Original Research Article

Effect of anticonvulsant drug sodium valproate on hepatic profile in children

Pradeep Minz[1], Asha Oroan[2], Samuel Lakra[3*], Ranjit Kaur Arora[4], Poonam Singh[5]

[1]Demonstrator, Department of Physiology, Department of Orthopedics, Rajendra Institute of Medical Sciences, Bariatu, Ranchi, Jharkhand, India

[2]Junior Resident, Department of Biochemistry, Department of Orthopedics, Rajendra Institute of Medical Sciences, Bariatu, Ranchi, Jharkhand, India

[3]Senior Resident, Department of Orthopedics, Rajendra Institute of Medical Sciences, Bariatu, Ranchi, Jharkhand, India

[4]Professor, Department of Physiology, Rajendra Institute of Medical Sciences, Bariatu, Ranchi, Jharkhand, India

[5]Professor & Head, Department of Physiology, Rajendra Institute of Medical Sciences, Bariatu, Ranchi, Jharkhand, India

Received: 13-11-2021 / Revised: 24-12-2021 / Accepted: 15-01-2022

Abstract

Background: Sodium valproate is one of the most common antiepileptic medications used in clinical practice. The period of treatment is commonly associated with benign alternation of the liver enzymes due to drug metabolism. Evaluation of asymptomatic enzymatic changes could be challenging to the expert clinician and may expose patients to unnecessary procedures or expenses. Thus, this article aims to focus on the frequency of liver enzyme abnormalities among epileptic children. **Materials & Methods:** The current prospective observational study was conducted on children with seizure disorder attending Pediatric OPD of Rajendra Institute of Medical Sciences, Ranchi. Period of study was extended from February 2014 to October 2015. Patient randomly selected from outdoor of department of Pediatric having seizure disorder. All children aged 2 years to 10 years, of either sex having partial or generalized seizure and who have recently started either phenytoin, valproate or carbamazapine were selected for study. Routine investigations like complete blood count, peripheral blood smear, CRP, blood glucose, CT Brain/Spine, EEG and hepatic profile like aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase, total serum bilirubin (direct & indirect), prothombin time or international normalized ratio (INR), serum albumin and Australia antigen (HbsAg) on valproate therapy were done. **Results:** The present study revealed that, the patients treated with valproate have shown significant increase mean ALP level after 1 year of treatment as p values were 0.03, 0.02 and 0.03 respectively. The patients treated with valproate have shown no significant increase mean SGPT and SGOT level after 1 year of treatment. It was also found that there was no significant increase in mean TSB and mean PT. Also there was no significant decrease in mean serum albumin. **Conclusion:** The significant increase was seen in mean ALP level these increase is probably due to enzyme-inducing or enzyme-inhibiting properties of drugs. SGPT, SGOT levels increases from the initial value but not to significant level. The study recommends obtaining baseline liver enzymes tests prior to commencement of treatment. However, the benefit of routine screening in asymptomatic patients has not proved. Further controlled studies with a large sample size are warranted.

Keywords: Epilepsy, anticonvulsant drug, sodium valproate, hepatic function, children

Introduction

Epilepsy is a chronic medical disorder or condition, usually resulting in unpredictable, unprovoked recurrent seizures that affect a variety of mental and physical functions. It is one of the most common neurological diseases, affecting 50 million people worldwide[1].

The term epilepsy is derived from the Greek word epilam-banein, meaning to attack or seize. A person is considered to have epilepsy when two or more unprovoked seizures occur that can't be explained by a medical condition such as fever or substance withdrawal. Seizures can be the result of a family tendency toward the disease, or they can occur after a brain injury, but the cause of epilepsy is largely unknown.

*Correspondence

Dr. Samuel Lakra

Senior Resident, Department of Orthopedics, Rajendra Institute of Medical Sciences, Bariatu, Ranchi, Jharkhand, India.

E-mail: drsamuellakra@gmail.com

Epileptic seizures are manifested by an abnormal, excessive, and hyper synchronous electrical discharge of neurons in the brain[2]. There are many kinds of seizures, each with characteristic behavioral changes and electrophysiological disturbances that can usually be detected in scalp electroencephalographic (EEG) recordings.

In paediatric population many different types of convulsions have been found but most common type of convulsion is febrile convulsion occurring in 3 or 4 out of every 100 children between six months and five years of age, but most often around twelve to eighteen months old[3]. Epilepsy requires long term and sometimes lifelong therapy. Thus, prolonged antiepileptic treatment could have some undesirable effects, and several reports have already shown that antiepileptic drugs (AEDS) influence on hepatic profile in children[4].

The liver is the main site of drug metabolism and is particularly susceptible to structural and functional injury after ingestion, parenteral administration, or inhalation of chemical agents, drugs, plant derivatives (home remedies), or environmental toxins. The clinical spectrum of illness can vary from asymptomatic biochemical abnormalities of liver function to fulminant failure. Liver injury may

be the only clinical feature of an adverse drug reaction or may be accompanied by systemic manifestations and damage to other organs[5].

