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Population Pharmacokinetic Analysis of Therapeutic Drug Monitoring Data in Optimizing Pharmacotherapy of Antiepileptic Drugs

Katarina Vučićević[1], Branislava Miljković[1], Sandra Vezmar Kovačević[1], Zoran Todorović[2], Milica Prostran[2] and Iztok Grabnar[3]
[1]*Department of Pharmacokinetics and Clinical Pharmacy, Faculty of Pharmacy, University of Belgrade,*
[2]*Department of Pharmacology, Clinical Pharmacology and Toxicology, School of Medicine, University of Belgrade,*
[3]*Chair of Biopharmaceutics and Pharmacokinetics, Faculty of Pharmacy, University of Ljubljana,*
[1,2]*Serbia*
[3]*Slovenia*

1. Introduction

Epilepsy is an episodic disease; hence the aim of the therapy is to minimize frequency of epileptic seizures and to improve the quality of patients' life with minimal adverse effects of antiepileptic drugs (AEDs) (Gidal & Garnett, 2005). Therapeutic Drug Monitoring (TDM) is a concept of individualisation of therapy based on drug concentration data, and application of pharmacokinetic (PK) and pharmacodynamic (PD) principles. It is not only a process of measuring drug concentration levels in biological fluids, but putting them into service of an optimized individual pharmacotherapy. The aim of TDM is to accomplish the optimal therapeutic drug response with minimal adverse drug effects e.g. better pharmaceutical care of patients (Bauer, 2008; Pokrajac, 2008).

Due to marked inter- and intraindividual PK characteristics of AEDs, TDM is indicated since the beginning of 1960s during the therapy of phenitoin (Buchthal et al., 1960). Shortly afterwards, it was recommended to monitor other AEDs, and correlate their concentrations with therapeutic effects (Kutt & Penry, 1974; Patsalos et al., 2008). Since PK and PD of AEDs demonstrate large interindividual variability, which is sometimes hard to identify, TDM of AEDs is incorporated into the therapy of epilepsy (Bauer, 2008; Commission on Antiepileptic Drugs, 1993; Dhillon & Kostrzewski, 2006). AEDs are being monitored also nowadays, but much of the available TDM data is insufficient due to inappropriate indication for performing the test, timing of samples collection, length of unchanged dosing regimen before measuring drug concentration, and unreliable documentation. Hence, TDM should be performed only if there is a clear indication: after initiation of treatment or after dose adjustment when the clinician decides to aim at preselected target concentration for that patient, to establish individual therapeutic range after achievement of desired clinical response, when there is suspicion of signs or symptoms of concentration-related toxicity,

when seizures persist despite apparently adequate dosage, if there is an alteration of PK (e.g. combination therapy, impairment of liver and/or renal function, paediatric population of patients, pregnancy), if there is change in drug formulation/switching to generic formulations, if there is unexpected change in clinical response, and if *non-compliance* is suspected (Patsalos et al., 2008). Throughout TDM, it is crucial to be aware of the dosing regimen, the duration of therapy, sample timing, as well as to keep high-quality recordings in patients' charts. In routine TDM of AEDs, it is recommended to obtain samples in steady-state corresponding to expected peak (maximum) and trough (minimum) concentration. Information from TDM must be interpreted in an adequate way since they could be used in rational pharmacotherapy of epilepsy (Bauer, 2008; Patsalos et al., 2008).
Owing to the fact that different factors affect individual PK parameters of AEDs, and consequently also the dosing regimen and clinical effects of a drug, identification of sources of intra- and interindividual variability among patients is essential for optimal drug therapy. Population modelling is a powerful tool to study whether demographic parameters (e.g. age, weight), pathophysiological conditions (e.g. other health problems, impairment of liver or/and renal function, concomitant therapy), and other sources of variability influence the dose-concentration relationship, and if so, to what extent. It is usually emphasized that population analysis is the analysis of variability, and it is more precise in determination of variability of PK parameters in the specific population over traditional PK analysis (Food and Drug Administration [FDA], 1999; Sheiner et al., 1977). Since many factors contribute to PK variability of AEDs, due to features of TDM data (1-2 plasma samples per patient), and characteristics of population analysis, population approach has irreplaceable role in PK analysis of TDM data. In this chapter, it the importance and advantages of population PK analysis in routine TDM of AEDs will be emphasized, the protocol of population studies explained, as well as the process of collecting and manipulating data, and finally the importance and application of the final population model in the clinical practice will be thoroughly discussed.

