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Total plasma protein effect on tacrolimus elimination in kidney transplant patients – Population pharmacokinetic approach

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ABSTRACT

Data from routine therapeutic drug monitoring of 105 adult kidney transplant recipients were used for population pharmacokinetic analysis which was performed using a non-linear mixed-effects modeling. The effect of demographic and clinical factors on tacrolimus clearance was evaluated.

Following the initiation of treatment with tacrolimus, the results of our study indicate a decrease of the drug clearance on day 15, 1 and 6 months after transplantation for 4.4%, 6.3% and 10.92%, respectively. Our model suggests a negative correlation between tacrolimus clearance and haematocrit. According to final model, clearance decreases with increasing of aspartate aminotransferase. Our results demonstrated that CL/F increases with patients' weight. This study reveals incensement for 10.4% in tacrolimus clearance with alteration of patients' minimal measured total protein levels to upper normal range.

The findings of this study explore various factors of tacrolimus pharmacokinetic variability and point out a relationship between tacrolimus clearance and total plasma protein. Developed model demonstrates the feasibility of estimation of individual tacrolimus clearance and may allow rational individualization of tacrolimus dosing in kidney transplant patients.

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1. Introduction

Tacrolimus is a potent, calcineurin inhibitor widely used for the prevention of acute and chronic allograft rejections in kidney transplant recipients (Bowman and Brennan, 2008). It has a narrow therapeutic window with wide inter-individual variability in clearance and other pharmacokinetic parameters (Staatz and Tett, 2004). In blood, it is extensively bound to erythrocytes with a mean blood to plasma ratio of about 15, while in plasma, tacrolimus is associated principally with α1-acid glycoprotein (AAG), lipoproteins, globulins and albumin (Staatz and Tett, 2004; Venkataramanan et al., 1995; Warty et al., 1991). Haematocrit is one of the factors that influence tacrolimus blood to plasma ratio (Staatz and Tett, 2004).Tacrolimus is a highly metabolised drug, with only about 0.5% unchanged parent drug appearing in urine or feces (Staatz and Tett, 2004; Venkataramanan et al., 1995). The drug is metabolized mainly by P450 3A isoenzymes (CYP3A) which expression varies widely (Koch et al., 2002; Staatz and Tett, 2004). Additionally, tacrolimus is a substrate of P-glycoprotein (Jeong and Chiou, 2006). The significant relation between the high within-patient variability in the clearance of tacrolimus and long-term graft failure was shown (Borra et al., 2010). There is evidence that low trough blood tacrolimus concentrations correlate with increased risk of rejection, whereas higher trough levels are associated with increased risk of toxicity (Borobia et al., 2009; Kershner and Fitzsimmons, 1996; Staatz et al., 2001; Venkataramanan et al., 2001). Nevertheless, some studies failed to establish a relation between tacrolimus trough concentration and graft rejection (Gaber et al., 1997; Jain et al., 1991). In addition, the correlation between tacrolimus dose and concentration is poor (Venkataramanan et al., 2001). These findings limit optimal titrations of the dosage regimen, and require additional information on the factors that affect the pharmacokinetic characteristics of the drug. The influence of some factors such as time after transplantation, haematocrit, albumin, corticosteroid therapy, liver function, diurnal variation, race and genetic polymorphism were acknowledged (Antignac et al., 2007; Han et al., 2013; Hesselink et al., 2003; Li et al., 2007; Macphee et al., 2002; Staatz and Tett, 2004; Staatz et al., 2002; Undre and Schafer, 1998). However, the results are often contradictory. Some studies correlated increase of clearance with post transplant day, whereas other had opposite results (Antignac et al., 2007, 2005; Han et al., 2013; Passey et al., 2011; Staatz et al., 2002). Furthermore, the effects of a variety of factors on tacrolimus elimination remain inconclusive. Therefore, we studied the effect of demographic and clinical factors such as

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graft origin, dialysis before transplantation, period after transplantation, serum creatinine, haematocrit, total proteins and hepatic enzymes, using data from routine therapeutic drug monitoring (TDM). Our objective was to define the significant factors of tacrolimus pharmacokinetic variability and develop a model for estimation of clearance to be used in transplant patient care.

2. Methods

2.1. Patients and data collection

A retrospective analysis of data from 105 adult kidney transplant recipients from the Nephrology Clinic, Clinical Center of Serbia, University of Belgrade, was performed. Patients' data during TDM were retrospectively collected. Approval for the study was obtained from the Ethics Committee of Clinical Center of Serbia. All data were collected from the patients' charts, and they included following covariates: gender (GEND), age, body weight (WT), day after transplantation (PDAY), graft origin (GRFT), dialysis before transplantation (DIAL), serum creatinine (SECR), haematocrit (HCT), hemoglobin (HGB), total protein (TP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and concomitant immunosuppressive drug doses.

2.2. Drug administration

Patients were on triple immunosuppressive therapy which included tacrolimus (Prograf®, Astellas Ireland CO. Ltd.), mycophenolate mofetil (MMF) and corticosteroids (CORT). The recommended initial dose of tacrolimus was 0.3 mg/kg per day. Subsequent doses were adjusted on the basis of achieving tacrolimus trough blood concentrations within target ranges and clinical evidence of efficacy and toxicity. Desired ranges of tacrolimus trough blood concentrations were between 15 and 20 ng/ml in the first two weeks following transplantation, 10–15 ng/ml till the end of the first month, 7–10 ng/ml in the period from the end of the first month to the end of the sixth month after transplantation.

