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Original Article

Serum concentrations of valproic acid in people with epilepsy: Clinical implication

[Concentraciones séricas de ácido valproico en personas con epilepsia: Implicación clínica]

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Abstract

Context: Therapeutic drug monitoring (TDM) allows personalizing the dose of valproic acid in patients with epilepsy to optimize drug therapy, minimize adverse effects and detect interactions.

Aims: To determine valproic acid concentrations in serum samples from people with epilepsy and to analyze its clinical implications.

Methods: Cloned donor enzyme immunoassay; descriptive, cross-sectional, non-randomized, convenience recruitment study of 57 voluntary patients with epilepsy (n = 39 male, 68.42%; n = 18 female, 31.58%) aged between 19 and 62 years. After three months of treatment with valproic acid, a single blood sample was collected from each volunteer at a minimal concentration.

Results: Serum drug concentrations 51.30-100.10 mg/L (SD 5.94) and level/dose 2.17-5.31 (SD 1.14) were observed. Association was shown between the dose ratio/dose of valproic acid (R^2 = 0.8693; p<0.05) and the Mann-Whitney U test (p<0.05). Valproic acid monotherapy and association with carbamazepine and phenytoin are not different between treatment groups (Mann-Whitney U test: p = 0.391 > α = 0.05).

Conclusions: Serum valproic acid concentrations are within the therapeutic range, and there is a significant inverse linear correlation between dose ratio/dose, which must be considered to personalize the dose and optimize the pharmacotherapeutic result.

Keywords: dose-dose relationship; epilepsy; serum concentration; therapeutic monitoring; valproic acid.

Resumen

Contexto: La monitorización terapéutica del fármaco (TDM) permite personalizar la dosis de ácido valproico en pacientes con epilepsia, para optimizar la terapia farmacológica, minimizar los efectos adversos y detectar interacciones.

Objetivos: Determinar las concentraciones de ácido valproico en muestras de suero de personas con epilepsia, y analizar su implicancia clínica.

Métodos: Inmunoensayo de enzima donante clonada; estudio descriptivo, transversal, reclutamiento por conveniencia y no aleatorizado de 57 pacientes voluntarios con epilepsia (n = 39 masculinos, 68,42%; n =18 femenino, 31,58%) edad entre 19 y 62 años. Después de tres meses de tratamiento con ácido valproico, se colectó una sola muestra de sangre de cada voluntario a concentración mínima.

Resultados: Se observó concentraciones de fármaco en suero 51,30-100,10 mg/L (SD 5,94), nivel/dosis 2,17-5,31 (SD 1,14). Se mostró asociación entre relación dosis/dosis de ácido valproico (R^2 = 0,8693; p<0,05), y Prueba U de Mann-Whitney (p<0,05). Monoterapia de ácido valproico y asociación con carbamazepina y fenitoína no son diferentes entre los grupos de tratamiento (Prueba U de Mann-Whitney: p = 0,391 > α = 0,05).

Conclusiones: Las concentraciones de ácido valproico en suero se encuentra dentro del intervalo terapéutico y existe una correlación lineal inversa significativa entre relación dosis/dosis, que se deben considerar para personalizar la dosis, y optimizar el resultado farmacoterapéutico.

Palabras Clave: ácido valproico; concentración sérica; relación dosis-dosis; epilepsia; seguimiento terapéutico.

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INTRODUCTION

Epilepsy is a chronic neurological disorder prevalent in developing countries, including Latin America, whose treatment must be through precision medicine, which is based on ethnicity, genotype/phenotype profile, and therapeutic drug monitoring, whose purpose is to maintain serum concentrations within the therapeutic index, minimizing adverse reactions and optimizing pharmacological therapy (Alvarado et al., 2018; Alvarado et al., 2022a; Alvarado et al., 2022b). Various anti-epileptic drugs (AEDs) are used in the treatment of this disease, including valproic acid (VPA). Said drug is specific for the treatment of primary generalized epilepsy, partial and myoclonic seizures (Li et al., 2021), bipolar disorder, mood, anxiety, and migraine prophylaxis (Doré et al., 2017; Ghodke-Puranik et al., 2013; Li et al., 2021; Wallenburg et al., 2017).

