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Minireview

Pharmacokinetics and Toxicity of Tacrolimus Early After Heart and Lung Transplantation

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Annually, about 8000 heart and lung transplantations are successfully performed worldwide. However, morbidity and mortality still pose a major concern. Renal failure in heart and lung transplant recipients is an essential adverse cause of morbidity and mortality, often originating in the early postoperative phase. At this time of clinical instability, the kidneys are exposed to numerous nephrotoxic stimuli. Among these, tacrolimus toxicity plays an important role, and its pharmacokinetics may be significantly altered in this critical phase by fluctuating drug absorption, changed protein metabolism, anemia and (multi-) organ failure. Limited understanding of tacrolimus pharmacokinetics in these circumstances is hampering daily practice. Tacrolimus dose adjustments are generally based on whole blood trough levels, which widely vary early after transplantation. Moreover, whole blood trough levels are difficult to predict and are poorly related to the area under the concentration-time curve. Even within the therapeutic range, toxicity may occur. These shortcomings of tacrolimus monitoring may not hold for the unbound tacrolimus plasma concentrations, which may better reflect tacrolimus toxicity. This review focuses on posttransplant tacrolimus pharmacokinetics, discusses relevant factors influencing the unbound tacrolimus concentrations and tacrolimus (nephro-) toxicity in heart and lung transplantation patients.

Abbreviations: ABCB1, ATP-binding cassette subfamily B member 1; ACE, angiotensin converting enzyme; AGP, α1-acid glycoprotein; ATP, adenosine triphosphate; AUC, area under the concentration-time curve; CF, cystic fibrosis; Cmax, maximum concentration; CYP, cytochrome P; FK506, tacrolimus; FKBP12, FK506 binding protein; HCO-60, polyoxyl 60 hydrogenated castor oil; HDL, high-density lipoprotein; IL-2, interleukin-2; LDL, low-density lipoprotein; MI, 13-desmethyl tacrolimus; MII, 15-desmethyl tacrolimus; MIII, 31-desmethyl tacrolimus; mTOR, mammalian target of rapamycin; NR1I2, nuclear receptor subfamily 1, group I, member 2; OATP-C, organic anion transporting polypeptide-C; Pgp, P-glycoprotein; SIRS, systemic inflammatory response syndrome; SLCO1B1, solute carrier organic anion transporter family member 1B1; SNP, single nucleotide polymorphism; Tmax, time to peak concentration; VLDL, very low-density lipoprotein

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Introduction

Heart and lung transplants are among the most successful solid organ transplantations in the world (1). However, long-term morbidity and mortality are significantly jeopardized by chronic kidney disease (2,3). It has been shown that chronic kidney disease often originates from kidney injury acquired early after transplantation (2,3). The underlying mechanisms of acute kidney injury are incompletely unraveled, but shock, systemic inflammation and tacrolimus nephrotoxicity are considered the most important factors. Serious clinical instability is frequently found in both heart and lung transplant recipients early after transplantation (4,5). These unfavorable clinical conditions set the stage for highly fluctuating pharmacokinetics of tacrolimus with increased unbound plasma concentrations, which potentiate the risk of kidney injury. Here, we summarize current knowledge regarding tacrolimus pharmacokinetics as derived from healthy persons and patients undergoing solid organ transplantation. Suggestions are made as to how altered

pharmacokinetics early after heart and lung transplantation affect the risk of tacrolimus (nephro-) toxicity.

Tacrolimus and Its Efficacy in Heart and Lung Transplantation

The immunosuppressant tacrolimus has been of paramount importance since the 1990s in the modern era of heart and lung transplantation. Tacrolimus acts as a potent calcineurin inhibitor and has significantly contributed to contemporary 5-year-survival rates of roughly 85% for heart and 60% for lung transplantation (6,7). In most studies, tacrolimus exhibits higher patient and organ survival rates than the calcineurin inhibitor cyclosporine. Moreover, tacrolimus leads to lower rejection rates and longer freedom from rejection (8–10). Sirolimus, an immunosuppressant of the mTOR inhibitor group, is discouraged in the early phase after transplantation owing to wound-healing complications, especially bronchial dehiscence in lung recipients (11). At present, when prioritizing efficacy, tacrolimus is the first choice immunosuppressive drug for heart and lung transplant recipients in the early phase post transplantation. Consequently, improving tacrolimus management in heart and lung transplant recipients is of utmost importance.

Pharmacokinetics of Tacrolimus in Healthy Persons

The pharmacokinetics of tacrolimus are best described by a 2-compartment model with first-order absorption and first-order elimination from the central compartment (12). The mean disposition half-life of tacrolimus is about 12 h (13). Therefore, steady state concentrations are expected in two to three days. The therapeutic levels of whole blood tacrolimus trough concentrations range from 5–20 μg/L, but to prevent toxicity the usual range is 5–15 μg/L (14,15). In daily practice, whole blood tacrolimus trough concentrations 12 h after administration are generally used for therapeutic drug monitoring, even though it has been demonstrated that 6 h postadministration concentrations better correlate with the 12 h area under the concentration-time curve (AUC) in stable transplantation patients (12,16–18).

Bioavailability of tacrolimus

Tacrolimus administered orally is rapidly absorbed with a mean time to maximal concentration (Tmax) of 1–2 h, while the composition of food may highly influence its absorption (19). High fat as well as high carbohydrate meals may substantially decrease the maximal concentration (Cmax) and increase Tmax (20). The highly lipophilic character of tacrolimus largely explains this phenomenon.

Another factor regulating tacrolimus bioavailability is P-glycoprotein (Pgp), which is an adenosine triphosphate (ATP)-driven efflux pump (Figure 1). Pgp is predominantly situated in the apical membrane of the mature epithelial cells but also in hepatocytes, renal proximal tubular cells, the blood-brain barrier and leucocytes (21,22). There is a pharmacokinetic linkage between Pgp and cytochrome P-450 enzyme 3A (CYP3A) (Figure 1). When tacrolimus passes Pgp and enters the enterocyte, it is metabolized by CYP3A. Hereafter, Pgp pumps tacrolimus and its metabolites into the gut lumen where it is transported into more distal segments of the bowel containing lower amounts of both enzymes (23–26).

The expression of Pgp and CYP3A is influenced by genetics. P-glycoprotein is encoded by the ABCB1 gene in humans. The single nucleotide polymorphisms (SNPs) 1199G>A and 2677G>T/A, 3435C>T and 1236C>T, whether present individually or in linkage, significantly minimize Pgp activity (0–28%) and result in a higher bioavailability of tacrolimus (27,28). The expression of ABCB1 is influenced by ethnicity. The combined haplotype (2677G>T/A, 3435C>T, 1236C>T) is present in approximately 35% of Mexican Americans, 32% of Caucasians, 27% of Asian Americans and 5% of African Americans (29–31). Another regulator of the ABCB1 genes is the pregnane X receptor (encoded by NR1I2). SNPs in the NR1I2 gene have been associated with reduced Pgp expression in the gut. Consequently, the pregnane X receptor 7635G>A and 8055T variant alleles may result in higher bioavailability of tacrolimus as well (32,33).