2. Traditional versus population pharmacokinetic approach

Traditional (classical) PK analysis refers to two-stage analysis using compartmental or noncompartmental PK approach. An accurate estimation of PK parameters requires frequent data sampling and concentration measurement in individual patients. In contrast, the population approach is based on one or more samples from an individual patient which are evaluated using model-dependent (compartmental) data analysis which, additionally, takes into account drug variability using specific statistical analysis. Hence, there are marked differences between these two approaches (Table 1). The subjects of traditional PK analysis are usually healthy volunteers or highly selected patients, whom drugs are being given by relatively simple dosing regimens (e.g. single bolus dose or single infusion). Protocol of the study with restrictive inclusion/exclusion criteria requires many samples per patient (sometimes as much as 10) – rich/dense data, which allows obtaining the individual PK profile of the drug. Sampling schedule is usually designed to obtain samples in short intervals and is the same for each individual in the study. Interindividual variability in PK is minimized in this way, and traditional controlled PK study focuses on the effect of a single factor on PK of a drug (FDA, 1999). In the first step of a two-stage approach, individual PK parameters are estimated through non-linear regression (e.g. one-compartment model) using individual dense concentration-time data. The individual values of PK parameters are used for the second stage, by calculating descriptive statistics typically average parameters values, standard deviation, coefficient of variation, or variance (Ette & Williams, 2004b).

Moreover, the dependencies between PK parameters and factor(s) that are not controlled by study design are calculated using classical statistic approaches such as linear stepwise regression, covariance analysis (Sun et al., 1999).

CHARACTERISTICS	TRADITIONAL (TWO-STAGE) ANALYSIS	POPULATION (NONLINEAR MIXED EFFECTS) ANALYSIS
Nature of the analysis	Pharmacokinetic model is fit to the data to each individual, whereas parameters are summarized	Pharmacokinetic model is fit to the data from all individuals, whereas based on empirical Bayes approach individual parameters are calculated
Experimental design	Stringent/controlled design is necessary	Stringent or non-stringent study design
Study population	Healthy volunteers or highly selected patients	Target patient population
Study size	Small	Large
Sampling data	Frequent sampling (usually 1-6 per patient – rich data)	Rich or sparse (1-2 samples) data within individuals with possibility of uneven number of data from different individuals
Interindividual variability	Minimized due to restrictive inclusion/exclusion criteria	Possible to identify sources of interindividual variability

Table 1. Characteristics of traditional and population pharmacokinetic analysis of data

On the other hand, in the population PK analysis individual patient is not the centre of the study; hence the aim is to develop population profile of a drug, whereas based on empirical Bayes approach individual parameters values are calculated. Study design allows large heterogeneous (e.g. by age, body weight, etc.) study population of patients from whom small number of samples – sparse/poor data are available. Sparse sampling in population PK analysis enables obtaining data from patient populations who are difficult to study due to ethical barriers, such as neonates, severely ill patients (Sheiner et al., 1977).
The protocol of the study is unbalanced, and it gives the opportunity to analyze data from individuals which differ in the number of samples per patient (FDA, 1999). Great advantage of population studies is that patients with insufficient data can be included in the study, whereas these subjects are usually excluded in traditional PK studies. Usual solutions to this problem include case imputation sample mean, median or estimation via linear regression values (e.g. total body weight can be predicted based on patients' age and gender) (Bonate, 2005). Concentrations bellow the limit of quantification (LOQ) of the assay are handled similarly. The usual strategy is not to exclude these data but to give them the value of LOQ/2. In order not to have doubts if the low concentrations is indication of noncompliance, the recommendation is to record the concentration even if it is below LOQ. This matter is a subject of much discussion, and there is no consensus on handling below LOQ data (Barrett, 2002; European Medicines Agency [EMEA], 2007). These alternative ways of treating problematic data give the possibility to maximally exploit the data, which is not possible in the traditional analysis. The milestone of population approach is the possibility to determine sources of variability with are usually consequence of a complex interaction of more factors (Vučićević et al., 2005; Sheiner et al., 1977). It is usually regarded as an analysis which is a study of drug variability, not only from a qualitative but also from quantitative aspect.