VPA is a short-chain branched fatty acid derivative, chemically called 2-propylpentanoic acid, whose mechanism of action is to block voltage-gated sodium and calcium channels, inhibit GABA transaminase (GABA-T), increasing γ-aminobutyric acid levels (GABA), increase 5-hydroxytryptamine (5-HT) levels, decrease dopamine and excitatory neurotransmissions (Doré et al., 2017; Li et al., 2021; Wallenburg et al., 2017). Due to the pKa of 4.8, it is absorbed through the gastrointestinal mucosa to obtain a bioavailability >95%, and a maximum plasma concentration (C_{max}) of 23.5-25.3 mg/L, in a maximum time (t_{max}) of 1.5 hours and an area under the curve ($AUC^{0-\infty}$) of 626-831 mg.h/L (Alvarado et al., 2018). It has a narrow therapeutic index with a minimum effective concentration (C_{mE}) of 50 mg/L (350 mM) and a minimum toxic concentration (C_{MT}) of 100 mg/L (700 mM) (Doré et al., 2017). After absorption, it circulates in the blood 90% bound to plasma proteins, mainly to albumin; this binding is saturable, 93% at 50 mg/L, and 70% at 150 mg/L (Doré et al., 2017; Ghodke-Puranik et al., 2013); the free fraction of the drug (7%) crosses the blood-brain barrier (BBB), more than 30% of the free fraction of VPA can generate adverse effects (Wallenburg et al., 2017). A steady state (C_{ss}) is reached in 3 to 50 days, the volume of distribution (Vd) is 0.1-0.4 L/kg in adults, 0.20-0.30 L/kg in children, half-life ($t_{1/2}$) is 4-20 h, the same that decreases due to the action of enzyme-inducing drugs (Alvarado et al., 2018). 40% of the VPA dose is metabolized by phase I oxidation, mainly with CYP2C9 and CYP2C19, giving rise to 4-hydroxy-VPA, 5-hydroxy-VPA, and 4-ene-VPA, which is involved in hepatotoxicity; CYP2A6 generates 3-hydroxy-VPA (Fig. 1A) (Alvarado et al., 2018; Ghodke-Puranik et al., 2013; Song et al., 2022). The most studied genes that encode proteins of the CYP2C subfamily are located on the long arm of chromosome 10 in the q24 region (10q24), whose allelic variants *CYP2C9**2, *3, *CYP2C19**2,* and *3 predict the poor metabolic phenotype, which are prone to generate side effects and toxicity, mainly hematological and hepatic (Fig. 1B) (Alvarado et al., 2018; Alvarado et al. 2019; Bartra et al., 2021; Doré et al., 2017). Between 30-50% is metabolized by conjugation phase II with UDP-glucuronosyl transferase (*UGT1A3, A4, A6, A8, A9, A10; UGT2B7, 2B15*), which transfers to the glucuronic cation of UDP-α-D-glucuronic acid (UDPGA) to VPA to generate the metabolite VPA O-β-glucuronide (Fig. 1A); metabolism is saturable, and metabolites are eliminated through the urine (Doré et al., 2017; Ghodke-Puranik et al., 2013; Song et al., 2022).

Therapeutic monitoring of VPA in clinical practice is justified by the type of three-compartment pharmacokinetic model followed by the drug, by its narrow therapeutic index, by the *CYP2C9, CYP2C19* and *UGT2B7* 802C>T allelic variants that express polymorphic enzymes (Alvarado et al., 2019; Zhao et al., 2020), by metabolism and binding to plasma proteins that are saturable (Shaikh et al., 2018; Taylor et al., 2019), by non-customized dose (Buoli et al., 2018) and for being an enzyme inhibitor drug; all of this generates unpredictable serum levels, and whose clinical implication is significant (Alvarado et al., 2020; Cotuá et al., 2017).

Through therapeutic drug monitoring (TDM), subtherapeutic and supratherapeutic plasma concentrations are detected, and by calculating the level/dose (N/D) index, a precise dose is proposed that allows maintaining plasma drug levels within the therapeutic index to control the symptoms of epilepsy (Shaikh et al., 2018); possible drug-drug or drug-nutrient interactions are identified, the incidence of adverse effects is minimized and non-compliance with pharmacological therapy, which are the causes of therapeutic failure (Alvarado et al., 2020).