Yet, another transporter of tacrolimus influencing oral bioavailability is the organic anion transporting polypeptide-C (OATP-C) (encoded by SLCO1B1), which is specifically

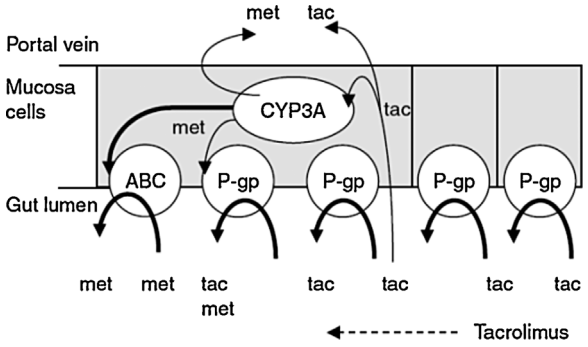

Figure 1: Proposed interactions between tacrolimus metabolism and active efflux of tacrolimus in the small intestinal mucosa. Two potential cooperative mechanisms between cytochrome P450 enzymes and active efflux transporters have been proposed: (A) P-glycoprotein regulates the access of tacrolimus to CYP3A enzymes and prevents CYP3A enzymes from being overwhelmed by the high drug concentrations in the intestine. With tacrolimus being repeatedly transported out of the mucosa cells and being reabsorbed again, leads to a higher exposure of CYP3A to tacrolimus and repeated exposure leads to a more efficient metabolism of tacrolimus in the intestine. (B) The metabolites of tacrolimus are better substrates of the active transporter than the parent drug, thus metabolite efflux is facilitated even if the parent drug is present in high concentrations. ABC, ATP-binding cassette transporter other than P-glycoprotein; met, tacrolimus metabolite; P-gp, P-glycoprotein; tac, tacrolimus (6).

expressed in the liver and takes part in the biliary excretion of tacrolimus. The SNP in the SLCO1B1 gene 521T>C significantly increases tacrolimus blood concentrations and the SNP 388A>G significantly decreases tacrolimus blood concentrations (28).

The bioavailability of tacrolimus has been found to be approximately 15%, though it may widely vary in healthy persons due to the aforementioned phenomena (34). In the first days after transplantation, the bioavailability may be even more variable (Figure 2).

Blood distribution of tacrolimus

The binding of tacrolimus to blood components is an important factor in its pharmacokinetics (35). Tacrolimus is mainly found within erythrocytes (85–95%), only a small part being localized in lymphocytes (roughly 0.5%). In plasma, approximately 60% of tacrolimus is bound to the proteins albumin and α1-acid glycoprotein (AGP), 30% to high-density lipoprotein (HDL), 8% to low-density lipoprotein (LDL) and 1% to very low-density lipoprotein (VLDL). Only 0.3–2% of plasma tacrolimus is unbound (36).

In more detail, tacrolimus is strongly bound to the cytosolic proteins cyclophilin and FK506 binding protein within the red blood cells (35,37). Due to the extensive distribution of tacrolimus into the erythrocytes, its apparent volume of distribution based on whole blood concentrations is much lower (1.0–1.5 L/kg) than that based on plasma concentrations (about 30 L/kg) (38). Additionally, influx and efflux of tacrolimus from plasma into red blood cells and vice versa is rapid with clearance rates of 0.276 mL/min and 1.70 mL/min, whereby equilibrium is established within 2 min (39). Because of this fast repartitioning, many authors prefer whole blood tacrolimus concentrations instead of tacrolimus plasma concentrations to monitor patients' treatment, which

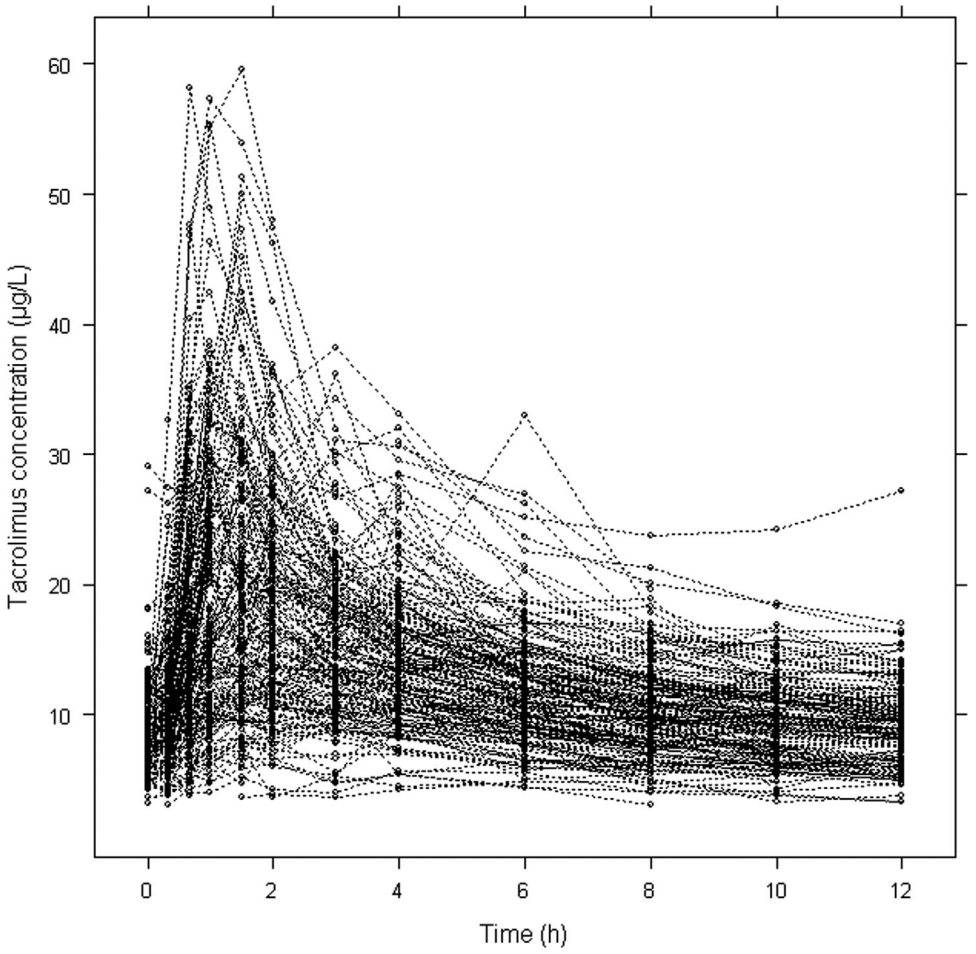

Figure 2: Whole blood tacrolimus concentration-time profiles obtained from 78 lung transplant patients during the first year posttransplantation showing a large variability in whole blood concentrations. The dots represent the observed concentration-time points (127).

seems adequate when erythrocytes and proteins are within normal limits (38).