The population approach to PK analysis of data was originally proposed for application to routinely collected clinical – TDM data (Sheiner et al., 1977), i.e. sparse and unbalanced observations from a large group of heterogeneous individuals. TDM data are heterogeneous (according to patients' characteristics, therapy, dosing regimens), but they are representative of the actual population of patients taking the drug of interest since they are gathered directly from such patients, and from the ethical perspective there is a justifiable purpose of patients' care. At the same time, heterogeneous data are the source of the information of drug behaviour (Barrett, 2002; Sheiner et al., 1977), and discovery of unexpected but important influences of various factors on PK is possible. However, in order to evaluate the effect of one factor on PK parameter, number of covariates in the studied group must be sufficient, so the results of the study would lead us to significant conclusions about the effect of the specific covariate on the PK parameter. In other words, if we want to estimate the effect of valproic acid (VPA) co-therapy on carbamazepine (CBZ) PK, the results of our study suggest that at least 10-20% of patients co-treated with VPA are needed (Vučićević et al., 2007, 2009). This is necessary in order to obtain a sufficient level of certainty in the results of the analysis. Thus, an analysis of routine TDM data possesses several advantages in terms of data availability, representativeness of patients, and richness of the data set. Therefore, it is not overestimated to claim that routine TDM data on AED is a very attractive and often unused source of drug information with a strong potential. The advantage is mainly in the quantity of samples, and the fact that they represent the population of all patients who are treated with that drug in a certain setting. Moreover, the study protocol is not as strict as in traditional PK studies and therefore much more viable in the daily routine, from the perspective of ethics (blood sampling is an invasive procedure which is not justified only for research purposes) and time management. Owing to the characteristics of population approach, and characteristics of routine data, population modelling serves as a logical extension of TDM of AEDs with possibility of identification and quantification of factors that contribute to PK variability (Sheiner et al., 1977).

3. Methodological aspects of population pharmacokinetic analysis

Term population analysis is used as a synonym for nonlinear mixed effects modelling. The same phrase, abbreviated, is used for the name of the widely used population pharmacokinetic analysis software – NONMEM® (ICON Developments, USA). In this section main methodological aspects will be addressed.

3.1 Nonlinear mixed effects models

The basis of nonlinear mixed effects modelling is one stage approach, which means that all parameters are being estimated simultaneously. The purpose of this analysis is to estimate: population and individual PK parameters, interindividual and residual variability, and to identify and investigate sources of variability that influence PK of a drug. All aspects are of great interests since they are required for the optimal dosage regimen design for individual patients, and they provide quantitative PK characteristics of a drug. Potential factors affecting PK behaviour of a drug (covariates) are:

- Demographic such as age, gender, body weight, race.
- Genetic due to polymorphism of cytochrome P (CYP) 450 isoenzymes (CYP2D6, CYP2C9, CYP2C19, etc.) involved in the metabolism of AEDs.
- Physiological and pathophysiological including pregnancy, gastrointestinal diseases, decreased function of elimination organs (liver, kidneys), acute and chronic diseases.

- Concomitant therapy as a result of drug-drug interactions, since two or more AEDs can be included in the therapy of epilepsy.
- Enviromental factors like smoking, alcohol intake or diets.
- Other factors such as drug formulation, biological rhythms, compliance (Ette & Williams, 2004a; Sun et al., 1999).

The main components of population PK model are given on Fig.1.

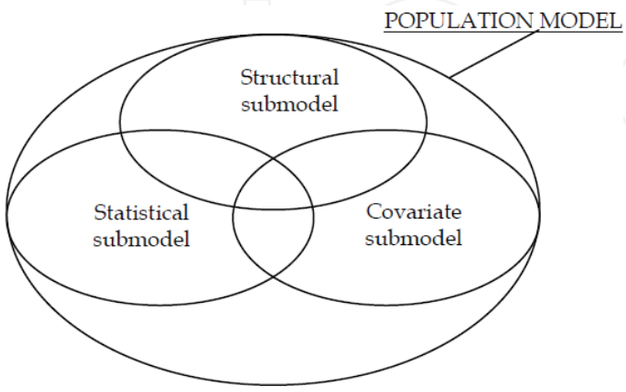

Fig. 1. Components of a nonlinear mixed effect (population) model

Term "mixed" stands for combination of fixed and random effects. Parameters of fixed effects represent population PK parameter values which are actually values of central tendency or typical values of parameters. These parameters are components of a structural PK model which refers to compartmental PK model. For example, intravenously given drug on a Fig. 1 follows one-compartment model with first-order elimination, and structural model is:

$$C_p = \frac{D}{V_d} \cdot e^{-\frac{CL}{Vd} \cdot t} \tag{1}$$

Dependent variable is observed drug concentration (Cp), whereas clearance (CL) and volume of distribution (Vd) are fixed parameters since they quantitatively describe the effect of a given dose (D) in specific time (t) on a drug level. Fixed effects parameters have symbols *theta* (θ). Population (typical) values of PK parameters (TV) can be explained in terms of covariates. As presented on Fig.2, patients' CL is defined in terms of a linear function of body weight (WT), given by:

$$TVCL = \theta_1 + \theta_2 \cdot WT \tag{2}$$

Parameters of random effects include: interindividual (between subject) variability which is partially but not completely possible to describe using available covariates and residual variability consisting of intraindividual (within subject) variability, measurement error, model misspecification, etc.

