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Appropriateness of Antiepileptic Drug-Level Monitoring at a Childrens' Hospital in Mexico

MARIBEL MÁRQUEZ-CRUZ[1], ALEJANDRO CHEHUE-ROMERO[1], MIRNA ELIZABETH RUIZ-ANAYA[2] and ANA LUISA ROBLES-PIEDRAS[1]*

[1]Universidad Autónoma del Estado de Hidalgo, Instituto de Ciencias de la Salud, Área Académica de Farmacia, Circuito Ex-Hacienda La Concepción, Km. 1.5, San Agustín Tlaxiaca, Hidalgo. México, c.p. 42160.
[2]Hospital del Niño DIF Hidalgo, Blvd. Felipe Ángeles Km 84.5, Venta Prieta, Pachuca de Soto, Hidalgo. México c.p. 42083
*Corresponding author E-mail: roblesa@uaeh.edu.mx

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ABSTRACT

In Mexico, plasma drug monitoring is being used to check toxicity, compliance, and dose titration in treatment with antipileptic drugs (AEDs), but without taking into account the principles of pharmacokinetics due to the absence of a clinical pharmacokinetic service with specialized pharmacists. The present retrospective study was performed to assess the proportion of AED serum level determinations for phenytoin, carbamazepine, phenobarbital and valproic acid fulfilling criteria for appropriate drug level monitoring in hospitalized patients, as well as the potential pharmacokinetic interactions between medications received. Only 40% of requests to measuring concentration levels of phenytoin in the patient were done having reached steady state, followed for 75% for phenobarbital, 79% for valproic acid and 91% for carbamazepine. Therapeutic levels were achieved in a much higher proportion of patients (60%) on phenobarbital treatment as compared to only 26% patients on phenytoin therapy. A total of 117 potential pharmacokinetic interactions were found. We recommend that the better clinical outcome can be evaluated only by monitoring the pharmacokinetic parameters for the variations appearing on individual patients, so that the overutilization or under-utilization or optimum TDM utilization service given to the patients can be analyzed and better patient outcomes can be maximized.

Keywords: Antiepileptic, Drug, Timing, Evaluation.

INTRODUCTION

In Mexico, plasma drug monitoring is being used to check toxicity, compliance, and dose titration in treatment with antipileptic drugs (AEDs), but without taking into account the principles of pharmacokinetics due to the absence of a clinical pharmacokinetic service with specialized pharmacists. Because AEDs have a narrow therapeutic index and complex pharmacokinetic properties, wide fluctuations in their plasma concentration can lead to either toxic effects or to loss of therapeutic efficacy. The development of technology for quantifying drug concentrations in biological fluids has rendered it possible to study the relationship among drug dosage, drug concentration in body fluids, and pharmacological effects. It has been observed that the desired therapeutic effect of many AEDs was usually achieved within a specific range of serum concentrations, with lower concentrations more likely to produce an insufficient effect and higher concentrations more often associated with adverse effects[1,2].

Phenytoin is utilized in the treatment of primary or secondary generalized tonic-clonic seizures, partial or complex partial seizures, and status epilepticus[3]. It leads to a reduction in central synaptic transmission, aiding in the control of abnormal neuronal excitability[4]. Long-term repeated exposure to high serum concentrations of phenytoin may predispose patients to irreversible neurotoxicity and may also exacerbate seizures[5].

Carbamazepine is currently considered a drug-of- choice for the treatment of partial and generalized tonic-clonic seizures[5]. Large interindividual differences in apparent plasma half-life linked with autoinduction and a narrow therapeutic range make this drug a suitable candidate for Therapeutic Drug Monitoring (TDM).

Valproic acid is one of the most widely employed AEDS in the treatment of both generalized and partial seizures in adults and children. The capability of treating many seizure types with a single anticonvulsant has resulted in the widespread use of valproic acid, particularly in children[6].

Phenobarbital is used for the treatment of all seizures, except for absence seizures. It reduces synaptic transmission, resulting in decreased excitability of entire nerve cell-inducing sedation. It potentiates synaptic inhibition through action on the Gamma-AminoButyric Acid-A (GABAA) receptor by increasing duration of chloride flow into the synapse[4].

Anticonvulsants such as phenytoin (Therapeutic Range (TR) = 10-20 mg/L), phenobarbital (TR = 15-40 mg/L), valproic acid (TR = 50-100 mg/L), and carbamazepine (TR = 4-8 mg/L) are generally monitored in plasma or serum because the concentrations are identical in these two biological matrices[7].

