Original Article

Evaluation of the Appropriateness of Valproic Acid-Levels Monitoring in Mexican Pediatric Patients

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Abstract

In Mexico, plasma drug quantitation is utilized to check dose titration, compliance, and toxicity in treatment with antiepileptic drugs like valproic acid (VPA), but without considering the pharmacokinetic principles due to the absence of clinical pharmacists in the Health System. This study analyzed the within-patient relationship between dosage and plasma VPA concentrations in different age groups, to evaluate the effect of enzyme-inducing co-medication, and to evaluate the efficiency of the monitoring process performed in a pediatric hospital, to make the pertinent recommendations. This retrospective observational analysis, lasted one year, performed in a pediatric hospital in Hidalgo, Mexico.

This retrospective analysis included the plasmatic concentration data of VPA in pediatric patients of 1 to 15 years old, who had received a reliable diagnosis of epilepsy. Microsoft Excel® was used for the statistical analysis of the data. Files of 260 patients were reviewed. It was found that only 56.5% of the patients had serum levels at a steady state. The plasma VPA levels were found in the sub-therapeutic level in 22% of patients and 15% had toxic levels. The analysis showed that children under five years of age appear as a heterogeneous group for the variables studied. However, the difference in plasma concentrations was not statistically significant ($p<0.05$). Due to the lack of recognition of clinical pharmacists in Mexico, we recommend that the best clinical outcome can only be assessed by monitoring pharmacokinetic parameters for changes occurring in each patient, and not just through trial and error dosing.

Keywords: Valproic, Evaluation, Monitoring, Process

Introduction

In Mexico, plasma drug quantitation is utilized to check dose titration, compliance, and toxicity in treatment with antiepileptic drugs like valproic acid (VPA), but without considering the pharmacokinetic principles due to the absence of clinical pharmacists in the Health System.

Because antiepileptic drugs (AEDs) have complex pharmacokinetics and a narrow therapeutic index, wide fluctuations in plasma concentration may cause either loss of therapeutic efficacy or toxic effects [1, 2].

Antiepileptic drugs (AEDs) have a narrow therapeutic window and a marked inter-individual variability. This can produce a variation in concentration levels in patients, leading to the presence of toxic effects or a lack of efficacy.

Technological advances have allowed the measurement of drug concentrations in biological fluids to aid in the study of the relationship between the administered dose and the pharmacological effect. In this sense, for drugs such as AEDs, it has been shown that low concentrations can produce insufficient effects, and that high concentrations may lead to adverse effects [3, 4]. VPA is a drug extensively used to treat epilepsy (recurrent seizures) in children due to its extensive anticonvulsant activity and the relatively low incidence of central nervous system toxicity [5-7]. It is effective for both generalized and partial seizures in children and especially important in treating absence, myoclonic, and tonic-clonic seizures [8].

Clinical trials have suggested that VPA may have the widest range of antiepileptic activity of all AEDs in both adults and children with epilepsy. In addition to being effective for treating partial seizures as well as generalized seizures, VPA

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has been shown to be effective in treating syndromes such as Gastalt's and West's [9].

This gives the VPA a special place for treating individuals with mixed types of seizures who have highly refractory symptoms. Moreover, due to its broad anticonvulsant spectrum, it is not contraindicated for the treatment of other types of epileptic seizures [9, 10].

In clinical practice, the plasma concentration and the efficacy of VPA vary greatly between individuals.[5] In addition to its broad anticonvulsant spectrum, there are other factors such as the patient's age, body weight, administered dose, pharmaceutical form and frequency of dosage, sampling time, concomitant medication, as well as genetic variations, which can modify the pharmacokinetics of VPA and as a result, modify the value of plasma concentration [11]. Therefore, the quantification and analysis of plasma concentrations of the drug are useful in the treatment of seizures and the decrease in the presence of adverse effects.

Over the years, Therapeutic Drug Monitoring (TDM) has proven its usefulness in the individualization of pharmacological treatments, mainly for drugs that have unpredictable pharmacokinetics. It has also shown its usefulness in special populations, such as pediatric. The use of therapeutic monitoring is recommended in those patients who are being dosed with AEDS since it is an extremely important tool for establishing dosage regimens adjusted to the needs of each patient [12, 13]. Thus, the pharmacokinetics through the TDM helps physicians understand why a patient may not be responding adequately to medication. Likewise, the TDM helps to detect non-compliance in patients, in addition to analyzing inter- and intra-individual variability in pharmacokinetics and the factors that contribute to this variation [3, 14].

Special care is necessary during the treatment of children because of their metabolic characteristics and growth-related changes in the incidence of epilepsy. For instance, the rate of metabolism may be much faster than that of non-elderly adults, and dose adjustment is needed to ensure adequate medication to control seizures. In young infants, drug distribution is reduced compared to older children and adults. During early postnatal development, the activity of liver enzymes increases rapidly and increases to a maximum of 2 to 6 times more than that of adults by the age of 6 months, and by the age of 6 years, it decreases to about twice the rate of adult activities and to adult levels at puberty [15].

