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Assessing Valproic Acid Monitoring Practices in Mexican Pediatric Patients

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ABSTRACT

Due to the lack of clinical pharmacists in the health system, plasma drug quantitation is used in Mexico to assess dosage titration, compliance, and toxicity during the treatment of patients with antiepileptic medications such as valproic acid (VPA). However, pharmacokinetic principles are not taken into account. To provide the necessary recommendations, this study investigated the intrapatient relationship between dosage and plasma VPA concentrations in different age groups, assessed the effect of co-medication that induces enzymes, and assessed the effectiveness of the monitoring procedure implemented in a pediatric hospital. A pediatric hospital in Hidalgo, Mexico, conducted this one-year retrospective observational study. In this retrospective investigation, VPA plasmatic concentration data were included from pediatric patients aged 1 to 15 years who had been conclusively diagnosed with epilepsy. The statistical analysis of the data was performed using Microsoft Excel®. A total of 260 patient files were examined. Serum levels were found to be constant in just 56.5% of the individuals. In 22% of patients, plasma VPA levels were found to be sub-therapeutic, and 15% had hazardous levels. Based on this study, children under the age of five years appear to be a diverse group for the factors studied. However, the change in plasma concentrations was not statistically significant ($P < 0.05$). We suggest that the optimum therapeutic outcome can only be assessed by tracking pharmacokinetic parameters for changes that occur in each patient, rather than merely using trial-and-error dosage because clinical pharmacists are not well-known in Mexico.

Keywords: Valproic, Evaluation, Monitoring, Process

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Introduction

Because the health system in Mexico lacks clinical pharmacists, plasma drug quantitation is used to assess dosage titration, compliance, and toxicity while treating patients with antiepileptic medications like valproic acid (VPA). However, pharmacokinetic principles are not taken into account.

Because antiepileptic drugs (AEDs) have complicated pharmacokinetics and a restricted therapeutic index, large changes in plasma concentration may induce either a loss of therapeutic effectiveness or toxic consequences [1, 2].

The therapeutic window for antiepileptic drugs (AEDs) is limited, and there is significant inter-individual variability. Patients may have a range of concentration levels as a result, which might result in harmful side effects or ineffectiveness.

The measurement of drug concentrations in biological fluids has been made possible by technological advancements, which can help with the investigation of the connection between the pharmacological action and the provided dose. Regarding medications like AEDs, it has been demonstrated that low dosages may not have

enough effects, while excessive dosages may have negative side effects [3, 4]. Since it has a broad anticonvulsant action and a low risk of central nervous system toxicity [5-7], VPA is a medication that is widely employed for managing epilepsy (recurrent seizures) in kids. It works well for both generalized and partial seizures in kids and is particularly useful in treating absence, myoclonic, and tonic-clonic seizures [8].

VPA may offer the broadest spectrum of antiepileptic action of any AED in treating epilepsy in people of all ages, according to clinical research. VPA was demonstrated to be useful in managing disorders including Gastalt's and West's, in addition to being successful in curing generalized seizures and partial seizures [9].

Because of this, the VPA has a unique position in curing patients with severely refractory symptoms and mixed forms of seizures. Furthermore, it is not contraindicated for the management of other forms of epileptic seizures because of its broad anticonvulsant range [9, 10].

VPA's plasma concentration and efficacy in clinical practice vary widely from person to person.5 As well as its wide range of anticonvulsant properties, other factors like the patient's age, body weight, administered dose, pharmaceutical form and frequency of dosage, sampling time, concurrent medication, and genetic variations can alter the pharmacokinetics of VPA and, consequently, alter the value of plasma concentration [11]. For this reason, measuring and analyzing the medication's plasma concentrations helps treat seizures and reduce the occurrence of side effects.

Therapeutic drug monitoring (TDM), especially for medications with erratic pharmacokinetics, has demonstrated its value in the customization of pharmaceutical therapies over time. Additionally, it has demonstrated its value in particular groups, such as children. It is advised that patients receiving AED dosages employ therapeutic monitoring as it is a crucial tool for creating dosage schedules adjusted to every patient's requirements [12, 13]. Therefore, the TDM's pharmacokinetics aids doctors in comprehending why a patient could not be reacting well to medicine. Similarly, in addition to assessing intra- and inter-individual variability in pharmacokinetics and the variables that influence this variation, the TDM assists in identifying non-compliance in patients [3, 14].

