

Effect of treatment and additional disease on pharmacokinetic of valproic acid in children with epilepsy[◆]

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ABSTRACT

Background. Most of bayesian pharmacokinetic studies and the influence of clinical variables have been carried out in adults. **Purpose.** The aim was to estimate population-based pharmacokinetic of valproic acid (VPA) and to determine the effect of treatment and additional disease on its performance in children with epilepsy. **Material and methods.** For the study steady-state serum concentrations of VPA were determined from 108 epileptic patients (44 females and 64 males) who were receiving the anticonvulsant as main drug of treatment with age range since 1 to 16 years (median 4y, 6m) and weight since 5.2 to 50 kg (median 17.5 kg). All patients had their renal, hepatic and nutritional functions normal. One compartment model using interactive two-stage Bayesian approach was employed in the analysis. **Results.** Population estimates of CL/F and V/F for VPA were 0.022 ± 0.013 L/h and 0.217 ± 0.134 L/kg, respectively. These estimates were significantly affected by weight, age, carbamazepine (CBZ) and gastroesophageal reflux (GER). The final regression models were: CL/F (L/h) = $0.0696 + 0.0031(\text{Age}) + 0.0075(\text{Weight})$; and V/F (L) = $0.674 + 0.0308(\text{Age}) + 0.0756(\text{Weight})$. Prediction of VPA serum concentration in other validation group revealed an important improvement in the predictive performance of VPA concentrations in comparison with the basic model that did not include any co-variables. **Conclusions.** Based on a population model of children with epilepsy, the pharmacokinetic of VPA could be altered by weight, age and the administration of CBZ and additional GER to epilepsy.

Key words. Anticonvulsants. Children. Epilepsy. Interactions. Pharmacokinetic.

Efecto del tratamiento y enfermedades adicionales sobre la farmacocinética de ácido valproico en niños con epilepsia

RESUMEN

Antecedentes. La mayoría de estudios sobre farmacocinética poblacional y la influencia de variables clínicas han sido realizados en adultos. **Objetivo.** Conocer la farmacocinética poblacional de ácido valproico (AVP) y evaluar el efecto del tratamiento y las enfermedades adicionales en niños con epilepsia. **Material y métodos.** Para el estudio se analizaron las concentraciones séricas de AVP alcanzadas en el estado estacionario de 108 pacientes con epilepsia (44 mujeres y 64 hombres) quienes recibieron AVP como principal medicamento para su tratamiento, en niños con un rango de edad de 1 a 16 años (mediana de 4a, 6m) y peso de 5.2 a 50 kg (mediana de 17.5 kg). Todos los pacientes tenían función renal, hepática y nutricional normal. Para el análisis farmacocinético se utilizó el modelo de un compartimiento aplicado en dos etapas. **Resultados.** Los estimados poblacionales de CL/F y V/F para AVP fueron 0.022 ± 0.013 L/h y de 0.217 ± 0.134 L/kg respectivamente. Estos valores fueron alterados significativamente por efecto del peso y la edad, así como por la coadministración de carbamazepina y presencia de reflujo gastroesofágico. Los modelos de regresión fueron: CL/F (L/h) = $0.0696 + 0.0031$ (edad) + 0.0075 (peso) y V/F (L) = $0.674 + 0.0308$ (edad) + 0.0756 (peso). La predicción de las concentraciones séricas de AVP en un segundo grupo incluido para la validación del modelo, mostraron mejoría en la predicción de las concentraciones de AVP en comparación con el modelo básico que no incluyó ninguna co-variable. **Conclusiones.** Se encontró que la farmacocinética poblacional de AVP en niños con epilepsia es alterada por el peso, edad, así como la co-administración de carbamazepina y del reflujo gastroesofágico, lo cual supone una interacción tanto farmacocinética como farmacodinámica.

Palabras clave. Anticonvulsivos. Niños. Epilepsia. Interacciones. Farmacocinética.

