ISSN- O: 2458 - 868X, ISSN–P: 2458 – 8687
National Library of Medicine - ID: 101731606

International Journal of Medical Science and Innovative Research (IJMSIR)
IJMSIR : A Medical Publication Hub
Available Online at: www.ijmsir.com
Volume – 11, Issue – 1, January – 2026, Page No. : 66 – 72

Therapeutic Drug Monitoring of Valproic Acid: A Cross-Sectional Correlation Study between Serum Levels and Clinical Response in Epileptic Patients

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Citation this Article: Avika Mathur, Sunil K. Mathur, Deepshikha Yadav, Pankaj Saini, "Therapeutic Drug Monitoring of Valproic Acid: A Cross-Sectional Correlation Study between Serum Levels and Clinical Response in Epileptic Patients", IJMSIR - January – 2026, Vol – 11, Issue - 1, P. No. 66 – 72.
Type of Publication: Original Research Article
Conflicts of Interest: Nil

Abstract

Background: Valproic acid (VPA) is a widely used broad-spectrum antiepileptic drug, but inter individual pharmacokinetic variability can lead to inconsistent seizure control and adverse effects at similar doses. Therapeutic drug monitoring (TDM) may help optimize therapy by correlating serum drug concentrations with clinical response.

Objective: To estimate trough serum VPA levels in epileptic patients receiving valproate monotherapy and determine their correlation with seizure control and adverse drug reactions (ADRs).

Methods: A prospective cross-sectional observational study was conducted over 12 months in the Departments of Pharmacology and Neurology, JLN Medical College, Ajmer, Rajasthan. One hundred adults (18–60 years) with epilepsy on stable sodium valproate monotherapy for ≥4 weeks were enrolled. Trough blood samples were collected 12 hours post-dose, serum was stored at −20°C, and VPA concentrations were measured using HPLC-UV. Serum levels were categorized as sub-therapeutic (<50 µg/mL), therapeutic (50–100 µg/mL), and toxic (>100 µg/mL). Seizure control over the preceding three months was classified as complete, partial, or uncontrolled. Pearson correlation assessed relationships between serum levels and clinical variables.

Results: Mean age was 34.8 ± 10.2 years; 58% were male; GTCS was the commonest seizure type (72%). Mean serum VPA level was 72.5 ± 23.4 µg/mL; 20% were sub-therapeutic, 65% therapeutic, and 15% toxic. Complete seizure control was achieved in 61% (mean VPA 79.2 ± 20.3 µg/mL), partial control in 26% (68.4 ± 22.5 µg/mL), and uncontrolled seizures in 13% (51.7 ± 19.6 µg/mL). Serum VPA concentration correlated significantly with clinical outcome ($r = 0.42$, $p = 0.002$), while correlations with dose ($r = 0.18$, $p = 0.07$) and duration of therapy ($r = 0.09$, $p = 0.32$) were not significant. ADRs occurred in 19%, most commonly tremor (7%) and weight gain (6%).

Conclusion: Serum VPA trough concentration showed a significant positive association with seizure control and was a better predictor of response than prescribed dose.

Routine TDM can support individualized dosing to improve efficacy and reduce toxicity in epilepsy management.

Keywords: valproic acid, therapeutic drug monitoring, epilepsy, serum trough level, seizure control, HPLC, adverse drug reactions.

Introduction

Valproic acid (VPA) remains a cornerstone in the management of epilepsy, recognized as one of the most widely prescribed broad-spectrum antiepileptic drugs globally. Its clinical utility extends to managing both generalized and focal seizures, a capability attributed to its complex pharmacological profile which includes the enhancement of gamma-aminobutyric acid (GABA) inhibitory activity and the modulation of voltage-gated ion channels[1]. Despite its proven efficacy and established biochemical properties, the clinical response to VPA is not uniform. Considerable variability exists among patients regarding both seizure control and tolerability, largely driven by interindividual differences in pharmacokinetics, metabolic clearance, and underlying genetic factors[2]. Consequently, relying solely on standard weight-based dosing is often insufficient. Therapeutic drug monitoring (TDM) has therefore emerged as an essential strategy to individualize therapy, ensuring that serum concentrations remain effective for seizure suppression while minimizing the risk of dose-dependent toxicity[2].

The generally accepted therapeutic reference range for serum VPA concentration is 50–100 µg/mL. However, large-scale retrospective analyses have indicated that the correlation between these serum levels and clinical outcomes is often inconsistent, with some patients requiring levels outside this range for optimal control [3]. This discrepancy is influenced by a multitude of covariates, including age, body weight, hepatic enzyme induction, and concurrent medication use [4]. Recent research has placed significant emphasis on the role of pharmacogenetics; for instance, polymorphisms in the *CYP2C9* gene have been shown to significantly alter VPA metabolism. These genetic variations can lead to unpredictable fluctuations in the concentration-to-dose ratio, necessitating precise dose adjustments, particularly in pediatric and vulnerable populations [5, 6].