Due to their metabolic characteristics and growth-related modifications to the incidence of epilepsy, children require special attention during treatment. For example, their metabolism may be significantly faster than that of non-elderly adults, and dose modification is required to make sure that they are taking enough medication to control seizures. Compared to older kids and adults, medication dispersion is lower in newborns. The liver enzyme activity rises quickly during the first six months of pregnancy and reaches a maximum of two to six times that of adults by the age of six months. By the age of six years, it falls to roughly twice the rate of adult activities and reaches adult levels during puberty [15].

Generally speaking, pharmacokinetic interactions are associated with modifications in metabolism caused by enzyme inducers or inhibitors. In the past, the majority of drug interactions have been identified as a consequence of an unanticipated shift in the patient's clinical state following the addition or removal of a medicine [16]. Through activation or inhibition via the cytochrome P450 enzymatic system, these metabolic pharmacokinetic interactions can result in significant changes to the plasma concentrations of AEDs [17].

It is impossible to establish a correlation between the administered dose and plasma concentration because of the wide interindividual variability in the rate of metabolism of AEDs, such as VPA. This is made even more difficult in patients receiving other AEDs, particularly if they have an enzyme-inducing effect. Higher dosages are thus needed for adolescents receiving combination treatment to achieve concentrations comparable to those seen in adults [3, 5]. Using the TDM to customize pharmacological treatments is necessary because of the unpredictability of the association between the dosage given to patients and the concentration of VPA [3]. The present investigation set out to examine the intra-patient association between plasma VPA levels and dose in various age groups with refractory epilepsy. To make the appropriate suggestions, it is necessary to assess the impact of co-medication caused by enzymes and the effectiveness of the AVP concentration monitoring procedure used in a pediatric hospital.

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 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. 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

As per **Table 1**, the patients were first divided into three groups based on their age. **Figure 1a** illustrates the correlation between the dose and plasma VPA levels for 147 patients.
63% of patients taking VPA had the medication at therapeutic levels, according to drug monitoring findings (defined therapeutic range: 50-100 mg/L).
It was discovered that 15% of patients had hazardous amounts of VPA plasma, whereas 22% of patients had sub-therapeutic levels. The levels of concentration attained in every age group are displayed in **Table 2**. A comparison of the three age groups revealed that greater amounts outside the therapeutic limit were seen in the group of 77 children aged 1 to 5 **(Figure 1b)**. These patient categories make up the largest proportion of those receiving AVP treatment for managing seizures.

Table 1. Characteristics of the patients

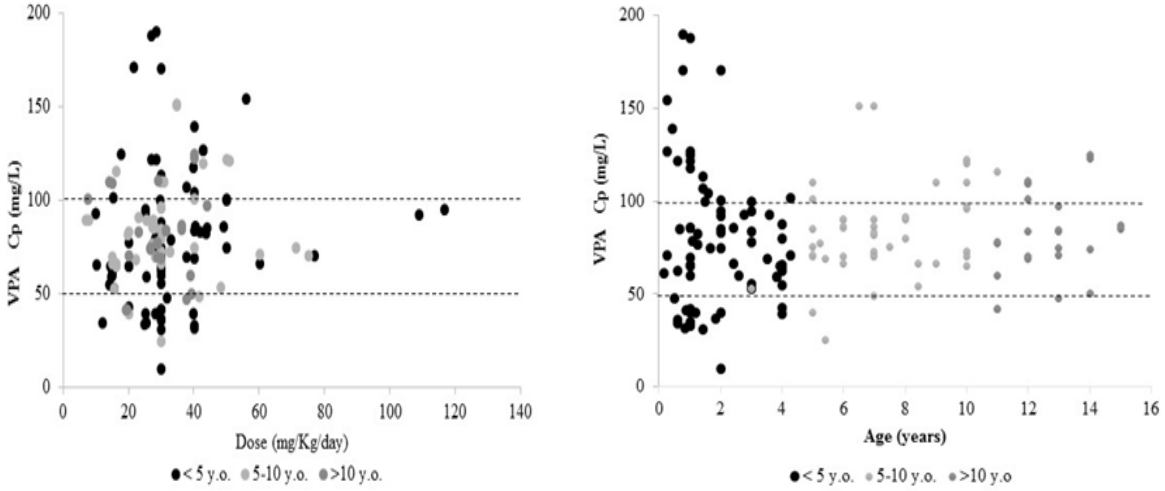
	Group 1	**Group 2**	**Group 3**
Number	77	46	24
Gender distribution (Male/Female)	26/51	26/20	9/15
Age (years), means (SD)	1.93 (1.26)	7.32 (1.97)	10.35 (2.73)
Body weight (Kg), means (SD)	11.22 (4.08)	25.12 (11.85)	42.77 (16.53)
Daily dosage at last assessment (mg/kg), means (SD)	33.17 (17.79)	30.80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

Data are presented as means ± SD for group 1 children (< 5 years old), group 2 children (5-10 years old), and group 3 children (10-15 years old).

