Dose-Response:
An International Journal
April-June 2020:1-7

DOI: 10.1177/1559325820918445
journals.sagepub.com/home/dos
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Non-Dose-Dependent Changes in Liver Enzyme Levels of Children With Epilepsy on Treatment With Sodium Valproate

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Abstract

Background: Sodium valproate (VPA) is considered as the drug of choice for the treatment of generalized epilepsy in children. Sodium Valproate may be hepatotoxic.

Aim: To assess the level of derangement of liver enzymes in children with epilepsy on treatment with sodium valproate.

Methods: A cohort study. One hundred fifty-three children, comprising 51 with epilepsy on treatment with VPA (group I), 51 with epilepsy on treatment with other antiepileptic drugs (AEDs) but not VPA (group II), and 51 with nonconvulsive disorders (group III) had liver function tests performed for them. Data were analyzed by SPSS version 23.0.

Results: There were 85 males and 68 females, aged 6 months to 14 years (median = 7.0 years). There was no significant difference in the mean plasma levels of alanine transaminase (ALT), alkaline phosphatase, and gamma glutamyl transferase across the three groups of children. The mean aspartate transaminase level was significantly higher in children in group III. There was a statistically significant negative correlation between the duration of AED therapy and the mean serum level of AST ($r = -0.266$, $P = 0.016$). The serum ALT level showed a statistically significant positive correlation with the duration of AED therapy ($r = 0.268$, $P = 0.015$).

Conclusion: Sodium valproate monotherapy does not appear to be associated with significant hepatotoxicity in children in our cohort.

Keywords

epilepsy, sodium valproate, antiepileptic drugs, liver function

Introduction

Epilepsy is defined as recurrent, unprovoked seizures.[1] It is one of the leading neurological disorders worldwide affecting about 50 million people, and two-thirds of them are children.[2-4] Epilepsy is considered to be quite disabling because of its unpredictability.[5,6] Hospital-based studies in Nigeria have shown that epilepsy remains the major reason for pediatric neurological consultation.[7] Sodium valproate (VPA) is considered as the drug of choice for the treatment of generalized epilepsy, the leading type of epilepsy seen in Nigerian children.[8,9] A serious adverse effect of the VPA is its effect on liver function with resultant drug-induced hepatotoxicity.[10,11] Liver enzymes can serve as markers of hepatocellular injury and this can be objectively diagnosed by the liver function test.

The pathogenesis of VPA hepatotoxicity is unclear but may relate to the accumulation of a toxic metabolite of valproic acid which impairs fatty acid oxidation.[12,13] Jeavon[14] reported that VPA hepatotoxicity appears to be an idiosyncratic reaction and it is most likely to appear within the first 6 months from the start of therapy. Long-term VPA therapy has also been reported to be associated with an increased risk for the development of nonalcoholic fatty liver disease.[15] There have been many studies to evaluate the effects of antiepileptic drugs (AEDs) on liver

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Received 16 September 2019; accepted 15 March 2020

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function in children with epilepsy; however, these studies revealed divergent results. Furthermore, there is limited information on the effect of VPA on the liver enzymes in pediatric patients with epilepsy in Nigeria. The study therefore set out to evaluate the changes in levels of liver enzymes in children with epilepsy on treatment with VPA.

Materials and Methods

This was a cohort study. A total of 153 children comprising 3 groups of children with 51 children in each group were studied. Group I comprised children with generalized epilepsy who had been on treatment with VPA for at least 6 months, group II had children with epilepsy who had been on treatment with other AEDs but not VPA for at least 6 months, while group III comprised children with nonconvulsive disorders, no known chronic illnesses, who were not on any medications, and had presented on routine follow-up after recovery from an acute illness. Ethical approval was obtained from the University of Ibadan/University College Hospital Ethical Committee. Informed consent was obtained from all the caregivers.

Basic demographic and clinical information was collected, including age, gender, schooling history, diagnosis, type of AED, dosages, and duration of treatment. Additional information obtained from caregivers of children with epilepsy and their seizure diaries included types of seizures, frequency of seizures, and date of last seizure.