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INTRODUCTION

Epilepsy is a neurological sickness which presently occupies second place in prevalence after cerebrovascular disease, and if not adequately controlled, could be incapacitating and mortal.¹ For the management of epilepsy, hundreds of antiepileptic drugs have been used, some of which have little or no advantage over others.²⁻⁴ In our country, valproic acid (VPA) is presently the most used anticonvulsant drug with 27%. This is attributable to the fact that it possesses some advantages in effectiveness over others, although, its use in pediatric population has not been long.⁵ Other anticonvulsants in use in a lesser degree are carbamazepine 18%, diphenylhydantoin 17% and phenobarbital 14%.

In spite of the advent of new anticonvulsants, VPA has continued to be the primary drug for the treatment of epilepsy in its different forms in most of the developing countries and with a relatively low cost. The efficiency as well as the toxicity depends on the blood concentration of the drug which in turn depends on the dose.

VPA (n-dipropyl-acetic acid) is rapidly absorbed and reaches its maximum concentration (C_{max}) between 2 and 4 hours. Its volume of distribution (V_d) is from 0.1 to 0.4 L/kg. It binds with blood proteins in 90% and its principal metabolite is an ester conjugated with glucuronide acid. It has a half life of 9 hours and its elimination is mainly renal.

The pharmacokinetic studies of anticonvulsant drugs have helped in establishing their optimum scheme of treatment and in making sure that their levels are maintained within therapeutic range by avoiding inadequate levels.^{6,7} In the same manner as above, the pharmacokinetic population models have contributed not only in anticonvulsants,^{8,9} but also in other drugs.^{10,11} Despite everything however, we still have very few reports on the pharmacokinetic studies of anticonvulsants in pediatric population using bayesian approach since the majority of the existing reports were in adults.^{12,13}

Some studies on formulation and/or dosage variables which tried to optimize their procedures using Bayesian population analysis with AVP in children have been reported.¹⁴⁻¹⁶ An important objective in the treatment of epileptic patients consists of opportune obtainment of the therapeutic concentration and with minimum uncertainty. However, various studies have showed ample variability in the pharmacokinetic of anticonvulsant among individuals in these patients. This variability is a limitation in the prediction of the relationship existing among doses,

blood concentration and therapeutic response in epileptic patients. One way of improving the predictive capacity of this relationship hinges on obtaining more information on the pharmacokinetic behavior of the drugs in the patients. The application of bayesian statistical technique of prediction gives way to improving the estimation of these therapeutic parameters for a particular patient.⁸

The bayesian method estimates the pharmacokinetic parameters for single patient using a priori the distribution and variability of population parameters.¹⁷ This method represents a very important and useful tool for drug therapeutic monitoring, even when the steady state of the drug has not been reached and only few samples per patient are needed.¹⁸ For this, the application of this method could be advantageous for pediatric patients for the mere reason that it eliminates ethical problems and the logistic of multiple samples.^{19,20}

The objective of the present study was apart from evaluating the effect of clinical variables as treatment and additional disease to epilepsy as well as biological variables as weight and age, is to describe the pharmacokinetic of valproic acid in a population of epileptic children using bayesian program of analysis.

MATERIAL AND METHODS

To establish the pharmacokinetic population model of valproic acid, the study was carried out with 108 patients (44 males and 64 females) with age range since 1 to 16 years (median 4y, 6 m) and weight since 5.2 to 50 kg (median 17.5 kg). The children were attended in the out-patient clinic of the Neurology service of National Institute of Pediatric. Only those with a diagnosis of epilepsy and who were treated with sodium valproate were selected for the study. The study was approved by the Institutional Research Committee and informed consent was obtained. The doses which were administered to the patients analyzed were on average 30 mg/kg/d of VPA given as tablets or oral solution. The liver, renal, and nutritional functions of the patients included in the study were normal. Serum levels of VPA were measured as a routine policy of drug sampling in the hospital. The samples (0.5 mL of blood) were obtained at steady state before the morning dose was given. Plasma levels were measured by using SYNCHRON LX system, (Beckman Coulter, Inc) which is based on a turbidimetric immune-inhibition of drug binding to particle (DBP). The sensitivity of method was 2 µg/mL with inter and intra-assay va-

riability of less than 10%. The pharmacokinetic parameters of each of the patients were estimated using PKS program (Abbott Lab), which uses non-parametric expectancy maximization algorithm (NPEM) by applying only the information from three samples of valproic acid per patient.