Pharmacokinetic interactions are typically related to changes in metabolism by enzyme inhibitors or inducers. Most drug interactions have been detected in the past as a result of an unexpected change in the patient's clinical condition after withdrawal or addition of a drug in their medication [16]. These pharmacokinetic interactions at the metabolic level can produce significant alterations of the plasma concentrations of AEDs, either due to induction or inhibition through the cytochrome P450 enzymatic system [17].

Due to the great interindividual variability in the rate of metabolism of AEDS such as VPA, it is not possible to establish a correlation between the administered dose and plasma concentration, and this is even more complicated in patients who are being comedicated with other AEDS, mainly if they exert an enzyme-inducing effect. Thus, children with combination therapy require higher doses to reach concentrations similar to those observed in adults [3, 5]. It is precisely the unpredictable relationship between the dose administered to patients and the concentration of VPA, which justifies the need to individualize pharmacological therapies through the TDM [3]. The purpose of this study was to analyze the within-patient relationship between dosage and plasma VPA concentration in different age groups with refractory epilepsy, to evaluate the effect of co-medication inducing by enzyme, and to evaluate the efficiency of the monitoring process of the AVP concentrations that are carried out in a pediatric hospital, in order to make the pertinent recommendations.

Materials and Methods

This retrospective analysis included the plasmatic concentration data of VPA in pediatric patients of 1 to 15 years old, diagnosed with epilepsy on clinical indication and monotherapy to receive adjunctive treatment with AEDs polytherapy over a period of twelve months, and absence of related neoplastic, gastrointestinal, endocrine, hepatic, or renal disease.

This study was solely observational and required no deviation from the clinical management plan adopted by the physicians. The main inclusion criterion was that for each patient the minimum concentration of VPA was at a steady state. All patients remained anonymous, and age, gender, weight, dose, concomitant use of other AED, and serum concentration were collected. The main reasons for requesting VPA concentration level measurement consisted of uncontrolled seizures, signs, and symptoms of toxicity, and suspected non-compliance in patients. In order to assess the suitability of the level determination, 2 criteria must be met: 1) correct sampling time (through the level at a steady-state condition) and 2) adequate indication for measurement. Plasmatic concentrations of VPA and the other AEDs were measured in the Biochemical Chemistry Laboratory using the AxSYM® II microparticle enzyme immunoassay (Abbott Laboratories, Abbott Park, IL, USA). Blood sampling in all patients was carried out in the morning, just before the next dose of the drug (through concentration).

The influence of age, bodyweight dose, and concomitant anti-epileptic therapy on plasma concentrations of VPA and potential interactions between AEDs in multidrug therapy for each patient under medical supervision were analyzed. Clinical records were reviewed for follow-up based on

laboratory reports. For the statistical analysis of the data, Microsoft Excel® was used.

Results and Discussion

The patients were initially classified, according to their age, into three groups **(Table 1)**. The relationship between plasma VPA concentration and dosage for 147 patients is shown in **Figure 1a**.

Drug monitoring results of VPA revealed that 63% of patients receiving VPA had the drug in therapeutic levels (established therapeutic range: 50-100 mg/L).

The VPA plasma levels were found in the sub-therapeutic level in 22% of patients and 15% of patients had been found in toxic levels. **Table 2** shows the concentration levels achieved in each age group. A comparison between the 3 age groups showed that in the 1 to 5-year-old group (n = 77), more concentrations were observed outside the therapeutic range **(Figure 1b)**. These groups represent the highest percentage of patients who are treated with AVP for seizure management.

Table 1. Characteristics of the patients

	Group 1	Group 2	Group 3
Number	77	46	24
Gender distribution (Male/Female)	26/51	26/20	9/15
Age(years)	1.93(1.26)	7.32(1.97)	10.35(2.73)
Body weight (Kg)	11.22(4.08)	25.12(11.85)	42.77(16.53)
Daily dosage at last assessment (mg/kg)	33.17(17.79)	30.80(14.18)	28.74(9.44)

Group 1 children aged <5 years; Group 2 children aged 5 to 10 years; Group 3 children aged 10-15 years old.
Data are expressed as means ± SD.

Table 2. Percentage of the plasma drug level of VPA in relation to therapeutic interval and to patients age group.

Group y.o.	Male/Female	Therapeutic Range n (%)	Sub-therapeutic Range n (%)	Toxic Range n (%)	Total of samples
1	26/51	43(56)	16 (21)	18(23)	77
2	26/20	34(74)	3(7)	9(20)	46
3	9/15	16(67)	3(13)	5(21)	24

Group 1 children aged <5 years; Group 2 children aged 5 to 10 years; Group 3 children aged 10-15 years old.