Metabolism of tacrolimus

Tacrolimus is mainly metabolized in the liver, but also in the gut and kidney. This process is mediated by, so called, phase I and II metabolism. Phase I metabolism occurs through the mixed-function oxidase system primarily by CYP3A4/5 (40,41). Phase II metabolism takes place in the liver by demethylation, glucuronidation, sulfation, acetylation, and conjugation. The resulting metabolites are only present in low concentrations in the blood and have minor pharmacological activity when compared to tacrolimus itself. Except for neurotoxicity, metabolites of tacrolimus are thought to be of minor clinical relevance (42).

Significant inter-patient variation is present in the expression and function of CYP3A4 and CYP3A5, which is caused by the SNPs of genes encoding for these enzymes.

The frequency of the CYP3A4-392A>G SNP, also known as CYP3A4*1B, is predominantly found in Africans (in approximately 50%) (43). The CYP3A4*1B variant allele increases CYP3A4 expression and decreases tacrolimus concentrations (44). Another SNP, CYP 3A4*18B: 82266G>A, is only expressed in Asians and also results in higher CYP3A4 expression (44). The CYP 3A4*22 SNP is only expressed in 5% of Caucasians and causes low CYP3A4 expression. The CYP3A4*22 SNP in combination with CYP3A5 nonexpression can easily result in supratherapeutic tacrolimus levels and hence in increased toxicity of tacrolimus (45).

The expression levels of CYP3A5*1 or *3 may influence metabolism of tacrolimus extensively and may be more important than CYP3A4 polymorphisms (26,44,46). The CYP3A5*1/*1 and CYP3A5*1/*3 genotype (CYP3A5 expressers) is associated with significantly lower whole blood tacrolimus concentrations when compared with the CYP3A5*3/*3 genotype (CYP3A5 nonexpressers) (32,47). The CYP3A5*3 allele also shows distinctive ethnic diversity with allelic frequencies of about 35% in African-Americans, 70% in Asians and 95% in Caucasians (48,49). Furthermore, the expression of CYP3A5 enzymes may differ between and within organs. For instance, CYP3A5 may be better expressed in the kidney than in the liver and within the kidney, CYP3A5 is predominantly expressed in the tubules metabolizing tacrolimus and decreasing nephrotoxicity (41). The metabolisation of tacrolimus in the gut may be affected by CYP3A5 expression affecting bioavailability, which may be around 50% lower in CYP3A5 expressers in comparison to CYP3A5 nonexpressers (46).

Due to these large differences in CYP3A expression between individuals, it may be beneficial to identify CYP3A expression before transplantation to better predict tacrolimus blood concentrations and reduce (nephro-) toxicity directly after transplantation (50).

Clearance of tacrolimus

Tacrolimus is mainly excreted via the bile, while the renal clearance rate amounts to less than 1% of the total body clearance (51). Approximately 80–95% of the total tacrolimus dose is excreted via feces and more than 99% is excreted as metabolite (51).

The systemic plasma clearance of tacrolimus is high (0.6–5.4 L/kg/hr), whereas whole body clearance, based on whole blood concentrations, is much lower (0.03–0.09 L/kg/hr). Thus, the binding to blood components such as erythrocytes or proteins plays a major role in tacrolimus pharmacokinetics (38).

Pharmacokinetics of Tacrolimus Early After Heart and Lung Transplantation

The complexity of tacrolimus pharmacokinetics is markedly increased by a diversity of influences occurring in the perioperative phase of heart and lung transplantation. The cardiopulmonary bypass itself alters pharmacokinetics by hemodilution, hypo-albuminemia and hypothermia as well as adsorption and sequestration in the bypass circuit (52–54). Furthermore, the surgical procedure itself, its duration and potential complications, the blood transfusions, as well as ischemia-reperfusion injury of the transplanted organ(s) may all contribute to subsequent systemic inflammation. This, in turn, may alter organ function as well as blood cell and protein concentrations influencing tacrolimus pharmacokinetics.

The early postoperative period is mainly characterized by hemodynamic instability, the need for blood transfusions and the occurrence of systemic inflammation, which all contribute to fluctuating tacrolimus pharmacokinetics and the increased risk of kidney injury. A subset of patients requires extended periods of extracorporeal support, i.e. veno-arterial or veno-venous extracorporeal membrane oxygenation, which has an additional impact on tacrolimus pharmacokinetics in the postoperative phase. In unstable patients especially, it is challenging to determine appropriate tacrolimus dosages as steady state concentration may not be reached given the prolonged mean disposition half-life time of up to 50 h (13,35).

As a result of these dosing difficulties in the first days after heart and lung transplantation, tacrolimus nephrotoxicity, which originates from vasoconstriction of afferent and efferent glomerular arterioles, often ensues (55). When whole blood and especially unbound tacrolimus plasma concentrations are increased, a stronger vaso-constrictive effect is suspected leading to acute kidney injury. The acute kidney injury is further aggravated by cardiac dysfunction, hypoxia, hypovolemia, large volume shifts and use of vasopressors (Table 1) (56). Pretransplant risk factors such as impaired renal

Table 1: Nephrotoxic drugs with mechanism of action in combination with tacrolimus

Drug	Hypothetical mechanisms of action	References
Aminoglycosides (gentamycin, neomycin, tobramycin)	Additive or synergistic: Tubular apoptosis and/or necrosis	(21,81–83)
Amphotericin B	Synergistic: Afferent vasoconstriction	(21,81,83)
Non-steroidal anti-inflammatory drugs (ibuprofen, diclofenac, aspirin)	Synergistic: Afferent vasoconstriction and/or interstitial nephritis and/or papillary necrosis	(21,81,83,84)
ACE inhibitors (captopril)	Synergistic: Efferent vasodilatation	(21,81)
Co-trimoxazole (sulfamethoxazole)	Additive: Interstitial nephritis	(85,86)
(Val) gancyclovir/acyclovir	Additive: Intra-tubular obstruction	(83)

function, hypertension, diabetes, renal hypoperfusion, poor nutritional status, low muscle mass, weight loss and edema increase the risk for postoperative kidney injury (57–59). Importantly, renal injury observed early after transplantation indicates an increased risk of developing chronic renal failure, which has been found in up to 50% after one year and 70% after five years (3,60). This underscores the need to address the unresolved clinical problem of maintaining whole blood tacrolimus trough concentrations within the therapeutic range to prevent nephrotoxicity.

Unfortunately, the relationship between whole blood tacrolimus trough concentrations and the AUC is highly variable, especially peri-operatively, making interpretation of the former very challenging (12,16–18). Even when tacrolimus concentrations are in the therapeutic range, toxicity may occur because of high unbound tacrolimus plasma concentrations (61). The variables influencing the bound and unbound tacrolimus concentrations may considerably change during the early postoperative phase.

Bioavailability of tacrolimus early after heart and lung transplantation

In hemodynamically unstable patients, the motility of the intestinal tract is significantly altered. This has a major impact on tacrolimus bioavailability, since intraluminal transport to the duodenum is limited, being its predominant site of intestinal absorption. On the other hand, a sudden increase in absorption may well occur when gut motility recovers upon hemodynamic improvement.

Furthermore, in situations of inflammation, ischemia-reperfusion injury, diarrhea and shock, Pgp expression in the gut wall may be reduced leading to decreased Pgp levels and an increase in whole blood tacrolimus trough concentrations up to 100% (17,19,25,62,63). Pgp levels generally normalize within 48 h after the insult (17,19,63).

