition, specifically variations in fat and muscle mass, significantly impacts drug distribution and clearance. Obesity, associated with altered CYP3A activity, results in decreased drug clearance, emphasizing the importance of accounting for body composition in dosing calculations. Pregnancy -induced physiological changes affect tacrolimus absorption, distribution, metabolism, and excretion, necessitating careful monitoring and dose adjustments in pregnant individuals. Dietary factors and drug interactions, particularly with CYP3A4 and P-glycoprotein, further contribute to the intricate web of variables influencing tacrolimus pharmacokinetics. In conclusion, this review sheds light on the multifaceted factors influencing tacrolimus pharmacokinetics, providing essential insights for clinicians to tailor individualized dosing regimens and enhance therapeutic efficacy while minimizing the risk of adverse events.

**Keywords:** Tacrolimus, Immunosuppression, Pharmacokinetics, Factors

INTRODUCTION

Tacrolimus, a 23 membered macrolide lactone isolated from Streptomyces tsukubaensis, is a potent calcineurin inhibitor (CNI) which is a backbone in immunosuppressive regimen. It was initially approved for immunosuppression in liver transplantation, but it is now used for prolonging allograft survival in case of kidney, lung, heart, pancreas, pancreatic islet, and intestinal transplants as well.[1] In comparison to cyclosporine, which was the first CNI used in kidney transplantation, tacrolimus has shown improved drug tolerance, lesser side effects, lower incidence of post-transplant rejection and an overall better graft survival rate.[2] Apart from serving as treatment and prophylaxis for organ rejection post-transplant, the immunosuppression provided by tacrolimus has also made it beneficial in other conditions like Crohn disease, Myasthenia gravis, Rheumatoid arthritis, Graft-versus-host disease and a few dermatological conditions like atopic dermatitis.[3] Understanding the various factors affecting tacrolimus pharmacokinetics (PK), is crucial for optimization of immunosuppression regimens, adjusting individual dosages and minimizing toxicity risks.

MECHANISM

Tacrolimus binds to FK-Binding protein 12 (FKBP12), which is a protein target of immunophilin family to form a complex which binds to calcineurin. Calcium and calmodulin are involved in regulating the enzymatic

activity of calcineurin in T- cell signal transduction. By inhibiting calcineurin, tacrolimus prevents dephosphorylation of transcription factor NFAT (nuclear factor of activated T-cells) and its subsequent translocation into nucleus. This leads to blockage of activation of various intracellular signalling pathways and release of cytokines such as TNF-α (tumour necrosis factor), GM-CSF (granulocyte-macrophage colony stimulating factor) and Interleukins, notably IL-2 (Figure 1).[4] Moreover, tacrolimus also has an effect on cellular events such as apoptosis and degranulation in leukocytes. These changes lead to suppression of immune response which is the therapeutic goal.[4,5]
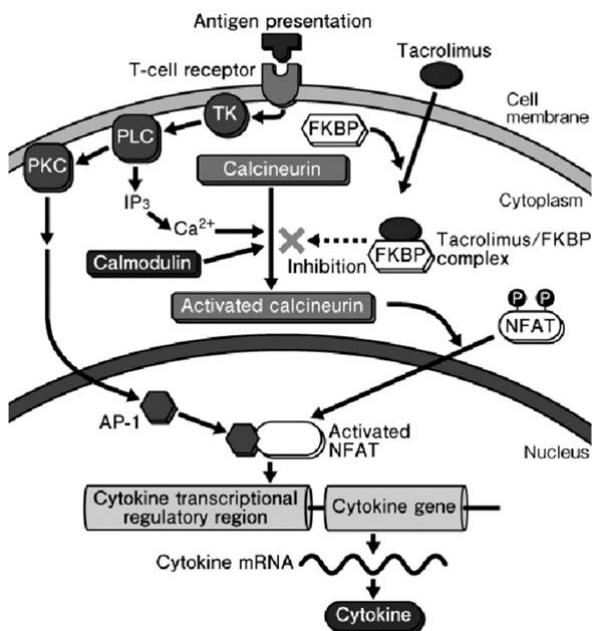
Figure 1: Mechanism of tacrolimus

FKBP - FK506-binding protein; NFAT - nuclear factor of activated T cells; PKC - protein kinase C; PLC - phospholipase C; TK - tyrosine kinase.

PHARMACOKINETICS

Tacrolimus is a highly lipophilic immunosuppressant. Absorption of tacrolimus occurs rapidly in most patients in the colon and small intestine, with peak plasma concentrations being attained in 0.5–1 hour. It is a saturable process following zero order kinetics. The oral bioavailability of tacrolimus is generally poor (average of 25%), but it can vary considerably among patients, ranging from 4 to 89%. In order to achieve equivalent drug exposure following administration, tacrolimus oral doses should typically be 3–4 times larger than intravenous doses.[6]

After entry into the systemic circulation, around 99% of the drug binds to erythrocytes. Tacrolimus can also bind to α1-acid glycoprotein (AAG), albumin, lipoprotein and globulin. Only the unbound portion enters into the lymphatic system and plays its role of immunosuppression. The volume of distribution (Vd) is around 30 l/kg based on plasma concentrations.