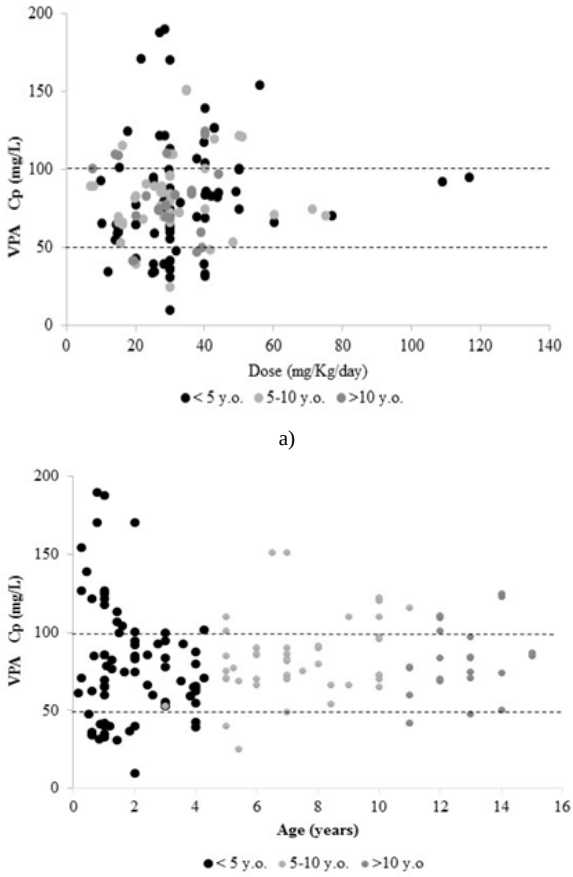

Figure 1. Relationship between plasma VPA concentration at steady state, prescribed daily dosage (panel a) and age (panel b), in 147 patients (divided in three age groups). The dotted line represents the established therapeutic range.

One of the probable reasons why a large percentage of VPA concentrations are below the therapeutic range may be non-compliance by patients. In this sense, one way to improve compliance is to track the doses patients are receiving, and monitor VPA levels on a regular basis, to ensure that therapy is being met. This is particularly useful in patients where non-compliance is a recidivist. Moreover, the measurement of the concentrations can also detect the interindividual variability in the pharmacokinetic behavior of the VPA according to age.

During childhood, the physiological changes that take place are very important and the kinetics of drug disposition can vary considerably with respect to adulthood, Different authors have found a decrease in plasma clearance of VPA with age, so that it is higher in children, as is the case in our population [18-20].

Although the measurements of VPA were made with the minimum concentration at a stationary state, this difference could be attributed to the different bioavailability of the commercialized pharmaceutical forms administered to the patients. In this study, the data shows that children under five

years of age appear as a heterogeneous group for the variables studied. However, the difference in plasma concentrations was not statistically significant ($p < 0.05$). Due to the great interindividual variability that VPA presents and the elevated percentage of concentrations that are outside the recommended therapeutic interval, it is suggested to know the value of VPA clearance in the defined age groups, since it is of great help in the programming of initial dosage guidelines or in the modification of already established dosage regimens. During the study period, files of 260 patients were reviewed. It was found that only 147 patients had serum levels of the drug measured at a steady-state (56.5%); 90% of the VPA prescriptions were for complex partial seizures and 61% received VPA as monotherapy, the remaining 39% included other AEDS in their treatment, such as phenytoin (n= 17), phenobarbital (n= 20), topiramate (n= 10), carbamazepine (n= 4), vigabatrin (n= 3), and clonazepam (n= 3).

While monotherapy remains the preferred treatment for epilepsy, combinations between AEDS are used very often, mainly in those who don't respond to a single drug, and similarly, these combinations are utilized to treat associated or intercurrent conditions [21]. Nevertheless, although combination therapy with AEDS may provide clinical benefits, it may also raise the risk of adverse effects due to pharmacological interactions and affect the well-being of patients [16]. Because only a small number of patients who received other enzyme-inducing AEDS were found during the duration of this study, it was not possible to compare the effect of comedication on VPA clearance within each age group.

In the population studied, 9.1% of the patients presented adverse reactions to the drug, which were drowsiness, headache, vomiting, gastritis and the most severe were leukopenia and thrombocytopenia. In this study, as in other studies conducted at the same center, there were some limitations [22]. Evaluation of the indication of an individual for whom AED measurement was requested was chiefly on the basis of data retrieved from the clinical records that may be incorrect or incomplete; moreover, there was no information regarding the relationship between the therapeutic range reported in patients and their response to AED therapy. Some important information, such as seizure recurrence or suspected side effects related to therapeutic AEDs, may not always be sufficiently listed in the charts as a reason for ordering a drug level. Therefore, based on this brief study, it is considered necessary to correct and adapt the current monitoring methodology used, including a clinical pharmacist who applies the principles of pharmacokinetics and TDM, which allows the optimization of VPA dosage for benefit of patients.

Conclusion

Due to the lack of recognition of clinical pharmacists in Mexico, it is recommended that the best clinical outcomes can be evaluated only by monitoring pharmacokinetic parameters for variations appearing in each patient, and not just through trial and error dosing. The recognition and inclusion of pharmacists in the health team are necessary.

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