Possible interaction between mycophenolate mofetil and tacrolimus in kidney transplant patients

Jan Strojil[1], Jiří Orság[2], Tomáš Fürst[3], Karel Urbánek[1], Pavel Anzenbacher[1], Karel Krejčí[2]
[1]Department of Pharmacology, Faculty of Medicine and Dentistry, Palacký University Olomouc, Czech Republic
[2]Department of Internal Medicine III – Nephrology, Rheumatology and Endocrinology, Faculty Hospital Olomouc, Czech Republic
[3]Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacký University Olomouc, Czech Republic

Aims: Tacrolimus is the mainstay of transplant immunosuppression in kidney graft recipients. It is most commonly used in combination with mycophenolate mofetil. Literature data on the existence and significance of drug-drug interaction of these two drugs is contradictory and inconclusive for kidney transplant patients. The aim of the study was to confirm and quantify the interaction in kidney transplant patients.
Methods: A total of 4,220 tacrolimus level measurements spanning 5 years in 181 renal graft recipients in a single transplant center were analyzed. Change in dose needed to achieve a unit concentration was used as a surrogate for drug clearance variability. A regression multivariate model was constructed to identify significant predictors of tacrolimus dose required to reach a unit concentration.
Results: The model identified significant predictors of tacrolimus dose, including hematocrit, liver function, body weight, prednisone dose, and age. The coefficient for mycophenolate mofetil dose was -8.76e-04 (standard error 1.35e-04, $p < 0.001$), i.e. each 1000 mg increase of mycophenolate dose lead on average to a 15.1 % reduction in the dose of tacrolimus required to reach the same concentration.
Conclusions: Based on our analysis, the interaction between mycophenolate mofetil and tacrolimus reported previously in liver transplant patients is present in kidney transplant patients as well. After prospective validation, a pharmacokinetic model could be used to predict tacrolimus level changes following adjustment of mycophenolate mofetil doses.

Key words: mycophenolate mofetil, tacrolimus, interaction, transplant, therapeutic drug monitoring.

Interakce mezi mykofenolát mofetilem a takrolimem u pacientů po transplantaci ledviny

Cíle: Takrolimus je základem imunosuprese u příjemců transplantované ledviny. Nejčastěji je užíván v kombinaci s mykofenolát mofetilem. Údaje o existenci a významu interakce těchto dvou léků u pacientů po transplantaci ledvin jsou protichůdné a nejednoznačné. Cílem této studie bylo potvrdit a kvantifikovat tuto interakci u pacientů po transplantaci ledvin.
Metody: Bylo analyzováno celkem 4 220 měření hladin takrolimu v období 5 let u 181 pacientů s renálním štěpem v jednom transplantačním centru. Změna dávky potřebné k dosažení jednotkové koncentrace byla použita jako náhradní parametr pro popis variability clearance léku. Regresní multivariační model byl sestaven tak, aby identifikoval významné prediktory dávky takrolimu potřebné k dosažení jednotkové koncentrace.
Výsledky: Model identifikoval významné prediktory dávky takrolimu jako hematokrit, jaterní funkce, tělesnou hmotnost, věk pacienta a jeho dávku prednisonu. Koeficient dávky mykofenolátmofetilu byl -8,76e-04 (standardní chyba 1,35e-04, $p < 0,001$). Každé zvýšení dávky mykofenolátu o 1 000 mg tedy vedlo v průměru k 15,1% snížení dávky takrolimu potřebné k dosažení stejné koncentrace.
Závěr: Na základě naší analýzy je interakce mezi mykofenolát mofetilem a takrolimem, identifikovaná již dříve u pacientů po transplantaci jater, přítomna také u pacientů po transplantaci ledviny. Po prospektivní validaci by pro stanovení změn hladiny takrolimu po úpravě dávky mykofenolát mofetilu mohl být použit farmakokinetický model.

Klíčová slova: mykofenolát mofetil, takrolimus, interakce, transplantace, terapeutické monitorování léků.

KORESPONDENČNÍ ADRESA AUTORA: Jan Strojil, MD, Jan.Strojil@upol.cz
Department of Pharmacology, Faculty of Medicine and Dentistry, Palacký University
Hněvotínská 3, 775 15 Olomouc

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Introduction

Tacrolimus is currently the mainstay of transplant immunosuppression in kidney graft recipients (1, 2). It is most commonly used in combination with mycophenolate mofetil. Literature data on the existence and significance of drug-drug interaction of these two drugs is contradictory (3–5).