Since each individual in the population has specific value of a PK parameter which differs to some extent from the population typical value, it is described in terms of interindividual unexplained variability. This variability is described using parameter *eta* (η), and a variety of error models can be used. As given in Fig. 2, all *eta*s in the studied population for a specific PK parameter (e.g. η_{CL}) are assumed to be normally distributed with a mean value of zero, and variance of ω^2_{CL}.

Residual error refers to the deviation of measured (observed) drug concentration from the predicted level in a specific time using structural PK model. This parameter uses the symbol *epsilon* (ε). All parameter values for residual variability are assumed to be normally distributed with a variance of σ^2 (Fig. 2).

Covariates, as previously mentioned, represent any variable/factor specific for a patient which can influence PK of a drug. Covariate submodels are integrated part of a structural part of a population model (Fig.1). A relationship between PK parameters and covariates depends on its nature, and range values (Jonsson & Karlsson, 1998; Mentre & Mallet, 1994). Therefore, there are:

- Categorical covariates that are qualitative, and they can be dichotomous with two values (e.g. gender: male or female; mono- or combination therapy) or polychotomous with more than two values (e.g. patients' race: white, black or yellow).
- Continuous covariates which have defined scale of its values and they are quantitative, such as body weight, age, creatinine clearance etc. Relationship between this covariate and PK parameter can be linear or nonlinear.

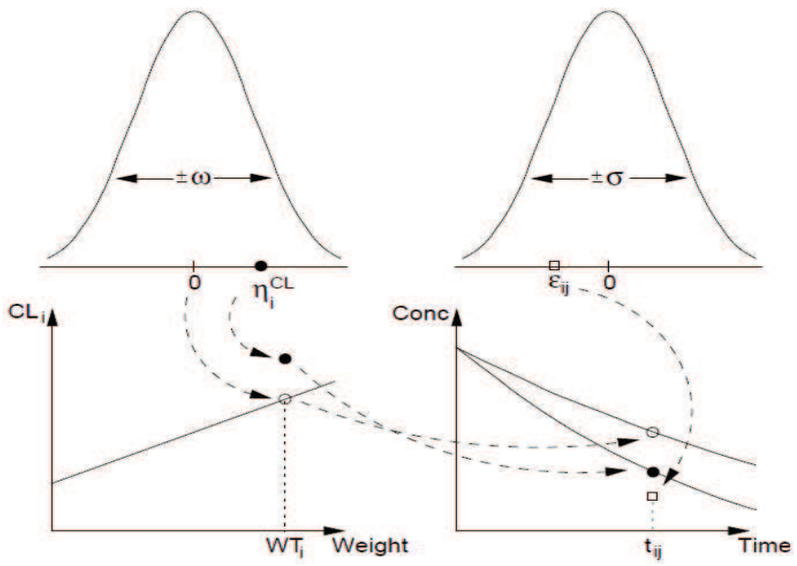

Fig. 2. Schema of nonlinear mixed effect model. Interindividual variability (left) and residual variability (right). Population (○) and individual (●) pharmacokinetic parameter/predicted and observed concentration (□) (Beal & Sheiner, 1989-2006)

Selection of an adequate model describing effect of a factor on PK parameter depends on preliminary modelling results. These results include individual values of PK parameters based on a distribution of base model parameters (empirical Bayes estimates), and its graphical dependences of covariates. Details of a modelling process will be explained in the following section.

3.2 Population model building and validation techniques

Since the aim of the population analysis is to describe interindividual variability in PK parameters, it can be done through the most commonly used stepwise covariates model building method, also known as forward inclusion-backward exclusion method. After defining the structural and statistical models (which form base model), influence of each covariate on PK parameter is examined (Bonate, 2005; Jonsson & Karlsson, 1998).

Software NONMEM® fits data to defined structural and error models according to principles based on maximum likelihood which is expressed via objective function value (OFV). Software performs iterative search of a parameters values that maximizes the probability of input data leading to minimization of OFV. OFV is proportional to double negative logarithm of data probability. Logarithm of data probability follows chi-squared (χ^2) distribution (Beal & Sheiner, 1989-2006).

