Cent. Eur. J. Med. • 8(4) • 2013 • 383-391
DOI: 10.2478/s11536-013-0158-5

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Central European Journal of **Medicine**

Population pharmacokinetic of antiepileptic drugs in different populations

Review Article

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Received 23 April 2012; Accepted 28 January 2013

Abstract: This article reviews a population pharmacokinetics studies conducted during the past few years in Serbia. Studies have included three the most frequently used antiepileptic drugs (valproate, carbamazepine and lamotrigine) and different populations of epileptic patients: children, adults and heterogeneous population composed of both children and adults. The review compares obtained values of population pharmacokinetic models of clearance of these drugs, and factors that are significantly determined, making brief comments on the results of other authors on the same topic. Individualization of drug dosage is the basis of rational therapy, and factors of variability will always be subject of scientific research.

Keywords: *Population pharmacokinetics • ENONMEM • Valproate • Carbamazepine • Lamotrigine*

1. Introduction

Epilepsy and antiepileptic drugs are subjects of intensive research for decades and often practical problem for physicians. Inspire of this many questions in this area remain open. One of the most important questions is how to improve patients' quality of life, reduce adverse effects and apply appropriate drug doses according to individual needs of each patient. The population pharmacokinetic (PPK) analysis has an important role in achieving these goals.

Nowadays, population pharmacokinetics (PPK) is an integral part of modern research in pharmacokinetics and its results could be applied in clinical practice. The development of PPK started in early seventies of the last century and continues to be methodologically improved [1]. At the beginning of the next decade principles relating to the PPK analysis have become generally accepted, but its role in the process of drug development were acknowledged by Government Regulatory Agencies later. Finally, in February 1999. FDA published the document with a title: "Guidance for Industry: Population Pharmacokinetics" [1,2].

A significant contribution to the development of the discipline had been given by Beal and Sheiner, who are the creators of the most commonly used software package in this field. This is the NONMEM (Non-linear Mixed Effects Modeling) software that contains a large library of subroutines to define the pharmacokinetic model of a target drug [3,4]. Also, it provides estimates of average values of pharmacokinetic parameters (clearance, volume of distribution, etc) and their variability (inter- and intraindividual).

2. Antiepileptic Drugs

Wide range of antiepileptic drugs is available to clinicians for treatment of epilepsy. Reviews of the literature shows that the most commonly used antiepileptics in clinical practice are carbamazepine (CBZ), valproate (VPA) and lamotrigine (LTG). This was the reason why these drugs were subject of our research for many

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years. Although there are many papers on this topic, our goal was to determine population value of clearance of these drugs and factors that contribute to its variability in different population of epileptic patients in Serbia: children, adults and heterogenous population.

3. Population Pharmacokinetic Studies

For this type of analysis it was necessary to make a detailed preliminary plan that included: knowledge about pharmacokinetic of investigated drugs, selection of the test population, choosing pharmacokinetic (PK) parameters and factors (related to the patients as well as factors related to the drug) that are considered to contribute to variability (inter – and intraindividual), detailed collection of relevant data from patients, accurately measuring concentrations of the drug and using the appropriate software [5].

Our first studies were devoted to testing two the most commonly used antiepileptic drugs in children and adults, valproate and carbamazepine, and were performed in a mixed population of children and adults [6,7]. Moreover, considering the known pharmacokinetic characteristics of children population and their differences compared to adults, we wanted to examine and evaluate the most important factors of variability of these drugs in more homogeneous populations (separate populations) [8,9]. On the other hand, PPK study of lamotrigine was performed only on a mixed population of patients with epilepsy due to small number of patients receiving this drug as compared to the previously mentioned drugs [10].

The protocol of our studies included the following data collected on the basis of interviews with the patients and their parents and attending physicians: total body weight (TBW), age (AGE), gender, total daily dose (DD), dosing schedule, time of the last drug intake and detailed information on concomitant therapy. Only patients on combination therapy (the target drug and another antiepileptic drug ie. bi-therapy) were included in analysis. Also, all studies were carried out on the basis of therapeutic drug monitoring programme in the Pediatric and Neurological Clinics of Clinical Center in Kragujevac, Serbia and approved by Ethics Committee [6-10].

3.1. Pharmacokinetic analysis

PPK analysis is consisted by three main stages that lead to obtaining the final, population model of pharmacokinetic parameters. Drug clearance and volume of distribution (the most important disposition parameters), are often the focus of pharmacokinetic investigations. Using the appropriate subroutine and POSTHOC option from NONMEM software, the data were fitted for estimation of typical mean value of drug clearance in the populations without testing covariates (the base model). Also, estimates of interindividual variability of clearance and residual error of the concentrations (intraindividual variability) were modeled by different error models (exponential and additive).

