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ORIGINAL RESEARCH ARTICLE

EFFECT OF DIFFERENT ANTICONVULSANTS ON LIVER ENZYME ACTIVITIES IN PATIENTS WITH SEIZURE DISORDER

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ABSTRACT

Background: Epilepsy is a common chronic neurological disorder characterized by recurrent unprovoked seizures, which has transient signs and/or symptoms of abnormal, synchronous neuronal activity in the brain. Antiepileptic drugs (AEDs) used for the prevention of seizure have been found to be an inducer of liver enzyme activity. So, the purpose of this study was to see the effect of antiepileptic drugs on hepatic enzymes activity.

Methods: An observational study was carried out in Kathmandu Medical College from October 2020 to April 2021 at neurology department. Sixty-seven seizure patients aged 19-89 years were included in the study. Liver function test was performed before medication, followed up and monitored for three and six months. Paired sample t-test was used to compare the means by using SPSS version 15.

Results: Among carbamazepine (CBZ) and sodium valproate (VPA) treated cases, 4.5% and 9.1% respectively showed raised Alanine aminotransferase (ALT) activity whereas, 13.6% and 4.5% respectively showed raised Alkaline Phosphatase (ALP) activity. ALT activity was higher in VPA treated patient compared to CBZ treated patient. However, ALP activity was raised in CBZ treated patient compared to VPA treated patients. No, change in liver enzyme activities was observed in patient treated with Levetiracetam

Conclusions: Anticonvulsant drugs used during the treatment have mild to moderate hepatotoxicity. Liver enzyme activity more than two to three-fold may increase. Levetiracetam has minimal hepatic metabolism while sodium valproate is more hepatotoxic. Therefore, routine screening of hepatic enzymes is recommended to the patients under antiepileptic therapy.

INTRODUCTION

Anti-convulsants or anti-epileptics are the diverse group of pharmacological agents used in the treatment of seizure.[1] A seizure is a paroxysmal time-limited change in motor activity and/or behavior that results from abnormal electrical activity in the brain.[2] Epilepsy is not a disease, but a syndrome of different cerebral disorders of the Central Nervous System which is characterized by excessive discharge of large numbers of neurons.[3] The common cause of seizure are head trauma, low blood sugar, alcohol consumption or as a drug withdrawal effect, infection, hypoxia and toxin.[4, 5]Liver is a primary organ for the metabolism and elimination of many antiepileptic drugs (AEDs) and thus is subjected to drug-induced toxicity. The use of AEDs induces hepatotoxic reactions, from mild and transient elevations of hepatic enzymes to fatal hepatic failure which are associated with mortality and morbidity.[6, 7]

Since, liver enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT)serve as markers of hepatocellular injury and are elevated in various forms of liver diseases. However, an elevation of these enzymes can also be due to secondary reasons, without the involvement of hepatic pathology.[8] One of the reasons behind hepatotoxicity is the use of antiepileptic drugs that may either cause the production of reactive toxic metabolite/s or induce immuno-allergic reactions.[9, 10]In such patients, if the increment in enzyme activity is progressive, an alternative AEDs can be prescribed.[8] Therefore, the purpose of this study was to observe the effect of antiepileptic drugs on hepatic enzymes activity.

METHODS

The present observational study was carried out in Kathmandu Medical College from October 2020 to April 2021 at neuro-medicine department where 67 diagnosed epileptic seizure cases, age ranging from 19-89 years was included using consecutive sampling technique. Ethical approval was obtained from institutional review committee(IRC), ref (2001202001) and written consent was taken from the patients who wished to participate in the study. Blood sample was collected from all the participants by venipuncture from cubital vein and sample was collected in a vial under aseptic condition for biochemical analysis. Liver enzymes, such as Alanine aminotransferase (ALT),Aspartate aminotransferase (AST) and Alkaline