Apart from finding important covariates, the functional relationship also has to be specified. There are several suggestions on covariate model building (Bonate, 2005; Jonsson & Karlsson, 1998; EMEA, 2007), but no consensus has been reached. Mainly graphics which demonstrate correlation of individual empirical Bayes parameter estimates of the base model versus selected covariates are used for identification of candidate covariates.

Each covariate was added in the base model, and examined for its effect on PK parameter by evaluating the drop in OFV. Each covariate was ranked against the base model by minimum decrease in OFV of 3.84 (χ^2 distribution, $p<0.05$ for 1 degree of freedom), and only significant covariates were introduced into the full model. The final model was determined by removing the covariates one by one from the full model, and a difference in the OFV more than 6.63 (χ^2 distribution, $p<0.01$ for 1 degree of freedom) was required to maintain covariate in the model (Beal, 2002; Beal & Sheiner, 1989-2006). Maintaining/excluding one covariate in/from the model in based on the combination of several considerations: statistical, graphical, and clinical relevance of the obtained relationship (Wählby et al., 2001). Additional indicators for the retention of a covariate in the model are decrease in interindividual and residual variability, minimal correlation between parameters, improvement in the precision of the parameter estimates, small standard errors of parameter estimates, gradients for each estimated parameter in final iteration step should be between 10^{-3} and 10^{2}. In each model-building step improvement of the model is assessed by the goodness-of-fit plots, including the agreement between the observed and predicted drug concentrations, reduction in the range of weighted residuals, and uniformity of the distribution of weighted residuals when plotted against predicted concentrations (Barrett, 2002; Beal & Sheiner, 1989-2006).

One of the most demanding tasks is the demonstration whether the final population PK model accurately represent the studied population. Depending on the objective of the analysis, the need for model validation may vary. There are generally two types of validation:

- Internal which is performed in the group of patients used for model development. Methods commonly used are data splitting, bootstrap, cross-validation.
- External which includes a separate, independent group of patients not included in model development (Bonate, 2006).

However, if developed population PK model is going to be used for dosage recommendations the predictive performance needs to be tested (Sun et al., 1999). To evaluate the performance of the final model in predicting drug concentrations, a second, validation group of patients is studied. Hence, external validation is performed. The measured drug concentrations in this group must be compared with the corresponding predicted values obtained using the final population PK model, patients' covariates and dosing information. Predictive performance of the model is assessed by calculating the mean error and its 95% confidence interval (CI) as an estimate of bias, and the root mean squared prediction error and 95% CI as an estimate of precision. CIs including the value of zero were considered unbiased (Sheiner & Beal, 1981; Wu, 1995).

3.3 Population pharmacokinetic modelling of routine therapeutic drug monitoring data

As previously stated, routine TDM data are particularly attractive and available source of information since they represent PK behaviour of a drug in the group of patients receiving

the drug for the therapeutic purposes. From economical perspective, an analysis of routine data is reasonable, since it reduces experimental costs (Sheiner et al., 1977). Nevertheless, the drug dosing history is often poorly recorded and the level of noncompliance is underestimated, which leads to biased estimation of population model parameters.

During TDM of AEDs, sampling enables mainly the collection of trough and to less extent peak drug concentrations. Commonly, from each patient a single blood sample is obtained at or close to trough concentration, shortly before the next dose. The relationship of patients' characteristics and minimum drug level can be explored by simple statistical analysis, but calculation of PK parameters seems almost impossible using traditional PK approach. Whereas, with population PK analysis it is possible to estimate PK parameters and two levels of variability (Sheiner et al., 1977).

However, the nature of the data influences the parameters that can be estimated in the analysis (Sun et al., 1999). In other words, a certain PK parameter cannot be calculated with any degree of a precision unless data used for analysis reflect the parameter. As reported by Sheiner & Beal, 1983, the use of mostly trough samples in the sampling design results in a good precision of the CL and its variability, and poorer precision of Vd and its variability. For that reason Vd is usually not estimated in population analysis of TDM data. Moreover, insufficient sampling during the absorption phase of *per os* given drugs, does not allow estimation of the parameters of the absorption process (rate constant of absorption); hence its values should be fixed to the literature value (Booth & Gobburu, 2003; Jiao et al., 2004; Wade et al., 1993). It has been shown (Wade et al., 1993) when no data were available from the absorption phase, misspecification of rate constant of absorption had no effect on other estimated parameters of the model. When doing this, a sensitivity analysis can be performed in order to confirm the effect of fixed parameter value on the final model parameter estimates. These methodological issues have been extensively applied during population PK analysis during the modelling of routine sparse TDM data of AEDs (Yukawa, 1999).

