MATHEMATICAL MODELS IN TREATMENT OF PATIENTS WITH KIDNEY TRANSPLANT

Abduarahman Essadeg*, Abduarahman Amer and Prof. Dr Jovan Popović

Faculty of Medicine - University of Novi Sad – Serbia.

*Corresponding Author: Dr. Abduarahman Essadeg
Faculty of Medicine - University of Novi Sad – Serbia.

ABSTRACT
Kidney transplantation represents the best method of treatment of end stage renal failure. One of the preconditions for successful renal transplantation is the optimal immunosuppressive therapy. The therapeutic goal of immunosuppression is achieving immune tolerance of the recipients while minimizing unwanted and toxic effects. The combination of immunosuppressive drugs with different mechanisms of action to reduce individual doses of drugs and minimize their side effects, which has great importance for the quality and extension of life of patients with kidney transplants. Optimal selection of immunosuppressive protocol should be harmonized with the individual characteristics of the patient, his primary renal disease, co-morbidities and drug therapy, degree of matching donors and recipients of organs.

KEYWORDS: Treatment, Kidney transplantation, Mathematical model.

INTRODUCTION
Pharmacokinetic analysis provides a mathematical model of the process of absorption, distribution, metabolism and excretion, monitoring the concentration of the drug and its metabolites in body fluids, especially blood plasma. The basic approach pharmacokinetic analysis presents is spacious compartmental model-dependent FK analysis. Lately, other approaches are gaining more and more significance, such as the FK model independent analysis, pharmacokinetic-pharmacodynamics (PK / PD) modeling, access time constants, especially the population pharmacokinetic analysis. Pharmacokinetic tests are conducted in order to determine FK parameters: drug clearance (Cl), volume of distribution (Vd), elimination half-life (t1 / 2), the area under the curve (AUC, AUC), rate constants of absorption and elimination (α, β) and other. Knowing FK parameters to determine the concentration of drug at the desired time (Cpt) and a better understanding of pharmacodynamics (FD) of the drug.

Pharmacokinetic studies are the basis for.
- calculating and modifying the dosage regimen of drugs
- Bio-availability of the drug
- Determination of pharmacokinetic-pharmacodynamics (PK / PD) correlations.

Types of pharmacokinetic analysis
Model - dependent (spatial) pharmacokinetic analysis
The basic type of test that is using in the pharmacokinetics of the model-dependent (spatial) FK analysis that quantitatively defines the processes through which the drug passes into the body. Spatial models are classified according to the number of spaces needed to describe the behavior of the drug in the body. The room or compartment is part of the body (sometimes it can be a whole organism) that the kinetic sense represents a unique and homogenous whole, while in essence hypothetical structure. The space is defined by the volume and concentration of the drug in it.

\[
\text{Drug concentration} = \frac{\text{Drug amount}}{\text{Volume in which the drug}}
\]

Figure 1.1. Schematic illustration of the relationship pharmacokinetics and pharmacodynamics of the drug.
Non-spatial pharmacokinetic analysis

The mathematical model obtained FK spatial analysis is too complicated when drug distribution takes place in a number of spaces, especially in the case of non-linear pharmacokinetic processes. Model-independent, non-spatial analysis FK itself as an approach that significantly more suited to clinical practice, and is often an integral part of the implementation of rational pharmacotherapy. This type of analysis is based on determining the concentration of the drug in the biological material and the calculation of pharmacokinetic parameters. Of the measurements, allow calculation of drug elimination rate constant (β) and time elimination half-life of the drug. For the same data, the method of trapezoidal cross section is obtained by the area under the curve (AUC), a measure of the amount of drug in the body. Mathematical calculations obtained a complete insight into the kinetics of the drug, where are avoided stringent test conditions that characterize spatial analysis.

If blood / blood plasma concentration are used as biological material, measured concentration of the drug allow mathematical obtaining of the drug elimination rate constant according to the following formula.

\[
\beta = \frac{\ln C_1 - \ln C_2}{t_2 - t_1}
\]

where \(C_1\) and \(C_2\) are the measured concentrations of the drug in time \(t_1\) and \(t_2\), respectively.