Biochemical Assay

Five milliliters of venous blood was withdrawn by the phlebotomist from each participant from the cubital vein, and this was carefully dispensed into lithium heparin bottle for the assay of plasma aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), and gamma glutamyl transferase (GGT) levels. Each specimen bottle was given an ID that corresponded with the participant's ID. Blood specimen bottle was then centrifuged at 3000*g* for 15 minutes within 30 minutes of blood collection. The plasma was decanted into plain bottles and stored at −20°C for not more than a month until analysis. Reference values used for the study were: ALT 10 to 56 IU/L, AST 0 to 45 IU/L, and GGT 0 to 40 IU/L.[16] The AST/ALT ratio was determined in children with elevated AST or ALT levels and an AST/ALT ratio <1 was regarded as a marker of hepatic toxicity.[17] The reference values used for classifying the plasma ALP levels depended on the age of the child, and the values ranged between 140 and 468 IU/L for males and 140 and 417 IU/L for females.[18] Plasma levels of liver enzymes in each study group were classified as normal or elevated. The distribution of children in each study group with plasma levels of liver enzymes within and outside the reference ranges was compared to assess the association between AED use and hepatotoxicity.

Table 1. Epilepsy Types in 102 Children With Epilepsy.

Type of Epilepsy	Number of Seizures	%
Generalized epilepsy		
Generalized tonic–clonic	50	49.1
Absence seizure	5	4.9
Atonic seizure	3	2.9
Myoclonic seizure	3	2.9
Focal seizure		
Complex partial seizure	38	37.3
Focal motor seizure	3	2.9
	102	100.0

Data Analysis

Data coded and entered into the computer were analyzed using Statistical Package for Social Sciences (SPSS) version 23.0. Frequency was expressed as proportion or percentage. Mean and standard deviation (SD) were used to summarize continuous variables. Student *t* test was used to test the association between mean values of normally distributed continuous variables, while Mann-Whitney *U* test was used for comparison of median if not normally distributed. Level of significance was set at a $P < .05$. Analysis of variance was calculated to assess the differences in mean enzymes level in the study group, with Duncan post hoc analysis used for pairwise comparison of group of means. Regression analysis and Pearson correlation were done.

Result

There were 85 males and 68 females, and their ages ranged from 6 months to 14 years (median = 7.0 years). Of the 102 children with epilepsy in groups I and II, 61 (59.8%) had generalized epilepsy, while 41 (40.2%) had partial epilepsy. Table 1 shows the distribution of epilepsy types in the 102 children with epilepsy. Thirty-seven (36.3%) of the children with epilepsy were in remission, defined as a seizure-free period of at least 12 months. The remaining 65 (63.7%) still had active epilepsy, defined as a seizure-free period <12 months, with seizure frequency ranging from daily to weekly seizures to once in 3 to 11 months. Twenty-one (20.6%) of the 102 children with epilepsy had associated neurological comorbidities, with multiple comorbidities in 5 of them. The comorbidities identified in the children were intellectual disability in 13 (12.7%), cerebral palsy in 8 (7.8%), and speech problems in 3 (2.9%). The parents of children recruited for this study were low-income earners: 39 (76.5%), 38 (74.5%), and 31 (60.8%) for group I, group II, and group III, respectively (Figure 1).

Antiepileptic Drug Therapy

All the children in group I were on VPA monotherapy, and the daily dose of VPA ranged from 400 to 2000 mg. The duration of treatment with VPA ranged from 6 months to 13 years, median 12.0 months. Carbamazepine (CBZ) was the most frequently prescribed AED for patients in group II: 46 (90.2%)

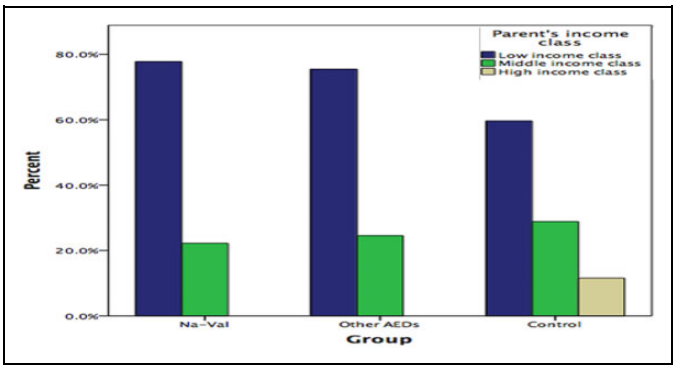

Figure 1. Income class of parents of children with or without epilepsy. AEDs indicates antiepileptic drugs; Na-Val, sodium valproate.

were on CBZ monotherapy, while 5 (9.8%) were on polytherapy, CBZ in combination with levetiracetam. The duration of treatment ranged from 6 months to 12 years, median 24.0 months.