If an absolute bioavailability of a drug is either unknown or very variable, it is possible to refer to apparent PK parameter values. Therefore, in the population PK studies of AEDs data, the only PK parameter which can be estimated with good precision from routine TDM data (mainly trough concentrations) is the apparent clearance (*CL/F*). Clearance is a vital PK parameter in dosage adjustment regimen, since the most widely used method of AEDs dosage adjustment is based upon the fact that in steady-state the rate of drug administration equals the rate of drug elimination (determined by a product of *CL/F* and the average steady-state drug concentration), given by equation (3).

$$R = \frac{D}{\tau} = CL / F \cdot C^{ss} \tag{3}$$

As reported (Sheiner & Beal, 1983) there is no significant loss in estimating *CL/F* and its variability by population modelling from routine type of data compared to better designed studies where more samples per patient are available.

4. Importance and application of population pharmacokinetic models from therapeutic drug monitoring of antiepileptic drugs

When a drug is marked and used for the treatment of a disease or condition, the main goal of therapy is to optimize dosage regimen in the individual patient. Degree of PK and/or PD variability of a drug influences the applicability of average dosing regimen for an individual

patient. Since AEDs show marked PK variability, poor correlation between plasma levels and dose was observed (Bauer, 2008; Miljković et al., 1991). Therefore, interindividual variability in drug disposition as well as in drug's response is often the reason for adverse drug reactions, as well as lack of therapeutic efficacy. Various factors contribute to large differences in plasma drug concentrations at steady-state among patients receiving the same dose, and consequently affect individual PK parameters of AEDs. For instance, patients' age or body weight are the commonly identified factors that affect AEDs' elimination since they show functional and physiological status of organs (e.g. liver, kidneys) involved in metabolism and/or excretion of a drug. Among other factors patients' race, gender, smoking status, drug formulation were found to affect PK parameters of some AEDs.

Consequently, evaluation and management of the variability is the aim of rational drug therapy with its individual approach to each patient. Understanding the factors which can influence AEDs PK characteristics throughout population modelling technique in combination with TDM is a valuable tool in designing a safe and effective dosing regimen for epileptic patients.

Therapy of epilepsy usually begins with one AED depending on the type of the seizure. When increasing the dose or substituting a drug with another AED does not give a desired therapeutic effect, a combination of AEDs might be considered. When another drug is added on, PK and/or PD drug-drug interactions may occur, leading to greater variability. However, the extent to which corresponding parameters are changed, indicate the need for the change of dosage regimen. It is a well known that some AEDs such as CBZ and PB are inducers of CYP450 isoenzymes, thus consequently affect PK parameters of elimination of AEDs that show CYP450 dependent elimination. In addition, VPA inhibits the metabolism of lamotrigine and PB, and a reduction in the dosage of the latter drugs is usually indicated when VPA is added on (Patsalos & Perucca, 2003a, 2003b; Perucca, 2006). To conclude, many drug-drug interactions between AEDs and AEDs with non-AEDs are proven by controlled PK studies; however population PK studies allow quantification of such interactions using sparse data. Drug interactions represent constant concern in the clinical practice owing to the fact that the treatment of epilepsy usually requires polytherapy, and that interindividual variability in PK can be caused by drug interactions (Patsalos & Perucca, 2003a, 2003b; Perucca, 2006). Therefore, it is logical the importance of population approach to identify and quantitatively describe drug-drug interactions in the clinical practice (Vučićević et al., 2007a, 2008, 2009a). It has been found that population PK analysis was powerful tool in detecting interaction, but also showed its' superiority over traditional PK approach (Grasela et al., 1987; Zhou, 2006). In the traditional PK studies it is possible to observe, under controlled conditions of the study, if one drug statistically significant changes the average PK parameter of another. Consequently, population-based analysis is particularly important to quantify known or suspected drug-drug interactions, as well as to detect any unexpected interactions. Several examples of developed population PK models for AEDs from routine TDM data in adult population are given in Table 2. Traditionally, TDM has mainly focused on the older antiepileptic drugs, such as CBZ, phenobarbital, phenytoin, primidone, and VPA, which all have been in clinical use for several decades. For that reason, population PK models are numerous, and some of them are presented in Table 2. Based on these population PK models, it is possible to observe quantitative effect of concomitant drugs in therapy with CBZ, or VPA.