In the first stage, the algorithm estimated the distributions of pharmacokinetic population parameter by relating the demographic data with serum concentration of valproic acid of each patient. This distribution was carried out under the assumption that the drug fits to one compartment open model.²¹ Samples were taken before the administration of the next dose at a time of minimum concentration, for the mere reason that this correlates better with the therapeutic effect of VPA.²²

To evaluate the pharmacokinetic population performance behavior, a second group of children consisting of 30 individuals who had the same inclusion criteria, but were not included in the original group of analysis used in the construction of pharmacokinetic model were recruited. The VPA concentrations measured in these patients were compared with the corresponding concentrations predicted by the basic and the final model. The predictor error was calculated as suggested by Sheiner and Beal.²³ Bias was assessed through the mean predictor error (MPE) and at its 95% confidence interval (CI). The values of the two models were compared. Optimum performance of the prediction is the bias of the median of prediction error calculated as follows:

$$MPE = \Sigma PE/n$$

Where ΣPE is the difference between the estimated value in each study group and n is the number of patients studied. A negative bias means that the bayesian method sub-estimated the parameters while a positive one indicates over-estimation of the same. The precision is calculated as the square

of the median value of errors (SME) using the equation:

$$SME = \Sigma (PE)^2/n$$

If the result of this is near to zero, this shows that the pharmacokinetic population model is adequate.

RESULTS

Table 1 shows the results of the laboratory test for the evaluation of liver and renal functions as well as the nutritional state of the patients under study. These results showed that these three conditions were normal. Among the principal diagnosis found in the patients included in the study were partial seizure crisis in 38% of the population; generalized crisis in 35% and others (Table 2). Although, the majority (56%) of the studied population had epilepsy as the only sickness, there were some patients with additional sickness like meningitis 10% and gastric reflux 10%. The rest of the sicknesses can be observed in table 2.

For the construction of pharmacokinetic model, some data like blood concentration of valproic acid, treatment scheme, duration, doses, and some laboratory examinations like blood creatinine and the levels of albumin of each and every one of the patients were registered.

The estimated parameters for pharmacokinetic population were as follows: apparent distribution volume (Vd/F) 0.217 ± 0.134 L/kg and clearance (Cl/F) 0.022 ± 0.013 L/kg/h. In these pharmacokinetic parameters, we did not observe any statistically significant difference ($p < 0.241$) among sex. The rest of the pharmacokinetic parameters obtained are reported in table 3.

The influence of some of the studied variables was analyzed with the intention of explaining the variation of the pharmacokinetic model in order to know those

Table 1. Laboratory data of the patients included in the population pharmacokinetic study of valproic acid (average \pm SD).

Total n = 108	Creatinin (mg/dL)	Haematocrit (%)	Proteins (g/dL)	Albumin (g/dL)	GOT (g/dL)	GPT (g/dL)
	0.44 ± 0.29	38.8 ± 3.64	6.46 ± 0.78	3.56 ± 0.56	35.73 ± 19.48	21.18 ± 17.53
Female n = 64, (60%)	0.41 ± 0.12	39.7 ± 3.41	6.5 ± 0.56	3.79 ± 0.44	36.18 ± 19.59	21.31 ± 17.7
Male n = 44, (40%)	0.46 ± 0.35	38.3 ± 3.73	6.42 ± 0.87	3.47 ± 0.59	35.51 ± 19.45	21.13 ± 17.32
Statistical difference	ns	ns	ns	ns	ns	ns

GOT: Glutamic oxaloacetic transaminase. GPT: Glutamic pyruvic transaminase. ns: not significant.

Table 2. The most common diagnoses of the patients in the pharmacokinetic population study of valproic acid.

Type of Seizure	n (%)	Additional disease*	n (%)
Generalized seizure	35 (33)	Gastroesophageal reflux	11 (10)
Partial seizure	38 (35)	Meningitis	11 (10)
Absence of seizure	12 (11)	Upper respiratory infection	10 (9)
West Syndrome**	23 (21)	Craniocerebral trauma	5 (4)
		Bronchopneumoniae	10 (9)
Patients with only seizure	61 (56)		

*Added to seizure. **Known as difficult to control.