Serum AED levels were estimated in 8 children in group I. The serum levels of VPA were within normal limits in 5 of them and above the therapeutic range in the remaining 3. On the other hand, 11 children in group II had their serum AED levels estimated. The mean serum levels of CBZ were within normal limits in 7 children and the mean serum levels of levetiracetam were within normal limits in 4 children.

Plasma Levels of Liver Enzymes

The mean plasma levels of AST in children in group I, group II, and group III were 34.7 (SD = 12.6) IU/L, 27.8 (SD = 10.3) IU/L, and 62.6 (46.9) IU/L, respectively. The plasma AST level was not significantly different in children with epilepsy on treatment with VPA compared with those on treatment with other AEDs, but not VPA ($P = 1.000$). The mean plasma AST level was significantly higher in children with nonconvulsive disorders (group III) who were just recovering from an acute illness than in those with epilepsy on treatment with VPA (group I; $P = .035$) or other AEDs (group II; $P = .006$). There was a statistically significant difference in the plasma AST levels across the 3 groups ($P = .005$).

The plasma levels of AST were significantly higher in 12 (23.5%) children, 2 (0.4%) children, and 16 (31.4%) children in group I, II, and III, respectively. With respect to plasma ALT levels, 2 (4.0%) children, none (0%), and 3 (5.9%) children had elevated ALT levels in groups I, II, and III, respectively. The mean plasma ALT levels in children in group I, group II, and group III were 29.8 (SD = 11.5) IU/L, 29.2 (SD = 11.0) IU/L, and 34.7 (SD = 24.0) IU/L, respectively. The plasma AST/ALT ratio was less than 1 in 2 (16.7%) of the 12 children with elevated AST levels in group I and 3 (18.8%) of the 16 children with elevated AST level in group III. The 2 children with elevated AST level in group II had AST/ALT ratio >1 and neither of them had an AST/ALT ratio less than 1. There was no statistically significant difference in the plasma ALT levels across the 3 groups ($P = .182$).

The mean plasma level of ALP in children in group I, II, and III were 207 (SD = 82.0) IU/L, 207 (SD = 138.2) IU/L, and 204.4 (SD = 96.2) IU/L. Based on the reference values for age and sex, 5 (9.8%), 10 (19.6%), and 4 (7.8%) children in group I, II, and III, respectively, had elevated levels of plasma ALP. There was no statistically significant difference in the plasma levels of ALP across the 3 groups ($P = .987$).

The plasma GGT level was not significantly different across the 3 groups ($P = .053$). The mean plasma GGT level was however significantly higher in children with nonconvulsive disorders compared with those in group II, but not when compared with the mean plasma GGT levels of children in group I. Tables 2 and 3 show the relationship in the liver enzymes across the 3 groups.

There was a statistically significant negative correlation between the duration of AED therapy and the mean plasma level of AST ($r = -0.266$, $P = .016$). The plasma ALT level showed a statistically significant positive correlation with the duration of AED and VPA therapy ($r = 0.268$, $P = .015$ and $r = 0.398$, $P = .008$) as well as dose of VPA ($r = 0.599$, $P < .001$).

Discussion

The study showed a preponderance of epilepsy in males compared to females. This is consistent with previous reports which have shown epilepsy to occur more frequently in males than females.[8,9] In consonance with previous reports from the developing countries, generalized epilepsy was the more common type of epilepsy seen in the cohort. The relatively higher prevalence of generalized epilepsy in the developing countries has been attributed to the high prevalence of symptomatic epilepsies resulting from perinatal brain injuries, traumatic brain injuries, and severe intracranial infections.[8-10] Most parents of children in the VPA group compared with those in other AED group and in the control group were low-income earners. It is estimated that 80% of the world's 33 million children with epilepsy live in resource-poor countries of the world.[19]

The most commonly prescribed AEDs in the study were VPA, CBZ and levetiracetam. Interestingly, none of the children was on treatment with phenobarbitone. These findings, though not generalizable, suggest an improvement in access to treatment with other AEDs apart from phenobarbitone, which has long been reported as the most widely available AED in resource-poor African countries.[20,21]

The median duration of treatment with VPA was 12 and 24 months for the other AEDs. This would have given sufficient time for any effect of the AED on the liver enzymes. Although the serum AED level was estimated in less than 20% of the children with epilepsy, none of them had suboptimal serum levels of the AED. It is usual to measure serum drug levels, since the plasma protein-bound drugs are inactive while the free drugs are the active drugs.