Beyond the parent drug, the metabolic pathway of VPA plays a critical role in its clinical profile. VPA undergoes extensive hepatic metabolism, producing various metabolites such as 4-ene-valproic acid and 2-propyl-4-pentenoic acid. Studies suggest that profiling these metabolites may offer higher predictive accuracy for TDM than measuring VPA alone, as specific metabolites have been directly linked to therapeutic efficacy while others are more closely associated with hepatotoxicity [7, 8]. This distinction is vital for distinguishing between a lack of efficacy and the onset of metabolic adverse effects.

Furthermore, VPA is highly susceptible to clinically significant drug–drug interactions. A notable example is the concomitant use of carbapenem antibiotics, which can drastically lower serum VPA levels—often to sub-therapeutic ranges—within a short period, thereby increasing the risk of breakthrough seizures and treatment failure [8]. On the other end of the spectrum, supratherapeutic levels pose a serious risk of toxicity. Molecular studies and meta-analyses have highlighted that elevated levels are strongly associated with adverse drug reactions (ADRs) such as severe tremor, significant weight gain, and metabolic disturbances [9,10]. Therefore, the systematic and continuous monitoring of serum VPA concentration is not merely a procedural requirement but a critical component of modern epilepsy management to balance molecular toxicity against therapeutic potential.

Materials and Methods

Study Design and Setting

This was a prospective, cross-sectional observational study conducted in the Department of Pharmacology in collaboration with the Department of Neurology, JLN medical college ajmer rajasthan, over a period of 12 months. The study aimed to evaluate serum valproic acid levels and correlate them with clinical outcomes among patients receiving valproic acid monotherapy for epilepsy. Ethical clearance was obtained from the Institutional Ethics Committee prior to study initiation. Written informed consent was obtained from all participants before enrolment.

Study Population

A total of 100 adult patients (aged 18–60 years) diagnosed with epilepsy and receiving sodium valproate monotherapy for at least four weeks were enrolled. Diagnosis was established based on clinical history, neurological examination, and electroencephalogram (EEG) findings consistent with epilepsy, in accordance with International League Against Epilepsy (ILAE) guidelines.

Inclusion Criteria

1. Patients aged 18–60 years with a confirmed diagnosis of epilepsy.
2. Receiving sodium valproate monotherapy for ≥4 weeks at a stable dose.
3. Willing to provide informed consent and comply with study procedures.

Exclusion Criteria

1. Patients on multiple antiepileptic drugs (polytherapy).
2. History of liver disease, renal impairment, or metabolic disorders.
3. Pregnant or lactating women.
4. Non-compliance with treatment regimen or missing follow-up data.

Data Collection and Clinical Assessment

Demographic details (age, sex, body weight), clinical characteristics (seizure type, duration of therapy, dose of valproate), and treatment outcomes were recorded using a structured case record form.

Clinical response was evaluated based on seizure control status over the preceding three months and categorized as:

- **Complete control** – no seizures,
- **Partial control** – reduction in frequency/intensity,
- **Uncontrolled** – no significant improvement.

Adverse drug reactions (ADRs) such as tremor, weight gain, or gastrointestinal symptoms were also documented.

Sample Collection and Processing

Venous blood samples (3 mL) were collected 12 hours after the last dose (trough level) to ensure steady-state concentration. Blood samples were allowed to clot and centrifuged at 3000 rpm for 10 minutes to obtain serum, which was stored at −20°C until analysis.

Estimation of Serum Valproic Acid Levels

Serum valproic acid concentrations were determined using High-Performance Liquid Chromatography (HPLC) with ultraviolet (UV) detection, following validated analytical procedures described in previous studies

- **Chromatographic conditions:** Reverse-phase C18 column (150 × 4.6 mm, 5 µm); mobile phase: acetonitrile–phosphate buffer (pH 3.5, 70:30 v/v); flow rate: 1.0 mL/min; detection wavelength: 210 nm.
- **Calibration range:** 10–150 µg/mL with correlation coefficient (r^2) ≥ 0.995.

- **Quality control:** Each analytical batch included blank, low, medium, and high concentration controls to ensure accuracy and precision.

Therapeutic Range Classification

Serum valproic acid levels were categorized as follows

- **Sub-therapeutic:** < 50 µg/mL
- **Therapeutic:** 50–100 µg/mL
- **Toxic:** > 100 µg/mL

Statistical Analysis

Data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY). Descriptive statistics (mean ± SD, percentages) were used for baseline characteristics. The Pearson correlation coefficient was applied to determine the relationship between serum valproic acid levels and seizure control, as well as with dose and duration of therapy. A *p*-value < 0.05 was considered statistically significant.