Tacrolimus has a narrow therapeutic index, variable absorption and interaction-prone metabolism and therefore requires routine therapeutic drug monitoring with frequent dose adjustments. It is a substrate for CYP3A4 (and 3A5, 3A7 and 3A43) and is almost completely metabolized with only less than half a percent of the dose appearing in urine and stool as unchanged compound (6). Unlike with its predecessor ciclosporin, serum concentrations of tacrolimus seem to be more affected by genetic polymorphism (7). Consequently, the systemic clearance (CL) and the oral bioavailability (F) vary widely and are susceptible to drug-drug and drug-food interactions that lead to large variability in oral clearance and in $T_{1/2}$ (8 h to over 100 h) (8).

For therapeutic drug monitoring (TDM) of tacrolimus, trough levels (C_0) seem to be a better predictor of total drug exposure (9, 10) and are traditionally used for routine TDM of tacrolimus. This is however still being challenged and consensus has not been reached yet on the optimal strategy for tacrolimus TDM (11).

Drug-drug interactions resulting in drug levels outside of the respective therapeutic ranges can lead to increased risk of graft rejection and/or toxicity (12, 13).

The drug label for mycophenolate mofetil lists interaction with tacrolimus as a recognized interaction that was observed in liver transplant patients while kidney transplant patients seemed to be unaffected (14).

The aim of this study was to confirm and try to quantify the interaction between tacrolimus and mycophenolate mofetil in kidney transplant recipients in the setting of routine clinical practice.

Methods

Blood levels collected as part of routine therapeutic drug monitoring of tacrolimus and mycophenolate mofetil at a single site transplant centre (University Hospital Olomouc, Czech Republic) between June 2006 and July 2012 were analyzed retrospectively. All transplanted patients who had at least two measurements or tacrolimus and mycophenolate levels during the study period were considered for the analysis. Due to high variability in the early post-transplant period (15) and limited availability of exact dosing information, we disregarded levels measured during the first 30 days following transplantation or until discharge from the initial hospitalization, whichever occurred later.

Tab. 1. *Target therapeutic ranges of tacrolimus*

Serum concentration (µg/L)		Time from transplantation
FK C_0	10–20	Days 1–14
	10–15	Days 15–30
	5–10	> 30 days

Abbreviations: FK C_0 – trough level of tacrolimus

Of a total of 185 transplanted patients considered for the study, 181 were included in the analysis, 4 were excluded because they did not meet the inclusion criteria (insufficient follow-up).

Drug levels were obtained from the hospital information system. All levels were measured using immunochemical methods used for routine clinical practice in the accredited hospital laboratory. Therapeutic ranges applicable for patients included in the study are listed in Table 1. Information on drug prescription was retrieved from drug prescription database managed by the Department of Pharmacology which includes all prescriptions filed in the hospital (16). All discharge reports and outpatient visit reports in the studied period were retrieved and information on dose adjustments and changes in prescribing that was not captured in the prescription database was recorded, i.e. temporary dose adjustments, pauses in medication and instructions given to the patient. All patients signed informed consent agreeing to data collection and analysis.

Data scrubbing

The primary dataset included 4,912 tacrolimus levels and 1,350 mycophenolate levels, from which levels measured in the early post-transplant period were excluded. Information from medical records was used to exclude measurements that were considered invalid by the nephrologist or the laboratory. The reasons for exclusion included – non C_0 levels in patients who took the drug before coming for the blood draw, laboratory errors and identified non-adherence. After exclusion of these measurements, 3,318 tacrolimus and 1,112 mycophenolate levels coming from 181 patients were for the final analysis.

Quantitative effect of drug interaction

For each data point, a dose per kilogram of body weight needed to achieve a unit concentration was calculated. This parameter was used as a surrogate for metabolic clearance of the drug, in a manner similar to the method used by Oteo et al (15):

$$\text{dose to reach unit concentration} = \frac{\text{dose [mg]}}{\text{body weight [kg]}} \div \text{concentration} \left[\frac{\mu g}{l}\right]$$

A multivariate linear regression model of this normalized dose of tacrolimus was then fitted to assess the variability of this normalized dose. The model included as predictors the dose of mycophenolate mofetil, the dose of prednisone, age, weight, hematocrit, AST, ALT, time from transplantation, patient sex, dose of prednisone, creatinine level, glomerular clearance, and body height. By iterative process the model eliminated non-significant predictors until only those significant remained.