Tacrolimus bioavailability is also importantly influenced by drug–drug interactions encompassing a large number of different drugs administered directly after heart and lung transplantation (Tables 2 and 3). A subset of these drugs significantly affects CYP3A and Pgp activity, e.g. corticosteroids induce the expression of intestinal and hepatic CYP3A and Pgp as does tacrolimus itself (64). The overall effect of higher Pgp and CYP3A levels is a reduced and delayed absorption of orally administered tacrolimus (23,25). By inhibiting intestinal Pgp as well as CYP3A activity, the absorption of tacrolimus increases and may result in very high blood concentrations.

Therefore, some authors prefer the sublingual or intravenous route over oral administration to obtain more stable tacrolimus concentrations (65,66). However, absorption is minimal when tacrolimus is administered sublingually and prolonged intravenous administration is limited by toxic concentrations of the solvent polyoxyl-60-hydrogenated castor oil (HCO-60), causing additional renal injury (67). At this moment, the preferred route of administration is oral, while sublingual or intravenous application is discouraged. When significant gut motility disturbances are observed, the intravenous route may be considered for a limited period of time.

Blood distribution of tacrolimus early after heart and lung transplantation

Under conditions of clinical instability, the resulting changes in blood composition alter plasma concentrations of unbound tacrolimus, e.g. through differences in erythrocytes concentrations, as mentioned before (39,68). Anemia, which is often encountered in this period, increases the unbound tacrolimus plasma concentrations, whereas red blood cell transfusions reduce it.

Furthermore, blood distribution of tacrolimus is affected by the concentrations of albumin, lipoproteins and AGP, which often change early after heart and lung transplantation. Hypo-albuminemia results from liver failure due to diminished production of proteins and from renal failure due to protein loss by the kidney. Decreased albumin concentrations may also be caused by a shortage of dietary protein, increased capillary permeability and hemodilution. Also, in renal failure, the number of tacrolimus-binding locations on the albumin molecule is reduced as a result of conformational changes and competitive binding of substances to albumin, such as fatty acids or uremic toxins (69). Additionally, lipoprotein concentrations in general decrease rapidly in the perioperative phase and may drop as low as 50%, being a result of decreased synthesis and enhanced catabolism.

Table 2: Interactions resulting in increased tacrolimus concentrations

Drug	Study	Route of drug administration	Effect on tacrolimus	Proposed mechanism of interaction	References
Glucocorticoids	*In vitro*: Human liver and intestinal microsomes	Tacrolimus oral, glucocorticoids oral or IV	Short term (first hours): inhibition of tacrolimus metabolism; Long term (after hours to days): Inducing of tacrolimus metabolism	Cortisol, dexamethasone, prednisone, prednisolone, methylprednisolone: CYP3A4 inhibitor, substrate and inducer, Pgp substrate and inducer; hydrocortisone: CYP3A4 substrate and inducer, Pgp substrate and inhibitor	(21,87–93)
Macrolide (erythromycin, clarithromycin)	*In vivo*: Human, case report and *In vitro*: Human liver and intestinal microsomes and rat liver microsomes	Tacrolimus oral, erythromycin oral or IV	Inhibition of tacrolimus metabolism, 2- to 6-fold increase in trough concentration	CYP3A4/5 substrate and inhibitor, Pgp substrate and inhibitor	(87–89,91,93,94)
Azoles (ketoconazole, fluconazole, itraconazole, voriconazole, posaconazole, clotrimazole, metronidazole)	*In vivo*: Human, prospective studies (healthy volunteers, patients)	Tacrolimus oral or IV and ketaconazole oral or IV, fluconazole oral or IV itraconazole oral or IV, voriconazole oral or IV, posaconazole oral, clotrimazole oral, metronidazole oral	Dose reduction 54–78% for oral and 42% for IV or 2- to 17.5-fold reduction in dose to maintain therapeutic trough concentrations or 2- to 9-fold increase in trough concentration, 2-fold increase in maximal plasma concentration, 2- to 5-fold increase in AUC and oral clearance decreased, no effects after IV administration	CYP3A substrate and inhibitor, Pgp substrate and inhibitor, CYP3A5 expresser is associated with a reduced susceptibility for the inhibitory effects of fluconazole on tacrolimus metabolism	(15,64,76,87–89,91,93,95–133)
Levofloxacin	*In vivo*: Human, prospective study (5 patients)	Tacrolimus oral and levofloxacin oral	25% increase in AUC	CYP3A substrate; only 5% hepatic metabolism, Pgp substrate	(93,134,135)
Basiliximab	*In vivo*: Human, retrospective data analysis (12 patients)	Tacrolimus oral and basiliximab IV	63% increase in trough concentration on day 3, 30% dose reduction in first week to maintain therapeutic trough concentrations	IL-2Rá-induced alteration of tacrolimus metabolism by downregulating the hepatic cytochrome P450 system	(136)
Calcium antagonists: Phenylalkamine: Verapamil, and benzothiazepine: Diltiazem, and dihydropiridines: Nifedipine, amlodipine, and nicardipine	*In vivo*: Human, prospective study (6 patients) and human, retrospective data analysis (150 patients); *In vitro*: Human liver, intestinal microsomes and rat liver microsomes	Tacrolimus oral and verapamil oral and diltiazem oral, nifedipine oral, nicardipine iv	No change to 4-fold increase or 55% increase in trough concentration, 21–38% decrease in daily dose to maintain therapeutic trough concentrations 25–82% increase in AUC and Cmax	CYP3A4/5 inhibitor, CYP3A4 substrate, Pgp substrate and inhibitor	(87–89,91,93,95,100,137–140)

Table 2: Continued

Drug	Study	Route of drug administration	Effect on tacrolimus	Proposed mechanism of interaction	References
Omeprazole	*In vivo*: Human, prospective study (51 patients) and case report (2 patients); *In vitro*: Human liver or intestinal microsomes	Tacrolimus oral and omeprazole oral or IV	No clinical effect or 2- to 3-fold increase in trough concentration	CYP3A4 substrate and inhibitor, Pgp substrate and inhibitor	(56)
Anti-retroviral drugs (HIV protease inhibitors)	*In vivo*: Human, prospective study (73 patients)	Tacrolimus oral and protease inhibitor oral (nelfinavir, ritonavir)	75-99% or 30–140-fold lower tacrolimus dose and 7-fold longer dosing interval to maintain therapeutic trough concentrations, 34–99% decrease in oral clearance	Amprenavir: CYP3A4 substrate and inhibitor, Pgp substrate; atazanavir and indinavir: CYP3A4 substrate and inhibitor, Pgp substrate, inhibitor and inducer; lopinavir and ritonavir: CYP3A4 substrate, inhibitor and inducer, Pgp substrate, inhibitor and inducer; Nelfinavir and saquinavir: CYP3A4 substrate and inhibitor, Pgp substrate and inhibitor	(65,66)
Amiodarone	*In vivo*: Human, case report	Tacrolimus oral and amiodarone oral or IV	75% dose reduction to maintain therapeutic trough concentrations	CYP3A4 substrate and inhibitor, Pgp inhibitor	(141)
Theophylline	*In vivo*: Human, case report,	Tacrolimus oral and theophylline oral	3-fold increase in trough concentration	CYP3A4 substrate and inhibitor	(93,142–144)
Grapefruit	*In vivo*: Human, 2 case reports	Tacrolimus oral and grape fruit juice oral	2- to 10-fold increase in trough concentration	CYP3A4 inhibitor	(145–147)

AUC, area under the concentration-time curve; Cmax, maximum concentration.