phosphatase (ALP) were estimated before the initiation of treatment. Then, patients were grouped under different anticonvulsant medication/therapy such as-carbamazepine (22 patients), sodium valproate (22 patients) and levetiracetam (23 patients)and were advised to follow up on consecutive three and six month with the laboratory report of their liver enzyme activity. Liver enzymes were estimated by Selectra pro S auto analyzer using Elitech reagents. Values of ALT>45IU/L, AST >45 IU/L and ALP >306IU/L were considered elevated. Epileptic patients having concomitant liver diseases, consuming other drugs which may elevate liver enzymes (e.g. antibiotics, anti-rheumatic drugs, statins and nonsteroidal anti-inflammatory drugs) and alcoholics were excluded from the study. Sample size was determined from the study conducted by Dewan et al.[11]

The sample size was calculated as follows:

Sample size (n) = Z^2 x pq/e^2

= (1.64)2 x 0.5 x (1-0.5)/(0.1)2

= 67

Where,
Confidence interval (CI)=90%
Margin of error (e) = 10%
p = prevalence which was taken as 50%
q = (1-p)
Statistical analysis was done by SPSS (Statistical package for social science) version 15. Paired sample t-test was used to compare the means between different groups.

RESULTS

In our study, a total of 241 patients admitted were diagnosed with dengue fever during the six months period. The age and sex distribution of the patients is depicted in Table 1. The mean age of the patients was calculated as 34.44 years on the basis of descriptive statistics.

This study included 55.2% of male and 44.8% female participants to whom different anticonvulsant drugs were prescribed for the treatment of seizure disorders. Among the treatment group, 9.1% showed raised ALT activity to whom sodium valporate was used and 13.6% showed raised ALP activityto whom Carbamazepine was used as depicted in table 1.

Table 1: Demographic and laboratory parameters of the study participants

	Male		Female
Age (Mean ±SD)	32.89±7.96		32.93±8.29
Sex	37(55.2%)		30 (44.8%)
Drugs Prescribed			
Carbamazepine	11 (50%)		11 (50%)
Sodium valporate	15 (68.2%)		7 (31.8%)
Levetiracetam	11 (47.8%)		12 (52.2%)
Raised Liver enzyme Activity after 6 month of treatment	Carbamazepine	Sodium valporate	Levetiracetam
ALT (>45 IU/L)	1(4.5%)	2(9.1%)	0
AST(>45 IU/L)	0	0	0
ALP(>306 IU/L)	3(13.6%)	1(4.5%)	0

Table 2: Laboratory parameter before and after treatment by carbamazepine on seizure patient

Parameter	Number of Patient	Mean ± S.D(IU/L)			p value primary 3 month treatment	p value primary 6 month treatment
		Before treatment	3 month treatment	6month Treatment		
Serum total bilirubin	22	0.60±0.13	0.66±0.14	0.72±0.10	0.190	0.003
Serum direct bilirubin	22	0.15±0.06	0.16±0.05	0.17±0.05	0.521	0.393
Serum total protein	22	6.86±0.42	6.72±0.45	6.89±0.32	0.336	0.829
Serum albumin	22	4.16±0.35	4.13±0.37	4.04±0.30	0.754	0.226
Serum ALT	22	24.79±2.91	27.75±3.76	32.11±5.57	0.014	0.000
Serum AST	22	26.83±3.77	29.31±4.47	28.43±4.95	0.078	0.240
Serum ALP	22	182.12±29.17	205.29±44.74	217.54±50.19	0.041	0.005

Serum ALT activity was raised significantly in patients who were under the treatment with carbamazepine when it is compared at different interval as p=0.014 and p=<0.001 respectively. Similarly, ALP activity was also raised significantly when compared at different interval that is p=0.041 and p=0.005 respectively as shown in table 2.

