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Original article

Therapeutic Drug Monitoring of Valproic Acid in Patients with Monotherapy at Steady State

[1]Mohsen Forooghipour, *[2]Amir Hooshang Mohammadpour, [2]Naser Vahdati Mashhadian, [3]Mohammad Hassanzadeh Khayyat, [1]Mahmood Reza Azarpajouh, [4]Naghmeh Mokhber, [2]Tamara Aghebati, [2]Jamal Shamsara

Abstract

Objective(s)
The role of therapeutic drug monitoring (TDM) in patient care has grown rapidly since its introduction three decades ago. The aim of present study was to evaluate the possible relationship between serum levels and the clinical response of valproic acid (VPA).
Materials and Methods
In the present study we evaluated a homogeneous group of adult patients receiving VPA monotherapy. A total of 18 epileptic patients who fulfilled inclusion and exclusion criteria were entered this prospective study. Steady state trough plasma concentration was determined by fluorescence polarization immunoassay (FPIA). The correlation between therapeutic response and VPA serum concentration was evaluated.
Results
Mean VPA dose and mean total VPA plasma concentrations were 8.35±1.49 mg/kg/day and 50.40±4.18 µg/ml respectively. Mean VPA clearance was 8.84±4.43 (ml/kg/h). Plasma levels within the therapeutic range were found in 33% of epileptic patients. Plasma levels were below the therapeutic range in 67% of study population. Of patients 75% and 17% with sub-therapeutic levels achieved complete control and partial control respectively.
Conclusion
Poor correlation was found between the plasma concentration of VPA and its therapeutic effects. Therefore, this study showed that TDM of VPA will be useful only when individuals are non-responsive to treatment or vulnerable to adverse reactions with standard doses.

Keywords: Therapeutic Drug Monitoring (TDM), Trough plasma concentration, Valproic acid

1- Department of Neurology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
2- Department of Pharmacodinamy & Toxicology, Pharmaceutical Research Center & School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
*Corresponding Author: Tel: +98-51-8823255; Fax: +98-511-8823251; email: mohamadpoorah@mums.ac.ir
3- Department of Medicinal Chemistry, Pharmaceutical Research Center & School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
4- Department of Psychiatry, Faculty of Medicine, Psychiatric Research Center, Ebn-sina Hospital, Mashhad University of Medical Sciences, Mashhad, Iran

Introduction

Therapeutic drug monitoring (TDM) or the measurement of drug concentrations in plasma, serum or blood, aims to improve clinical activity, avoid toxicity, and reduce the costs of drug treatment. Specific conditions for TDM to be reasonably applied include the availability of a validated assay, a considerable inter-individual pharmacokinetic variability, a high correlation between drug concentration and toxicity, and a narrow therapeutic index (1). Because clinical effects are more closely related to drug levels than dose, clinicians can use therapeutic drug monitoring to optimize dosage decisions, in order to maximize efficacy and prevent toxicity (2). In the last 10-20 years therapeutic monitoring of antiepileptic drugs (AED_s) has had a major impact on epilepsy management due to enhance understanding of AED_s pharmacokinetics (3). This article discusses TDM for valproic acid (VPA) which has the widest spectrum of activity among the available antiepileptic drugs. Valproic acid is chemically related to free fatty acids. This drug is one of the most widely used AEDs in treatment of both generalized and partial seizures in adults and children. The capability of treating many type of seizure with a single anticonvulsant has resulted in the wide-spread use of VPA particularly in children (4). Furthermore, it is increasingly used for therapy of bipolar and schizoaffective disorders, neuropathic pain and for prophylactic treatment of migraine headache (5, 6). Monitoring of VPA is helpful when its toxicity and efficacy are doubtful. Because of significant inter-individual pharmacokinetic variability and concentration-dependent, plasma protein binding pharmacokinetic of VPA, the clearance of VPA is not a constant as it is the case for linear pharmacokinetics and is reported to be concentration or dose-dependent (3, 4, 7). In addition, clinical effects of VPA bear a relatively close relation to serum drug concentration. Its appropriate serum concentration depends on different factors such as age, total body weight, VPA dosage and co-administration of the other drugs which affect pharmacokinetics of VPA. Determination of serum concentration of VPA is valuable to improve clinical decisions and avoid adverse drug reactions (ADR_s) (4, 8, 9). It also provide clinicians with important information for making quantitative therapeutic decision, that is, titration of drug dose according to the individual patients, thus avoiding ADR_s (10). Therefore, in the the present study we investigated the TDM of VPA in epileptic patients.