Table 3. Population pharmacokinetic parameter of valproic acid in the patients included (average \pm SD).

Patients	Volume of distribution Vd (L/kg)	Clearance Cl (L/kg/h)
Total n = 108	0.205 \pm 0.137	0.020 \pm 0.014
Female n = 64 (60%)	0.217 \pm 0.134	0.022 \pm 0.013
Male n = 44 (40%)	0.200 \pm 0.141	0.020 \pm 0.014
Statistical difference	ns	ns

ns: not significant.

Table 4. Effect of drug treatment on volume of distribution (Vd) and clearance (Cl) of valproic acid (VPA) in the patients included in the study (average \pm SD).

Parameter/treatment	VPA (only)	VPA + CBZ	VPA + DPH	VPA + PB	Significance*
N (%)	35 (32)	36 (33)	24 (22)	13 (12)	
Vd (L/kg)	0.205 \pm 0.14	0.234 \pm 0.162	0.178 \pm 0.117	0.173 \pm 0.131	p < 0.001
Cl (L/kg/h)	0.021 \pm 0.014	0.023 \pm 0.014	0.018 \pm 0.011	0.017 \pm 0.013	p < 0.001

*After Student-t test, comparisons were made when VAP was given alone vs. rest of treatments. CBZ: Carbamazepine. DPH: Diphenylhydantoin. PB: Phenobarbital.

that significantly alter Cl and Vd parameters. On constructing the model that explained clearance variability we obtained the following objective equation:

$$Cl = 0.0696 + 0.0031 \times (\text{age}) + 0.0075 \times (\text{weight})$$

When these variables are considered, it is possible to explain the clearance value of 85%, reason why the rest of the established variables could contribute little or nothing in this aspect. The equation that describes the tendency of distribution volume is as shown below:

$$Vd = 0.674 + 0.0308 \times (\text{age}) + 0.0756 \times (\text{weight})$$

The value of the distribution volume can be applied to the tune of 81% to the age of the pa-

tient, and when the weight variable is included, a 95% of response over the distribution value could be reached. Moreover, the analysis of the variables which were considered to be small could increase the response value of the said pharmacokinetic population parameter. Later, the effect of treatment with other drugs on Vd and Cl was evaluated with the observation that the simultaneous administration of VPA and carbamazepine (CBZ) tends to increase the parameters of Vd from 0.205 \pm 0.140 to 0.234 \pm 0.162 L/kg (p < 0.001), while Cl increased from 0.021 \pm 0.014 to 0.023 \pm 0.014 L/kg/h (p < 0.001).

On the other hand, simultaneous administration of VPA and diphenylhydantoin (DPH) or phenobarbital (PB) tended to decrease both parameters with Vd value of 0.178 \pm 0.117 L/kg for VPA with DPH

Table 5. Effect of some diseases on volume of distribution (Vd) and clearance (Cl) of valproic acid (VPA) in the patients included in the study (average \pm SD).

Parameter/treatment	Seizure only	Seizure + GER	Seizure + MN	Seizure + URI	Seizure + CCT	Seizure + BP	Significance
N (%)	61 (56)	11 (10)	11 (10)	10 (9)	5 (4)	10 (9)	
Vd (L/kg)	0.236 \pm 0.153	0.128 \pm 0.029	0.132 \pm 0.072	0.137 \pm 0.117	0.118 \pm 0.075	0.192 \pm 0.155	p < 0.001
Cl (L/kg/h)	0.024 \pm 0.015	0.013 \pm 0.002	0.013 \pm 0.007	0.014 \pm 0.011	0.032 \pm 0.015	0.019 \pm 0.015	p < 0.001

*After student-t test, comparisons were made when patients had seizures only vs. rest of additional disease. GER: Gastroesophageal reflux. MN: Meningitis. URI: Upper respiratory infection. CCT: Craniocerebral trauma. BP: Bronchopneumoniae.

Table 6. Relationship between the analyzed samples and treatment with valproic acid to patients included for construction of model and those for validation group.