Table 3: Interactions resulting in decreased tacrolimus concentrations

Drug	Study	Route of administration	Effect on tacrolimus	Proposed mechanism of interaction	References
Glucocorticoids	*In vivo*: Human, prospective study (778 patients); *In vitro*: Rat liver microsomes	Tacrolimus oral or IV and corticosteroids oral	Short term (first hours): inhibition of tacrolimus metabolism; Long term (after hours to days): Inducing of tacrolimus metabolism, a concomitant prednisolone dose of more than 10 mg/d increases the apparent clearance of tacrolimus by 15–36% (and thus a 15% lower bioavailability) at 5 mg/d 12–14% decrease in AUC	Cortisol, dexamethasone, prednisone, prednisolone, methylprednisolone: CYP3A4 inhibitor, substrate and inducer, Pgp substrate and inducer; hydrocortisone: CYP3A4 substrate and inducer, Pgp inhibitor and substrate	(21,37,44,63,90–93,100,148–155)
Carbamazepine	*In vivo*: Human, case report	Tacrolimus oral and carbamazepine oral	AUC/dose ratio reduces with 50–70%	CYP3A4 induction	(93)
Phenytoin	*In vivo*: Human, case report (6 patients)	Tacrolimus oral and phenytoin oral or IV	Decrease in tacrolimus whole blood levels, 2- to 3-fold increase in dose to maintain therapeutic trough concentrations	CYP3A4 induction	(93)
Phenobarbital	*In vivo*: Human, case reports (2 patients)	Tacrolimus oral and phenobarbital IV	Increase clearance	CYP3A4 inducer, Pgp inhibitor	(93)
Rifampicin	*In vivo*: Human, case report (10 patients); *In vitro*: Rat liver microsomes	Tacrolimus oral and rifampicin oral or IV	5- to >10-fold increase in dose to maintain therapeutic trough concentrations, 50% increased clearance, 50% decrease in oral bio-availability, no effect on rat liver metabolism	CYP3A4 and Pgp induction	(102,138,156–160)
St John's wort	*In vivo*: Human, prospective study (10 healthy volunteers and 11 patients)	Tacrolimus oral and St John's wort oral	34–50% decrease in AUC, 2- to 5-fold decrease in trough concentration	CYP3A4 and Pgp inducer	(161–166)

AUC, area under the concentration-time curve.

As a consequence, the decrease of the primary tacrolimus-binding lipoprotein HDL results in increased unbound tacrolimus plasma concentrations (70,71). In contrast, the acute phase protein AGP is often increased in case of inflammation and also after administration of corticosteroids, macrolide antibiotics and tacrolimus (72,73). As a result, increased AGP concentrations may result in reduced unbound tacrolimus plasma concentrations (74).

Thus, early after transplantation, the unbound tacrolimus plasma concentrations may change due to an altered blood composition, while the whole blood concentrations may remain unchanged (Table 4). These conditions favor the measurement of the unbound plasma concentrations in unstable patients.

Metabolism of tacrolimus early after heart and lung transplantation

The metabolism of tacrolimus depends not only on hepatic intrinsic clearance, but also on hepatic blood flow as reflected by an intermediate extraction ratio (69). Therefore, under conditions of shock, tacrolimus metabolism is impaired, which may substantially increase its concentrations (75).

Another phenomenon arising during periods of shock is the predominance of tacrolimus metabolisation in the gut as compared to the liver. Intestinal CYP3A levels are usually 10–50% of the concentration found in the liver, but during shock or systemic inflammation intestinal CYP3A, expressed primarily in the duodenum, may equalize or even exceed the hepatic levels (76).

These high CYP3A concentrations in the proximal intestine increase tacrolimus metabolism and decrease whole blood concentrations in times of shock.

Clearance of tacrolimus early after heart and lung transplantation

In the unstable clinical phase, whole body clearance of tacrolimus and its metabolites is influenced by a diversity of factors, among which severe cholestasis, anemia and hypo-albuminemia may all substantially alter the clearance (75). Cholestasis reflects hepatic dysfunction, which decreases the metabolism and transport of tacrolimus into the bile, resulting in a reduced clearance of tacrolimus. Anemia and hypo-albuminemia increase the unbound concentrations, which could augment the uptake of tacrolimus into the liver resulting in a higher clearance. This may explain the finding that patients with a low hematocrit (<0.35) have a higher whole body clearance of tacrolimus (up to 46%) than patients with a higher hematocrit (77,78). Also, in patients with hypo-albuminemia (albumin level <35 mg/L), clearance of tacrolimus is much higher (up to 16%) than in patients with albumin concentrations >35 mg/L (77). These changes in whole body clearance support the theory that steady state concentrations are often not reached within the first days after the initial dose of tacrolimus in unstable transplantation patients (51).

Drug–Drug Interaction of Tacrolimus

Heart and lung transplant recipients often receive a large number of different drugs that interfere with tacrolimus

Table 4: Influencing factors on tacrolimus blood concentrations early after heart and lung transplantation. The effects are assumptions based on literature and physiological concepts: ⇔ no effect, ↑ and ↓ small effect, ↑↑ and ↓↓ mild effect, ↑↑↑ and ↓↓↓ large effect

Factor	Effect on tacrolimus whole blood concentrations	Effect on unbound tacrolimus plasma concentrations	Reference
Bio-variables			
Anemia	↓⇔	↑↑↑	(38,39,74,77,149)
Blood transfusion	↑⇔	↓↓↓	(74)
Hypo-albuminemia	⇔	↑↑↑	(74,77)
High AGP	⇔	↓	(74,167)
Low HDL	⇔	↑	(74,168)
Low LDL	⇔	↑	(74,168)
Low VLDL	⇔	↑	(74,168)
Organ dysfunction			
Ileus	↓↓↓	⇔	(14,54)
Restored gut motility	↑↑↑	⇔	(14)
Diarrhea	↑↑	⇔	(17,19,63,169)
Low Pgp (shock, inflammation)	↑↑	⇔	(40,62,63)
ECMO	↓↓	↓	(52–54)
Liver dysfunction	↑	⇔	(75)
Cholestasis	↑	⇔	(75)
Kidney dysfunction	⇔	↑	(170)

AGP, α1-acid glycoprotein; ECMO, Extracorporeal Membrane Oxygenation; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

(Tables 2 and 3). A subset of these drugs may influence CYP3A, which metabolizes >90% of tacrolimus. Thus, inhibition or induction of CYP3A will lead to clinically significant changes in tacrolimus metabolism, whereby CYP3A inhibition is almost immediately effective and CYP3A induction is a slow process (25). Therefore, when a drug interacting with tacrolimus pharmacokinetics is initiated or withdrawn, careful monitoring of the whole blood tacrolimus concentrations and prompt adjustment of the dose is recommended.