Hepatic metabolism of drugs and toxins is mediated by a sequence of enzymatic reactions that, in large part, transform hydrophobic, less soluble molecules into more nontoxic, hydrophilic compounds that can be readily excreted in urine or bile. Relative liver size, liver blood flow, and extent of protein binding also influence drug metabolism. Phase 1 of the process involves enzymatic activation of the substrate to reactive intermediates containing a carboxyl, phenol, epoxide, or hydroxyl group. Mixed-function mono-oxygenase, cytochrome-*c* reductase, various hydrolases, and the cytochrome P450 (CYP) system are involved in this process. Nonspecific induction of these enzymatic pathways, which can occur during intercurrent viral infection, with starvation, and with administration of certain drugs such as anticonvulsants, can alter drug metabolism and increase the potential for hepatotoxicity. A single agent can be metabolized by more than one biochemical reaction. The reactive intermediates that are potentially damaging to the cell are enzymatically conjugated in phase 2 reactions with glucuronic acid, sulfate, acetate, glycine, or glutathione. Some drugs may be directly metabolized by these conjugating reactions without 1st undergoing phase-1 activation. Phase 3 is the energy-dependent excretion of drug metabolites[6, 7]. The liver is the primary organ for drug metabolism and elimination for many antiepileptic drugs (AEDs) and thus is subjected to drug-induced toxicity. There is a wide range of hepatotoxic reactions, from mild and transient elevations of hepatic enzymes to fatal hepatic failure[8].

Antiepileptic drugs may alter liver function and increase the activity of hepatic microsomal enzyme. This may alter the metabolism of various substances such as drugs and lipids[9]. The present study investigated hepatic profile status in children with epilepsy who had been receiving valproate**.**

Aims & Objectives

1. To know the effect of anticonvulsant drug (sodium valproate) on hepatics profile in children between 2 years to 10 years.
2. To establish the relationship between the change in hepatic profile with the type of anticonvulsant drug.

Materials & Methods

The current prospective observational study was conducted on children with seizure disorder attending Pediatric OPD of Rajendra Institute of Medical Sciences, Ranchi. Period of study was extended from February 2014 to October 2015. Patient randomly selected from outdoor of department of Pediatric having seizure disorder. Normal subjects of both sexes & of different age group were selected who did not have seizure.

Selection of cases

All children aged 2 years to 10 years, of either sex having partial or generalized seizure and who have recently started either phenytoin, valproate or carbamazapine were selected for study. Cases have been selected randomly on the basic of detailed systematic scheme of history taking, general and systemic examination & through routine investigation including specific investigations where necessary. Written informed consent has been taken from each patient /attendant before selecting them as subject in this study.

Presenting problems like abnormal movement suggesting of seizures along with type of seizures, duration, day of onset & frequency/alteredsensorium/unconsciousness/lethargy/irritability/starring look/ excessive crying/vomiting/refusal to feed/fever/t achypnea/ respiratory distress/ any other were noted. Antenatal history – antenatal check up history of mother, maternal nutrition, antepartum history. H/O premature rupture of membrane/fetal distress/meconium stained liquor/any other were noted.

Birth history like place of delivery & mode of delivery, immunization history, family history, history of past illness, treatment history, developmental history, social history, personal history, drug history and allergic history was noted.

Routine investigations like complete blood count, peripheral blood smear, CRP, blood glucose, CT Brain/Spine, EEG and hepatic profile like aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase, total serum bilirubin (direct & indirect), prothombin time or international normalized ratio (INR), serum albumin and Australia antigen (HbsAg) were done.

Inclusion criteria

All children aged 2years to 10 years having newly diagnosed or untreated seizure disorder after detailed history taking & examination, have been included in the study to eliminate the confounding effects (if any) of treatment medication on the study.

Exclusion criteria

1) All children who did not have seizure.
2) Patients who had received any other anticonvulsant before VAL therapy or were receiving two or more anticonvulsants were excluded from the study
3) Children with hepatic or renal disease, those receiving medications which may alter liver functions and those with a family history of obesity, atherosclerosis or metabolic disease were excluded.
4) Patients with gross developmental delay or congenital abnormalities were also excluded from the study.
5) Patients or attendant who did not give valid consent for the study.
6) Those cases which did not cooperate and did not come for follow up were also excluded from the study.

Selection of control

Normal subjects of age group 2 years to 10 years of both sexes, who are not on any drugs including anticonvulsant drugs, were selected randomly from the cohort of - patient's attendants, hospital /department staff's home.

Selection criteria

- Subjects declared healthy & did not have seizure.
- Not having any condition known to alter hepatic profile level.
- Subjects /attendants willing voluntarily to participate in the study.

Hepatic profile

Blood sample collection

Venous blood sample (5 mL) was drawn from antecubital vein and serum was collected in the morning (between 9.00 and 10.00 am) after a fasting period of 8-12 hours in both cases and controls. The blood sample was analyzed on same day in the department of biochemistry by using chem. 5x auto analyzer.

