Original Article

Evaluation Of Therapeutic Drug Monitoring Services In Duhok, Kurdistan Region, Iraq: Valproic Acid As Example

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Abstract

Introduction:
Therapeutic drug monitoring (TDM) measures the level of medications within the biological fluids. Valproic acid (VPA) is a narrow therapeutic index anti-epileptic. Measurement of its level is essential for the evaluation of safety and efficacy. Aim was to evaluate the benefit of TDM services in patients taking Valproic acid with respect to outcome improvement and prevention of adverse events linked to dosage errors,

Methodology
The cohort was designed to take random samples of patients taking Valproic acid, measuring their VAP blood levels at the correct time. Patient demographic data were collected through face-to-face and phone interviews and from patient charts.

Results
Results indicated that most patients were male and below 18 years of age. No toxicity was observed in the patient. Very few patients experienced side effects and attacks per week. Patients had no knowledge of medical history, Renal Function Test (RFT), Liver Function Test (LFT), Protein Level, and other medications.

Discussion
The study found poor education of patients about therapeutic drug monitoring, and TDM is available in private facilities only. The patient had no education about Renal and liver function test protein levels and other medications being used by them. The study also found that side effects and frequency of attacks per week were not effects by valproic acid blood levels.

Keywords: Valproic acid, VPA, Therapeutic Drug monitoring, TDM, Duhok

1. Introduction

1.1 Background

Therapeutic drug monitoring (TDM) is not a universal solution. The therapeutic index for most medications is broad; consequently, they can be administered safely and effectively within the dosing ranges established from testing and research (Alffenaar et al. 2019). A broad therapeutic index means that variations in dosing ranges can yield the same effectivity. In addition, medications with a broad therapeutic index have less toxicity and adverse side effects (Oellerich & Dasgupta 2015). Contrastingly, medications with a narrow therapeutic index need TDM to enhance their

effectiveness and prevent toxicity (Clarke and Dasgupta 2016). In addition, some drugs need TDM because the amounts reaching blood plasma might be lower than the amounts being administered.

Valproic acid (VPA) is a broad-spectrum anticonvulsive medication. The therapeutic range of VPA is narrow (50-100 mcg/mL), and its toxicity increases in concentrations that exceed 100 mcg/mL. The absorption of VPA is rapid when taken orally, with peak concentrations attained in one-four hours (Oellerich and Dasgupta 2015). VPA is safe and effective for most patients when the therapeutic window of 50-100 mcg/mL is maintained (Hiemke et al. 2018). The side effects are few and non-serious in this therapeutic range. They include headaches, hair thinning, weight gain, swelling of gums, diarrhea, and tremors. Nevertheless, even when VPA is administered in the established therapeutic window, patients report outcomes of considerable variations (Hussin & Rzoqi 2018). Adverse side effects, including jaundice, nausea, vomiting, stomach pain, abnormal bleeding, and suicidal thoughts, have been reported in some patients (Xu et al. 2018: Stringer 2020).

Free VPA contributes to the pharmacological effects of the medication and its toxic effects. The unpredictable and unfavorable relationships between the dose and blood concentration of VPA emphasize the need for routine TDM to ensure its effectiveness and safety. VPA has a high binding capacity to albumin, which increases with the growth of serum concentration leading to higher concentrations of unbound/free VPA (Oellerich and Dasgupta 2015: Epilepsy Foundation 2020). When the albumin concentration is normal and the total serum concentration is low at 20-60 mcg/mL, free VPA is about ten percent of the serum concentration (Stringer 2020). This free VPA might rise above 15 percent in higher serum concentrations that exceed 100 mcg/mL. Besides the high VPA concentration of VPA in blood serum, hypoalbuminemia is another crucial factor contributing to the high amount of free VPA. In such a manner, increasing toxicity Patients with lower albumin levels tend to have a higher fraction of free VPA than those with higher albumin levels. Other factors that might contribute to a high fraction of free VPA in patients include concurrent medications (for example, lipid infusions of clevidipine, propofol, warfarin, phenytoin, nonsteroidal anti-inflammatory drugs, and aspirin) and the availability of endogenous substances competing for albumin with VPA (for example, urea nitrogen, fatty acids, and bilirubin) (Choi et al. 2019). All these factors increase the fraction of free VPA, thus leading to a high risk of toxicity and inadequate total VPA concentration in blood serum. The concentration of free VPA has been reported to predict adverse neurological symptoms accurately (Hussin and Rzoqi 2018). VPA is used to ensure that seizures do not spread in the brain. Anti-epileptic medications treat symptoms but do not change the course of epilepsy (de Biase et al. 2019). Overall, TDM is recommended as a clinical approach to ensure that VPA is safe and effective.