Furthermore, serum ALT activity was raised significantly in patients who were under the treatment with Sodium valporate. An increase in ALT activity was observed when compared at different interval as p=0.004 and p=<0.001 respectively. Similarly serum AST activity was also increased significantly when measured at different intervals as p=0.002 and p=<0.001 respectively. Serum activity of ALP was also elevated significantly when it was measured after 6 month with p=0.010 as shown in table 3.

Table 3: Laboratory parameter before and after treatment by sodium valporate on seizure patient

Parameter	Number of Patient	Mean ± S.D (IU/L)			p value primary 3 month treatment	p value primary 6 month treatment
		Before treatment	3month treatment	6 month Treatment		
Serum total bilirubin	22	0.66±0.11	0.69±0.16	0.76±0.98	0.541	0.007
Serum direct bilirubin	22	0.15±0.06	0.18±0.07	0.17±0.06	0.064	0.165
Serum total protein	22	6.85±0.47	7.00±0.43	6.86±0.27	0.091	0.870
Serum albumin	22	3.94±0.33	4.09±0.28	3.94±0.25	0.044	0.916
Serum ALT	22	26.35±3.97	29.17±3.72	34.72±6.20	0.004	0.000
Serum AST	22	24.86±2.82	27.26±3.87	31.03±4.81	0.002	0.000
Serum ALP	22	181.55±21.68	195.62±27.62	210.54±40.10	0.053	0.010

Table 4: Laboratory parameter before and after treatment by Levetiracetam on seizure patient

Parameter	Number of Patient	Mean ± S.D (IU/L)			p value primary 3 month treatment	p value primary 6 month treatment
		Before treatment	3 month treatment	6 month Treatment		
Serum total bilirubin	23	0.62±0.15	0.65±0.15	0.67±0.10	0.559	0.193
Serum direct bilirubin	23	0.19±0.06	0.16±0.07	0.16±0.07	0.089	0.038
Serum total protein	23	6.95±0.44	6.86±0.46	6.91±0.34	0.475	0.752
Serum albumin	23	4.35±0.39	4.22±0.37	4.16±0.31	0.193	0.067
Serum ALT	23	23.17±2.66	24.72±3.28	21.87±2.68	0.002	0.057
Serum AST	23	25.12±3.97	26.18±4.38	23.90±2.50	0.452	0.155
Serum ALP	23	191.05±19.29	184.31±18.00	188.82±21.72	0.257	0.680

However, table 4 showed the activity of liver enzymes were within normal range in the group of patients treated with Levetiracetam. Serum ALT, AST and ALP activity was statistically insignificant when compared in the interval of six months with p value noted as 0.057, 0.155 and 0.680 respectively.