Variable	Construction group	Validation group
No. analyzed samples	108 (2.4)* = 260	30 (1.4)* = 42
Analyzed simple per patient	2.40 \pm 0.82	1.42 \pm 0.36
Doses administered (mg/kg/d)	38.60 \pm 12.31	32.30 \pm 4.72
Concentration (μ g/mL)	74.97 \pm 31.59	70.88 \pm 18.2
Duration of treatment (days)	122.01 \pm 47.85	32.13 \pm 12.45

*Average of samples analyzed in each group, X \pm SD, Mean \pm Standard Deviation.

and 0.1739 ± 0.131 L/kg for VPA in combination with FB. The effect of phenobarbital and other drugs was analyzed too. This was examined as bimodal (yes or no). The complete value of this interaction is shown in table 4. Finally, it was found that the presence of other diseases could also alter the pharmacokinetic parameters. For example, the presence of seizure together with gastroesophageal reflux (GER), meningitis, airway infections, or pneumonia all tended to decrease significantly the value of Vd to 0.128 ± 0.029 , 0.132 ± 0.072 , 0.137 ± 0.117 and 0.192 ± 0.155 L/kg respectively. In the same way, the value of Cl was also significantly reduced to the tune of 0.013 ± 0.002 , 0.013 ± 0.007 , 0.014 ± 0.011 and 0.019 ± 0.015 L/kg/h respectively. The complete data of this information is shown in table 5.

In table 6, the summary of the samples analyzed in each of the study groups as well as the doses and concentrations found are presented. It is necessary to point out that some patients had been on treatment for some months while others were just for some days. The only requirement to be enlisted in the study was to have had at least more than three days of treatment which is the time required to obtain VPA stationary state.

On making prediction of the concentrations, a correlation index of $r = 0.61$ was obtained bet-

ween the concentrations observed and the predicted concentration with a standard error of 07.1% as shown in figure 1. Besides, the correlation between age and weight for Vd and Cl was investigated and this was found to be good for the two variables in children under monotherapy. This correlation between Vd and weight had $r = 0.865$, while the correlation of Vd and age is found to be $r = 0.903$. Other important correlations were Cl vs. weight and Cl vs. age with $r = 0.748$ and 0.816 respectively.

In order to estimate the predictive performance of the selected final mode, prediction of the VPA serum concentration was calculated and compared with VPA measured concentrations in the validation group. This assessment revealed an important improvement in the predictive performance of VPA concentrations in comparison with the basic model that did not include any covariates.

DISCUSSION

In adult population, the application of bayesian method for the estimation of pharmacokinetic parameters and individualization of doses has proved to be a valuable tool in clinical practice for different drugs.^{21,24} However, the evidence in pediatric patients is limited.²⁵ The bayesian method combines

the information on statistical distribution of pharmacokinetic parameters (*a priori*) with that of serum concentration of drugs obtained from the patient. The pharmacokinetic population parameters ought to be representative of the population in which the patient belongs.²⁶ This is important, especially when there is a limited sample per patient due to the fact that under this circumstance, the value of the function depends more on the population parameters over and above a bayesian predictor's performance in specific subpopulation.

It is even more relevant due to logistic and ethical limitations to carry out an extensive blood sample in order to have a specific pharmacokinetic model for the drugs and the population of interest in an epileptic pediatric patient.¹⁹

In this study, the population parameters of valproic acid were compared in two groups of pediatric patients suffering from epilepsy. In one group, the parameters were based on the information obtained only from the defined behavior on the included proper characteristics of the population with the parameters determined in the second group. In this, we take into account the influence of the variables that mostly affect *a priori* the determined pharmacokinetic in the initial population group. Our comparison showed that the clearance and the distribution volume can be estimated with a bias and clinically acceptable precision with bayesian method. The clinical implication of these findings will depend on the determination of the primary pharmacodynamic related to the therapeutic efficiency, for example, the control or absence of seizure. In this way, an important bias and a poor precision in the estimation of

Vd and Cl could lead to a suboptimum therapy. For the mere reason that $AUC = \text{doses divided by } K_{el} \times V_d$, the precise and unbiased estimation of these parameters could be therapeutically relevant.