1.2 Problem Statement

Drug dosage errors represent a crucial clinical issue that can cause adverse side effects and negative patient outcomes (Choi et al. 2019). Dosage errors are still a problem despite the availability of clinical measures that can mitigate this problem, such as training physicians and pharmacists to ensure that they oversee the administration and dispensation of drugs (Stringer 2020). The risk for dosage errors is high in VPA.

The therapeutic index for VPA is low. Therefore, monitoring is needed to mitigate toxicity and enhance therapeutic effectiveness. When administered orally, VPA is absorbed well, bound to albumin, and is eliminated through metabolism. The pharmacokinetic characteristics of VPA are complex since its elimination kinetics tend to be non-linear (Choi et al. 2019). In addition, the pharmacokinetics of VPA reveals considerable individual variability stemming from pharmacogenetics differences in transport and enzyme activities (Hussin & Rzoqi 2018:Guo et al. 2019). VPA has high inter-patient variability when it comes to plasma protein binding.

1.3 Purpose Statement

This study aims to evaluate the benefits of TDM for patients who take VPA. In this study, patients taking VPA were monitored to determine whether TDM would benefit them in preventing side effects. Patients visited private clinics in Duhok and undertook mono-therapy of VPA. Their levels of VPA were monitored. Other observed aspects included the dosage form, doses per day, duration of using the medication in years, side effects, reasons for visiting the

physician, frequency of the attack per week, medical history, plasma protein level, and concurrent medications being taken by patients.

2. Methodology

2.1 Study Design

This study adopted the cohort design to evaluate TDM Services of VPA on patients regarding improved outcomes and prevention of side effects associated with dosing errors. This design helps determine outcomes' incidence, calculate relative risk (RR), and examine relationships between exposure and outcomes (Sharma 2018). This research involved a sample of patients being treated with VPA. a survey of patients was executed to examine the occurrence of any patient-related factors that hinder TDM. The objective was to evaluate whether the cohort of patients benefited from monitoring their VPA levels concerning safety and efficacy.

2.2 Sample and setting

The population for this research consisted of patients in the Duhok governorate being treated using VPA. Random sampling was used to select participants. In this research, participants were selected randomly from the two neurologist clinics to ensure the diversity of the sample. The sample consisted of 25 patients being treated with VPA. These patients were on mono-therapy with VPA. Patients were sent to private laboratories to take a blood sample to measure VPA levels using the Roche Cobas 6000 Machine for TDM services.

2.3 Data collection procedures

Data for this research was gathered from reports of Valproic acid blood levels test, face-to-face, phone interviews, and the clinical records of patients. The patient taking VPA were carefully monitored. Samples for TDM were collected at the right time (30 minutes) before the administration of the second dose since all the patients were on medications having half-lives of three-five hours. Various forms of data were collected, including their gender, age, level of VPA, a form of dosage, dose per day, side effects experienced, reasons for visiting the physician, frequency of seizure attacks per week, medical history, liver function tests, renal function tests, protein level, and other medications being taken by patients.

2.4 Inclusion and exclusion Criteria

Inclusion criteria were adopted.

1- A blood sample was taken within (30 minutes) of the next dose.
2- Mono-therapy of VAP

Exclusion criteria were adopted.

1-Samples not taken within (30 minutes) of the next dose.
2-People with diminished autonomy, such as the mentally ill, were protected by excluding from the research due to their inability to supply informed consent.

2.5 Duration of study

The cohort study started in October 2021. Arrangements were made with Neurologists and laboratories in Duhok, as only three private laboratories in Duhok provide TDM services. Blood samples of Patients visiting these clinics from February 2022 to May 2022 were taken.

2.6 Ethics

Before the study was conducted, approval was obtained from the University Of Duhok College Of Pharmacy and the Directorate General of Health Duhok Ethics committee reference number 24102021-10-45 dated 24/10/2021, which their conditions were respectfully followed. The ethical principles considered in this research include respect for

persons and beneficence. This research was low-risk. No social, financial, legal, physiological, or psychological harm was associated with participating in this research. Respect for persons requires taking steps to protect the confidentiality and anonymity of participants (Tappen 2022). The data collected was kept in a secure computer only accessed by the researcher. This research was purely observational. No interventions were adopted in the research.

2.7 statistical analysis

The statistical package for social sciences (SPSS) was used to analyze data. The data analysis was performed as a single cohort based on the respondents' demographics. The appropriate statistical test was selected based on the data type and normality of sample distribution.

2.8 Limitations

A limitation of this study stems from

1- TDM services aren't available in public hospitals, and private laboratories aren't available 24 hours; patients must wait until opening hours.