The next step, building of the final pharmacokinetic model, was performed by adding each examined covariate (total body weight, age, gender, total daily dose of the drug, comedication with other antiepileptic drugs) in the base model by the linear or nonlinear regression. This acquired several univariate regression models. The value of minimum objective function (MOF), the main statistical parameter for PPK analysis, was used to compare the validity of these regression models. MOF is defined as -2loglikelihood (-2LL) and the reduction of 3.841 or 6.64 (difference in the MOF of more then 3.841 for $P<0.05$, df=1 or 6.64 for $P<0.01$, df=1) for each covariate was necessary [3,11]. Only covariates which accomplished these statistical requirements were estimated as significant and were included simultaneously in the model, leading to the full model. At the and, a process of backward deletion of each covariate from this model was performed. A more restricive statistical criterion (difference in the MOF of more then 6.64 for $P<0.01$, df=1 or 10.83 for $P<0.001$, df=1) was requested to maintain a significant covariate in the final pharmacokinetic model. Finally, the final model was obtained by including all covariates which fulfilled the mentioned statistical criterion. Also, in all stages of PPK analysis it was important to fulfill other demands: reduction in interindividual and residual variability, improvement of scatter-plots of predicted values (PRED) versus observed concentrations (DV) and of weighted residuals (WRES) versus predicted concentrations (PRED), from the base to the final model.

The last stage was the validation of the final pharmacokinetics model. It was used to estimate predictive performance of derived model. The validation set was the control group of patients whose data were not included in the process of building the pharmacokinetic model but their demografic and medication data should be similar to the target population. To assess bias and precision of our final model we calculated prediction errors (MPE, MSPE, RMSE) as recomended by NONMEM software creators [12].

In our studies valproate, carbamazepine and lamotrigine were administered orally, one to three times per day, and all patients were on therapy for at least two

weeks or one month; the steady-states were reached. Blood samples were taken from patients either at the end of the dose interval or when maximal drug concentration had been reached but most of the samples were collected at the end of the dose intervals.

Serum VPA concentrations were measured using fluorescent polarised immunoenzyme technique (TDx analyser; Abbot Laboratories Co; USA), whereas the values of serum CBZ and LTG concentrations have been obtained by HPLC analysis at the Pharmacology Department, Faculty of Medical Sciences in Kragujevac [6,8].

The data were analysed with subroutine ADVAN 1 (one-compartment model without absorption) from the NONMEM software (version 5, level 1.1, double precision) for development of population pharmacokinetical models of clearance of the target drugs. Absolute bioavailability (F) was not assesed because all doses were given orally and F was included in clearance (the apparent oral drug clearance) for the aims of these analysis.

Our derived pharmacokinetics models of investigated drugs clearances were confirmed in validations sets for all examined populations and good predictive performances were obtained. It was shown by improvement of data fit between the base and the final models, by decrease in inter- and residual variability and by calculated predictive errors from validation sets [6-10].

4. Valproate

Valproate is used to treat different types of seizures, neuropathic pain, migraines and for prophylaxis and treatment of bipolar disorder, too [13,14].

Our first PPK examination of population VPA clearance has been started in the period between 2003-2005. The data we have used for analysis were collected from 93 epileptic patients (34 adult and 59 pediatric patients were consisted this heterogeneous population) and the mean value of age was 16.88±12.69 years [6].

As a result of performed analysis the final population pharmacokinetic model of VPA clearance was [6]:

$CL\ (l\ h^{-1}) = 0.164 + 0.00365 \times TBW + 0.00464 \times AGE$

The model described the values of population clearance in terms of specific patients´ characteristics: total body weight and age of patients. The linear relationship of TBW and age with CL of valproate was shown in the study. The facts that age and total body weight are the important factors that influence a change of VPA CL in children and also in heterogeneous patient populations were in accordance with reports of other authors [15-17].

Further research was carried out in separate populations: children and adult epileptic patients during 2007-2009 [8]. For purposes of our analysis were used 65 and 63 steady state concentrations of VPA collected from 58 children (age mean 7.21±3.63 years) and 60 adult epileptic patients (33.97±16.41 years), respectively. In total 34 patients of the children population were on VPA monotherapy while 24 patients were on combination of VPA and carbamazepine or lamotrigine: 17 patients on VPA+CBZ and 7 patients on VPA+LTG. The adult population included 19 patients on concomitant therapy: 8 with carbamazepine, 3 with lamotrigine, 8 with phenobarbital and 41 patients were on VPA monotherapy.