It is necessary to have methods and techniques that allow monitoring AEDs in hospital clinical practice in the city of Mérida-Venezuela, and in other Latin American countries such as Peru, where clinical pharmacokinetics is still not a routine practice, so it is necessary to do research to increase scientific evidence and thereby promote the implementation of clinical pharmacokinetics in our Latin American hospitals. Additionally, the pharmacogenetic profile of the ethnic groups and mestizos of Latin America should be considered, the same ones that are different from other populations. In this sense, through the plasma levels of the drug and the metabolic pheno-

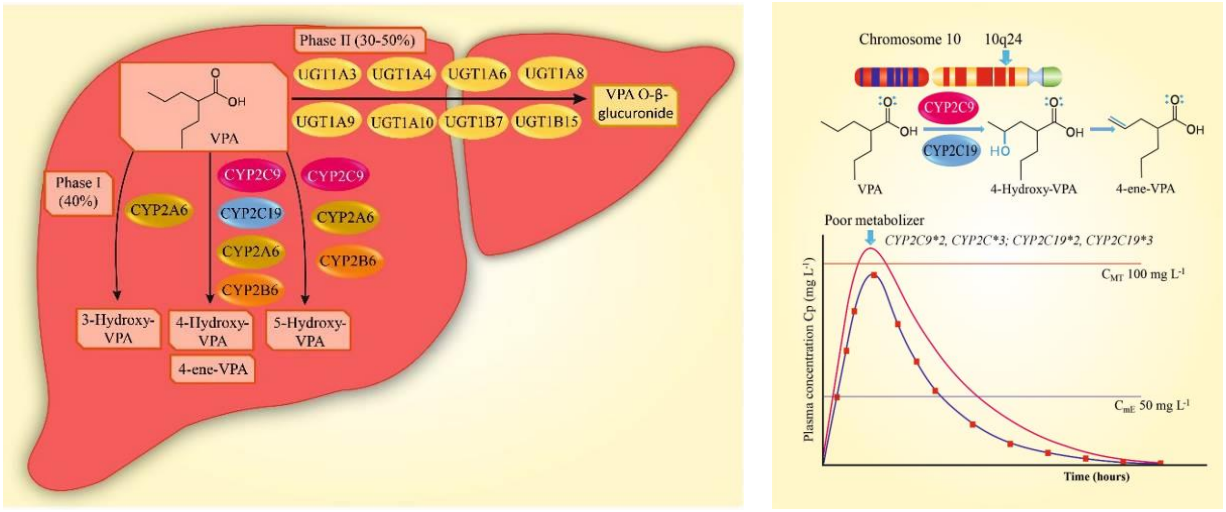

Figure 1. Metabolism of phase I oxidation with the participation of CYP2C9 and CYP2C19; and serum level of valproic acid in people with poor metabolic phenotype.

Figure 1B shows the metabolism of VPA by the two enzymes of greatest clinical importance until it forms the metabolite 4-ene-VPA involved in hepatotoxicity; the serum level of VPA is proposed in patients who present allelic variants of *CYP2C9* and *CYP2C19* for which it exceeds the minimum toxic concentration (C_{MT}) 100 mg/L. Figure made by the authors.

type typical of Latin Americans, a safe and effective therapeutic regimen will be designed for epileptic patients (Alvarado et al. 2021b).

The objective was to determine the concentrations of valproic acid in serum samples from people with epilepsy, and to analyze its clinical implications.

MATERIAL AND METHODS

Design and type of study

Descriptive, cross-sectional, and prospective recruitment for convenience and non-randomized study (Alvarado et al., 2021a; Alvarado et al., 2022a; Bonalde et al., 2021).

Study population and biological sample

The study population was patients with epilepsy who attended the outpatient clinic of the Neurology Service of a Hospital in Mérida, Venezuela, from January 2019 to February 2022. The patients were categorized as volunteers with a diagnosis of epilepsy according to the guidelines of the International League Against Epilepsy (ILAE) (Berg et al., 2010).