3. Results

3.1 Demographic Characteristics

Participants in this study varied in terms of gender and age. Most participants were males, 72% (n = 18); the age of participants was a categorical variable consisting of participants aged above 18 years and 60% (n=15) below 18 years. Table 3.1 summarizes the participants' gender and age.

Table 3.1: The Age and Gender of Patients

		Frequency	Percent
Gender	Male	18	72
	Female	7	28
Age	<18 yrs	15	60
	>18yrs	10	40
Total		25	100

3.2 VPA Level

The therapeutic range of VPA is narrow (50-100 mcg/mL), and its toxicity increases in concentrations that exceed 100 mcg/mL. Of eight patients, 32% had lower VPA levels below the recommended therapeutic range. The remaining 17, 68% of patients were within the recommended therapeutic range for VPA. Table 3.2 show the details.

Table 3.2: Frequency of the VPA level

	Frequency	Percent
Low level	8	32
Normal level	17	68
Total	25	100

3.3 Dosage Form

The dosage Form was also examined in this research: syrup or tablet. Thirteen participants (44%) reported taking VPA syrup, while 14 (56%) took VPA tablets. These findings are presented in Table 3.3.

Table 3.3: The Use of the Dosage Form

	Frequency	Percent
Tablet	14	56
Syrup	11	44
Total	25	100

3.4 Duration of Using Medication in Years

Data regarding the duration of using the medication in years was also collected. The majority of participants had used VPA for two to five years. Table 3.4 summarizes the frequency statistics for the duration of using VPA.

Table 3.4: Duration of Using VPA in Years

Years	Frequency	Percent
<2	6	24
2-5	11	44
5-10	6	24
>10	2	8
Total	25	100

3.5 Side Effects reported

Side effects of patients were also examined in the study. In this regard, most participants 72% (n = 18) did not experience any side effects. Two participants (8%) experienced nausea, while five (20%) experienced headaches. These findings are summarized in Table 3.5.

Table 3.5: Frequency of Side Effects Experienced by Participants

	Frequency	Percent
No Side effect	18	72.0
Nausea	2	8.0
Headache	5	20.0
Total	25	100.0

3.6 Reason for visiting physician

Regarding the reason for visiting the physician, follow-up was the most common reason, as reported by 60% (n = 15) of participants. Ten participants (40%) visited the physician because they experienced an epilepsy attack. Table 3.6 presents these findings.

Table 3.6: Reasons for Visiting Physician

	Frequency	Percent
Follow up	15	60
Epilepsy Attack	10	40
Total	25	100

3.7 Frequency of attacks per week

Lastly, the frequency of attacks per week was examined. The maximum number of attacks reported was three, while the minimum was attach-free. Most respondents were attack free, 60% (n = 15). One attack per week was reported by 8 participants, while 2 and 3 attacks each per week were reported by one participant. Table 3.7 presents a summary of these findings.

Table 3.7: Frequency of Attacks per Week

	Frequency	Percent
Attack free	15	60
1	8	32
2	1	4
3	1	4
Total	25	100

3.8 Education on medical history, Renal Function Test (RFT), Liver Function Test (LFT), Protein Level, and other medications

The findings indicate none of the participants received education regarding their medical history, RFT, LFT, protein level, and other medications. These results are presented in Table 3.8

Table 3.8

	Frequency	Percent
Medical history	0	0
RFT	0	0
LFT	0	0
Protein level	0	0
Other medications	0	0

4. Discussion

The findings from this study evaluated the beneficial influence of monitoring VPA in epileptic patients. The results suggest a low prevalence of side effects and frequency of attacks among the group of monitored patients. The low prevalence of side effects is attributable to the VPA levels within the therapeutic range. This finding is expected considering TDM of VPA is associated with improved effectiveness and safety of the medication. The improved safety of TDM explains the low prevalence of side effects. At the same time, the improved effectiveness of TDM of VPA explains the low frequency of attacks among the studied cohort of patients. By establishing and evaluating the concentration of VPA in the blood plasma, seizures can be treated, and adverse side effects can be prevented (Methaneethorn 2018). TDM helps to modify and individualize treatment to consider the unpredictable pharmacokinetic characteristics of VPA (Hunt et al. 2021).

Providing communication and education to patients about TDM is essential in enhancing their acceptance of TDM and encouraging adherence (Methaneethorn 2018). A notable observation in this study was that all the 25 patients who participated were not educated about medical history, renal function test, liver function test, protein level, and other medications being taken. As a result, they did not have any information about these aspects. This observation suggests insufficient knowledge of TDM among patients who participated in this research, possibly explained by the fact that their providers did not educate them about TDM.