The final pharmacokinetic models could be described using following equations [8]:

A. the children population:

$CL\ (l\ h^{-1}) = 0.137 + 0.00258 \times TBW + 0.159 \times CBZ$

B. the adult population:

$CL\ (l\ h^{-1}) = 0.0712 + 0.00502 \times TBW + 0.539 \times PB$

Our results noted significant differences in typical values of VPA clearance among children and adults. The clearance of valproate in adults being much higher (almost 2.5 times) than that in children. The populations mean value for clearance of the investigated drug was also determined by body weight of patients and co-medication with carbamazepine in the children population, whereas in the adult population body and concomitant therapy with phenobarbital were important determinants [8].

Total body weight is an important cause of interindividual variability of pharmacokinetics of valproate, particularly in the children populations. The significant influence of this factor has been confirmed in studies by other authors that reports point to the possibility of both linear and non-linear increase in VPA clearance with increasing body weight of patients in different populations [15,16,18-21]. Also, numerous studies have showed the existence of a linear increase of VPA clearance with body weight in mixed populations of children and adults [6,22]. That is in agreement with our results.

Nowadays, there are different reports about the influence of age on valproate. Some researchers explained an increasing clearance of VPA with age in the children population in correlation to developmental changes in hepatic drug metabolism [6,17]. There is a very close correlation between total body weight and age of the patient, especially in the children population, but also in heterogeneous populations [6,16]. However, our research clearly showed that the age within the subpopulations of children and adults was not important

characteristic that influenced the clearance of valproate which is in accordance with reports by other authors [15,18-20,23]. Moreover, some researchers have noted that body weight is a better indicator of metabolic capacity and general physiological condition of the body then age [21,24].

Pharmacokinetic interactions of valproate with other antiepileptic drugs are common and clinically significant to physicians and researchers. These drug-drug interactions occur in the all pharmacokinetics phases and are followed by changes in the plasma concentration of drugs. The main place of interactions is often their metabolism.

Valproate is extensively metabolized in the liver by the process of glucuronidation and β and Ω oxidation [8]. The drug is an enzyme inhibitor and is subject to enzyme induction. It is substrate for different cytochrome (CYP) P450 isoenzymes, such as: CYP2C9, CYP2C19 and CYP2A6. Co-administration of enzyme inductors such as carbamazepine and phenobarbital increase the elimination of VPA via induction of these isoenzymes. Namely, carbamazepine is a potent enzyme inducer, CYP3A4, CYP1A2 and CYP2C9 isoenzymes [9]. Trough a similar mechanism, phenobarbital also induced VPA metabolism. The most important induction occurs via CYP2C9 and CYP2C19 isoenzymes. As the result of these pharmacokinetic interactions are increasing the rate of metabolism of valproate and a subsequent reduction its half-life.

In agreement with our findings, results of numerous studies have shown that the relative clearance of valproate is increased in concomitant therapy with carbamazepine [15-19]. In children the increase in VPA clearance ranged from 35.9% to 61% [16,18]. El Desoky et al. have shown that influence of carbamazepine was +0.151 lh^{-1} in a population with equal number of children and adults [17]. Furthermore, the current study reported an increase in VPA clearance in the adult population when phenobarbital was included in therapy. Similar results were obtained by other researchers [15,19,21,22]. The magnitude of its effect was different and ranged from 10% to 40% in a heterogenous and adult population, respectively [15,19]. On the other hand, estimate of CBZ influence on VPA clearance was not shown in the adult population because this covariate was not well represented (only 7.5% of the total population).

5. Carbamazepine

Carbamazepine is one of the traditional antiepileptic drugs used in the treatment of epilepsy for half a century. It is particularly effective for simple or complex partial and generalized tonic-clonic seizures in children and adults [25,26]. However, therapy with carbamazepine is complicated due to its complex pharmacokinetics properties, presence a high inter- and intraindivudual variability, an active metabolite (CBZ-10,11 epoxide) as well as drug interaction profile. The drug is capable of inducing its own metabolism via CYP3A4 isoform and metabolism of many drugs that are metabolized by the same isoenzyme. The main metabolic pathway of CBZ is process of oxidation by CYP3A4, CYP2C8 and CYP1A2. Consequently CBZ metabolism may be affected by the drugs that induce or inhibit liver microsomal enzymes. Other metabolic pathways included process of hydroxylation and conjugation with glucuronic acid [9].