Tacrolimus Pharmacokinetics in Cystic Fibrosis

Cystic fibrosis (CF) constitutes a multi-system disorder, which may affect the liver, pancreas and intestinal tract potentially causing a large scale of metabolic derangements. Therefore, the pharmacokinetics of tacrolimus in CF patients substantially differ from that in non-CF patients. Two underlying mechanisms are suggested. First, fat absorption is severely hampered due to pancreatic insufficiency resulting in high-fat containing stools. As a consequence, the absorption of tacrolimus, which is highly lipophilic, may be lowered to as much as 40%, whereas the rate of absorption is slower increasing the Tmax (16). Next, total body clearance of tacrolimus is increased, likely by an increased phase II metabolism in these patients leading to reduced whole blood tacrolimus concentrations (79). Subsequently, in CF patients much higher doses of tacrolimus are generally required to achieve equivalent blood concentrations (20).

Conclusions and Future Perspectives

Tacrolimus toxicity is an important determinant of morbidity and mortality after heart and lung transplantation. Clinical instability, especially in the early phase after transplantation, gives rise to fluctuating tacrolimus pharmacokinetics and subsequent nephrotoxicity. Clinicians should be aware of the spectrum of clinical conditions that influences tacrolimus pharmacokinetics, such as systemic inflammation, hemorrhage and shock, all of which result in higher variations of tacrolimus concentrations and therefore complicate adequate dosing.

In clinical practice, it remains cumbersome and unsatisfactory to prescribe well-titrated individualized daily administration of tacrolimus early after transplantation to prevent toxic levels in this phase. Even when the whole blood tacrolimus concentrations are in the therapeutic range, toxicity may develop because the unbound plasma concentrations can accidentally increase to high levels. The unbound concentration has been shown to be an important factor in cellular uptake, and may increase glomerular vasoconstriction leading to nephrotoxicity in the early days after transplantation (77,80).

Thus, from a mechanistic point of view, the plasma concentration of unbound tacrolimus is a more reasonable parameter to monitor to achieve optimal tacrolimus dosing in the unstable patient. This concept of tacrolimus monitoring is novel and will help to avoid toxic tacrolimus concentrations but it necessitates the development of an effective analytical method to determine the unbound plasma concentrations. Unfortunately, at present, current assays used for routine tacrolimus monitoring lack the sensitivity to adequately measure the low unbound plasma concentrations. Until such analyses become available, unbound tacrolimus plasma concentrations can be predicted based on the concentrations of a subset of known bio-variables influencing them. Although pharmacokinetic modeling has been performed, these formulas are not appropriate for the unstable transplantation patient. Creating such a model is of utmost importance to decrease tacrolimus toxicity in the early days after transplantation. The erythrocyte count and the plasma protein concentrations of albumin, AGP and HDL all are pivotal variables, which have to be considered in this complex computation. This review provides initial guidance to clinicians in adjusting tacrolimus dosing regimens on the basis of these bio-variables.

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Authors' Contributions

M. A. Sikma and J. Meulenbelt performed data analysis. M. A. Sikma, E. M. van Maarseveen, E. A. van de Graaf, J. H. Kirkels, M. C. Verhaar, D. W. Donker, J. Kesecioglu, and J. Meulenbelt contributed to the writing of the manuscript.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

References

1. Christie JD, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: 29th adult lung and heart-lung transplant report-2012. J Heart Lung Transplant 2012; 31: 1073–1086.