Estimation of serum alkaline phosphatase

Methodology

Alkaline phosphatase in serum is determined by measuring the rate of hydrolysis of various phosphate esters under specified conditions. ρ-Nitrophenyl Phosphate is one such phosphate ester. The present method is based on that of Wilkinson et al[10].

Principle

$$\rho\text{-NPP} + H_2O \xrightarrow[Mg]{\text{Alk Phos}} \rho\text{-Nitrophenol} + H_3PO_4$$

ρ-Nitrophenyl phosphate is hydrolyzed to ρ-nitrophenol and inorganicphosphate. The rate at which the ρ-NPP is hydrolyzed, measured at 405nm, is directly proportional to the alkaline phosphatase activity.

Calculation

One international Unit (IU/L) is defined as the amount of enzyme that catalyzes the transformation of one micromole of substrate per minute under specified conditions.

$$(IU/L) = \frac{\Delta Abs./Min. \times TV \times 1000}{SV \times absorptivity \times P}$$

Where

ΔAbs./Min. = Average absorbance change per minute

TV =Total reaction volume in (microL)
SV= Sample Volume (microL)
absorptivity= Millimolar absorptivity of ρ-Nitrophenol At 405nm=18.8
p= cuvette Light path in cm=1cm
Activity of ALP AT37°C = ΔAbs405./min. x 2713

Conversion factor
1000 = Conversion of IU/ml to IU/L

Table 1: Reference value of serum alkaline phosphatase (IU/L)

Age group	Alkaline Phosphatase (IU/L)
0-5 years	60-320
5-10 years	110-360
10-12 years	103-373
12-16 years	67-382
>16 years	36-112

Estimation of SGPT
Methodology
International Federation of Clinical Chemistry (IFCC) - Uv Kinetic Method[11]

Principle
SGPT (ALAT) catalyzes the transfer of amino group between L-Alanine and aoxoglutarate to form pyruvate and glutamate. The Pyruvate formed reacts with NADH in the presence of lactate dehydrogenase to form NAD. The rate of oxidation of NADH to NAD is measured as a decrease in absorbance at340 nm, which is proportional to the SGPT (ALAT) activity in the sample.
L-Alanine + 2-Oxoglutarate ----------►Pyruvate + L-Glutamate

LDH
Pyruvate + NADH ----------►L-Lactate + NAD+

The rate of NADH consumption is measured photometrically and is directly proportional to the ALT concentration in the sample.

Calculation
The general formula for converting absorbance change into international units(IU)of activity is (IU/L) = $\frac{\Delta Abs./Min. \times TV \times 1000}{SV \times absorptivity \times P}$

Where
ΔAbs./Min. = Average absorbance change per minute
TV =Total reaction volume in (microL)
SV = Sample Volume (microL)
absorptivity= Millimolar absorptivity of NADHl At 340nm=6.22
p= cuvette Light path in cm=1cm
Activity of SGPT AT 37°C = ΔAbs405./min. x 1768

Table 2: Reference Value Of SGPT (IU/L)

Age	SGPT (IU/L)
1-3 Years	< 57
4-6 Years	<52
7-12 Years	<45
13-17 Years	<42
Adult Male	<41
Adult Female	<39

Estimation of SGOT
Methodology
L – Aspartate + 2-oxoglutarate---------► Oxaloacetate +L- Glutamate

SGOT
Oxaloacetate + NADH----------►L-Malate + NAD

MDH
Sample Pyruvate + NADH----------►L-Lactate + NAD

LDH
AST present in the sample catalyses the transfer of the amino group from L-aspartate to 2-oxoglutarate forming oxaloacetate and L-glutamate.
Oxaloacetate in the presence of NADH and malate dehydrogenase (MDH), is reduced to L-malate. In this reaction NADH is oxidized to NAD. The reaction is monitored by measuring the rate of decrease in absorbance at 340nm due to the oxidation of NADH to NAD[12].
Addition of lactate dehydrogenase (LDH) to the reagent is necessary to achieve rapid and complete reduction of endogenous pyruvate so that it does not interfere with the assay.
Calculation – Δ A /min. x Factor = ALT/GPT activity in U/L

Table 3: Reference value of SGOT (IU/L)

Children 2-10	SGOT(U/L)
Male	upto 35
Female	upto 31

Estimation of serum albumin[13]
Principle
Albumin is bound by the BCG dye to procedure an increase in the blue-green color measured at 630 nm. The color increase is proportional to the concentration of albumin present.