The mean plasma AST level was significantly higher in children in group III with nonconvulsive disorders, while the mean plasma AST level did not show any significant

Table 2. Relationship Between the Serum Liver Enzymes in the 3 Groups of Children Studies.

		ANOVA				
		Sum of Squares	*df*	Mean Square	*F*	Significance
AST	Between groups	35 369.840	2	17 684.920	5.589	.005
	Within groups	490 487.610	155	3164.436		
	Total	525 857.449	157			
ALP	Between groups	292.960	2	146.480	.013	.987
	Within groups	1 802 462.458	155	11 628.790		
	Total	1 802 755.418	157			
ALT	Between groups	947.274	2	473.637	1.725	.182
	Within groups	42 557.644	155	274.565		
	Total	43 504.918	157			
GGT	Between groups	7825.375	2	3912.688	2.999	.053
	Within groups	202 237.872	155	1304.760		
	Total	210 063.247	157			

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; ANOVA, analysis of variance; AST, aspartate transaminase; GGT, gamma glutamyl transferase.

Table 3. Post Hoc Analysis on the Relationship Between the Serum Liver Enzymes Across the 3 Groups.

					95% Confidence Interval	
Dependent Variable	(I) Group_2	(J) Group_2	Mean Difference (I − J)	Significance	Lower Bound	Upper Bound
AST	Na-Val	Others	6.85826	1.000	−19.5939	33.3104
		Control	−27.91097[a]	.035	−54.3631	−1.4588
	Others	Na-Val	−6.85826	1.000	−33.3104	19.5939
		Control	−34.76923[a]	.006	−61.4698	−8.0687
	Control	Na-Val	27.91097[a]	.035	1.4588	54.3631
		Others	34.76923[a]	.006	8.0687	61.4698
ALP	Na-Val	Others	−0.25499	1.000	−50.9634	50.4535
		Control	2.76425	1.000	−47.9442	53.4727
	Others	Na-Val	0.25499	1.000	−50.4535	50.9634
		Control	3.01923	1.000	−48.1654	54.2038
	Control	Na-Val	−2.76425	1.000	−53.4727	47.9442
		Others	−3.01923	1.000	−54.2038	48.1654
ALT	Na-Val	Others	0.62322	1.000	−7.1685	8.4150
		Control	−4.87678	.396	−12.6685	2.9150
	Others	Na-Val	−0.62322	1.000	−8.4150	7.1685
		Control	−5.50000	.278	−13.3649	2.3649
	Control	Na-Val	4.87678	.396	−2.9150	12.6685
		Others	5.50000	.278	−2.3649	13.3649
GGT	Na-Val	Others	−8.42094	.696	−25.4064	8.5646
		Control	8.92521	.616	−8.0603	25.9107
	Others	Na-Val	8.42094	.696	−8.5646	25.4064
		Control	17.34615[a]	.046	0.2012	34.4912
	Control	Na-Val	−8.92521	.616	−25.9107	8.0603
		Others	−17.34615[a]	.046	−34.4912	−0.2012

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma glutamyl transferase; Na-Val, sodium valproate.
[a]$P < .05$.

difference between children with epilepsy on treatment with VPA compared with those on treatment with other AEDs. Of the liver enzymes, AST is the least specific and may be elevated in other diseases affecting other organs apart from the liver and these include acute hemolytic anemias, musculoskeletal disease, burns, acute renal disease, and so on.[17] The children in group III did not have epilepsy but were on follow-up visit to the clinic following recovery from an acute illness. This may therefore explain the elevated levels of AST in about a third of them. It has been suggested that the plasma AST/ALT ratio could be a better marker of hepatic injury rather than the absolute AST level, with a ratio less than 1

indicating hepatocellular injury.[22] Only 3 of the 18 children with elevated AST levels in group III has an AST/ALT ratio <1, and this raises the possibility of the elevated AST being largely from a nonhepatic source in the cohort.

The mean plasma levels of AST did not show any significant elevation in children with epilepsy on treatment with VPA. This is consistent with reports by Haznedar and colleagues who did not observe any evidence of hepatotoxicity in a cohort of patients with epilepsy on treatment with therapeutic doses of VPA.[23] The study also did not show any significant elevation in AST levels in children with epilepsy on other AEDs, CBZ and levetiracetam. This observation is at variance with the report by Haznedar and colleagues. The authors reported evidence for oxidative liver damage in children on treatment with levetiracetam. The small number of children on levetiracetam in our study and the fact that levetiracetam was given in combination with CBZ might account for the variance in the observations. The underlying mechanisms behind hepatotoxicity induced by AED are not clear. Reactive metabolites from AED can in some cases lead to direct cytotoxicity, liver cell necrosis, or sometimes neoantigen formation, inducing immune-allergic mechanisms.[24] Recent studies have postulated that mitochondrial dysfunction plays a major role in AED-induced liver damage. Patients with Alpers-Huttenlocher syndrome, a neuronal mitochondrial disease, have increased susceptibility to VPA-induced hepatotoxicity.[25] It is therefore likely that genetic factors play a significant role in the predisposition to hepatotoxicity in patients undergoing treatment with VPA.