The study in a heterogeneous population of epileptic patients was performed between the years 2003 and 2005 [7]. The data were collected from 97 adult and pediatric patients with the following age distribution: 2-14 years 67.3% of patients, 15-18 years 1.9%, 19-57 years 19.8% of patients and over 60 years 1% of patients. There were 14 patients taking combination of carbamazepine and valproate.

The equation for the final model was [7]:

$$\mathbf{CL\ (l\ h^{-1}) = 1.73 \times TBW^{0.1} \times AGE^{0.1} + 0.874 \times VPA}$$

There were three significant predictors of CBZ clearance in the target population: total body weight and age of patients and comedication with valproate. The results shown nonlinear relationship between these physiological factors and CBZ clearance. These findings were supported by other reports [24,27]. Also, the influence of concomitant therapy with valproate was observed. Nowadays, there are different reports about the influence of VPA on CBZ clearance [11,24,28]. It is generally known that valproate is highly bound to plasma protein and increases the unbound fraction both carbamazepine and its metabolite (CBZ epoxide) as well as inhibits its metabolism via hepatic microsomal hydrolase. As a result of these facts CBZ concentration could be increased, decreased or remain unchanged [11]. In our study was measured total (bound and unbound) CBZ concentration and has been noted slight increase on CBZ clearance which could be caused by displacement from plasma protein in presence concomitant therapy with VPA. Consequently, clearance of CBZ was increased by 7% in Japanese population and by 23% in the population of Chinese children when VPA was introduced [29,30], but Delgado and Gray did not observe effect of VPA in their studies [27,31].

Treatment of pediatric and adult patients with carbamazepine could be complicated due to various factors influenced on its disposition. Apart from physiological

factors, numerous factors may alter CBZ pharmacokinetics [8,32], like specific diseases, nutritional habits or prior exposure to drug therapy. Many of these factors correlate with age and could be masked or passed unnoticed if pharmacokinetic modelling is based only on one population consisted of both children and adults. That was the reason for our next studies which included a separate populations of children and adults [9].

Analyses were conducted using 114 and 53 steady state concentrations of CBZ collected from 98 epileptic children (age mean 8 ± 3 years) and 53 epileptic adults (age mean 32 ± 15 years), respectively. The pediatric population included patients on concomitant therapy with VPA or LTG, whereas the adult population consisted of patients on combination therapy with carbamazepine and phenobarbital (PB), topiramate (TPM), valproate or lamotrigine.

The final models of population value of CBZ clerance were described by the following equations [9]:

A. the children population:

$CL\ (l\ h^{-1}) = 1.01 + 0.0667 \times AGE + 0.0022 \times DD$

B. the adult population:

$CL\ (l\ h^{-1}) = 1.15 + 0.0195 \times AGE + 0.0029 \times DD + 1.61 \times PB$

The main covariates of derived PK models were age of patients and total daily dose of CBZ in both populations studied, and co-medication with PB in the adult population. The influence of total daily dose of CBZ was similar in both populations. On the other hand, the influence of patient's age in children was much higher than that in adults – almost 3.4 times. Many authors have shown increase in values of CBZ clearance with the age of the patients in both pediatric and mixed (children and adults) populations [7,27,33], which is in agreement with our results.

As a second significant factor of both models, we have noted total daily dose of CBZ. Although some authors reported nonlinear influence of total daily dose on CBZ clearance [24,29,30], our findings have shown that the relationship was linear. That is in agreement with results from the studies carried out in children, adolescents and adults [27,34]. Our derived results may be explained by the decrease of CBZ bioavailability and the increase of its clearance through auto-induction of metabolism at higher doses [24,27,30,34]. On the other hand, some autors have shown inherent correlation between dose and clearance [35-37].

Phenobarbital is the third important determinante of the final model, which increases clearance of CBZ in the adult population. This drug-drug interaction is occurs in the phase of metabolism of carbamazepine trough cytochrome P450 enzyme systems. Phenobarbital is a very potent inducer CYP3A4, CYP2C8 and CYP1A2 isoenzymes that are active participate in metabolism of CBZ. As demonstrated in previous studies, the effect concomitant therapy PB with CBZ led to significant increase in CBZ clearance and it is very important for clinical practice in the treatment of epilepsy [27,29-31,33].

6. Lamotrigine

Lamotrigine is used for various types of epilepsy and epilepsy syndromes as mono- or adjunctive therapy, both in children and adults [38,39]. It has pronounced interindividual variability in pharmacokinetics. Furthermore, its dosing is frequently complicated by comedication with other antiepileptic drugs (enzyme inductors or inhibitors) [40]. These predominantly pharmacokinetics but also and pharmacodynamics interactions are clinicaly relevant for patients with epilepsy. Particularly interesting are drug-drug interactions between lamotrigine and carbamazepine or valproate which are often use in clinical practice.