The concentration of phenytoin should be measured a few days after treatment initiation but, but in practice, the concentration is measured after 3-4 weeks of continuous dosing[8].

Other AEDs also should be monitored when they reach steady states. For example, phenobarbital is monitored after 3-4 weeks, carbamazepine after 2-3 weeks, and valproic acid, on day 2. However, patients should be monitored in the case of the worsening of the epilepsy or when they exhibit signs of drug toxicity[9].

It has been reported by some authors that there is no significant difference in clinical outcome in terms of seizure control and the frequency of side effects in patients with doses adjusted on a clinical basis alone or by achieving serum levels within predefined target ranges[10].

AEDs are widely utilized as long-term adjunctive therapy or as monotherapy in epilepsy[11]. When multidrug therapy is employed, there is a possibility of clinically relevant drug interactions that, in patients with epilepsy, are particularly common for a variety of reasons as follows: (i) AEDs are administered for prolonged periods, often over a lifetime, thereby increasing the probability of co-prescription; (ii) the majority of AEDs possess a narrow therapeutic index, and even relatively modest alterations in their pharmacokinetics can result in loss of response or toxic effects; (iii) the most widely used AEDs (carbamazepine, valproic acid, phenytoin, and phenobarbital) exert prominent effects on the activity of the enzymes that metabolize the majority of existing medication, and (iv) the majority of AEDs are substrates of the same enzymes[11].

Pharmacokinetic interactions are usually related with alterations in metabolism by enzyme inducers or inhibitors and are often well described in preclinical models. The majority of drug interactions in the past were discovered due to an unexpected change in the clinical status of a patient after addition or withdrawal from a drug in their existing medication[12]. These pharmacokinetic interactions may result in alterations in serum concentrations of the actual AEDs or the other drug or drugs, often caused by induction or inhibition of cytochrome P450 (CYP) enzymes[13].

Accordingly, the present retrospective study was performed to assess the proportion of AED serum-level determinations for phenytoin, carbamazepine, phenobarbital, and valproic acid, complying with criteria for appropriate drug-level

monitoring in hospitalized patients. The main outcome measure comprised the proportion of measurements with an appropriate indication and sampling times. In addition, the potential pharmacokinetic interactions among the medications received by the patients were analyzed.

MATERIALS AND METHODS

The present study is a retrospective analysis including the (TDM) data of phenobarbital, carbamazepine, valproic acid, and phenytoin in pediatric patients who had received a reliable diagnosis of epilepsy on monotherapy (Single AED) and AEDs polytherapy over a period of 6 months. These patients continued to be followed up at the Childrens' Hospital in Pachuca, Mexico. The main indications for carrying out TDM in these pediatric patients with epilepsy were uncontrolled seizures, symptoms and signs of toxicity-associated overdosage toxicity, or suspected non-compliance. Criteria for appropriate AED-level monitoring were defined a priori, combining criteria previously described in the literature[14-18].

The following two criteria had to be complied with in order to assess an AED drug-level determination as appropriate: (1) adequate indication for the measurement, and (2) correct sampling time (through the level, i.e., steady-state conditions):

Therapeutic

Plasma levels within the normal therapeutic range (10-20 mg/L for phenytoin, 4-8 mg/L for carbamazepine, 50-100 mg/L for valproic acid, and 15-40 mg/L for phenobarbital).

Subtherapeutic

The plasma levels below the minimum value of range i.e. below 10 mg/L for phenytoin, 4 mg/L for carbamazepine, 50 mg/L for valproic acid and 15 mg/L for phenobarbital.

Toxic

The plasma levels more than the maximum value of normal range i.e. more than 20 mg/L for phenytoin, 8mg/L for carbamazepine, 100 mg/L for valproic acid and 40 mg/L for phenobarbital.

Serum levels of phenytoin, carbamazepine, valproic acid, and phenobarbital were measured by personnel in the Biochemical Chemistry Laboratory utilizing the AxSYM® II microparticle enzyme immunoassay (Abbott Laboratories, Abbott Park, IL, USA). Blood samples were collected from patients in the morning immediately prior to the next drug dose being due (through concentration). The potential interactions between AEDs in multidrug treatment for each patient who had undergone drug monitoring were analyzed. Clinical records were examined for the follow-up action taken based on the laboratory reports.