Statistical methods

All statistical analyses were performed in the R software (R Foundation for Statistical Computing, Vienna, Austria) and MatLab (The MathWorks Inc., Natick, Massachusetts). Significance level was set to 5 %.

Results

The analysis included 111 male and 70 female kidney transplant recipients, two of which were recipients of live-donor grafts.

Average age of the population was 45.5 years at the time of transplantation (46.6 for men; 43.9 for women; $p > 0$); the youngest patient was 13.5 years old and the oldest was 72.8.

Tab. 2. *Demographic parametrs of the patient population*

Parameter	N (%)	Min	Max	Median
Patient age [years]	181 (100.0)	13.5	72.8	52.2
Men	111 (61.3)	16.9	68.5	47.9
Women	70 (38.7)	13.5	72.8	45.3
Time from Tx [years]		0.1	20.7	3.8
Body weight [kg]		37	126	75
Tacrolimus level [µg/L]		0.1	32.8	6.4
Daily tacrolimus dose/b.w. [mg/kg]		0.001	0.18	0.04
Prednisone dose [mg]		0.0	30	6,25
Mycophenolate dose [g]		0.0	2.0	1.0
Mycophenolate level [mg/L]		0.2	12.4	2.2
ALT [µkat/L]		0.07	5.59	0.35
AST [µkat/L]		0.08	5.85	0.38
Hematocrit		0.19	0.54	0.38
Creatinine [µmol/L]		52	879	149
GFR (MDRD) [mL/sec]		0.08	1.99	0.58

Tx – transplantation; ALT – Alanine aminotransferase; AST – Aspartate transaminase; GFR – glomerular filtration rate; MDRD – Modification of Diet in Renal Disease

Tab. 3. *Coefficients of the model estimating the effect of significant predictors*

	Baseline	Estimate	Standard Error	Significance
Intercept		5.80e–03	3.31e–04	< 0.001
Prednisone dose [mg]	0	-4.93e–05	2.15e–05	0.02
Mycophenolate dose [g]	0	-8.76e–04	1.35e–04	< 0.001
Time from Tx [years]	0	1.59e–04	1.99e–05	< 0.001
Body weight [kg]	75	-1.33e–05	6.45e–06	0.03
Anti-infective treatment	0	-7.24e–04	2.63e–04	0.005
Presence of a metabolic inhibitor	0	-3.01e–03	5.14e–04	< 0.001
Tacrolimus dose/b.w. [mg/kg]	40	1.48e–04	3.26e–06	< 0.001
Age [years]	50	-2.26e–05	7.08e–06	0.001
Sex	0	5.89e–04	1.99e–04	0.003
Dosing interval (12 or 24 hr)	12	1.15e–03	2.07e–04	< 0.001
ALT [µkat/L]	0.35	-1.47e–03	4.38e–04	< 0.001
AST[µkat/L]	0.38	2.83e–03	6.82e–04	< 0.001
Hematocrit	0.38	-1.15e–02	1.61e–03	< 0.001

Tx – transplantation; ALT – Alanine aminotransferase; AST – Aspartate transaminase; b.w. – body weight; presence of anti-infective treatment and presence of metabolic interaction take values of 0 or 1 (absent or present); sex takes values 0 or 1 (male or female); dosing interval takes values 1 or 2 (once or twice daily); the intercept then refers to dose required to reach a unit concentration in a patient with baseline characteristics

A total of 3,318 measurements of trough concentrations (C_0) were included in the analysis. The average period covered by data 3.1 years, on average each patient had 19 data points with drug levels (4–60).

The average dose to achieve a unit concentration of tacrolimus group was 8.3 l/kg (± 6.6), this value was not significantly affected by concomitant prescription of a non-interacting anti-infective (8.37 ± 5.90, p = 0.63).

Table 2 summarizes the parameters describing the variation of normalized dose of tacrolimus, their standard errors and statistical significance.

The effect of mycophenolate mofetil dose was statistically significant (p < 0.001); every 1000 mg of dose increase resulted in a reduction of the dose of tacrolimus required to reach the same concentration by 0.88 l/kg (15.1 % of the baseline dose, p < 0.001).

The other significant predictors (full list and values in Table 3) were included in the model to separate the effect of mycophenolate mofetil from the other expected predictors of tacrolimus dose required to reach concentration.