The speed of elimination of the drug is determined by the time for which the drug concentration decreases to half the initial value and it represents the half-life time of the drug (half-life of the drug).

\[
t_{1/2} = \frac{0.693}{\beta}
\]

The total amount of drug in the body, and thus the exposure of the organism drug can be calculated using the method trapezoidal data on drug concentration and time measurement of concentration. In this way gets the FK parameter area under the curve - AUC (PIK), which represents the mathematical expression.

\[
AUC = \sum_{n=1}^{\infty} \frac{(C_n + 1 + C_n)}{2} (t_{n+1} - t_n)
\]

\(t_n\) - measurement time drug concentration
\(C_n\) - the concentration of drug in a given time

The clearance of the drug represents a theoretical volume of bodily fluids that are clean of drug per unit time. Knowing the volume of drug distribution and elimination half-life weather it is possible to calculate the clearance of the drug. Decreased renal function causes a change of the FK parameter; it is of particular importance for patients with kidney presaCenim for drugs that show nephrotoxicity, what tacrolimus is. The clearance of the drug presented a mathematical equation.

\(C_l = \frac{K_{el} \cdot V_d}{V_d}
\)

**Kel** - constant drug elimination

**Cl** - clearance

**Vd** - volume of distribution

The advantage of FK non-spatial analysis is not required strict requirements research as a classic, spacious FK access. Pharmacokinetic parameters obtained Nonspatial FK analysis shows continuity despite minor changes the test conditions. This Pharmacokinetic approach is suitable for the analysis of FK tacrolimus in patients with kidney presaCenim. Knowledge of the pharmacokinetic parameters of tacrolimus allows adequate transplant patients with immunosuppression minimization nephrotoxicity, and is significantly FK analysis performed after the administration of the first dose. To facilitate individualization anu dosing regimens of tacrolimus in transplant patients is essential during the analysis to establish the correlation between the concentration of TAC to give up in the blood and AUC. Defining the time in which the concentration of TAC provides the most accurate AUC would represent a total exposure indicator organism drug, which would allow the setting up of optimal dosing regimens TAC in transplant patients.

Population pharmacokinetic analysis

Population pharmacokinetic analysis (PPA) has found its place in contemporary pharmacotherapy due to finding a single model for a given population of subjects. With the development of clinical pharmacokinetics growing importance of population access to FK analysis, which is retained the classic FK access with additional defining pathophysiological, demographic, inter- and intra-individual variability of factors. By defining the mathematical model of population approach is a correlation between the so-called input and output information for a given system. The very process of modeling is a search function that best predicts the output of the estimated model parameters. When we talk about therapy tacrolimus, input may represent dosing regimen or dose while the output of information concentration TAC or a clearance in a given time. Population FK trial of tacrolimus is of importance for
clinical practice because it provides specific, population PK parameters of the tested population of transplanted patients and define the factors that may affect the value of FK parameters. Knowing the value of FK population parameters and factors defining the variability contributes to proper dosing regimens for new transplant patients.

It is characteristic for Population FK analysis is that an individual patient is the center of the test, but the weight of obtaining population profile of the drug, which is why it requires numerous and heterogeneous group of patients. Respondents among themselves differ according to gender, age, body weight, presence / absence of other diseases and the implementation of other drugs. The demographic and FK analysis Tac next sex, age and body weight, the variable representing the time period elapsed since the transplant, the daily dose of corticosteroids which is part of the immunosuppressive therapy, the relationship of liver enzymes, the presence of other drugs in therapy.

Population FK analysis is base on the knowledge of the parameters obtained by the classical spatial analysis. The main difference is in the number, terms and duration of the test. The spatial analysis of the participating small number of respondents who constitute a homogenous group and predominantly healthy volunteers, while in a population approach to testing is performed in a large, heterogeneous group of patients. Classical analysis is implementing out quickly, in a controlled environment, while population analysis uses data obtained during routine checks for a longer period. Number of data per subject, which are essential for spatial analysis, is pre-defined and still significantly higher than the number of data per patient for Population Analysis (one through six). Because of these differences, population FK analysis provides new information on medicinal products and to some clinically relevant data on the pharmacokinetics of the drug in the target population of respondents. Identification of demographic, pathophysiological mental and other factors that affect the value of FK parameters gives a more complete consideration of the possibility of a renal patient and greater security setting optimal therapeutic regimen of tacrolimus special value indicates FK population analysis that uses and pharmacodynamic (FD) par Ametra drug and PK / PD analysis and population.

Setting the basis of population model makes statistical data processing of the patient population. There are three basic statistical approaches in population analysis.
1. Access to integrated data
2. two-stage approach
3. The method combined effects

Each of these approaches is aim at obtaining value FK population parameters based on individual data, but differ in the way of obtaining these values and opportunities assessment of intraindividual and interindivial variability. In our study, we used Nonlinear Mixed Effect.

The method name is derived from the combined effects of two levels of effects that have an impact on the value of FK parameters: fixed and random. Ongoing effects have only one parameter value, and that is typical, the average value of the population, while the random effects have a range of values and a certain distribution of parameter values. If the distribution of population parameters of the model comes preset on the parameter, linear population approach, otherwise it is non-parametric and non-linear approach. Access to the combined effects of nonlinear modeling - Nonlinear Mixed Effects Modelling - (NONMEM) is now the most used and introduced in 1979 by Lewis B Sheiner and Stuart L Beal.