Table 2. Percentage of the plasma drug level of VPA about 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 n (%)**
1	26/51	43 (56%)	16 (21%)	18 (23%)	77 (100%)
2	26/20	34 (74%)	3 (7%)	9 (20%)	46 (100%)
3	9/15	16 (67%)	3 (13%)	5 (21%)	24 (100%)

Group 1 children aged < 5 years, group 2 children aged 5-10 years, and group 3 children aged 10-15 years old.



a) b)

Figure 1. Correlation between age (panel b), prescribed daily dose (panel a), and plasma VPA levels at steady state in 147 patients (split into three age groups). The recognized therapeutic range is shown by the dotted line.

Patient non-compliance could have been one of the likely causes of the high proportion of VPA values that fall below the therapeutic limit. In this regard, keeping track of the dosages that patients are taking and routinely checking VPA levels to make sure that treatment is being fulfilled are two ways to increase compliance. For patients whose non-compliance is recidivist, this is very helpful. Furthermore, the interindividual heterogeneity in the pharmacokinetic behavior of the VPA according to age may also be detected by measuring the concentrations.

The physiological changes that occur during youth are crucial, and the kinetics of drug disposal might differ significantly from those of maturity. As is the case in our group, several publications have discovered that the plasma clearance of VPA decreases with age, making it greater in children [18-20].

This discrepancy may be explained by the varying bioavailability of the commercially available pharmacological forms that were given to the patients, even though the VPA measurements were performed at the lowest concentration possible while the subjects were stationary. Children under five years old appear to be a diverse group for the characteristics examined in this study, according to the data. Nonetheless, there was no statistically significant change in plasma concentrations ($P < 0.05$). It is advised to ascertain the value of VPA clearance in the designated age groups due to the significant interindividual variability that VPA exhibits and the high percentage of concentrations that fall outside the recommended therapeutic interval. This is because it is very helpful when creating initial dosage guidelines or modifying existing dosage regimens. A total of 260 patients' files were examined during the research period. The results showed that only 147 patients had steady-state serum levels of the medication (56.5%); 90% of VPA prescriptions were for complex partial seizures, and 61% of patients received VPA as monotherapy; 39% of patients also received other AEDs, including phenytoin (n = 17), phenobarbital (n = 20), topiramate (n = 10), carbamazepine (n = 4), vigabatrin (n = 3), and clonazepam (n = 3).

Although monotherapy is still the recommended treatment for epilepsy, AED combinations are utilized frequently, mostly for patients who do not react to a single medication. These combinations are also used to treat related or coexisting diseases [21]. However, while combination therapy with AEDS may have therapeutic advantages, it may also increase the likelihood of negative consequences from pharmacological interactions and have an impact on patients' health [16]. It was not feasible to compare the impact of medication on VPA clearance within each age group since there were so few patients who took additional enzyme-inducing AEDS throughout this trial.

Leukopenia and thrombocytopenia were the most severe adverse medication responses, with 9.1% of the patients in the population under study experiencing tiredness, headaches, vomiting, and gastritis. There were several restrictions in this investigation, much like in earlier research projects carried out at the same facility [22]. There was no information about the connection between the therapeutic range reported in patients and their response to AED therapy, and the assessment of an individual's indication for whom an AED estimation was needed was primarily based on data taken from clinical records that might be inaccurate or lacking. Certain crucial details, such as seizure recurrence or possible adverse effects associated with therapeutic AEDs, would not always be

adequately indicated in the charts as justifications for prescribing a medication level. Therefore, based on this small study, it is thought that the present monitoring system has to be corrected and modified. This includes hiring a clinical pharmacist who uses TDM and pharmacokinetics concepts to optimize VPA dosage for patients' benefit.

Conclusion

Because clinical pharmacists are not recognized in Mexico, it is advised that the best clinical results be assessed only by tracking pharmacokinetic parameters for differences that may arise in each patient, rather than relying solely on trial-and-error dosage. Pharmacists must be acknowledged and included in the health team.

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