International Journal of Contemporary Pediatrics
Swathi SM et al. Int J Contemp Pediatr. 2025 Dec;12(12):1975-1978
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20253779

Original Research Article

A comparative study on the effect of sodium valproate therapy on liver enzyme levels in children with seizure disorder compared to other antiepileptic drugs

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Received: 10 September 2025
Revised: 09 October 2025
Accepted: 25 October 2025

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ABSTRACT

Background: Sodium valproate is a commonly prescribed antiepileptic drug known for its effectiveness in controlling seizures in pediatric patients but is also associated with concerns over altered liver enzyme levels and rarely hepatotoxicity. Comparisons with other antiepileptic drugs are essential to understand their relative impacts on hepatic function in children with seizure disorder.
Methods: A prospective study was conducted in the department of paediatrics at the Government Cuddalore Medical College Hospital over a one-year period, enrolling children aged 1 to 12 years diagnosed with seizure disorder and on sodium valproate, phenytoin or levetiracetam therapy. Liver function was assessed by measuring serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and alkaline phosphatase (ALP) measured at baseline and after 12 months. Inclusion and exclusion criteria ensured well-defined cohorts, and enzyme levels were measured using standard clinical laboratory techniques. Data was collected via structured proforma and analysed by SPSS version 25 software.
Results: Among the 40 recruited children, those receiving sodium valproate demonstrated significant elevations in SGOT, SGPT, and ALP levels after one year of therapy. In contrast, children receiving levetiracetam showed increased ALP levels only, while no significant changes were observed in the phenytoin group. Statistical analysis confirmed the significance of these findings, underscoring sodium valproate's stronger association with hepatic enzyme elevation compared to the other drugs.
Conclusions: The study indicates that sodium valproate therapy in children with seizure disorder is associated with significant elevations in liver enzyme levels compared to phenytoin and levetiracetam. Regular liver function monitoring, particularly before and at six-month intervals during sodium valproate therapy, is recommended to detect early signs of hepatotoxicity.

Keywords: Levetiracetam, Liver enzymes, Phenytoin, Sodium valproate

INTRODUCTION

Sodium valproate is an antiepileptic medication primarily used to treat epilepsy and bipolar disorder. It works by stabilizing the electrical activity in the brain via sodium channels. It is often prescribed as a first-line treatment for epilepsy due to its effectiveness in controlling seizures. Sodium valproate can have adverse effects like weight gain, fatigability, tremors, hepatotoxicity, reversible thrombocytopenia, etc. Altered liver enzymes is one of the common adverse effects of sodium valproate demanding dose adjustment or discontinuation of therapy. The drug is metabolized primarily in the liver.[1] The mechanism by which sodium valproate causes

changes in liver enzymes is unclear, but some contributing factors include the accumulation of toxic metabolites of sodium valproate that can interrupt fatty acid oxidation and cause mitochondrial toxicity. Sodium valproate is metabolized in the liver by glucuronidation, beta-oxidation, conjugation with carnitine or glycine, and less by cytochrome 450. Phenytoin is metabolized mainly by the cytochrome p450 enzyme system in the liver to inactive metabolites. On the other hand, levetiracetam is extensively metabolized in kidneys and 66% excreted unchanged.

Aims and objectives

This study aimed at determining the changes in liver enzyme levels in children with seizure disorder on sodium valproate compared to children on phenytoin and levetiracetam.

To evaluate the changes in liver enzyme levels, specifically serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and alkaline phosphatase (ALP) in children with seizure disorder who are undergoing sodium valproate therapy compared to children on phenytoin and levetiracetam.

METHODS

This study was conducted in government Cuddalore medical college hospital, Annamalai Nagar, Chidambaram over a period of one year from February 2023 to march 2024.

Type of study

It was a prospective study.

Ethical approval

The study was approved by the Institutional Ethical Committee.

Inclusion criteria

Children aged 1 to 12 years of both male and female diagnosed with seizure disorder regardless of form (e.g., focal or generalized seizures). Children who have been on antiepileptic medication- sodium valproate, phenytoin and levetiracetam for at least a year. Children who are stable on their present antiepileptic treatment regimen and have not recently changed medication or dosage. Children whose caregivers or legal guardians should give informed consent to participate in the study.

Exclusion criteria

Children with chronic hepatic disorders, such as cirrhosis or hepatitis, may have varying treatment outcomes due to medication metabolism. Children with chronic renal diseases, such as chronic kidney disease or renal insufficiency, may have altered medication clearance and pharmacokinetics. Children with neurodegenerative diseases and brain tumors. Children with a history of non-compliance with antiepileptic drugs or prescription non-adherence.

Lab parameters

SGOT and SGPT were estimated by international federation of clinical chemistry recommended UV kinetic method. Alkaline phosphatase was estimated by 4-nitrophenyl phosphate (pNPP) method.

Sampling method

Convenient sampling method was employed for this study.

Study method

The study was conducted over one-year period at Government Cuddalore Medical College Hospital, enrolling children aged 1 to 12 years with seizure disorder on sodium valproate, phenytoin, or levetiracetam therapy. Liver function tests (SGOT, SGPT, ALP) were measured at baseline and after 12 months using standard biochemical methods.