DRUG	POPULATION PHARMACOKINETIC MODEL	REFERENCE
Carbamazepine		
$CL/F[l/h] = 5.35 \cdot \left(\frac{DCBZ}{15}\right)^{0.591} \cdot \left(1 + 0.414 \cdot \frac{DPB}{2}\right) \cdot \left(\frac{WT}{70}\right)^{0.564} \cdot 1.18^{VPA}$, where *DCBZ* and *DPB* are daily doses of carbamazepine and phenobarbitone in mg/kg; *VPA*=1 if valproic acid dose is greater 750 mg/day, or 0 if else		Vučićević et al., 2007b
$CL/F[l/h] = 0.141 \cdot DCBZ^{0.406} \cdot WT^{0.117} \cdot 1.23^{VPA} \cdot 1.44^{PHT} \cdot 1.26^{PB}$, where *DCBZ* is daily dose of carbamazepine in mg; *VPA*=1, *PHT*=1, *PB*=1 if valproic acid dose greater than 18 mg/kg, phenytoin, phenobarbitone are present in therapy, or 0 if else		Jiao et al., 2004
$CL/F[ml/h \cdot kg] = 64.9 \cdot DCBZ^{0.465} \cdot WT^{-0.336} \cdot 1.03^{VPA} \cdot 1.44^{POLY} \cdot 1.16^{PB}$, where *DCBZ* is daily dose of carbamazepine in mg/kg; *VPA*=1, *PB*=1, *POLY*=1 if valproic acid, phenobarbitone or more than two AEDs are present in therapy, or 0 if else		Yukawa & Aoyama, 1996
$CL/F[l/day \cdot kg] = 40.7 \cdot AGE^{0.494} \cdot WT^{-1.17} \cdot 1.44^{PB}$, where AGE is in years, *PB*=1 if phenobarbitone is present in therapy, or 0 if else		Chan et al., 2000
$CL/F[l/h] = (0.0134 \cdot WT + 3.58) \cdot 1.42^{PHT} \cdot 1.17^{PB/FEL} \cdot 1.62^{PHT+PB/FEL} \cdot 0.749^{AGE}$, where *PHT*=1, *PB/FEL*=1, *PHT+PB/FEL*=1, *AGE*=1 if patient is treated with phenytoin, phenobarbitone or felbamate, phenytoin and phenobarbitone/felbamate, or is older than 70 years, or 0 if else		Graves et al., 1998
Valproic acid		
$CL/F[l/h] = 0.517 \cdot \left(\frac{WT}{70}\right)^{0.556} \cdot 1.43^{VPA} \cdot 0.765^{TPR}$, where *VPA*=1 if *VPA* dose is greater 1000 mg/day, and *TPR*=1 in co-therapy with topiramate, or 0 if else.		Vučićević et al., 2009b
$CL/F[l/h] = 0.105 + 0.151 \cdot CBZ + 0.000248 \cdot DVPA + 0.0968 \cdot \frac{AGE}{20} + 0.0803 \cdot INDI$, where *DVPA* is valproic acid dose in mg/day; *CBZ*=1 in co-therapy with carbamazepine, or 0 if else; *INDI* is uncontrolled epilepsy		El Desoky et al., 2004
$CL/F[ml/h \cdot kg] = 17.2 \cdot DVPA^{0.159} \cdot WT^{-0.264} \cdot 0.821^{CZP} \cdot 0.896^{GEN}$, where *DVPA* is daily valproic acid dose in mg/kg; *CZP*=1 for concomitant therapy with clonazepam, *GEN*=1 for female, or 0 if else		Yukawa et al., 2003
$CL/F[l/h] = 0.004 \cdot WT \cdot DVPA^{0.304} \cdot 1.363^{CBZ} \cdot 1.541^{PHT} \cdot 1.397^{PB}$, where *DVPA* is daily dose of valproic acid in mg/kg; *CBZ*=1, *PHT*=1, *PB*=1 if carbamazepine, phenytoin, phenobarbitone are present in therapy, or 0 if else		Blanco-Serrano et al., 1999.