The big advantage of this approach is the way to collect data for analysis. The data are collect over a longer period during routine clinical control patients. Despite the complexity of the algorithms and the necessary experience in modeling, NONMEM population represents more commonplace FK access.

Benefits NONMEM analysis in patients with kidney transplant

- Data obtained at different times can be included in the database and used for analysis FK population of patients with kidney presaCenim.
- The data are representative of the population and help in setting up the dosage regimen with the de novo patients.
- allows the examination of differences in the pharmacokinetics of taking into account the age, genetics, factors outside her environment, physiological and pathophysiological factors ke.
- allows the examination of the existence and importance of the influence of other drugs necessary for the treatment of transplant patients with the determination of the minimum dose that achieves impact on the concentration of TAC.

Disadvantages NONMEM analysis in patients with kidney transplant

- Software essential for NONMEM analysis is complex and requires expertise and training.
- The reliability of the data obtained required a large number of patients (over forty, and it is considerably larger number - about 100 patients).
- Data collection process takes a long time, sometimes years.

In NONMEM, population pharmacokinetic analysis, there are three basic steps.
I step- collecting the data required for analysis in the population of transplanted patients.
II step-development model.
III step- validation of the final model.
Data collection requires persistence and thoroughness as it takes place during a routine inspection of transplanted patients. The development model is the most complex process in a population study. For Population FK Tac analysis used a respective subroutine of PREDPP (PRED Population Pharmacokinetics) software library selected based on its pharmacokinetic characteristics and mode of application. Connecting such a defined model with an executive model to some population parameter values FK TAC and definition of variables that have an impact on the pharmacokinetics of TAC in the study population. Validation provides reliability and demonstrates the correctness of the resulting model of population TAC.

NONMEM is composed of three parts: structural (describes PK parameters of the drug), covariate (describes the impact of demographic and other characteristics of the PK parameters of the drug) and statistical (described interindividual and within-person variability). The final step in PFK modeling validation using patient groups belonging to the studied population or are not involved in the process of building the model. If it proves reliable population levels PK parameters obtained in the process of model building on a new group of data can be considering to have successfully completed NONMEM modeling and factors intra- and inter-variability within populations isipitivane defined.

Physiological (perfusion) pharmacokinetic model analysis
The main feature of this approach is the integration of FK analysis of factors hemodynamics of the human body. Premises with the physiological model of determined velocity of blood flow and tissue perfusion with beating, this is the main difference compared to spatial analysis. Physiological model is suitable for analysis of FK primarily in preclinical studies of the drug to the experimental animals, as it can contribute to forecasts FK drug in humans. FK This analytical approach provides the possibility of extrapolation between different animal species and between humans and experimental animals; it is not possible for spatial modeling because of the definition of the apparent volume.

Access time constants (the time constant approach)
This approach is characteristic in that it represents a synthesis of spatial and no spatial FK analysis, including statistical processing. Access time constants e time constant defined as the time it takes to equivalent drug to move from one area to another. This is obtaining by a combination of physiological ka space and FK process that makes the uniqueness of this approach. As a result of the analysis establishes a correlation between FK descriptive parameters (maximum measured concentration of the drug, biological half-life when the weather and the apparent volume of distribution), and duration of the individual process through which still crossed release of the drug from the pharmaceutical form, absorption, drug distribution, retention in the body, duration the effect of the drug. The correlation between the pharmacokinetic variables of the process and gives the possibility of adaptation of the therapy according to the characteristics or organism (eg. if the increased resorption of the drug, it is necessary not to give a lower dose than usual to prevent side effects of therapy showed.

FK/FD Modeling
The main objective of PK / PD testing is to establish a PK / PD relationship for a given drug. Considerig how this relationship is complex, so are the mathematical models. Using PK / PD modeling is possible to identify the key characteristics of the drug that will enable quantification and prediction of the time course of the effect of the drug under physiological and pathological conditions. Pharmacokinetic / pharmacodynamic model combines the FK model that gives the relationship between dose and concentration depending on the weather and the FD model, which gives the relationship between drug concentration and effect over time. The task is to find FK analysis tool that connects these models and statistical describes them. Because of PK / PD tests will construct sigmoidal model showing the effects of drug addiction drug effect of its concentration in a selected biological fluids. PK / PD modeling is simplified when a drug is directly measurable pharmacodynamic effect. Modern FK tests put emphasis on PK / PD population analysis which gives an assessment of the impact of variables (demographic factors and pharmacotherapeutic target population) determining or verifying relationships Dose-effect of the drug in the target population and assessment adjustments dose for specific patient populations.