Reagents
Bromocresol Green (BCG) 0.O8 Mmmol/L,succinate Buffer, pH 4.2± 0.1, surfactant, sodium azide 1 gm/L
Albumin Standard-3.6g/dl
Albu concentration (g/dL)= $\frac{\text{Absorbance. of test x Conc. of std (g/dL)}}{\text{Absorbance of Standard Std.}}$

Table 4: Reference value of albumin concentration (g/dL)

Age	Albumin concentration (g/dL)
2-14 Years	3.2-5.1
14-18 years	3.2-4.8
>18 years	3.5-5

Estimation of serum bilirubin
Methodology
Diazo Method, End Point[14]
Bilibuin is coupled with diazotized sulphanilic acid in acidic medium to form the pink colored azobilirubin which absorbs at 540/630 nm. The intensity of the color produced is directly proportional to bilirubin concentration present in the sample. Direct bilirubin or conjugated bilirubin is water soluble and it directly reacts inacidic medium. However, for indirect bilirubin or unconjugated bilirubin a surfactant is used for dissolving it inwater and then the dissolved material reacts similar to direct bilirubin.
Bilirubin + DPD----------►Azobilirubin

surfactant
Calculation
Calculation With Factor
Total bilirubin = Absorbance of Test Sample X Factor
Calculation with standard/calibrator:
Total bilirubin = $\frac{\text{Absorbance of Test Sample X concentrationof standard}}{\text{Absorbance of standard}}$

Table 5: Reference value of TSB concentration (mg/dL)

	TSB concentration (mg/dL)
Infants	1.2-6
Adults	0.2-1

Estimation of PT
Principle of the Method[15]
The coagulation process is triggered by incubation of plasma with the optimal amount of thromboplastin and calcium. The time to formation of a fibrin clot is then measured.

Reagents
Thromborel® S Reagent: lyophilized human placental thromboplastin (≤ 60 g/L), calcium chloride (approx. 1.5 g/L).
Calculation
The results can be reported in seconds, in % of norm, as prothrombin ratio (PR) or as International Normalized Ratio (INR). To obtain the

prothrombin ratio, the reaction time of the sample is divided by the reaction time of the normal plasma pool (e.g., Standard Human Plasma):

$$PR = \frac{\text{Reaction time of sample (seconds)}}{\text{Reaction time of normal plasma (seconds)}}$$

The prothrombin ratio can be converted into internationally comparable values by means of the International Sensitivity Index (ISI). The result obtained is in International Normalized Ratio (INR): INR= PR (ISI)

PT was calculated by semi auto analyzer machine, synmex CA-50 reference interval: 12.6 to 18.2 seconds control: 14.4 seconds

Statistical analysis

Based on previous study, Data was analyzed by using SPSS version 20.0. POST HOC and TUKEY test was applied to difference in means of various parameters in the two groups (significance of P <0.05). Data were compared in patients and controls using Chi-square test.

Results

In this present study observation based on hepatic profile done on in 100 subjects aged 2 years to 10 years. About 50 study cases of seizure disorder taking oral antiepilectics drugs. Another 50 Control, normal subjects of both sexes were selected who did not have seizure[6].

Table 6: Range and mean of serum hepatic profile in control group (n=50)

Range age	(2-10) years	Normal Values
Mean age	6.02±2.41 years	
Range of serum ALP	100-320U/L	100-320U/L
Mean serum ALP	171.15±38.315U/L	
Range of SGPT	5-45U/L	5-45U/L
Mean SGPT	30.70±6.63U/L	
Range of SGOT	15-40U/L	15-40U/L
Mean SGOT	25.84±5.23U/L	
Range of serum Albu	2.3-6.5 mg/dl	2.3-6.5 mg/dl
Mean serum albumin	4.14±0.23mg/dl	
Range of PT	14.1- 16.8 sec	14.1- 16.8 sec
Mean PT	15.14±0.51 sec	
Range of TSB	<1.2 mg/dl	<1.2 mg/dl
Mean TSB	0.51±0.08 mg/dl	

Table 7: Shows male female ratio in case group

Gender	Male	Female
Total No. of Patients	33	17

Out of 50 cases 33 cases were male and 17 cases were female child [Table 7].

Table 8: Showing economical status of the cases

Status	Good	Average	Poor
No. of Child	5	34	11

Table 8 showing out of total 50 cases socioeconomic status of patients were 11 poor, 34 average and 5 good.