Materials and Methods

Patients

This study was carried out prospectively during the course of a therapeutic drug monitoring program in the Psychiatric and Neurologic Clinic of Ebn Sina and Ghaem hospitals of Mashhad University of Medical Sciences in Iran between July 2005 and April 2006. All of the patients fulfilled the following inclusion criteria: a) Receiving a constant dose of VPA at least for 5 days. b) Taking VPA alone or with other drugs which have no effect on VPA pharmacokinetic. Exclusion criteria were: a) Patients with abnormal renal function tests. b) Patients with abnormal liver function tests. Whenever a blood sample was taken, all relevant demographic data (e.g. age, gender, body weight), and medication details (sampling time, duration of therapy, concurrent medication and adverse drug reactions) were recorded. Therapeutic response also was evaluated when complete control referred to patients free of seizures and partial control referred to reduction in frequency and intensity of seizures. In addition, several laboratory tests (CBC, BUN, ALT, and AST) were performed.

Blood sampling and drug assays

Trough Serum samples were taken before the administration of the morning dose. Fluorescence polarization immunoassay (FPIA) method was used for determination of the serum VPA concentration. An acceptable VPA assay calibration curve should meet the following criteria: Polarization Error (PERR) of -2.00 to +2.00 for all calibration and Root Mean Squared Error (RMSE) less than or equal to 1.00. Descriptive analysis was carried out by SPSS software for windows (version 11.5, USA).

Results

Characteristics of the study populations

The study population consisted of 18 epileptic patients. Demographic and medication details for the patients are summarized in Table 1. All of the patients were on monotherapy.

Table 1. Characteristics of the study population

Patients (n)	18
Male	32%
Female	68%
Age (yr)	28.64±9.22[1]
Total body weight (kg)	63.95±6.82
VPA dosage (mg/kg/day)	8.35±1.49
Serum VPA concentration (µg/ml)	50.40±24.18
VPA CL /F (ml/kg/hr)	8.84±4.43

1. Mean±SD

VPA plasma level fluctuation in patients

Our results showed high inter-individual variability in VPA serum level (Table 2).

Table 2. Mean of inter-individual variability in VPA serum concentrations

VPA dose	CV%
400 (mg/day)	38.96%
600 (mg/ml)	45.75%
800 (mg/ml)	14.25%

TDM of VPA

The high portion of epileptic patients in whom VPA level was in sub-therapeutic range showed the partial or complete response and 34% of patients who had a VPA level in therapeutic range didn't show complete response (Figure 1 and Table 3).

Table 3. TDM of VPA

33%	**Therapeutic rang**
66%	Complete response
17%	Partial response
17%	No response
67%	**Sub-therapeutic rang**
75%	Complete response
17%	Partial response
8%	No response
0	**Toxic level**

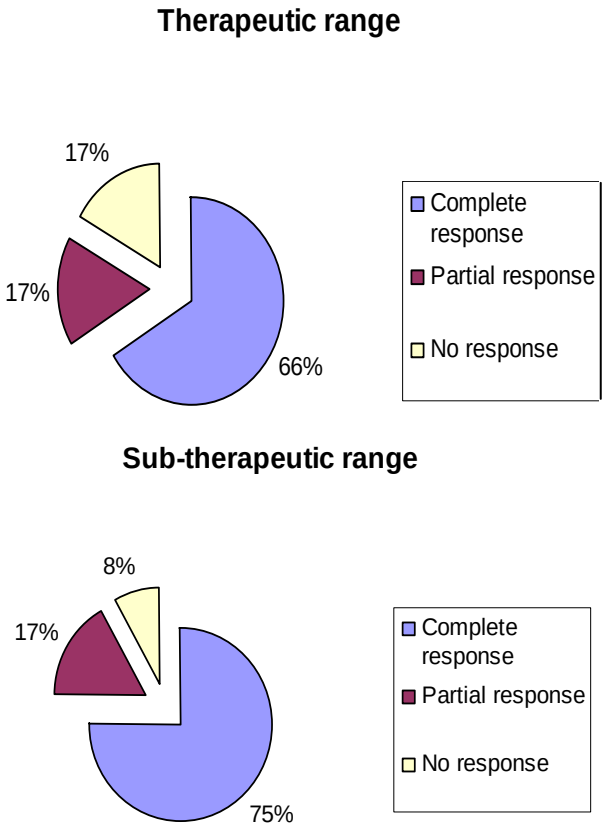

Figure 1. The ratio of patients with partial, complete or no response which their VPA levels are in therapeutic or sub-therapeutic ranges.