Therapeutic drugs monitoring (TDM)
Therapeutic monitoring of drugs constitutes a precise and pre-planned monitoring of the concentration of the drug and / or its metabolites in blood plasma or other biological fluids kim, where the measured concentration is clearly related to the effect of the drug. TDM is recommending when there is a large inter-individual variability in drug FK, it requires individualization of therapy. Monitoring is of great importance when the drug shows a small therapeutic index, saturation kinetics in patients with pathologic conditions that may affect the drug FK processes, such as the kidney transplantation.

Tacrolimus, due to the low therapeutic index, variable kinetics and high interaction potential requires regular monitoring of the concentration in the blood of patients after kidney transplantation. Therapeutic monitoring enables modification of the treatment regimen depending on individual patient characteristics. Tacrolimus shows linear kinetics within the therapeutic concentration, which enables modification of the dose based on the measured concentration of the drug in the blood in a state of equilibrium.
Figure 1.2: Schematic representation of a TDM-tacrolimus

Figure 2 schematically shows the proper TDM of tacrolimus in a few basic steps. After application of the initial dose TAC, Chechens held based on body weight of the patient, perform the clinical assessment and measurement of the concentration of drug in the blood. Pharmacokinetic analysis enables the modification of the existing dosing regimen in accordance with the individual characteristics of the patient. FK population modeling data on measured concentrations TAC during therapeutic monitoring obtained specific, population PK parameter values and determine significant variables, it is the basis for the creation of the dosage regimen in de novo transplant patients.

Immunosuppressive drugs in the treatment of patients with kidney transplant

The importance of the immunosuppressive therapy in transplantation

The aim of immunosuppressive therapy is to achieve immune tolerance in the recipient's body transplanted organ while minimizing adverse effects of selected drugs. A large number of immunosuppressive drugs can cause acute and chronic intoxication, especially nephrotoxicity, which is why they need to be rational application. The immune response organism to the transplanted kidney is achieved through three phases. These are: the induction phase, the phase maintenance and treatment of episodes of acute kidney rejection. Immunosuppressive drugs are used in all three phases.

The most important group of immunosuppressive drugs are:
1. corticosteroids
2. calcineurin inhibitors
3. inhibitors of lymphocyte proliferation
4. antilymphocite antibodies

In order to achieve the effectiveness of the immunosuppressive therapy, with satisfactory a safety profile should these drugs have the following features:
- mechanism of action has to be selective
- needs to demonstrate adaptive specificity
- target the drug molecule has to be cytotoxic T cells
- biotransformation of the drug should be carried out independently of the cytochrome P450 enzymes
- synergistic effects in combination with other immunosuppressants.

Immunosuppressive drugs have serious side effects and a high interaction potential, which is why it requires monitoring and evaluation of the therapeutic dose regimen at sensitive transplant patients. A precondition of correct choice of medicines that will make optimal immunosuppression after transplantation Kidney is knowledge of their pharmacological characteristics. The choice of immunosuppressive therapy is done individually according to the patient, in order to find optimal combination of immunosuppressive drugs.

Corticosteroids

Prednisone and methylprednisolone are the corticosteroids (KS), which are successfully used for the development of Immune Tolerance transplant patient. Corticosteroids are effective in the prevention and treatment of organ transplant rejection are therefore used immediately before and after prolonged transplantation (Tx). Prednisolone and its derivatives is inhibition of methylprednisolone transcription factors, thereby reducing the transcription of the gene for interleukin-2 (IL-2) and other cytokines (IL-1, pyrogen-free collagenase, elastase, plasminogen activator and Tumor necrosis). Corticosteroids are related to cytoplasmic receptors through cell membrane to form the drug-receptor complex was traveling up to the cell nucleus. Anti-inflammatory and limfiliticco operation is based on the prevention of the proliferation of T - lymphocytes,
stabilizing the lysosomal membrane and blocking the synthesis of antibodies. Direct and indirect preventing the synthesis of interferon and interleukin IL-1, IL-2, IL-6, corticosteroids interfere with the sensitization of the cells that produce the antibody and reduce the release of antigens from of the transplanted tissue and disposed revascularization.

In the pharmacotherapy of patients transplanted KS doses significantly changes depending on the time elapsed from transplantation (the day of transplantation is applied loading dose 500 mg methylprednisolone, while 15 days after Tx dose prednisone is reduced to 40-60mg). Of particular importance is the determination of the dose KS terminating significant impact KS 60mg). Of particular importanc is applied loading dose

REFERENCES