Analysis

Data analysis was performed using SPSS software version 25.0, with paired t-tests applied to assess significant differences in liver enzyme levels.

RESULTS

This study on the effect of sodium valproate on changes in liver enzyme levels was done over a period of one year in government medical college and hospital, Cuddalore district. Totally 84 children with seizure disorder were screened out of which 40 children satisfied the inclusion criteria and recruited as study participants. Out of these, 20 participants were only on sodium valproate and 12 participants were on phenytoin and 8 participants were on levetiracetam. The major study participants were toddlers and school going each contributing 27.5% (Table 1). The duration of illness in 55% of the study participants were more than one year (Table 2). The type of seizures in 90% of the participants were generalized tonic clonic seizures (Table 3).

Table 1: Age group among the study participants.

Age group	Female (%)	Male (%)	Total (%)
Toddlers	2 (18.2)	9 (81.8)	11 (100)
Pre school	3 (37.5)	5 (62.5)	8 (100)
Early adolescence	3 (30)	7 (70)	10 (100)
School going	4 (36.4)	7 (63.6)	11 (100)
Total	12 (30)	28 (70)	40 (100)

Table 2: Duration of illness among the study participants.

Duration of illness	Female (%)	Male (%)	Total (%)
Newly diagnosed	3 (33.3)	6 (6.7)	9 (100)
Less than or equal to one year	2 (22.2)	7 (77.8)	9 (100)
More than one year	7 (31.8)	15 (68.2)	22 (100)
Total	12 (30)	28 (70)	40 (100)

Table 3: Type of seizures among the study participants.

Type of seizures	Female (%)	Male (%)	Total (%)
GTCS	12 (33.3)	24 (66.7)	36 (100)
Focal seizures	0	4 (100)	4 (100)
Total	12 (30)	28 (70)	40 (100)

Results revealed significant elevation of SGOT, SGPT and ALP in all children taking sodium valproate. Elevation of ALP levels alone in children taking levetiracetam and no significant changes in children taking phenytoin (Table 4).

Table 4: Liver enzyme levels.

Drug	At the time of recruitment	After 1 year	P value
SGOT			
Sodium valproate	29.90±12.95	49.75±17.32	0.003*
Phenytoin	31.58±9.85	36.00±9.49	0.23
Levetiracetam	31.25±7.59	33.25±4.68	0.26
SGPT			
Sodium valproate	27.10±12.15	45.60±15.61	0.002*
Phenytoin	26.92±11.94	33.25±9.21	0.13
Levetiracetam	27.75±11.81	22.25±6.62	0.39
ALP			
Sodium valproate	151.85±70.41	247.30±75.32	0.001*
Phenytoin	68.17±23.71	94.58±38.45	0.05
Levetiracetam	73.63±28.66	91.38±23.96	0.02*

*Statistically significant by paired t test

DISCUSSION

There are only limited studies on the mechanism by which sodium valproate causes changes in liver enzyme levels. Many studies have reported significant elevation of liver enzymes and hepatotoxicity in children treated with sodium valproate compared to other antiepileptic drugs.[2-6]

In this study, liver enzyme levels were monitored before and after one year in the study group. The results demonstrated a significant increase in serum glutamate oxaloacetic transaminase (SGOT), serum glutamate pyruvic transaminase (SGPT), and alkaline phosphatase (ALP) in children receiving sodium valproate. Similar findings were reported by Divya et al who observed significant elevation in SGOT and SGPT in children taking sodium valproate, elevated SGPT in children taking phenytoin and no significant changes in liver enzymes in children taking levetiracetam.[2] Hadzagić-Catebusić et al also found a significant increase in both SGOT and SGPT levels in the sodium valproate group compared to children on carbamazepine.[3] Wang et al observed a significant elevation of SGOT levels in 25.8% of the children treated with sodium valproate.[4] Sridharan et al observed a significant proportion of critically ill children taking antiepileptic drugs like sodium valproate, carbamazepine, and phenytoin experienced drug-induced liver injury.[5] Shahi et al observed a notable rise in SGPT levels in children on sodium valproate.[6]

However, in contrast to these findings, Adedapo et al reported no significant elevation in plasma liver enzyme levels in children treated with sodium valproate.[7] Mahgoub et al observed no significant changes in liver enzymes in children taking sodium valproate.[8]

Smaller sample size is a limitation to come to a conclusion. A longer duration of study is needed to understand the exact mechanism behind the effect of sodium valproate on liver enzymes. A wide age group range (1 to 12 years) was included. Age group classification could give further understanding if a larger sample size is included.

CONCLUSION

This study demonstrated that sodium valproate therapy in children with seizure disorder is associated with a significant elevation of liver enzymes compared to phenytoin and levetiracetam. These findings emphasize the importance of routine liver function monitoring in children receiving sodium valproate to detect possible hepatotoxicity early. This study provides knowledge on impacts of common antiepileptic drugs on liver enzyme levels and aids for safer pediatric epilepsy management. Larger studies with extended follow-up are warranted to elucidate underlying mechanisms and long-term outcomes.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Swathi sri M, Chidambaranathan S. A comparative study on the effect of sodium valproate therapy on liver enzyme levels in children with seizure disorder compared to other antiepileptic drugs. Int J Contemp Pediatr 2025;12:1975-8.