The baseline patient to whom the predictors are related is described in Table 2. As expected the effect of concurrent prescription of an interacting CYP inhibitors was largest in magnitude; reduction of dose required by up 50 %. The estimate for effect of hematocrit was the largest (-1.15e-02) but since the range of hematocrit is limited to a narrow range of values with small absolute difference, the absolute effect on the dose was relatively small.

The dose to reach a unit concentration also increased with treatment duration, each year from the time of transplantation increased the required dose from baseline dose by 2.8 %.

Discussion

The reported interaction between prednisone and tacrolimus was found in our population (4), but the effect was small and significance was not as high as with the other predictors. This could be partially explained by the fact that most patients were treated by the same dose of prednisone throughout the studied period there was therefore little data that could support the effect.

Interacting medication (esp. at the level of hepatic metabolism) is an expected powerful predictor of tacrolimus levels. A much smaller effect was observed in the presence of systemic anti-infective treatment without a described drug-drug interaction, possibly due to changes in pharmacokinetic parameters during acute infection.

Most of the published literature concerning tacrolimus and mycophenolate interaction deals with effects of tacrolimus on mycophenolate levels (17–19) where an increase in exposure to mycophenolic acid (MPA) is observed. The suggested mechanism is a possible effect on enterohepatic cycling of MMF with possible renal impairment resulting from increased levels. The literature data is scarcer on the presence of aninteraction in the opposite direction.

The drug label of mycophenolate mofetil lists interaction with tacrolimus as a recognized interaction that was observed in liver transplant patients while kidney transplant patients seemed to be unaffected (14). In liver transplant recipients, twice daily dosing of 1.5 g of mycophenolate mofetil led to an approx. 20 % increase in tacrolimus AUC. The effect we observed in our population of kidney transplant recipients is in the same direction and of similar magnitude as the one reported for liver transplant patients.

A study by Kagaya et al. investigated drug interaction between MPA and tacrolimus in 71 Japanese kidney transplant recipients and found no significant effect of MPA on tacrolimus levels, but failed to confirm the effect of tacrolimus on MPA as well (3). The same study also found no

effect of UGT2B7 genotype and CYP3A5 genotype on the kinetics of MPA.

Pirsch et al. reported a non-significant increase in tacrolimus AUC_{0-12} following introduction of 1, 1.5, or 2 g/day of MMF to a tacrolimus based immunosuppression in stable kidney transplant recipients (5).

Drawbacks of the study include its non-intervention retrospective design which on the other hand allowed us to include a larger population with longer follow-up then would be feasible for a prospective study. However, the data from the prescription database was meticulously hand-checked for validity against patient's clinical files, noting of any temporary dose adjustments, patient instructions, mentions of reported non-compliance or non C_0 level measurements that were excluded from the final analysis. This time-consuming process ensured that the analysed dataset was of higher quality than simply combining laboratory and prescription database without validation of the data.

The data points are most likely not fully independent and patients with longer follow-up and more data points will have higher weight in the model. This drawback was accepted to keep the model simple and avoid introducing further bias by manual selection of "interesting" data points.

Due to the effect of healthy survivors we would expect patients with the longest follow-up to be those with stable levels and low incidence of toxicity/rejection, therefore skewing the data away from large effects.

In this case, a retrospective analysis can never fully distinguish between cause and effect, but the change in dose/level ratio observed for tacrolimus suggests that tacrolimus is indeed the victim drug.

Possible mechanisms of this interaction include an effect on absorption of tacrolimus or possibly interaction at the level of CYP3A4 and CYP3A5 which are involved in the metabolism of both tacrolimus and mycophenolic acid (MPA); converting MPA to 6-O-desmethyl-MPA (CYP2C8 is also involved in this transformation) (20).

Strengths of this study include a reasonably large population (over 180 transplanted patients) and validated prescription and laboratory data checked against clinical documentation. Because pharmacokinetics can change in the presence of disease and complex medication as seen in transplanted patients, having a real-life patient population can be more informative for clinical practice than small studies done on healthy volunteers. A more thorough examination of the dataset using a population PK model developed by Åsberg et al (21) is being prepared for publication.

Conclusion

A possible drug-drug interaction between mycophenolate mofetil and tacrolimus leading to higher levels of tacrolimus had been previously reported in liver-transplant patients but not in kidney graft recipients. Based on our analysis, the interaction of similar magnitude and the same direction seems to be present in kidney transplant population. Routine therapeutic drug monitoring of both drugs can mitigate the significance of this interaction. The presence of the interaction needs to be confirmed using a validated PK model.

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