2. Wehbe E, Duncan AE, Dar G, Budev M, Stephany B. Recovery from AKI and short- and long-term outcomes after lung transplatation. Clin J Am Soc Nephrol 2013; 8: 19–25.
3. La Morena De MP, Bravos MDLT, Prado RF, et al. Chronic kidney disease after lung transplantation: Incidence, risk factors, and treatment. Transplant Proc 2010; 42: 3217–3219.
4. Taylor DO, Edwards LB, Aurora P, et al. Registry of the international society for heart and lung transplantation: Twenty-fifth official adult heart transplant report—2008. J Heart Lung Transplant 2008; 27: 943–956.
5. Vicente R, Morales P, Ramos F, Solé A, Mayo M, Villalain C. Perioperative complications of lung transplantation in patients with emphysema and fibrosis: Experience from 1992–2002. Transplant Proc 2006; 38: 2560–2562.
6. Kaczmarek I, Zaruba M-M, Beiras-Fernandez A, et al. Tacrolimus with mycophenolate mofetil or sirolimus compared with calcineurin inhibitor-free immunosuppression (sirolimus/mycophenolate mofetil) after heart transplantation: 5-year results. J Heart Lung Transplant 2013; 32: 277–284.
7. Neurohr C, Huppmann P, Zimmermann G, et al. Tacrolimus and mycophenolate mofetil as first line immunosuppression after lung transplantation. Transpl Int Blackwell Publishing Ltd 2009; 22: 635–643.
8. Griffith BP, Bando K, Hardesty RL, Armitage JM. A prospective randomized trial of FK506 versus cyclosporine after human pulmonary transplantation. Transplantation 1994; 57: 848–851.
9. Treede H, Glanville AR, Klepetko W, et al. Tacrolimus and cyclosporine have differential effects on the risk of development of bronchiolitis obliterans syndrome: Results of a prospective, randomized international trial in lung transplantation. J Heart Lung Transplant 2012; 31: 797–804.
10. Guethoff S, Meiser BM, Groetzner J, et al. Ten-year results of a randomized trial comparing tacrolimus versus cyclosporine a in combination with mycophenolate mofetil after heart transplantation. Transplantation 2013; 95: 629–634.
11. Groetzner J, Kur F, Spelsberg F, et al. Airway anastomosis complications in de novo lung transplantation with sirolimus-based immunosuppression. HEALUN 2004; 23: 632–638.
12. Monchaud C, de Winter BC, Knoop C, et al. Population pharmacokinetic modelling and design of a Bayesian estimator for therapeutic drug monitoring of tacrolimus in lung transplantation. Clin Pharmacokinet 2012; 51: 175–186.
13. Phapale PB, Kim S-D, Lee HW, et al. An integrative approach for identifying ametabolic phenotype predictive of individualizedpharmacokinetics of tacrolimus. Clin Pharmacol Ther 2010; 87: 426–436.
14. Undre NA, Meiser BM, Uberfuhr P, et al. Pharmacokinetics of tacrolimus (FK506) in primary orthoropic heart transplant patients. Transplant Proc 1998; 30: 1112–1115.
15. Berge M, Chevalier P, Benammar M, et al. Safe management of tacrolimus together with posaconazole in lung transplant patients with cystic fibrosis. Ther Drug Monit 2009; 31: 396–399.
16. Saint-Marcoux F, Knoop C, Debord J, et al. Pharmacokinetic study of tacrolimus in cystic fibrosis and non-cystic fibrosis lung transplant patients and design of bayesian estimators using limited sampling strategies. clinical pharmacokinetics. Clin Pharmacokinet 2005; 44: 1317–1328.
17. Kuypers D. Clinical efficacy and toxicity profile of tacrolimus and mycophenolic acid in relation to combined long-term pharmacokinetics in de novo renal allograft recipients. Clin Pharmacol Ther 2004; 75: 434–447.
18. Mendonza AE, Zahir H, Gohh RY, Akhlaghi F. Tacrolimus in diabetic kidney transplant recipients: Pharmacokinetics and application of a limited sampling strategy. Ther Drug Monit 2007; 29: 391–398.
19. Maes BD, Lemahieu W, Kuypers D, et al. Differential effect of diarrhea on FK506 versus cyclosporine a trough levels and resultant prevention of allograft rejection in renal transplant recipients. Am J Transplant 2002; 2: 989–992.
20. Bekersky I, Dressler D, Mekki QA. Effect of low- and high-fat meals on tacrolimus absorption following 5mg single oral doses to healthy human subjects. J Clin Pharmacol 2001; 41: 176–182.
21. Christians U, Jacobsen W, Benet LZ. Mechanisms of clinically relevant drug interactions associated with tacrolimus. Clin Pharmacokinet 2002; 41: 813–851.
22. Shitara Y, Maeda K, Ikejiri K, Yoshida K, Horie T, Sugiyama Y. Clinical significance of organic anion transporting polypeptides (OATPs) in drug disposition: their roles in hepatic clearance and intestinal absorption. Biopharm Drug Dispos 2013; 34: 45–78.
23. Christians U, Jacobsen W, Benet LZ, Lampen A. Mechanisms of clinically relevant drug interactions associated with tacrolimus. Clin Pharmacokinet 2002; 41: 813–851.
24. Paine MF, Khalighi M, Fisher JM, Shen DD. Characterization of interintestinal and intraintestinal variations in human CYP3A-dependent metabolism. J Pharmacol Exp Ther 1997; 283: 1–11.
25. Masuda S. Tacrolimus therapy according to mucosal MDR1 levels in small-bowel transplant recipients*1. Clin Pharmacol Ther 2004; 75: 352–361.
26. Goto M, Masuda S, Kiuchi T, et al. CYP3A5*1-carrying graft liver reduces the concentration/oral dose ratio of tacrolimus in recipients of living-donor liver transplantation. Pharmacogenetics 2004; 14: 471–478.
27. Staatz DCE, Goodman LK, Tett SE. Effect of CYP3A and ABCB1 single nucleotide polymorphisms on the pharmacokinetics and pharmacodynamics of calcineurin inhibitors: Part II. Clin Pharmacokinet 2010; 49: 141–175.
28. Elens L, Capron A, Van Kerckhove VR, et al. 1199G > A and 2677G > T/A polymorphisms of ABCB1 independently affect tacrolimus concentration in hepatic tissue after liver transplantation. Pharmacogenet Genomics 2007; 17: 873–883.
29. Kroetz DL, Pauli-Magnus C, Hodges LM, et al. Sequence diversity and haplotype structure in the human ABCB1 (MDR1, multidrug resistance transporter) gene. Pharmacogenetics 2003; 13: 481–494.
30. Cho JH, Yoon YD, Park JY, et al. Impact of cytochrome P450 3A and ATP-Binding cassette subfamily B member 1 polymorphisms on tacrolimus dose-adjusted trough concentrations among Korean renal transplant recipients. Transplant Proc 2012; 44: 109–114.
31. Mancinelli L. The pharmacokinetics and metabolic disposition of tacrolimus: A comparison across ethnic groups. Clin Pharmacol Ther 2001; 69: 24–31.
32. Press RR, Ploeger BA, Hartigh JD, et al. Explaining variability in tacrolimus pharmacokinetics to optimize early exposure in adult kidney transplant recipients. Ther Drug Monit 2009; 31: 187–197.
33. Barraclough KA, Staatz CE, Johnson DW, et al. Kidney transplant outcomes are related to tacrolimus, mycophenolic acid and prednisolone exposure in the first week. Transpl Int 2012; 25: 1182–1193.
34. Karamperis N, Povlsen JV, Højskov C, Poulsen JH, Pedersen AR, Jørgensen KA. Comparison of the pharmacokinetics of tacrolimus and cyclosporine at equivalent molecular doses. Transplant Proc 2003; 35: 1314–1318.
35. Jusko WJ, Piekoszewski W, Klintmalm GB. Pharmacokinetics of tacrolimus in liver transplant patients. Clin Pharmacol Ther 1995; 57: 281–290.
36. Zahir H, Nand RA, Brown KF, Tattam BN. Validation of methods to study the distribution and protein binding of tacrolimus in human blood. J Pharmacol Toxicol Methods 2001; 46: 27–35.
37. Fung JJ. Tacrolimus and transplantation. Transplantation 2004; 77: (Supplement) S41–S43.