2.3. Blood sampling and bioanalytical assay

All collected blood samples were pre-dose and were analyzed in the same laboratory. In the immediate post transplantation period, blood samples were collected two or three times per week until concentrations were stabilized. Thereafter, samples were collected once weekly in the first month after transplantation, and once monthly afterward. If physician suspected the rejection of graft or adverse reactions, drug monitoring was performed more frequently.

Concentrations of tacrolimus in whole blood were assessed using Architect system® (Abbott Laboratories), a chemiluminescent microparticle immunoassay (CMIA) (ARCHITECT System, 2009). According to the manufacturer's information the measurement range for assay is 2–30 ng/ml. Blood samples exceeding this range were diluted according to manufacturer's protocol.

2.4. Population pharmacokinetic analysis

Population pharmacokinetic analysis was performed using a non-linear mixed-effects modeling program NONMEM® (version 7 level 2, GloboMax LLC, Ellicott City, MD, USA) and Perl speaks NONMEM (version 3.5.3, http://psn.sourceforge.net), Xpose® (version 4, http://xpose.sourceforge.net/) and R® (version 2.15.0, http://r-project.org) were used for graphical presentations. Additionally, Pirana® (version 2.5.0, http://www.pirana-software.com/) was used for model evaluation and graphical presentation as well.

Population pharmacokinetic analyses were performed using the first order conditional estimation with interaction (FOCEI) method to improve the estimation of pharmacokinetic parameters and their variability. A one-compartment pharmacokinetic model with first-order absorption and elimination as implemented in NONMEM subroutine ADVAN2 and TRANS2 was used to describe the concentration–time data. Since all data were trough concentrations, estimation of the volume of distribution (V/F) and rate constant of absorption (k_a) was not possible and therefore they were fixed at 0.68 l/kg and 1.3 h^{-1} (Summary of Product Characteristics, 2012). Based on the literature value of tacrolimus $t_{1/2}$ of 15.6 h, and tmax of 2.5 h, k_a was estimated using the following equation: $\text{tmax} = \ln(k_a/k_{el})/(k_a - k_{el})$(Booth and Gobburu, 2003; Vucicevic et al., 2009).

In the first step, the base model was derived. The interindividual variability of tacrolimus CL/F (ϖ^2) was described by exponential model:

$$CL/F_j = TVCL \cdot \exp(\eta_{jCL})$$

where CL/F_j is total body clearance for the jth individual, TVCL is typical population value of CL/F and η_j is random variable for the jth individual distributed with zero means and respective variances of ϖ^2_{CL}. Residual variability of tacrolimus concentration (σ^2), the additive, the proportional, and the slope-intercept error models were tested as follows:

$$C_{ij} = C_{predij} + \varepsilon_{ij}$$
$$C_{ij} = C_{predij} + C_{predij} \cdot \varepsilon_{ij}$$
$$C_{ij} = C_{predij} + C_{predij} \cdot \varepsilon_{1ij} + \varepsilon_{2ij}$$

where C_{ij} is the ith observed concentration for the jth individual, C_{predij} is predicted concentration for the jth individual and ε_{ij} is a randomly distributed variable with zero mean and variance σ^2. Once the base model was established, the effects of covariates on relevant pharmacokinetic parameter variability were explored. Tested covariates were: PDAY, WT, AGE, GRFT, GEND, DIAL, SECR, HCT, UP, ALP, AST, MMF and CORT. Missing covariate data for SECR (0.3%), HGB (1.55%), HCT (2.1%) and TP (6.8%) were treated with multiple imputation of median per day. An imputation method for missing data for ALP (29.46%), AST (28.26%) and ALT (28.51%) was last-observation carried forward (LOCF) (Bonate, 2006; Harrel, 2001).

Statistical significance of the covariates was evaluated based on the objective function value (OFV), which is equal to minus twice the log likelihood. Covariates were introduced sequentially into the population models to develop a full model. In each step of the covariate model building the covariate with the highest drop in objective function value (ΔOFV), at least 3.84 ($p < 0.05$), was included in the model. The full model was obtained when the effects of all the remaining covariates were insignificant (ΔOFV < 3.84). The final model was determined by backward elimination of covariates in a stepwise manner. Covariates were kept in the final population pharmacokinetic model when the removal of the covariate resulted in an OFV increase of at least 6.63 ($p < 0.01$). An additional criterion for the retention of a covariate in the model was reduction in unexplained interindividual variability. The model appropriateness was evaluated by standard diagnostic plots (Karlsson and Savic, 2007), convergence of minimization, number of significant digits more than 3, successful covariance step, gradients in the final iteration being in the range 10^{-3} to 10^2 and absence of substantial η- and ε-shrinkage (Savic and Karlsson, 2009). Conditional weighted residuals (CWRES) were calculated for standard diagnostic plots (Hooker et al., 2007).

A nonparametric bootstrap of 1000 samples was used for assessing the accuracy and robustness of the final population model (Parke et al., 1999). Additionally, performance of final model was

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