Table 9: Types of seizure found in patients

Types of Seizure	FC	GTC
No of Patients	7	43

Above table 9/Fig.1 showing types of seizure found in patients

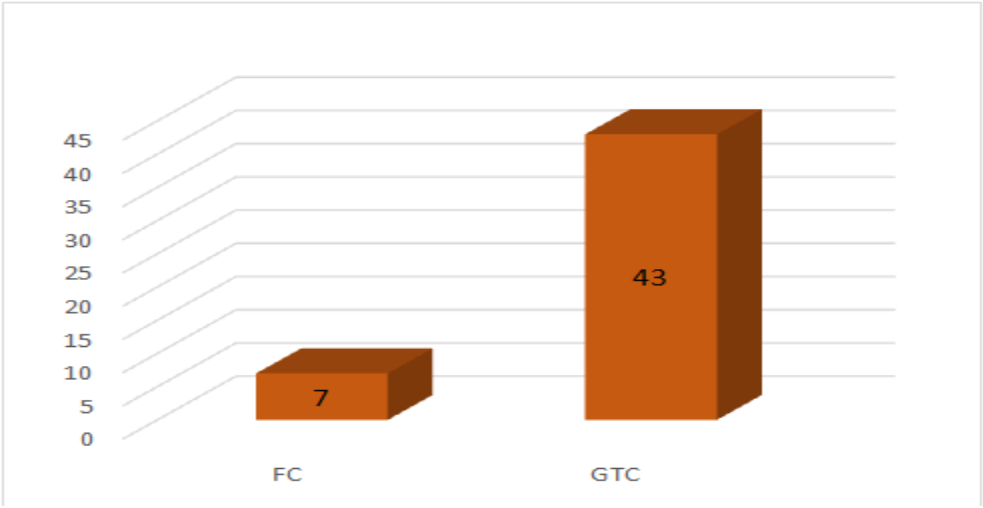

FiG 1: Showing distribution of seizure according to types of seizure out of 50 cases 43 had GTC type seizure and 7 had FC type seizure.

Table 10: Showing total numbers of patient on corresponding drugs

Drugs	Phenytoin	Valproate	Carbamazepine
No. of Patients	16	27	7

Above table 10 showing distribution of patient according to advised drugs, out of 50 cases 27 cases were T/t with VAL, 16 were T/t with PHY and 7 were T/t with CAR.

Table 11: Range and mean of serum hepatic profile in case group of valporic acid group (n=27)

Range age	(2-10) years	Normal Values
Mean age	6.59±2.44years	-
Range of serum ALP	100-602U/L	100-320U/L
Mean serum ALP	388.57±110.28U/L	-
Range of SGPT	5-82U/L	5-45U/L
Mean SGPT	48.63±15.70U/L	-
Range of SGOT	15-62U/L	15-40U/L
Mean SGOT	39.49±10.47U/L	
Range of serum Albu	2.3 mg/dl-6.5 mg/dl	2.3-6.5 mg/dl
Mean serum albumin	4.03±0.25mg/dl	
Range of PT	14.1- 16.8 sec	14.1- 16.8 sec
Mean PT	15.35±0.50 sec	
Range of TSB	<1.2 mg/dl	<1.2 mg/dl
Mean TSB	0.58±0.09 mg/dl	

Table 12: Mean and SD of alkaline phosphatase (U/L) at the start and after 1 year in control and case group of valproate treatment (n=27)

Alkaline phosphatase				
	Mean initially	Mean after 1 year	SD initially	SD after 1 year
Control (healthy)	168.59	171.15	±31.45	±38.31
Cases	178.65	388.57	±37.33	±110.28

P value-0.03

Above Table 12/Fig 2 show significant increase mean ALP level after treatment with valproate as p value is 0.03. Out of 27 cases 6 cases shows 1.5 fold ,6 cases shows 2 fold ,8 cases shows 3 fold increase in ALP after 1 year of Treatment from the initial value.

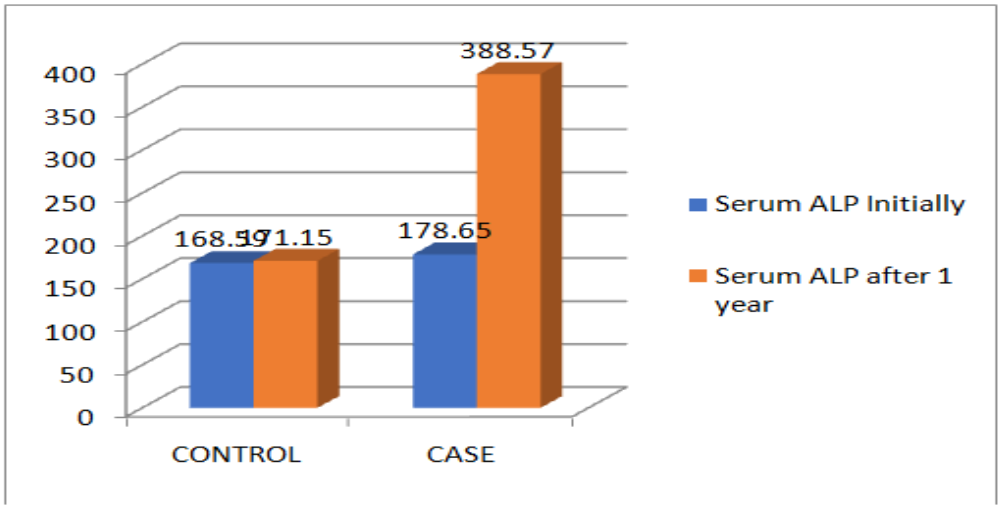

Fig 2: Showing significant increase mean ALP level after treatment with valproate

Table 13: Mean and SD of SGPT (U/L) at the start and after 1 year in control and case group of valproate treatment (n=27)

SGPT (U/L)				
	Mean initially	Mean after after 1 year	SD initially	SD after after 1 year
Control (Healthy)	22.51	28.16	±6.65	±6.63
Case	25.01	50.49	±7.20	±15.70

P value-0.25

Above Table 13/Fig. 3 shows no significant increase mean SGPT level after treatment with valproate as p value is 0.25. Out of 27 cases 10 cases shows 1.5 fold, 9 cases shows 2 fold ,3 cases shows 3 fold increase in SGPT after 1 year of treatment from the initial value.