The sample consisted of 57 volunteer patients (male 39; female 18) aged between 19 and 62 years. A single blood sample was collected from each volunteer who attended for control and as part of normal medical practice (Alvarado et al., 2022b). The extraction of the blood sample was carried out in the morning before the VPA dose (Minimum concentration); 3 mL of venous blood was collected in Vacutainer tubes, BD Bioscience previously coded (Alvarado et al., 2022a; Alvarado et al., 2022b; Guk et al., 2019; Hernández-Jerónimo et al., 2022).

Selection criteria

The patients who attended the medical control were informed of the objectives and importance of the study, and all those who agreed to participate in the study met the following selection criteria: patients receiving monotherapy with valproic acid (1500-2000 mg/day) or in combination AVP with carbamazepine (CBZ) and AVP plus phenytoin (PHT); with no less than three months of treatment, comply with the dose and frequency of administration of anti-epileptics, and not self-medicate (Alvarado et al., 2019; Alvarado et al., 2022a; Alvarado et al., 2022b).

Valproic acid quantification

The samples were centrifuged at 8,000 rpm for 10 min and performed within two hours of sampling. Then, 0.5 mL of the supernatant was measured (no other special treatment was necessary), determining AVP in the serum by the CEDIA method (Cloned Donor Enzyme Immunoassay) on the Indiko Thermo Fisher Scientific (Waltham, Massachusetts, USA) equipment (Alvarado et al., 2020).

Table 1. Characteristics of the volunteer patients.

Statistic	Male (n = 39; 68.42%)			Female (n = 18; 31.58%)		
	Age (years)	Weight (kg)	Dose (mg/day)	Age (years)	Weight (kg)	Dose (mg/day)
Median	36	77	2000	30.50	68	1000
Minimum	22	68	1000	19	63	1000
Maximum	52	93	2000	62	73	2000
Mean	35.90	77.33	1564.10	36.89	68.44	1222.22
SD	7.93	4.90	502.36	13.63	2.64	427.79

SD: standard deviation; Cp: serum concentration; n: number of volunteer patients.

Ethical aspects

The entire study process was developed in strict compliance with Good Clinical Practices (GCP) and national and international ethical criteria that are based on the Belmont Report, Declaration of Helsinki with the current revision. The Institutional Medical Board approved this study as a minimal-risk investigation for using blood samples from routine clinical practice, through certificate 002-JMI-2019. The patients who agreed to participate in the study signed the informed consent form prior to the collection of the blood sample, immediately assigned a code to guarantee confidentiality and anonymity. The information obtained will be published for scientific purposes (Alvarado et al., 2018).

Statistical analysis

Data were collected in an Excel document, and analysis of variance (ANOVA), non-parametric Mann-Whitney U test, and Pearson's correlation test were performed. A value of $p<0.05$ was considered statistically significant. The Statistical Software GraphPad Prism 9. Version 9.1.2 was used.

RESULTS

One hundred patients were reported and evaluated according to prospective, convenience, and non-randomized recruitment; 57 met the inclusion criteria, being classified according to sex (male 39; female 18), age (19-62 years), weight, and age (Fig. 2 and Table 1). It is noted that the daily dose of AVP was 1000-2000 mg (Table 1).

Serum concentrations were determined in patients with monotherapy and in association with other anti-epileptic drugs (AVP + CBZ and AVP + PHT). It was observed that only 1.75% was within the limit of the minimum toxic concentration (100.10 mg/L). The Kolmogorov-Smirnov test for plasma concentration does not have a normal distribution. Therefore, the non-parametric Mann-Whitney U test was performed ($p>0.05$). The analysis of variance (ANOVA) concludes that the mean serum concentrations are not different in patients of different weights ($p = 0.821 > \alpha = 0.05$); Using the Pearson correlation test, it was determined that the dose (mg/day)/weight (kg) relationship for each patient is low ($r = 0.317$) and statistically significant ($p = 0.016 < \alpha = 0.05$). The therapeutic serum levels, Level/Dose (ND), and proposed maintenance dose of AVP are shown in Table 2.

The relationship between dose (mg/day)-concentration (mg/L) and the therapeutic range is shown in Fig.3. A positive correlation and a low, statistically significant coefficient of determination ($p<0.05$) were found.