Our study did not show any significant difference in the plasma levels of other liver enzymes: ALT, ALP, and GGT in the 3 groups of children studied. This is at variance with several other reports that have described hepatotoxicity as a common adverse reaction to VPA. Star and his colleagues[26] retrieved the individual case safety reports (ICSRs) for children <17 years with valproic acid and fatal outcome from the World Health Organization Global ICSR database. The report found hepatotoxicity to occur more frequently in children than in adults, with a higher risk in children under the age of 6 years. The observed significantly low risk of hepatotoxicity to VPA in our study might be related to the fact that these children were on VPA monotherapy. Polytherapy, with administration of VPA in combination with other AEDs, has been identified as a risk factor for fatal hepatotoxicity.[26]

A statistically significant increase in AST level and GGT was observed in all 3 groups throughout the study period. Sodium valproate mediated hepatic injury is associated with dose dependent rise in serum liver enzymes.[22]

Most notably is the fact that GGT was significantly increased in children on other AEDs (with CBZ as the most prescribed drug in this group) compared to children on VPA group and controls. Gamma glutamyl transferase is more specific than the rest since is an inducible enzyme, the only inducible enzyme in this class of enzymes, buttressing the fact that CBZ is a liver enzyme inducer which can precipitate attacks likely via an increase in catabolism of hydroxymethylbilane synthase and uroporphyrinogen decarboxylase affecting heme synthesis.

A comparative cohort study evaluated and compared the effect of phenobarbital (PB; 5 mg/kg/d) versus VPA (20 mg/kg/d) on liver function of children with epilepsy. They measured serum levels of AST, ALT, and ALP before starting the treatment, then after 3 and 6 months of treatment. There was a significant increase in AST, ALT, and ALP levels in both groups, and the increases were higher in the PB-treated group. It was suggested PB being one of the potent enzyme-inducing AEDs may explain the higher increases observed in liver enzymes in patients compared to that seen in patients treated with VPA.[27]

In our study, the mean AED dose and duration were longer for the group on other AEDs compared to the group on VPA; this explains why the group on other AED had a longer seizure-free period. We found a negative correlation between VPA dose and ALP and AST/ALT ratio, though ALT had a positive correlation with duration of therapy. However, Huang and colleagues found that there was no significant correlation between hepatotoxicity and the dose or duration of VPA therapy.[28] Others reported no correlation between the duration of therapy with CBZ and elevated liver enzymes.[24] However, some authors found that AED-induced hepatotoxicity was related to dose of the drug used; for example, Perucca and colleagues found a dose-dependent degree of enzyme induction in patients with epilepsy receiving therapeutic doses of CBZ, leading to elevation in liver enzymes.[29] Kalapos found that enzyme induction and hepatotoxicity caused by CBZ were not dose related.[30] Elmasry et al found that enzyme induction and hepatotoxicity caused by CBZ were not dose related.[31] Studies to investigate valproic acid impact on liver transaminases (AST, ALP, and AST) across nations still have divergent inconsistent results including nonstatistically significant decrease and then increase in liver enzymes.[32] Granted that the divergent reports on liver enzyme levels may be related to pharmacogenetic variations in the different populations, however, the ratio of the liver enzymes AST/ALT may be more informative.

Our study showed a significant, though weak negative correlation between the duration of AED therapy and AST levels. This observation might be related to the fact that severe VPA hepatotoxicity most commonly arises in children within the first 3 months of treatment.[33,34]

Conclusion

Our study suggests that VPA monotherapy does not cause a significant increase in plasma levels of liver enzymes and may be not largely hepatotoxic.

Limitation

The absence of baseline liver enzyme estimation however poses some limitation to our study.

Acknowledgments

The assistance of Prof. A. E. Orimadegun in the statistical analysis of the data is acknowledged. The resident doctors in the pediatric neurology clinic, patients, the parents, and all the caregivers are acknowledged and appreciated.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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