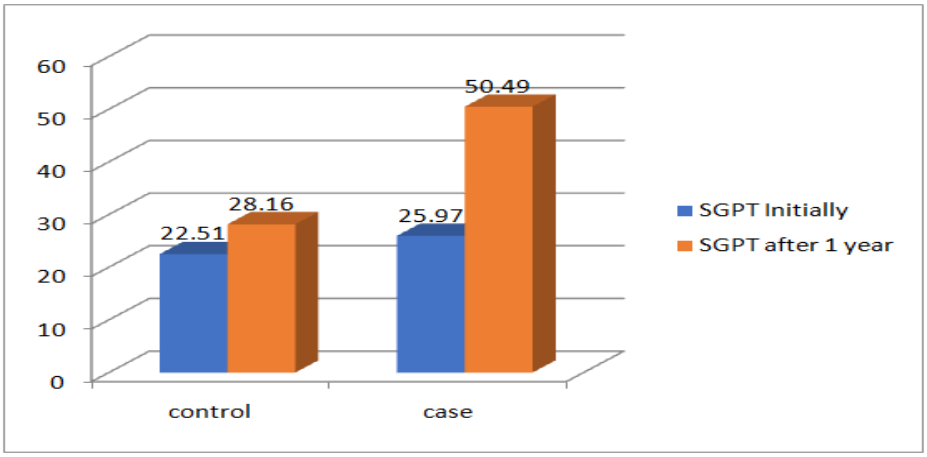

Fig 3: Shows no significant increase in mean SGPT after valproate treatment.

Table 14: Mean and SD of SGOT (U/L) at the start and after 1 year in control and case group of valproate treatment (n=27)

	SGOT (U/L)			
	Mean initially	**Mean after after 1 year**	**SD initially**	**SD after after 1 year**
Control (Healthy)	23.13	25.84	±4.42	±5.23
Case	21.36	39.49	±4.05	±10.47

P value-0.2

Above Table 14 shows no significant increase mean SGOT level after treatment with valproate as p value is 0.2. Out of 27 cases 10 cases shows 1.5 fold ,7 cases shows 2 fold ,4 cases shows 3 fold increase in SGOT after 1 year from the initial value.

Table 15: Mean and SD of S. Albu (mg/dL) at the start and after 1 year in control and case group of valproate treatment (n=27)

	S. Albu (mg/dL)			
	Mean initially	**Mean after after 1 year**	**SD initially**	**SD after after 1 year**
Control (healthy)	4.2	4.24	±0.24	±0.23
Case	4.23	4.18	±0.27	±0.25

P value-0.14

Above table 15 shows no significant decrease mean serum Albumin level after treatment with valproate as p value is 0.14.

Table 16: Mean and SD of PT(sec) at the start and after 1 year in control and case group of valproate treatment (n=27)

	S. Albu (mg/dL)			
	Mean initially	**Mean after 1 year**	**SD initially**	**SD after after 1 year**
Control(healthy)	15.12	15.14	±0.52	±0.51
Case	15.13	15.35	±0.47	±0.50

P value-0.082

Above table 16 shows no significant decrease mean PT level after treatment with valproate as p value is 0.082.

Table 17: Mean and SD of TSB(mg/dL) at the start and after 1 year in control and case group of valproate treatment (n=27)

	S. TSB (mg/dL)			
	Mean initially	**Mean after 1 year**	**SD initially**	**SD after 1 year**
Control(healthy)	0.47	0.49	±0.08	±0.09
case	0.47	0.58	±0.08	±0.09

P value-0.10

Above table 17 shows no significant decrease mean TSB level after treatment with valproate as p value is 0.10

Discussion

The present study was undertaken to study the effect of commonly used anticonvulsant drug valproate on serum level of hepatic profile in outdoor patients of department of pediatrics, Rajendra Institute of Medical Sciences, Ranchi. The study was a hospital based study, conducted on 100 patients over a period of 1 year. Out of total 100 cases observed, 50 were normal healthy controls and 50 were of seizure disorder. Out of 50 patients of seizure disorder, 27 were given valproate, 16 were given phenytoin and 7 were given carbamazepine. In the present study we have analyzed and represented only subjects' data on valproate therapy. Antiepileptic drugs may alter liver function and increase the activity of hepatic microsomal enzyme. This may alter the metabolism of various substances such as drugs and lipids[9]. The clinical spectrum of illness can vary from asymptomatic biochemical abnormalities of liver function to fulminant failure. There is a wide range of hepatotoxic reactions, from mild and transient elevations of hepatic enzymes to fatal hepatic failure[10].In the present study we have found out that there was no significant alteration of hepatic profile except serum alkaline phosphatase from the initial value which was significantly higher than control group. The study done by Kotsopoulos IA et al (2002)[16] in Systematic review and meta-analysis of incidence studies of epilepsy and unprovoked seizures and Irene Kotsopoulos et al (2005)[17] in incidence of epilepsy and predictive factors of epileptic and non-epileptic seizures seen that males had a slightly higher incidence of epilepsy than the females and partial seizures seemed to occur more often than generalized seizures. In my study there is also seizure was more common in male but the generalized seizure seemed to occur more often than focal/ partial seizures.