Metabolism of tacrolimus occurs extensively in the liver and small intestine by CYP3A isoenzymes. Among the 15 potential metabolites that have been identified, 13-O-demethyl-tacrolimus is the chief breakdown product. The expression of the main isoforms of the CYP3A subfamily – CYP3A4, CYP3A5, CYP3A7 and CYP3A47 – is variable between individuals and their overlapping specificity to substrate makes it challenging to pinpoint their distinct roles in the biotransformation of tacrolimus. P-glycoprotein, which is also called multi drug resistance protein–1, can cause efflux of drug in the intestine which can further contribute to pharmacokinetic variability.[3,7,8]

The total body clearance is quite low, roughly 0.06 l/h/kg, whereas the half-life is long and variable ranging from 4 to 41 h (12 hours on average). Bile excretes roughly 95% of tacrolimus metabolites, while urine only excretes about 2% of them. Urine and faeces only expel 0.5% of the original drug.[9] The fluctuations in pharmacokinetic variability occurs due to the influence of a wide range of factors and it is crucial to understand them for the purpose of safety, efficacy and dose optimization.

FACTORS AFFECTING PHARMACOKINETICS

Genetics

Genetics has been identified to be responsible for about 20-95% of the variability in drug effects. It is suggested that the expression of metabolizing enzymes (especially CYP3A5 and CYP3A4) and efflux pumps like P-gp are closely related to Tacrolimus pharmacokinetics, especially the metabolism, and therefore, genetic polymorphisms in these proteins can cause inter-individual variability. It has been identified that CYP3A5 expressers (CYP3A5*1/*1 or *3/*1 genotype) have higher tacrolimus dosage requirements compared to CYP3A5 non- expressers (CYP3A5*3/*3 genotype) while the trough levels and dose adjusted trough levels are comparatively lower. This was further supported by a study by Lesche et al, involving heart transplant patients, where the required elevation in tacrolimus dose to attain desired concentration was found to be about 2.2 to 2.6 folds higher in expressers. This could be due to the higher apparent clearance rate in expressers. Other single nucleotide polymorphisms (SNP) such as CYP3A5*6 and CYP3A5*7 have resulted in non-functional enzyme.[9,10,11]

Among the 28 SNP's identified for CYP3A4, the SNP's CYP3A4*1B and CYP3A4*22 were studied more extensively. On comparison with the wild type genotype (*1/*1), those with the *1B mutation showed a lower dose adjusted trough levels by 35%, while expressors of *22 genotype had higher dose adjusted trough levels indicating need for tacrolimus dose reduction by 30%. The influence of CYP3A5 genotype however, has resulted in an uncertainty regarding the actual impact of CYP3A4*1B

genotype on Tacrolimus pharmacokinetics, while CYP3A4*22 genotype is independent of such influence. Higher plasma drug concentration and tacrolimus clearance rate has been associated with CYP3A4*18 carriers. A rare variant CYP3A4*26, has been found to produce a non-functional enzyme causing very high tacrolimus exposure. The variations in tacrolimus exposure among different CYP3A metabolisers has been summarized in Table 1.[9,10]

Table 1: Impact on tacrolimus exposure by different CYP3A metabolizers.

CYP3A metabolizers	CY3A5	CYP3A4	Dose adjusted trough levels	Tacrolimus dose requirements
Ultra rapid	Expressers (*1/*1 or *3/*1)	*1B carriers	Lower	Higher
Poor	Non –expressers (*3/*3)	*22 carriers	Higher	Lower
Non functional	*6 carrier; *7 carrier	*26 carrier	Very high	Very low

P-glycoprotein is encoded by the ABCB1 gene and over 50 SNP's have been identified for it. Variation in ABCB1 3435C>T can alter the function of P-gp in duodenum and reduce its function causing variation in tacrolimus pharmacokinetics. The dose adjusted concentration was decreased by 36% in wild type patients when compared with those having 2677G>T/A SNP. Several studies have failed to demonstrate a link between ABCB1 1236C>T SNP and kinetics of tacrolimus.[10,12]

Ethnicity

In a study by Machphee et al, it was identified that the attainment of target blood concentration required higher tacrolimus doses in black and non- white South American patients and this disparity is attributed to lower bioavailability.[13] Taking genetics into consideration, the association between CYP3A4*1B and target level concentration could also be influenced by ethnicity as a certain study showed no specific difference when a solely white patient group was considered. Moreover, inability to attain target concentrations was more pronounced among CYP3A5 expressors in white population, suggesting that the potential genetic linkage in black patients is less complete. It is also possible that some black patients' CYP3A5 expressor status was incorrectly assigned due to the presence of the null allele CYP3A5*6, which is found in 10% of black patients and very few white patients. CYP3A5*6 can coexist with CYP3A5*1 and change an expressor genotype to a non expressor.