38. Wallemacq DPE, Verbeeck RK. Comparative clinical pharmacokinetics of tacrolimus in paediatric and adult patients. Clin Pharmacokinet 2001; 40: 283–295.
39. Chow F-S, Piekoszewski W, Jusko WJ. Effect of hematocrit and albumin concentration on hepatic clearance of tacrolimus (FK506) during rabbit liver perfusion. Drug Metab Dispos 1997; 25: 610–616.
40. Masuda S. Effect of intestinal P-glycoprotein on daily tacrolimus trough level in a living-donor small bowel recipient. Clin Pharmacol Ther 2000; 68: 98–103.
41. Joy MS, Hogan SL, Thompson BD, Finn WF, Nickeleit V. Cytochrome P450 3A5 expression in the kidneys of patients with calcineurin inhibitor nephrotoxicity. Nephrol Dial Transplant 2007; 22: 1963–1968.
42. Yanagimachi M, Naruto T, Tanoshima R, et al. Influence of CYP3A5 and ABCB1 gene polymorphisms on calcineurin inhibitor-related neurotoxicity after hematopoietic stem cell transplantation. Clin Transplant 2010; 24: 855–861.
43. Lamba JK, Lin YS, Thummel K, et al. Common allelic variants of cytochrome P4503A4 and their prevalence in different populations. Pharmacogenetics 2002; 12: 121–132.
44. Hesselink D. Genetic polymorphisms of the CYP3A4, CYP3A5, and MDR-1 genes and pharmacokinetics of the calcineurin inhibitors cyclosporine and tacrolimus. Clin Pharmacol Ther 2003; 74: 245–254.
45. Elens L, Van Schaik RH, Panin N, et al. Effect of a new functional CYP3A4 polymorphism on calcineurin inhibitors' dose requirements and trough blood levels in stable renal transplant patients. Pharmacogenomics 2011; 12: 1383–1396.
46. Størset E, Holford N, Hennig S, et al. Improved prediction of tacrolimus concentrations early after kidney transplantation using theory-based pharmacokinetic modelling. Br J Clin Pharmacol 2014; 78: 509–523.
47. Gervasini G, Garcia M, Macias RM, Cubero JJ, Caravaca F, Benitez J. Impact of genetic polymorphisms on tacrolimus pharmacokinetics and the clinical outcome of renal transplantation. Transpl Int 2012; 25: 471–480.
48. Kuehl P, Zhang J, Lin Y, Lamba J, Assem M. Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. Nat Genet 2001; 27: 383–391.
49. Hustert E, Haberl M, Burk O, et al. The genetic determinants of the CYP3A5 polymorphism. Pharmacogenetics 2001; 11: 773–779.
50. Sy SKB, Heuberger J, Shilbayeh S, Conrado DJ, Derendorf H. A Markov chain model to evaluate the effect of CYP3A5 and ABCB1 polymorphisms on adverse events associated with tacrolimus in pediatric renal transplantation. AAPS J 2013; 15: 1189–1199.
51. Moller A, Iwasaki K, Kawamura A, Teramura Y. The disposition of 14C-labeled tacrolimus after intravenous and oral administration in healthy human subjects. Drug Metab Dispos 1999; 27: 633–636.
52. Shekar K, Roberts JA, Welch S, et al. ASAP ECMO: Antibiotic, sedative and analgesic pharmacokinetics during extracorporeal membrane oxygenation: A multi-centre study to optimise drug therapy during ECMO. BMC Anesthesiol 2012; 12: 29.
53. Van Saet A, de Wildt SN, Knibbe CAJ, Bogers ADJJC, Stolker RJ, Tibboel D. The effect of adult and pediatric cardiopulmonary bypass on pharmacokinetic and pharmacodynamic parameters. Curr Clin Pharmacol 2013; 8: 297–318.
54. Pea F, Pavan F, Furlanut M. Clinical relevance of pharmacokinetics and pharmacodynamics in cardiac critical care patients. Clin Pharmacokinet 2008; 47: 449–462.
55. Textor SC, Wiesner R, Wilson DJ, et al. Systemic and renal hemodynamic differences between FK506 and cyclosporine in liver transplant recipients. Transplantation 1993; 55: 1332–1339.
56. De Lima JJ, Xue H, Coburn L, et al. Effects of FK506 in rat and human resistance arteries. Kidney International. Nature Publishing Group 1999; 55: 1518–1527.
57. Bloom RD, Reese PP. Chronic kidney disease after nonrenal solid-organ transplantation. J Am Soc Nephrol 2007; 18: 3031–3041.
58. Bloom RD, Doyle AM. Kidney disease after heart and lung transplantation. Am J Transplant 2006; 6: 671–679.
59. Ishani A, Erturk S, Hertz MI, Matas AJ, Savik K, Rosenberg ME. Predictors of renal function following lung or heart-lung transplantation. Kidney Int 2002; 61: 2228–2234.
60. Stehlik J, Edwards LB, Kucheryavaya AY, et al. The registry of the international society for heart and lung transplantation: 29th official adult heart transplant report—2012. J Heart Lung Transplant 2012; 31: 1052–1064.
61. Lefaucheur C, Nochy D, Amrein C, et al. Renal histopathological lesions after lung transplantation in patients with cystic fibrosis. Am J Transplant 2008; 8: 1901–1910.
62. Omae T, Goto M, Shimomura M, et al. Transient up-regulation of P-glycoprotein reduces tacrolimus absorption after ischemia-reperfusion injury in rat ileum. Biochem Pharmacol 2005; 69: 561–568.
63. Lemahieu W, Maes B, Verbeke K, Rutgeerts P, Geboes K, Vanrenterghem Y. Cytochrome P450 3A4 and P-glycoprotein activity and assimilation of tacrolimus in transplant patients with persistent diarrhea. Am J Transplant 2005; 5: 1383–1391.
64. Kuypers DR. Influence of interactions between immunosuppressive drugs on therapeutic drug monitoring. Ann Transplant 2008; 13: 11–18.
65. Reams BD, Palmer SM. Sublingual tacrolimus for immunosuppresion in lung transplantation. Am J Respir Med 2002; 1: 91–98.
66. Knoop C, Thiry P, Saint-Marcoux F, Rousseau A, Marquet P, Estenne M. Tacrolimus pharmacokinetics and dose monitoring after lung transplantation for cystic fibrosis and other conditions. Am J Transplant 2005; 5: 1477–1482.
67. Jiang T, Acosta D. An in vitro model of cyclosporine-induced nephrotoxicity. Fundam Appl Toxicol 1993; 20: 486–495.
68. Sharina H, Kek TL, Kwong SJS, et al. Pharmacogenotyping of CYP3A5 in predicting dose-adjusted trough levels of tacrolimus among Malaysian kidney-transplant patients. Br J Clin Pharmacol 2003; 57: 298–309.
69. Otagiri M. A molecular functional study on the interactions of drugs with plasma. Drug Metab Pharmacokinite 2005; 20: 309–323.
70. Lüthold S, Berneis K, Bady P, Müller B. Effects of infectious disease on plasma lipids. Eur J Clin Invest 2007; 37: 573–579.
71. Van Leeuwen HJ, Heezius ECJM, Dallinga GM, van Strijp JAG, Verhoef J, van Kessel KPM. Lipoprotein metabolism in patients with severe sepsis. Crit Care Med 2003; 31: 1359–1366.
72. Piekoszewski W, Jusko WJ. Plasma protein binding of tacrolimus in humans. J Pharm Sci 1993; 82: 340–341.
73. Zsila F. Overlapping ligand specificity of P-glycoprotein and serum 1-Acid glycoprotein: Evidences and potential implications. Curr Drug Metab 2007; 8: 563–593.
74. Zahir H, McCaughan G, Gleeson M, Nand RA, McLachlan AJ. Factors affecting variability in distribution of tacrolimus in liver transplant recipients. Br J Clin Pharmacol 2004; 57: 298–309.
75. Gonschior A-K, Christians U, Winkler M, Linck A, Baumann J, Sewing K-F. Tacrolimus (FK506) metabolite patterns in blood from liver and kidney transplant patients. Clin Chem 1996; 42: 1426–1432.
76. Capone D, Gentile A, Imperatore P, Palmiero G, Basile V. Effects of itraconazole on tacrolimus blood concentrations in a renal transplant recipient. Ann .Pharmacother 1999; 33: 1124–1125.
77. Zahir H, McLachlan AJ, Nelson A, McCaughan G, Gleeson M, Akhlagi F. Population pharmacokinetic estimation of tacrolimus apparent clearance in adult liver transplant recipients. Ther Drug Monit 2005; 27: 422–430.

78. Staatz C. Population pharmacokinetics of tacrolimus in adult kidney transplant recipients. Clin Pharmacol 2002; 72: 660–669.
79. Rey E, Tréluyer JM, Pons G. Drug disposition in cystic fibrosis. Clin Pharmacokinet 1998; 35: 314–329.
80. Rifai N, Chao F-F, Pham Q, Thiessen J, S, oldin SJ. The role of lipoproproteins in the transport and uptake of cyclosporine and dihydro-tacrolimus into HepG2 and JURKAT cell lines. Clin Biochem 2013; 29: 1–7.

Supporting Information

Additional Supporting Information may be found in the online version of this article.

Supplementary References