As per study Anju Aggarwal et al in 2004[18] showed that ratio of bilirubin and SGPT were not significantly different except for raised alkaline phosphatase. CBZ is considered to increase vitamin D metabolism, and risk of bone disease. Decreased vitamin D levels in subjects on CBZ might result in increased blood levels of alkaline phosphatase. In present study, it was also found that there was no significant increase in mean TSB and mean PT, also there was no significant decrease in mean serum albumin.G.P Mendis et al in 1998[19] conducted study on plasma activities of hepatic enzymes in patients on anticonvulsant therapy, it was concluded that plasma activities of AST and ALT were similar in control and test group and raised ALT and GGT were not an indication to alter anticonvulsant therapy. The study done by Manisha Naithani et al (2010)[20] on adverse metabolic effects of antiepileptic drugs and their correlation with blood components, has shown that there was increase in mean alkaline phosphatase and thyroid stimulating hormone concentration as compared to healthy age and sex matched individuals but these metabolic alterations were mostly mild and clinically insignificant. In my study also there was no significant increase in hepatic profile except in mean alkaline phosphatase. In a study by Mohammad Reza Salehiomran et al (2010)[21] on the effect of anticonvulsant drugs (phenobarbital and valproic acid) on the serum level of cholesterol, triglyceride, lipoprotein and liver enzymes in convulsive children, It was found that In children receiving sodium valproate, HDL, ALP, SGOT, SGPT significantly increased after treatment but there were no statistically significant changes in total cholesterol, LDL and TG. In my study also there was No significant increase in SGPT and SGOT.

Abdelmoneim Mahgoub et al study[22], an analytic cross-sectional study was conducted in 100 epileptic patients who received carbamazepine or sodium valproate for 1 year. Those with healthy pretreatment liver enzymes were recruited for the study. The results showed an elevation of Aspartate Aminotransferase (AST) in 24% of the patients treated with sodium valproate ($p = 0.01$) and 20% of the patients treated with carbamazepine. Alanine Aminotransferase (ALT) was elevated in both groups to a similar extent, 6% ($p = 0.01$). In conclusion, the study showed a lower proportion of liver enzyme abnormalities, since AST is a less sensitive biomarker when compared to ALT. No measurement exceeds twice the average value, nor are there any clinical abnormalities. There is no proven value of routine liver enzyme measurement in asymptomatic patients in our study.L. J. Willmore et al (1978)[23] in his study on Effect of valproic acid on hepatic function concluded that Altered hepatic function tests occurred in four of 25 patients treated with valproic acid. An average dose reduction in three patients of 10 mg per kilogram per day resulted in reversion of serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) to normal. Hence, careful monitoring of hepatic function is required of patients being treated with valproic acid, and that dose reduction alone may be effective in preventing untoward hepatic side effects.

Strengths of Study

The main strength of our study was prospective study design and inference that there was no significant alteration of hepatic profile except serum alkaline phosphatase which was significantly higher than control group. These mild elevations did not appear to be clinically significant and were probably due to enzyme induction.

Limitations of the study

The main limitations of our study were non blinded study design, shorter follow up period and enrollment from a single centre. We recommend serial monitoring of changes of hepatic profile from the beginning of therapy to completion of therapy and beyond. As the duration of the therapy was minimum of 3 years.

Conclusion

The study was hospital based study, conducted on 100 children over a period of 1 year. All children aged 2 years to 10 years, of either sex. Out of total 100 children observed, 50 were normal healthy controls. About 50 were having partial or generalized seizure and who have recently started either phenytoin, valproate or carbamazapine were errolled as case after clinical examination and laboratory confirmation. Out of 50 cases 33 cases were male and 17 cases were female child. Out of 50 patients of seizure disorder, 27 were given valproate,16 were given phenytoin and 7 were given carbamazepine for at least 1 year. The present study revealed that, the patients treated with valproate have shown significant increase mean ALP level after 1 year of treatment as p values were 0.03, 0.02 and 0.03 respectively. It was found that there was elevation of ALP was more and attained higher values in those receiving phenytoin than valproate, and carbamazepine.The patients treated with valproate have shown no significant increase mean SGPT and SGOT level after 1 year of treatment. It was also found that there was No significant increase in mean TSB and mean PT also there was No significant decrease in mean serum albumin.

The adverse effects of AEDs develop insidiously over many years, they might either be overlooked or not associated with the drug therapy. It was seen that there was increase in ALP, SGPT, SGOT level in 1 year. The significant increase was seen in mean ALP level these increase is probably due to enzyme-inducing or enzyme-inhibiting properties of drugs. SGPT, SGOT levels increases from the initial value but not to significant level. These drugs are safe to use in children up to 1 year. The future studies will either corroborate or contradict the present findings and strengthen the observation made in the present study.