The relationship between the dose ratio (mg/L/mg/day) and dose (mg/day) of AVP is shown in Fig. 4. The Kolmogórov-Smirnov test for this variable showed that there is no normal distribution, so the non-parametric Mann-Whitney U test was performed ($p<0.05$).

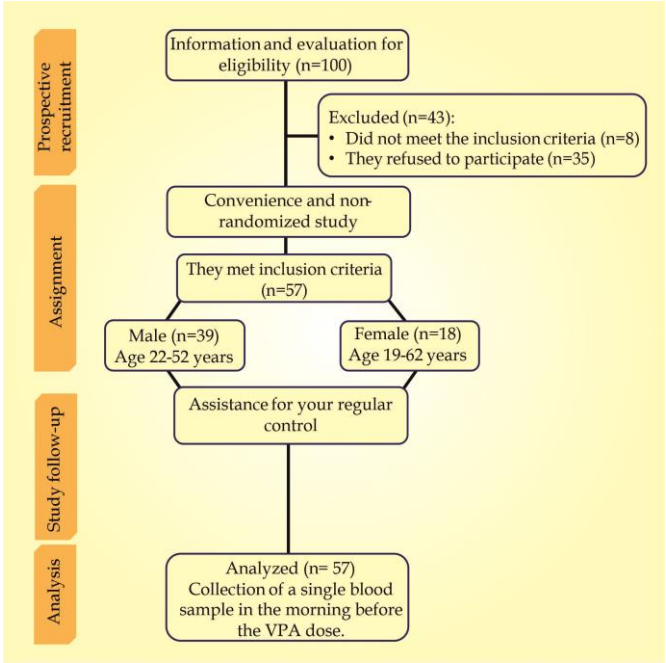

Figure 2. Flow diagram of subjects' progress through the phases of a non-randomized study.

Table 2. Therapeutic level, level/dose, and maintenance dose of valproic acid.

Statistic	Therapeutic level (50-100 mg/L)	Level/Dose	Maintenance dose (**Dm:** mg)
Median	65.74	3.76	1445.00
Minimum	51.30	2.17	1445.00
Maximum	100.10	5.31	2890.00
Mean	65.75	3.73	2104.12
SD	5.94	1.14	726.11

Level/Dose (N/D) was determined by dividing the serum concentration value by the dose (mg/kg/day) [N/D = (C/Dose mg/kg/day)]; the proposed maintenance dose (Dm) was determined with the following equation $Dm = (Cl)(C_{ss})(tau)/S.F.$ Clearance (Cl), steady-state concentration (C_{ss}), administration interval (tau), drug salt (S), and bioavailability value (F).

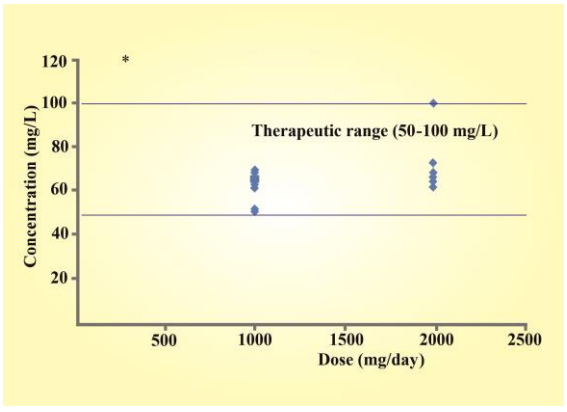

Figure 3. Dose-concentration relationship of valproic acid showing the therapeutic range.

*Pearson's correlation value (r = 0.264; R^2 0.0699; p = 0.047 < α = 0.05).

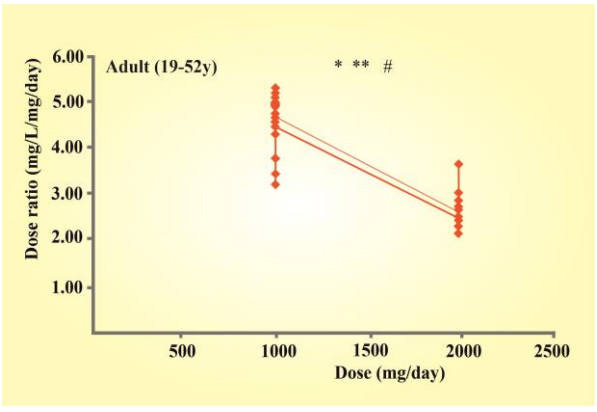

Figure 4. Dose ratio/dose of valproic acid obtained from 57 volunteer patients.