Table 2. Population pharmacokinetic models of carbamazepine and valproic acid derived from routine therapeutic drug monitoring data in adult population of epileptic patients

The importance of a population PK models is best shown in an example. It is a well known fact that PB acts as an inductor of CYP450 isoenzymes, thus consequently it effects CBZ elimination (Patsalos & Perucca, 2003a). Since induction process requires synthesis of new enzymes, time course of an induction is a function of enzyme synthesis rate. Hence, time course of induction is dose dependent (Patsalos & Perucca, 2003a). Using the population PK approach, the possibility to examine the influence of various PB doses on CBZ metabolism (CL/F) was shown, and the results indicate a linear relationship (Table 2).

Clinical significance in population modelling converts the estimated values of population PK models into potential benefits for an individual patient. In modelling, clinical relevance of the covariate effect usually assumes reduction in the interindividual variability of the specific PK parameter while adding a covariate/factor to a model. On the other hand, clinical relevance can also be evaluated by estimating the change in the predicted individual parameter values. For example, if predicted CL/F of a CBZ in a patient increases by 20% after adding PB (as a covariate) in the model, PB co-therapy may be regarded as a clinically relevant predictor of CBZ CL/F. In order to make the effect of a covariate on PK parameter robust, 95% CI of the value of parameter explaining covariate effect should be addressed. Finally, what is regarded as clinically relevant varies between investigators, physicians and regulators (EMEA, 2007).

Knowledge of population PK models can assist in choosing initial dosing regimen of a drug, modifying dosing regimens according to observed drug levels, and they can elucidate certain clinical questions. Identification of the factors which contribute to PK variability of AEDs provides a foundation for individualization of the therapy. An adjustment of drug therapy is directed by individual values of PK parameters which depend on patient and disease characteristics.

In order to optimize dosing regimen for a specific patient, individual PK parameters are needed. Hence, patient's CL/F represents fundamental PK parameter for individualization of therapy (given by equation (3)). Bayes approach is used to determine individual PK parameters using mutually the data from individual patient and population PK models of a drug defined via population typical values of PK parameters and their variability (Bonate, 2006; Jelliffe et al., 1993; Sheiner et al., 1979). This prediction is possible to perform using different PK softwares. Though, in Bayes regression approach it is of a great importance to use population PK model that represents individual patients. Furthermore, if population PK behaviour of AEDs is integrated with pharmacological and clinical effects, it would provide a better rationale for the proper selection of optimal dose, type and duration of administration of AED therapy in different patient populations.

5. Conclusion

Clinical experience demonstrated the need of therapeutic drug monitoring in optimizing therapy of epilepsy. Identification of sources of intra- and interindividual variability among patients is essential for individualization of drug therapy, and it can be accomplished by population approach to data analysis. The major strength of the population pharmacokinetics approach is that useful information can be extracted from sparse data collected during routine clinical care. Therefore, population approach serves as a natural and expected extension of therapeutic drug monitoring and it can significantly contribute to more rational pharmacotherapy of antiepileptic drugs. Knowledge of population

pharmacokinetic models can assist in selecting an initial dosing regimen, and modifying dosing regimen appropriately according to the observed drug level and patients' characteristics. In order to truly individualize dosing regimen, patient's individual PK parameters are required, and they can be estimated as a function of significant covariates by Bayes analysis and the population pharmacokinetic model.

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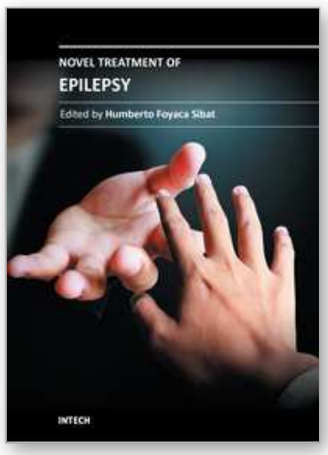

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Epilepsy continues to be a major health problem throughout the planet, affecting millions of people, mainly in developing countries where parasitic zoonoses are more common and cysticercosis, as a leading cause, is endemic. There is epidemiological evidence for an increasing prevalence of epilepsy throughout the world, and evidence of increasing morbidity and mortality in many countries as a consequence of higher incidence of infectious diseases, head injury and stroke. We decided to edit this book because we identified another way to approach this problem, covering aspects of the treatment of epilepsy based on the most recent technological results â€œin vitroâ€ from developed countries, and the basic treatment of epilepsy at the primary care level in rural areas of South Africa. Therefore, apart from the classic issues that cannot be missing in any book about epilepsy, we introduced novel aspects related with epilepsy and neurocysticercosis, as a leading cause of epilepsy in developing countries. Many experts from the field of epilepsy worked hard on this publication to provide valuable updated information about the treatment of epilepsy and other related problems.

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