In this study, eight patients had lower VPA levels below the recommended therapeutic range. Amongst these patients, five had attacked, while three did not have attacks. The variations in outcomes, despite having low VPA

levels, can be explained using the pharmacokinetic variability of VPA. The unpredictable and unfavorable relationships between the dose and blood concentration of VPA might explain the variable response in patients. The pharmacokinetics of VPA reveals considerable individual variability stemming from pharmacogenetic differences in transport and enzyme activities (Hussin & Rzoqi 2018). The remaining 17 participants were within the recommended therapeutic range for VPA; however, attacks were witnessed in four of them. Again, the differences in outcomes in terms of attacks amongst patients with regular VPA readings can be explained using the pharmaco-genetic variability of the medication. Overall, pharmaco-genetic differences explain the variations in the drug response in patients with low and normal VPA levels.

Another interesting observation in this study is that some patients had low VPA levels despite using the medication for the long term. Six patients had low VPA levels while taking the medication for long-term causes. A possible explanation for this low VPA level in these patients is poor adherence. As noted earlier, all the patients in this study did not receive education on medical history, renal function test, liver function test, albumin level, and other medications being taken, which can lead to poor adherence. Non-compliance with the dosage can cause low levels of the drug. In addition, VPA has high inter-patient variability regarding plasma protein binding (Meethaneethorn 2019). It leads to a poor correlation between plasma concentration and the amount of drug administered. Moreover, the differences in VPA levels can also be potentially explained using the individualization of treatment. Efforts to improve adherence to the recommended dosage, such as educating patients, should be implemented.

An analysis of the patients who had attacks revealed that five had normal VPA levels while the other five had low medication levels. These findings suggest different patient responses irrespective of the dose level due to pharmaco-genetic differences. Ideally, patients within the normal VPA range are not expected to experience any attacks. However, genetic factors play a role in the drug response of VPA in terms of drug targets, transport, and metabolism (Meethaneethorn 2019). Therefore, genetic differences across these patients contributed to differences in how they responded to the medication.

In this study, most participants did not experience any side effects. There was no difference in dosage per day between patients with side effects and those without, which suggests that the dosage per day did not impact side effects. Additionally, there was no significant difference in VPA levels across patients with and without side effects, suggesting that the VPA level did not impact side effects. Explained for this is the patients in the sample had VPA levels either below or within the therapeutic range. Similar findings were found for side effects based on the medication's duration. There were no significant differences in the medication duration between patients with side effects and those without. Most patients did not experience side effects since the VPA level was either low or within the therapeutic range; hence, drug toxicity was not observed.

TDM is an essential aspect of epilepsy treatment using VPA. By establishing and evaluating the concentration of VPA in the blood plasma, seizures can be treated, and adverse side effects can be prevented (Methaneethorn 2018). TDM helps to modify and individualize treatment to consider the unpredictable pharmacokinetic characteristics of VPA (Hunt et al. 2021). When treating epileptic seizures, monitoring drug concentration is pivotal since VPA affects the central nervous system, and associated side effects can be severe. While trial and error were previously used to compute the optimal dosage for VPA, the advent of modern methods to determine drug concentrations in blood plasma helped to examine the correlation between response and dosage accurately to improve the overall efficacy of treatment (Shaikh et al. 2018). Low concentrations of medications can result in insufficient effect, while high concentrations are toxic (Shaikh et al. 2018). Current guidelines require TDM to be performed for VPA to establish the optimal dose, evaluate non-adherence, and assess pharmacokinetic variations. Most cases of epilepsy can be managed safely and effectively using 50-100 mcg/mL of VPA in the blood (Methaneethorn 2018). It is also imperative to note that the pharmacokinetic attributes of VPA are influenced by the patient's age (Romoli et al. 2019). In children, VPA has a shorter half-life and a higher distribution volume. It means that the medication amount might be tripled or doubled in comparison to the required dosage. In addition, the unpredictable association between clinical response, dosage, and concentration in blood plasma, necessitates TDM (Hunt et al. 2021). Overall, the treatment using VPA needs constant monitoring of the drug's concentrations in the blood.

Current guidelines require TDM to be performed for VPA to establish the optimal dose, evaluate non-adherence, and assess pharmacokinetic variations. Most cases of epilepsy can be managed safely and effectively using

50-100 mcg/mL of VPA in the blood (Methaneethorn 2018). It is also imperative to note that the pharmacokinetic attributes of VPA are influenced by the patient's age (Romoli et al. 2019). In this study, the VPA level for most participants was within the recommended target range, which explains the low frequency of attacks per week and the low prevalence of side effects.

5-Conclusion

This study concluded that TDM services are beneficial for the safety and efficacy of medication, Preventing toxicity, and it also plays a major for in finding patinet complaince. TDM help adjust and control side effect in patients.

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