*Pearson's correlation value (r = -0.9323; R^2 0.8693; p = 0.000 < α = 0.05). **Non-parametric Mann-Whitney U test (p = 0.000 < α = 0.05). #Mann-Whitney U non-parametric test for the medians of monotherapy (AVP) and two drugs (AVP + CBZ; AVP + PHT) (p = 0.391 > α = 0.05).

DISCUSSION

The concentration of valproic acid in serum has been evaluated, observing that they are within the therapeutic range; for this study, values of 50-100 mg/L recommended by existing guidelines were considered (Lan et al., 2021; Patsalos et al., 2018). The value of the Mann-Whitney U Test for the median serum concentrations ($p = 0.952$ $\alpha>0.05$) was not different between the male and female sex groups. In this investigation, the patients voluntarily donated a single blood sample after three months of treatment, the purpose of which was for the drugs to reach the concentration in the steady state (C_{ss}); and the time of extraction was carried out at a minimum concentration (Alvarado et al., 2020; Alvarado et al., 2022a; Alvarado et al., 2022b; Guk et al., 2019; Hernández-Jerónimo et al., 2022). In a previous study carried out by Cotuá et al. (2017), it is indicated that the blood sample is taken before the morning dose of the drug, whose serum concentration obtained is called the minimum, basal, trough or pre-dose concentration. Subsequently, Taylor et al. (2019) proposed that VPA can be quantified between the third or fourth day of starting a treatment or the adjusted dose and 12 hours after the last dose received. Regarding the therapeutic interval, Lampón and Tutor (2013) proposed that values less than 81 mg/L should be considered as subtherapeutic concentrations implicated in pharmacotherapeutic failure; and values greater than 147 mg/L as supratherapeutic factors responsible for drug toxicity. While Tseng et al. (2020) observed that a free VPA concentration >14.67 mg/L is related to the appearance of thrombocytopenia (27.6%), hyperammonemia and hepatotoxicity were not related. Buoli et al. (2018) reported that age, sex, and high doses are factors that generate VPA levels higher than the minimum toxic concentrations (100-130 mg/L), which are related to thrombocytopenias.

In the present study, the therapeutic levels for both patients with monotherapy and with two antiepileptic drugs: AVP + CBZ (n = 2; 51.75 mg/L) and AVP + PHT (n = 4; 62.43 mg/L) are within the therapeutic index. However, in a previous study, Ben Mahmoud et al. (2017) reported that subtherapeutic serum levels of VPA increase in young patients ($p<0.02$), when several medications are associated ($p<0.007$) and due to the concomitant consumption of enzyme-inducing drugs ($p<0.02$). Other pharmacological interactions should also be considered, as suggested by Hernández-Ramos et al. (2021), who observed an interaction of valproic acid, meropenem or ertapenem, so they recommend avoiding this combination whenever there is a viable alternative. Regarding the association between administered doses (mg/day)/serum concentrations (mg/L), a low positive linear correlation was observed for each patient at the 5% level of significance. The level/dose index was also determined to know the hypothetical serum level reached with a theoretical dose of 1 mg/kg, and with these values, the precise dose is adjusted (Alvarado et al., 2020). Regarding the VPA dose ratio (mg/L/mg/day)/dose (mg/day), an inverse association was obtained according to the Pearson correlation coefficient (-0.9323) at the 5% level of significance ($p = 0.000 < \alpha$ 0.05) and a coefficient of determination ($R^2 = 0.8693$), which indicates an 86.93% relationship at the linear level of both variables, that is, there is a decrease in the dose relationship with the increase in the dose of acid valproic; according to the value of the Mann-Whitney U Test for the medians of this variable, it is different between the dose groups (mg/day) p = value 0.000<0.05. This same test was applied to find out if there was a difference in those patients who received monotherapy (n = 51) and two antiepileptic drugs (AVP + CBZ; AVP + PHT). It was found that the medians were not different between the treatment groups ($p = 0.391 > 0.05$).