A priori, the obtained Vd in our study is 0.217 ± 0.134 L/kg which is similar to that reported in the literature for valproic acid in a pediatric population.²⁷ Studies in epileptic pediatric patients showed that the sub-therapeutic concentrations of anticonvulsants are associated with a high presence of seizure crisis in the patients which denotes a usage of an anticonvulsant agent in a form that is not effective.

An ample inter-individual variability was observed in the pharmacokinetic parameters of valproic acid in our patients who were *a priori* analyzed. This ample inter-individual variability is described for various drugs in epileptic patients.^{28,29} As shown in figure 1, the relationship between observed and predicted plasma valproic acid concentrations appeared to be poor at highest concentrations. This observation can reflect the peculiar pharmacokinetic behavior of VPA, which is highly bound to serum albumin, and at plasma therapeutic concentrations, saturates plasma protein binding sites.³⁰ This capacity limited plasma protein binding may result in non-linear changes in the plasma concentrations of valproic acid, especially when concentrations are higher than 50 mg/L.³¹ Variables with significant effects and which, in a better form explain the variability of the clearance value were the weight and the age of the patients. The rest of the variables analyzed did not affect the clearance value in an important way.

The construction of population model will be of service in evaluating the performance of VPA in a group of smaller patients with similar characteristics to those which were used for the development of pharmacokinetic population model. In such group, we added other variables with the intention of establishing the optimization of anticonvulsive treatment by means of the correlation of pharmacokinetic and pharmacodynamic model, considering some clinical variables as well as the presence of seizure and its duration or the absence of the same.³² Although, these are preliminary results, but they seem to confirm the importance of considering very simple variables like the weight, the age and the treatment of the children before establishing a scheme of anticonvulsive treatment with a drug of common use like VPA in the neurology service using bayesian pharmacokinetic analysis.³³⁻³⁴ The result of our study provides a pharmacokinetic model of valproic acid

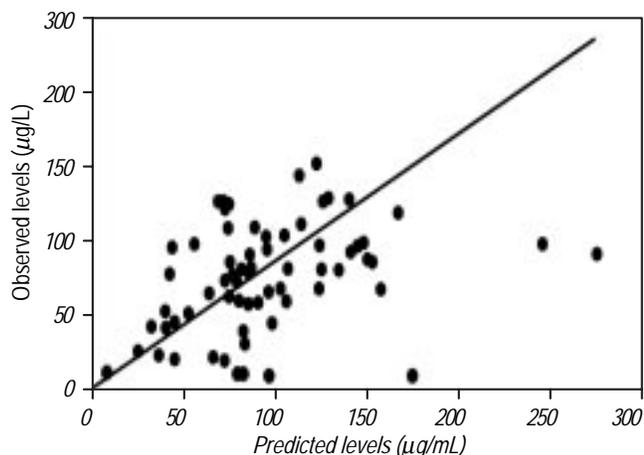


Figure 1. Correlation between observed and predicted concentrations in children with epilepsy treated with VPA. Correlation had a standard error of 7.1%, slanting = $17.4 \mu\text{g/mL}$ and exactness = $67.5 \mu\text{g/mL}$.

for epileptic patients which can be integrated to a bayesian predictor for the design of a regime of individualized doses. Based on a population model proposed to estimate the individual CL/F and V/F for pediatric patients, weight, age and concomitant anti-convulsants or additional disease simultaneous to epilepsy alter pharmacokinetic parameters of VPA.

We specifically observed that patients with gastroesophageal reflux significantly alternate VPA kinetic, i.e. those patents had increased the elimination rate of VPA. Since there are no reported works in this respect to support our results, it would sound adventurous to make definite conclusions, reason why we think that is necessary to carry out new controlled studies in which patients with both involved pathologies. This is vital in making conclusion on the concomitant sicknesses to epilepsy in children. The present work could serve as a point of reference in such a field with scarce studies. However, the clinical recommendation is to monitor the levels of VPA by subjecting the patients to a strict clinical vigilance in order to minimize the effects as consequences of pharmacokinetic alterations.

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