Our earlier study (in period from 2007 to 2008) included 38 patients with epilepsy whose mean age was 25.78 ± 13.15 years [10]. The target population consisted of both children and adult patients (7-62 years). In addition to the previosly mentioned factors, the study examined the influence of concomitant therapy with valproate, carbamazepine, phenobarbital, and topiramate (the numbers of patients with comedication were 13, 8, 2, 3, respectively, whereas on LTG monotherapy were 12 epileptic patients).

Equation for the final model which described value of population LTG clearance was as following [10]:

$CL\ (l\ h^{-1}) = 0.615 + 0.01 \times TBW + 0.00445 \times DD + 1.13 \times CBZ - 1\ xVPA$

Derived model clearly showed four significant predictors of LTG clearance in the target population: total body weight, daily dose of lamotrigine and comedication with carbamazepine and /or valproate.

Previous studies have shown that total body weight described part of the interindividual variability of LTG clearance in other studies, too [41-46]. Increase of CL LTG with increase in TBW was noted in a heterogenous Spanish population and also in pediatric and elderly population of epileptic patients [41,42,44,46].

Inclusion of total daily dose of LTG in the final model is possible indication for a certain degree of

autoinduction of drug metabolism in the target population. Nowadays, there are contradictory reports about the presence of autoinduction of LTG metabolism. Several studies suggested an absence of autoinduction [47,48]. However, Hussein and Posner [49] reported increased lamotrigine clearance by 17.3% during 48 weeks of therapy due to autoinduction of the drug. This is in agreement with other authors who noted the presence of a slight autoinduction of LTG [50-52].

A large part of lamotrigine variability could be explained by the influence of concomitant AEL therapy, especially with enzyme inductors or inhibitors [43-46]. Although LTG is neither an enzyme inducer nor inhibitor CYP P450 isoenzyme, the proces of its metabolism is the main location for numerous drug interactions when they are added in therapy. Lamotrigine is metabolised to inactive metabolites by conjugation in the liver via enzyme uridine diphosphate glucuronosyl transferase (UGT). The normal half-life of LTG elimination is between 24 and 37 hours. However, that time can be twice or more reduced (12-15h) or increased (70h) in presence potent enzyme inductors i.e. carbamazepine, phenobarbital, phenytoin or inhibitor such as valproate [10]. These interactions is clinicaly most significant due to the possibility of loss of therapeutic effect or the occurrence of adverse reactions of LTG. These enzyme inducers led to increase activity of varius CYP P450 and UGT isoenzymes. Our findings suggested that concomitant administration with carbamazepine resulted in an increase of lamotrigine clearance. Total body weight was also included in our final model of CL LTG and because of that the influence of carbamazepine will be greater in patients with lower total body weight. On the other hand, the effects of phenobarbital on CL LTG was not shown (this covariate was not well represented in our population). Earlier studies have reported about significant influence of phenobarbital on mean population value of lamotrigine clearance [43,45].

It is known that the serum concentration of lamotrigine could be significantly increased in the presence of concomitant therapy with valproate. Because of drug-drug interaction, the manufacturer recommended a specific dosing regimen due to increased risk for toxic effects of lamotrigine and cutaneous rash in the patients [53]. Valproate predominatly inhibites CYP 2C9 isoform and metabolism of the drugs that are metabolised via the same isoenzyme. Possible mechanism for the interaction of valproate with lamotrigine is the competition of these drugs for a reaction of conjugation (glucuronidation). As a result, the metabolism of LTG is inhibited and consequently increased serum concentration and half-life of LTG. The dose of lamotrigine should be carefully titrated and reduced in patients on therapy with valproate, resulting in avoiding problems with toxicity and many adverse events of lamotrigine. Several studies have shown that this drug combination have a potentially sinergistic effect on refractory epilepsy [54-56]. Furthermore, other authors reported a significant decrease in lamotrigine clearance caused by concomitant administration of valproate, as it was confirmed in our study [43-45].

7. Conclusions

Numerous population pharmacokinetic studies worldwide are performed in order to provide the basis for the implementation of individual dosage regimens of antiepileptic drugs. This is a brief review of our earlier PPK analysis of valproate, carbamazepine and lamotrigine conducted on different epileptic populations in Serbia. We hope that our research over the past few years provided a good basis for clinicians to improve treatment of epilepsy. Individualization of drug dosage is the basis of rational therapy, and therefore the factors of pharmacokinetic variability will always be subject of intense research.

Acknowledgements

This study was partially funded by grant No 175007 from Serbian Ministry of Education.

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