Our findings must be corroborated with pharmacogenetic studies by genotype, ethnicity, and miscegenation, as shown by Zhao et al. (2020), who observed that the allelic variant *UGT2B7* 802C>T and age influence the concentration levels of VPA and suggested administering the anti-epileptic with caution in young patients who are poor metabolizers. In a recent study by Wu et al. (2021) daily VPA doses and free drug concentrations were found to be significantly lower in patients with *CYP2C9*3/*3* allelic variants versus *CYP2C9*1/*3* groups and *CYP2C9 *1/*1* ($p<0.05$), pharmacogenetic and TDM studies are recommended.

Therapeutic drug monitoring (TDM) of VPA is justified by the three-compartment pharmacokinetic model, protein binding and saturable metabolism (Shaikh et al., 2018; Taylor et al., 2019), enzymes expressed by genes that present allelic variants (Alvarado et al. al., 2019), due to age, sex, non-personalized doses (Buoli et al., 2018) and due to pharmacological interactions (Hernández-Ramos et al., 2021) that generate unpredictable serum levels, and whose clinical implication is significant (Alvarado et al., 2020; Cotuá et al., 2017). With the values of the serum concentration of the drug, it is interpreted if the drug is within the therapeutic index to control the symptoms of epilepsy (Shaikh et al., 2018); when the drug does not reach the minimum effective concentration (C_{mE}), the symptoms of epilepsy are not adequately controlled, and pharmacological treatment is likely to fail (Lan et al., 2021), and when the free drug exceeds the minimum toxic concentration (C_{MT}) predisposes to hepatic, hematological, neuro-

logical toxicity and metabolic syndrome (Carmona-Vázquez et al., 2015; Lan et al., 2021). As there are subtherapeutic and supratherapeutic levels, the level/dose index is determined to adjust and individualize the dose for each patient; additionally, through pharmacotherapeutic follow-up, side effects, toxicity, and non-compliance with pharmacological therapy are detected (Alvarado et al., 2020; Canisius et al., 2020; Cotuá et al., 2017). Pharmacogenetics and clinical pharmacokinetics (clinical monitoring) are the basic sciences of precision medicine that need to be implemented in Latin American countries due to their ancestry, miscegenation, and ethnic groups (Alvarado et al., 2021a).

The results of this research must be considered in the context of various limitations. The main one is in the oral declaration of the patients of having met the selection criteria. Other biases that can lead to confusion are the size of the sample (n = 57), which was not calculated based on the population of patients with epilepsy who attend the Neurology Department, recruitment for convenience and non-randomized, and not designing a case-control study, which are being considered for future studies by our research team; another limitation is the cloned donor enzyme immunoassay method (CEDIA); however, it should be mentioned that these kits are available in hospitals in Mérida, Venezuela.

CONCLUSION

It is concluded that serum valproic acid concentrations are within the therapeutic range, and there is a significant inverse linear correlation between dose ratio/dose, which should be considered to personalize the dose and optimize the pharmacotherapeutic result. It is suggested that TDM should be a clinical and routine practice in Latin American hospitals, given their own ethnicity and miscegenation, for which scientific evidence is required so that the health authorities of each country have the academic and technical foundations to implement these studies in our hospitals.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Alvarado AT	Cotuá J	Delgado M	Morales A	Muñoz AM	Li C	Bendezú MR	García JA	Laos-Anchante D	Surco-Laos F	Loja B	Bolarte-Arteaga M	Pineda-Pérez M
Concepts or ideas	x	x	x	x	x	x	x	x	x	x	x	x	x
Design	x	x	x	x	x	x	x	x	x	x	x	x	x
Definition of intellectual content	x	x	x	x	x	x							
Literature search					x	x	x	x	x	x	x	x	x
Experimental studies	x	x	x	x						x		x	x
Data acquisition		x	x	x									
Data analysis	x			x			x	x	x	x	x	x	x
Statistical analysis	x				x	x	x	x					
Manuscript preparation	x	x	x	x	x								
Manuscript editing	x					x	x	x	x	x	x	x	x
Manuscript review	x	x	x	x	x	x	x	x	x	x	x	x	x

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