References

1. Epilepsy.20 June 2019. https://www.who.int/news-room/fact-sheets/detail/epilepsy [Accessed on 19th October 2021]
2. Goldenberg MM. Overview of drugs used for epilepsy and seizures: etiology, diagnosis, and treatment. P T. 2010;35(7):392-415.
3. Leung AK, Hon KL, Leung TN. Febrile seizures: an overview. Drugs Context. 2018;7:212536.
4. French JA, Gazzola DM. New generation antiepileptic drugs: what do they offer in terms of improved tolerability and safety?. Ther Adv Drug Saf. 2011;2(4):141-158.
5. Piñeiro-Carrero VM, Piñeiro EO. Liver. Pediatrics. 2004 Apr;113(4 Suppl):1097-106.
6. Mazaleuskaya LL, Sangkuhl K, Thorn CF, FitzGerald GA, Altman RB, Klein TE. PharmGKB summary: pathways of acetaminophen metabolism at the therapeutic versus toxic doses. Pharmacogenet Genomics. 2015;25(8):416-426.
7. Esteves F, Rueff J, Kranendonk M. The Central Role of Cytochrome P450 in Xenobiotic Metabolism—A Brief Review on a Fascinating Enzyme Family. J. Xenobiot. 2021; 11: 94–114.
8. Arroyo S, de la Morena A. Life-threatening adverse events of antiepileptic drugs. Epilepsy Res. 2001 Nov;47(1-2):155-74.
9. Hackman A M, Bricker J T. Preventive cardiology, hypertension, and dyslipidemia. In: The Science and Practice of Pediatric Cardiology. Garson A., Bricker J. T., Fisher D. J., Neish S. R. (eds.). Baltimore : Williams & Wilkins, 1998, 2243-2260.
10. Wilkinson J H, Boutwell J H, Winsten S. Evaluation of a new system for the kinetic measurement of serum alkaline phosphatase. Clin. Chem. 1969;15:487.
11. Bergmeyer HU, Herder M, Rej R. Approved recommendation (1985) on IFCC methods for the measurement of Catalytic concentration of enzymes. Part 3. (FCC Method for alanine aminotransferase. J Clin Chem Clin Biochem 1986;24:481-489.
12. Huang XJ, Choi YK, Im HS, Yarimaga O, Yoon E, Kim HS. Aspartate Aminotransferase (AST/GOT) and Alanine Aminotransferase (ALT/GPT) Detection Techniques. Sensors (Basel). 2006;6(7):756-782.
13. Tietz. N.W. Fundamentals of Clinical Chemistry, p. 940. W.B. Saunders Co. Philadelphia, PA. (1987).
14. Gambino SR, Golden WRC, Smith AW. Bilirubin (Modified Jendrassik and Grof)—Provisional. Editor(s): Samuel Meites, Standard Methods of Clinical Chemistry, Elsevier 1965;5: 55-64.

15. Maxwell M, Wintrobe G, Lee R, Boggs DR, Bithell TC, Athens JW, Foerster J, Lukens J. Clinical hematology. 8th ed. Philadelphia: Lea & Febiger, 1981.
16. Kotsopoulos IA,Kessels FG, Knottnerus JA. Systematic review and meta-analysis of incidence studies of epilepsy and unprovoked seizures. Epilepsia. 2002;43(11):1402-9.
17. Kotsopoulos I, de Krom M, Kessels F, Lodder J, Troost J, Twellaar M, van Merode T, Knottnerus A. Incidence of epilepsy and predictive factors of epileptic and non-epileptic seizures. Seizure. 2005 Apr;14(3):175-82.
18. Aggarwal A, Kumar M, Faridi MMA. Effect of Carbamazepine on Serum Lipids and Liver Function Tests. Indian Pediatrics 2005; 42:913-918.
19. Mendis GP,Hunt HA. Plasma activities of hepatic enzymes in patients on anticonvulsant therapy. Seizure. 1993 ;2(4):319-23
20. Naithani M, Chopra S, Somani BL, Singh RK. Studies on adverse metabolic effects of antiepileptics and their correlation with blood components. Current Neurobiology .2010;1(2):9.
21. Salehiomran MR, Kordkheily SHE. The effect of anticonvulsant drugs (phenobarbital and valproic acid) on the serum level of cholesterol, triglyceride, lipoprotein and liver enzymes in convulsive children. Iranian Journal of Child Neurology (IJCN) Nov 2010; 4(3): 33-38.
22. Mahgoub A et al. Effect of Carbamazepine and Sodium Valproate on Liver Enzymes of Epileptic Children. Dr. Sulaiman Al Habib Medical Journal.2020; 2(3): 123–127.
23. Willmore LJ, Wilder BJ, Bruni J, Villarreal HJ. Effect of valproic acid on hepatic function. Neurology. 1978;28(9 Pt 1):961-4.

Conflict of Interest: Nil Source of support: Nil