RESULTS AND DISCUSSION

A total of 303 patients with 672 plasma drug concentration-measurement requests were collected (2.2 requests per patient) over the 6-month study period. The majority of plasma concentrations requested were 335 (49.9%) for valproic acid, followed by 172 (25.6%) for phenytoin, 131 (19.5%) for phenobarbital, and 34 (5%) for carbamazepine.

In our study as well as other studies, inappropriate indications were identified in patients with routine monitoring (i.e., drug-level measurement in a patient with good clinical response to AED therapy, no change of dose, clinical condition, or co-medication)[14]. Another common reason for inappropriate AED-level measurement was drug-level determination after dose adjustment without having reached steady state.

Measuring a serum concentration of an antiepileptic drug is most appropriate when the blood sample is drawn after steady-state conditions have been achieved, i.e., after 4-5 half-lives on an unchanged dose regimen. Only 40% of requests to measure phenytoin-concentration levels in the patient were effected on having reached steady state (n = 172), followed by 75% for phenobarbital (n = 131), 79% for valproic acid (n = 335), and 91% for carbamazepine (n = 34).

If a plasma sample is obtained prior to distribution of the drug into the tissues is complete,

the plasma concentration will be higher than predicted on the basis of dose and response. Concentrations measured at these times can be compared with published therapeutic ranges, which are usually based on prospective studies that related through drug concentrations measured at steady state to pharmacodynamic responses. If a given dose of a drug produced the same plasma concentration in all patients, there would be no need to measure the plasma concentration of the drug. However, individuals vary considerably in the extent to which they absorb, distribute, and eliminate drugs. Ten-fold or even greater differences in steady-state plasma concentrations have been found among patients treated with the same dose of important drugs such as phenytoin[19].

Table 1: Percentage of the plasma drug level of AEDs in relation to therapeutic interval

Drug	Total of samples	Antiepileptic drug levels		
		Therapeutic	Sub-therapeutic	Toxic
Phenytoin	172	44 (25.5%)	94 (54.7%)	34 (19.8%)
Carbamazepine	34	19 (55.9%)	8 (23.5%)	7 (20.6%)
Valproic acid	335	166 (49.6%)	113 (33.7%)	56 (16.7%)
Phenobarbital	131	78 (59.6%)	48 (36.6%)	5 (3.8%)

Table 2: Expected changes in plasma concentrations when an AED is added to a preexisting regimen an incidence

Potential Interaction	Effect	Incidence
AVP-DFH	↓ AVP	18
CBZ-DFH	↓ CBZ	1
AVP-DFH	↓ DFH	1
DFH-CBZ	↓ DFH	1
DFH-AVP	↓ DFH	22
DFH-FNB	↓ DFH	24
CBZ-Clobazam	↓ Clobazam	2
FNB-Clobazam	↓ Clobazam	1
DFH-Clobazam	↓ Clobazam	11
DFH-Clonazepam	↓ Clonazepam	2
CBZ-Diazepam	↓ Diazepam	4
DFH-Diazepam	↓ Diazepam	17
DFH-Topiramate	↓ Topiramate	2
DFH-AVP	↓ DFH	1
DFH-FNB	↓ DFH	3
DFH-FNB	↓ DFH	3
AVP-Lamotrigine	↓ Lamotrigine	4
	TOTAL	117

AVP= valproic acid; CBZ= carbamazepine; DFH= phenytoin; FNB= phenobarbital.

Therapeutic levels were achieved in a much higher proportion of patients (60%) on phenobarbital treatment as compared with only 26% in patients on phenytoin therapy (Table 1).

These differences can possibly be ascribed to a more complex pharmacokinetic behavior of phenytoin in terms of the drug's physicochemical characteristics and to saturable kinetics, as well as to problems of bioavailability. The overall skew toward subtherapeutic levels is to be expected, because requests for TDM were frequently made in patients experiencing uncontrolled seizures. This confirms the propensity of patients to undergo break-through seizures when plasma-drug levels are subtherapeutic. The trend might be different in the general epileptic population, which cannot be commented upon based on the present analysis.

The protein binding of valproic acid is concentration- dependent and decreases with an increasing dose. However, the variation in the free fraction of valproic acid begins acquire significance only at a total drug concentration >100 mg/L. Therefore, assuming linear kinetics and bearing in mind the previously cited limitations, drug levels

can easily be estimated. It is therefore generally not necessary to perform an additional drug-level measurement after dosage adjustment unless there are signs of adverse effects, or unless co-medication or liver function has changed[20,21].