Tornatore et al, showed that 88% of black patients were intermediate or extensive metabolizers due to CYP3A5*1 genotype, and irrespective of gender, they showed higher tacrolimus clearance with greater trough levels which may indicate need for higher tacrolimus dosages.[14]

Due to increased awareness of ethnic variations in tacrolimus response, some centres have initiated the practice of administering two fold higher doses to black patients. However, it is crucial to understand that race is not a reliable indicator of underlying genotype influencing tacrolimus kinetics as more white CYP3A5 expressors undergo transplantation resulting in need for tacrolimus usage, than black patients with this genotype.[13,14]

On the other hand, the frequency of CYP3A5*3 allele is 77.8% in Chinese population, and they require a lower dosage when compared with black patients.[9] Thus, ethnic variations in tacrolimus pharmacokinetics further highlights the impact of genetic factors on drug metabolism. However, it is not a reliable factor and solely relying on race for dose adjustments can be completely misleading.

Age

Through comparison of elderly and middle aged transplant recipients, a decline in tacrolimus clearance per body mass index was identified in elderly due to possible association with declining hepatic function and structural changes in ageing liver. Reduced metabolic clearance was indicated by higher dose adjusted trough levels. However, on long term tacrolimus pharmacokinetic investigations, several inconsistencies were seen in the results.[15]

In children, maintaining target tacrolimus trough concentrations requires doses that are 2- to 3-fold higher compared to adults. The differences in tacrolimus clearance across various age groups may be explained by the age-dependent activity of CYP3A enzymes and P-gp. In vivo studies indicate that CYP3A activity is low after birth, peaks in young/mature adults, and decreases with advanced age. Research involving 90 healthy volunteers aged 0 to 86 demonstrated that p-glycoprotein activity in peripheral blood lymphocytes is highest in cord blood and declines progressively with age. However, there is some conflicting data suggesting that p-glycoprotein function might be well preserved during advanced age, raising uncertainties regarding p-glycoprotein-mediated drug transport in the gut and liver.[7,16] The intricate relationship between age and tacrolimus clearance warrants further investigation for personalised and effective treatment strategies in diverse age groups.

Gender

Predicting gender dependent changes in pharmacokinetics of tacrolimus is difficult and complex due to its association with various other factors like genetics, hormonal status, concomitant diseases and socio-economic status of patients. The activity of CYP3A in women was found to

exceed men population, but there is no sufficient evidence. In postmenopausal female patients, the CYP3A4 activity was increased compared to men of same age. Moreover, a difference in CYP3A4 activity in pre and postmenopausal women was also observed.[17,18]

Body composition

Body composition can influence the distribution and blood levels of tacrolimus, due to its highly lipophilic nature. Variations in fat mass composition of an individual can affect tacrolimus pharmacokinetics, with obese and overweight patients exhibiting lower activity of CYP3A leading to decreased clearance. Increased tacrolimus whole blood concentrations were found in patients with higher muscle mass when compared to patients with lower muscle mass. Therefore, low dose is sufficient to attain desired tacrolimus trough levels in obese patients when compared to that of lean patients.[19,20]

Pregnancy

Tacrolimus is considered safe during pregnancy even though it crosses the placenta and enters fetal circulation because the blood levels detected in the fetus are about half that of the mother.[21] During pregnancy, several physiological changes occurs altering absorption, distribution, metabolism and excretion of tacrolimus.[22,23]

The absorption of tacrolimus from the small intestine and colon gets countered by efflux which is mediated by P-glycoprotein. This protein gets further induced in renal tissue, placental tissue and intestinal epithelial cells in pregnancy due to the increased production of oestradiol and oestrogen resulting in decreased tacrolimus bioavailability. In pregnancy, both albumin and AAG concentrations in plasma decreases and since tacrolimus binds to both, this leads to increased plasma tacrolimus free fraction. The volume of distribution (Vd) of tacrolimus increases as a result of an increase in the total blood volume of ~50%.

Moreover, increased oestrogen concentrations decrease CYP3A4 and increase CYP3A5 activity throughout gestation, and since tacrolimus metabolism is carried out mainly by CYP450 enzyme system, it can lead to increase in the mean tacrolimus CL/F (oral clearance) by 39% compared to postpartum. Gestational age and haematocrit also affect the CL/F (Table 2).[22,23]

Haematocrit is inversely correlated with CL/F. Therefore, decreased haematocrit due to pregnancy leads to increased CL/F which reduces tacrolimus whole blood concentrations. Due to vasodilatation during pregnancy, the renal plasma flow is increased by 50 -85%, which leads to an increased glomerular filtration rate (GFR) resulting in higher renal excretion of non-metabolized tacrolimus.[22,23]

Table 2: Oral clearance at different gestational age.