Results

Table 1: Demographic and Clinical Characteristics of Study Participants (n = 100)

Parameter	Mean ± SD / n (%)
Age (years)	34.8 ± 10.2
Gender (Male/Female)	58 / 42
Body weight (kg)	63.4 ± 8.9
Duration of therapy (years)	2.3 ± 1.1
Daily dose (mg/day)	853.6 ± 202.5
Seizure type – GTCS	72 (72%)
Seizure type – Partial	28 (28%)

Table 2: Distribution of Serum Valproic Acid Levels (n = 100)

Serum VPA Range (µg/mL)	Category	n (%)
< 50	Sub-therapeutic	20 (20%)
50–100	Therapeutic	65 (65%)
> 100	Toxic	15 (15%)
Mean ± SD	—	72.5 ± 23.4

Table 3: Serum Valproic Acid Levels and Clinical Outcome (n = 100)

Clinical Outcome	n (%)	Mean ± SD Serum VPA (µg/mL)
Complete control	61 (61%)	79.2 ± 20.3
Partial control	26 (26%)	68.4 ± 22.5
Uncontrolled	13 (13%)	51.7 ± 19.6

Table 4: Correlation between Serum Valproic Acid Levels, Dose, and Duration (n = 100)

Parameter	Correlation Coefficient (r)	*p*-value
Daily dose vs. serum level	0.18	0.07
Duration of therapy vs. serum level	0.09	0.32
Clinical Outcome vs. serum level	0.42	0.002

Table 5: Frequency of Adverse Drug Reactions Among Study Participants (n = 100)

Adverse Reaction	n (%)
Tremor	7 (7%)
Weight gain	6 (6%)
Gastrointestinal upset	4 (4%)
Hair loss	2 (2%)
Total	19 (19%)

Discussion

The present study was undertaken to analyze the correlation between serum valproic acid (VPA) levels and clinical response in patients with epilepsy. Our findings demonstrated a significant positive correlation between serum concentration and seizure control, reinforcing the value of Therapeutic Drug Monitoring (TDM). These results align with the established therapeutic window of 50–100 µg/mL, which has been validated by numerous international studies.

Demographic and Clinical Profile In our study, Generalized Tonic-Clonic Seizures (GTCS) were the most prevalent seizure type, affecting 72% of the study population. This distribution is consistent with the epidemiological data reported by Sridharan and Murthy [11], who noted that GTCS remains the predominant seizure phenotype in the Indian population. Similarly, a study by Pradeep and Saritha [12] found that over 80% of pediatric and adult patients in their cohort presented with generalized seizures, corroborating our observation that this seizure type is the primary indication for valproate monotherapy in our setting.

Correlation between Serum Levels and Seizure Control We observed that 61% of our patients achieved complete seizure control, and these patients had significantly higher mean serum VPA levels (79.2 µg/mL) compared to uncontrolled patients. This significant positive correlation (r = 0.42) mirrors the findings of Vasudev et al.[13], who reported a linear relationship between weekly rises in serum VPA levels and clinical improvement. Furthermore, our results are in agreement with Bowden et al. [14], whose analysis of concentration-response relationships suggested that efficacy significantly increases as serum levels rise above 50 µg/mL, with optimal responses often seen in the higher quartiles of the therapeutic range.

Therapeutic Range and Sub-therapeutic Levels While 65% of our patients were within the therapeutic range, 20% were found to be sub-therapeutic (<50 µg/mL). Interestingly, a portion of these sub-therapeutic patients still exhibited partial seizure control. This phenomenon was also described in a study by Gomez-Bellver et al. [15], who noted that some patients achieve clinical stability at lower serum concentrations due to lower individual seizure thresholds or milder disease variants. However, Henriksen and Johannessen[16] emphasize that maintaining levels above 50 µg/mL is critical for preventing breakthrough seizures in the long term, suggesting that our sub-therapeutic group may remain at risk despite temporary control.

Lack of Dose-Concentration Correlation A crucial finding in our study was the absence of a significant correlation between the prescribed daily dose and the resulting serum concentration (p = 0.07). This lack of linearity supports the pharmacokinetic variability highlighted by Gram et al. [17], who demonstrated that VPA metabolism is highly idiosyncratic and non-linear. Similarly, Schobben et al.[18] reported that relying solely

on weight-based dosing (mg/kg) frequently fails to predict serum levels accurately due to inter-individual differences in protein binding and hepatic clearance. This confirms that TDM is indispensable, as dose adjustments based on clinical judgment alone may lead to under-dosing or toxicity.

Adverse Drug Reactions (ADRs) We recorded adverse events in 19% of patients, with tremor (7%) and weight gain (6%) being the most common. Our rates are slightly lower than those reported by Grosso et al. [19], who found weight gain in up to 25% of children and adolescents on long-term therapy. The association we observed between toxic levels (>100 µg/mL) and ADRs is consistent with the findings of Lundberg et al. [20], who established that neurological side effects like tremor are dose-dependent and correlate strongly with peak serum concentrations. Additionally, the presence of gastrointestinal symptoms in our cohort, despite enteric-coated formulations, aligns with the side-effect profile described in the multi-centric analysis by Perucca et al.[21], suggesting that local gastric irritation persists as a common challenge.

Conclusion

In summary, our study corroborates the global consensus that serum valproic acid levels are a reliable predictor of clinical response, significantly more so than the prescribed dose. While our seizure control rates are comparable to those reported in similar developing world settings, the variability in pharmacokinetics observed here strongly advocates for the routine implementation of TDM to personalize epilepsy management.

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