Discussion

Our results indicate that in a large number of epileptic patients (67%), VPA levels were in the sub-therapeutic range whereas 75% and 17% of these patients achieved complete control and partial control respectively. In our experiments we found that a new therapeutic range for VPA in the Iranian population should be determined.

VPA is used increasingly in neurology for the treatment of epilepsy, patients with bipolar mood disorders and other neuralgia. Clinical effects are more closely related to drug levels than to dose. TDM is particularly useful in determination of drug levels and identification of therapeutic failure due to under dosage, and -even in the presence of optimal dosage- for identification of serious toxicity, inter-individual pharmacokinetic variability (Rapid or Slow metabolism of drug) and detection of pharmacokinetic interactions (10). VPA shows diurnal variation in serum concentration. Therefore, the serum samples should be collected at the same time of days, trough levels are preferred (11).

In spite of high fluctuation in serum level of VPA (Table 2) indicating the TDM of VPA for defining the therapeutic range of VPA, the TDM results showed that there was no significant correlation between VPA serum level and the therapeutic response.

Conclusion

This study suggests that the therapeutic range should be defined for Iranian population. In addition, based on the finding of the present study, despite TDM usefulness in therapy by determination of sub-therapeutic levels in a time course, TDM of VPA will be useful only when individuals are non-responsive to treatment or vulnerable to adverse reactions with standard doses.

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References

1. Joerger M, Schellens JH, Beijnen JH. Therapeutic drug monitoring of non-anticancer drugs in cancer patients. Methods Find Exp Clin Pharmacol 2004; 26:531-545.
2. Eilers R. Therapeutic drug monitoring for the treatment of psychiatric disorders. Clinical use and cost effectiveness. Clin Pharmacokinet 1995; 29:442-450.
3. Reith DM, Andrews J, McLaughlin D. Valproic acid has temporal variability in urinary clearance of metabolites. Chronobiol Int 2001; 18:123-129.
4. Evans WE, Schentag JJ, Jasko WJ. Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring. 3rd ed. Lippincott Williams & Wilkins; 1992.
5. DeVane CL. Pharmacokinetics, drug interactions, and tolerability of valproate. Psychopharmacol Bull 2003; 37:25-42.
6. Lagace DC, O'Brien WT, Gurvich N, Nachtigal MW, Klein PS. Valproic acid: How it works. Or not. Clin Neurosci Res 2004; 4:215-225.
7. Fattore C, Messina S, Battino D, Croci D, Mamoli D, Perucca E. The influence of old age and enzyme inducing comedication on the pharmacokinetics of valproic acid at steady-state: A case-matched evaluation based on therapeutic drug monitoring data. Epilepsy Res 2006; 70:153-160.
8. Jiang Z, Zhang J, Liao HM, Tang JW, Peng QL. Influence of age, body weight and dose on sodium valproate plasma concentrations in children with epilepsy. Zhongguo Dang Dai Er Ke Za Zhi 2008; 10:325-328.
9. Perucca E, Aldenkamp A, Tallis R, Kramer G. Role of valproate across the ages. Treatment of epilepsy in the elderly. Acta Neurol Scand Suppl 2006; 184:28-37.
10. Sharma S, Joshi S, Mukherji S, Bala K, Tripathi CB.Therapeutic Drug Monitoring: Appropriateness and Clinical Utility in Neuropsychiatry Practice. Am J Ther 2008 (In Press).
11. Gidal BE, Pitterle ME, Spencer NW, Maly MM. Relationship between valproic acid dosage, plasma concentration and clearance in adult monotherapy patients with epilepsy. J Clin Pharm Ther 1995; 20:215-519.