Gestational age	Increase in oral clearance (%)
First trimester	15
Second trimester	19
Third trimester	21

Diet

The impact of diet on the absorption of tacrolimus was investigated in a study by Bekersky et al, and the pharmacokinetic parameters of tacrolimus for fasting, low-fat/high carbohydrate and high fat meals were compared. In the fasting state, tacrolimus showed a significantly higher maximum concentration (C_{max}) and Area under the curve (AUC), with a shorter time to reach C_{max} (t_{max}) compared to the fed states.

Both high-fat and low-fat/high-carbohydrate meals led to reduced bioavailability, as evidenced by fasting AUC being 1.50- and 1.35-fold greater. In comparison to the high-fat and low-fat/high-carbohydrate meals, the C_{max} values during the fasting state were 4.35 and 2.83 times higher, respectively. The corresponding increases in t_{max} values were 2.34 for low-fat/high-carbohydrate and 4.72 for high-fat meals. Comparing the two fed states, the high-fat meal further decreased the rate of tacrolimus absorption compared to the low-fat/high-carbohydrate meal, with a 2.02-fold increase in t_{max} and 1.11- and 1.54-fold increases in AUC(0-∞) and C_{max} following the low-fat/high-carbohydrate meal.[24]

In terms of timing of drug ingestion relative to meals, taking tacrolimus immediately after a meal or 1.5 hours later significantly reduced absorption extent, with AUC ratios of around 1.5 compared to fasting state. Additionally, the increased mean t_{max} indicated that absorption of tacrolimus after a meal was prolonged. The distinction between immediate and delayed post-meal drug ingestion was visually apparent but not statistically significant, except for C_{max}.[25]

Drug interactions

The pharmacokinetic pathways of tacrolimus involve CYP3A4 and P-glycoprotein, and medications that interact with these systems will affect tacrolimus concentrations. The oral bioavailability of tacrolimus can be enhanced by concurrently administering CYP3A or P-glycoprotein inhibitors, while inducers of these systems can reduce it.

Moreover, substrates of these systems can occupy active places in them leading to higher absorption and bioavailability of tacrolimus. The various drugs interacting with tacrolimus have been summarized in Table 3 and Table 4.[26,27]

Table 3: Drugs interacting with tacrolimus via P-glycoprotein.

P-glycoprotein		Drugs	
	Inhibitors	Azithromycin, Amiodarone, conivaptan, verapamil, diltiazem, dronaderone, erythromycin, clarithromycin, indinavir, lopinavir, ranolazine, ritonavir, itraconazole, ketoconazole, captopril, carvedilol, quinidine, felodipine, cyclosporin	Increased bioavailability of tacrolimus
	Inducers	Avasimibe, ambrisentan, dabigatran, everolimus, imatinib, carbamazepine, ranolazine, ritonavir, rifampin, rifampicin, sirolimus, talinolol, tipranavir, topotecan, conivaptan	Decreased bioavailability of tacrolimus
	Substrates	Azithromycin, actinomycin, vinblastine, vincristine, dexamethasone, digoxin, doxorubicin, etoposide, colchicine, cortisol, lovastatin, paclitaxel, terfenadine, fexofenadine, phenytoin	Increased bioavailability of tacrolimus

Table 4: Drugs interacting with tacrolimus via CYP3A enzyme system.

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

Liver disease

Liver function can significantly influence tacrolimus pharmacokinetics as it is directly involved in its bioavailability and elimination. This has led to a need for careful monitoring and dosage adjustment particularly in patients with compromised liver function, with both intravenous and oral formulations. In patients with moderate to severe liver impairment, tacrolimus infusion or oral therapy resulted in elevated bioavailability (35%), a longer half-life of around 38.5 hrs and reduced clearance. Liver dysfunction causes impairment of biliary excretion of metabolites and this can also contribute towards elevation in plasma tacrolimus concentrations in patients, which is associated with a higher risk of nephrotoxicity. In a study carried out in liver transplant recipient, it was identified that the the pharmacokinetic parameters showed a significant degree of variability, which was linked to the patients' varying functional liver condition following transplantation.[28]

CONCLUSION

In conclusion, the pharmacokinetics of tacrolimus can be influenced by multifaceted factors, and understanding these factors are imperative for optimizing dosage, ensuring efficacy, and maintaining safety. Tacrolimus's intricate interplay with diverse physiological and genetic elements necessitates personalized approaches in dosing, particularly in vulnerable populations, emphasizing the importance of tailored therapeutic strategies for enhanced outcomes in transplant recipients and individuals with immunological disorders.

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