On the other hand, even though carbamazepine exhibits the dose-dependent induction of its own metabolism (autoinduction), drug clearance remains constant after reaching maximal autoinduction, which occurs approximately 1-2 weeks after initiating carbamazepine therapy[22,23].

The study results demonstrated 39.1% (n = 672) subtherapeutic ranges in a single AED with phenytoin and valproic acid. In a similar study conducted by Shakya et al., a total of 88 patients of 417 (21.10%) were found at under subtherapeutic range[24].

During this study, a total of 102 concentration levels fell within toxic range: 17% of valproic acid levels, 21% carbamazepine, 20% of phenytoin levels, and 4% of those of phenobarbital. This may be due to inappropriate dosage and non-compliance. Likewise, the addition or deletion of other AED with dose adjustments may lead the therapeutic range to decrease under subtherapeutic and toxic range[11,12].

Thirty nine percent of total samples were found to be below therapeutic range (Table 1). The high percentage of subtherapeutic levels for phenytoin, carbamazepine, valproic acid, and phenobarbital may be expected, in that TDM requests were frequently made in patients having uncontrolled seizures. Another cause that could attribute to the increase or decrease in serum level of AED could be the co-administration of other drugs along with the AED.

Although monotherapy remains the mainstay for treatment of epilepsy, combinations of AEDs are employed frequently in patients not responding to a single medication. AEDs may also be combined with drugs used to treat intercurrent or associated conditions[11]. However, combination therapy may have adverse effects. When two or more AEDs are utilized, the potential for drug interactions is substantial, and such interactions may exert a profound effect on the patient's well-being[12].

Based on AEDs monotherapy and polytherapy, there was a greater percentage of patients taking monotherapy (67%) compared with polytherapy AEDs. A similar study was conducted by Räty et al.[25]. Table 2 depicts the combinations of AEDs administered to the patients involved in this study.

For example, when phenytoin is used in combination with either carbamazepine or valproic acid, it was found that its level was either subtherapeutic or at toxic level[10,11]. Phenytoin can extensively bind with plasma protein and can be subjected to displacement by other drugs that compete for their binding sites. Many acidic drugs, e.g., salicylates, sodium valproate, some Non-Steroidal Anti-Inflammatory Drugs (NSAID), and warfarin could also strongly bind with albumin, and displacement of phenytoin can take place. The main clinical problem arising from this type of interaction was that the decrease in the measured phenytoin may be misinterpreted as a need to increase the drug, thus increasing phenytoin toxicity[12].

Carbamazepine causes decreased concentrations of phenytoin and valproic acid. Phenobarbital stimulates P450 enzymes, leading to enhanced metabolism, therefore lower concentrations of primidone, phenytoin, carbamazepine, and valproic acid leads to increased phenobarbital concentrations. Acidification of urine by valproic acid enhances the reabsorption of phenobarbital, which is also acidic. The resulting increase in the $t_{1/2}$ of phenobarbital leads to a 10-20% (up to 40%) increase in its concentration after 24-26 days[26].

It has been shown that patients treated with a combination of two AEDs more often exhibited poor epilepsy control compared with those on monotherapy, and medication-free patients did not demonstrate a significantly higher frequency of seizures than patients on AEDs. These findings can be explained by the fact that treatment reflects the intractability of the epilepsy[24].

In this study, there were some limitations. Assessment of the indication of an individual for whom AED measurement was requested was mainly based on information retrieved from the clinical record, which may contain incomplete or incorrect information; furthermore, there was no data on the relationship between the response of patients toward AED therapy and the therapeutic range reported in the patients.

Some important information, such as suspected adverse effects associated with AEDs therapy or seizure recurrence, may not always have been adequately noted in the charts as a reason for ordering a drug level.

Based on this retrospective evaluation, there is an immediate need to require 100% appropriateness of plasma-drug monitoring by means TDM utilization and optimization of the drug dosage by validating the data employing the screening checklist by the TDM pharmacist in a TDM laboratory.

CONCLUSION

We recommend that best clinical outcome can be evaluated only by monitoring pharmacokinetic parameters for variations appearing in individual patients. Thus, overutilization, or underutilization, or the optimal TDM utilization service afforded to patients can be analyzed, and better patient outcomes can be maximized.

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