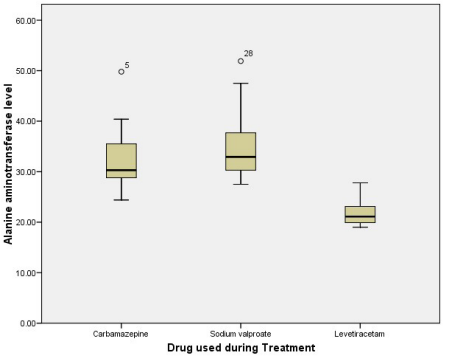

Figure 1: Comaprison of ALT activity in different AEDs after 6 month

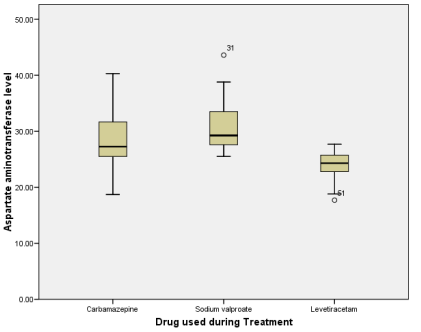

Figure 2: Comparison of AST activity in different AEDs after 6 month

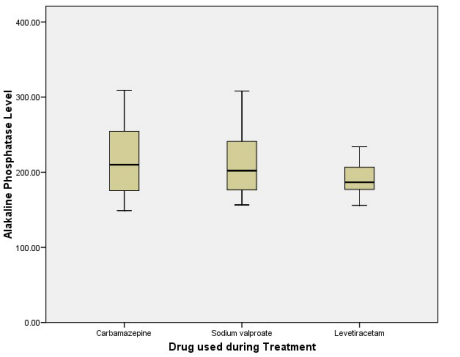

Figure 3: Comparison of ALP activity in different AEDs after 6 month

DISCUSSION

The present study included 67 patients with seizure disorder, among which 22 patients were prescribed with carbamazepine, the same number of patients using sodium valporate and 23 patients were prescribed with levetiracetam**.** The liver function tests of the patients were performed prior to the treatment and the same tests were repeated to the patients after treating them with anticonvulsants for three months and six months respectively.

In this study ALT activity was increased in 4.5% and ALP activity was increased in 13.6% patients treated with carbamazepine (CBZ). In a similar study Heinz Grobe[12] observed that serum ALT activity was increased in 9% of cases and serum ALP was raised in 14% of cases. Another study conducted by Hussein

et al[13]it was observed that 50% patients who were treated with CBZ had increased ALP activity. This study showed a raised activity of ALT (mean ± SD 27.75±3.76 IU/L and 32.11±5.57 IU/L) as well as ALP (mean ± SD 205.29±44.74 IU/L and 217.54±50.19 IU/L) in the patients treated with CBZ for three months and six months respectively. CBZ is an older-generation sodium channel blocker and is extensively bio-transformed and is oxidized in the liver into carbamazepine-10,11-epoxide (CBZ-E), which possesses anti-convulsant properties that is generated through the action of CYP3A4, CYP3A5 and CYP2C8 via the action of enzyme of cytochrome P 450 system (CYP 450).[14-16] CYP450 isoenzymes are induced by AEDs, especially the classical AEDs, such as benzodiazepines (BZDs), carbamazepine (CBZ), phenytoin (PT), phenobarbital (PB) and valproic acid. Serum aminotransferase have been transiently elevated in the patients who are prescribed with the considerable amounts of carbamazepine (ranging from 1% to 22%). These elevations are usually benign, not associated with liver histological abnormalities and usually resolve even with drug continuation.[17] This study showed a moderate rise in serum ALP in the patients treated with CBZ as shown in table 2. CYP450 induced by CBZ may lead to bone metabolism abnormalities, reflected by an increased concentration of biochemical markers of bone resorption and degradation in both serum and urine. Since, dysregulation of CYP450 causes vitamin D deficiency and side effects such as decreased calcitonin, reduced calcium levels, and elevated ALP, suggesting the existence of bone destruction.[18]

Among the patients treated with Sodium Valproate (VPA), liver enzyme activity was higher. The ALT activity was increased in 9.1% and ALP activity was increased in 4.5% of the patient treated with VPA. In consistent with the present study, a study conducted by Hussein et al[13], showed that there was an increase in ALT activity among the patient (6.25%) treated with VPA. However, unlike the findings of the present study, Hussein et al. showed huge number of patients (62.5%) having increased ALP activity. Another study conducted by Willmore et al[19] and Felker et al[20] observed transient elevation of ALT and AST activity in seizure patients treated with VPA. Prospective studies suggest that 5% to 10% of persons develop ALT elevations during long term valproate therapy, but these abnormalities are usually asymptomatic and can resolve even with continuation of drug.[21] VPA has very complicated biotransformation of which hepatic biotransformation is the major route for its elimination, therefore a transient elevation of liver enzymes occurs in patients receiving VPA. The medication can be continued even if there is rise in enzyme levels to moderate; up to two to three times the baseline levels and till the patient has remained asymptomatic. If the changes in hepatic functions are clinically symptomatic it is recommended to discontinue the drug with supportive therapy such as maintaining serum glucose, Vitamin K supplement and carnitine therapy.[8] This study found a moderate increase in ALP activity which is shown in Table 3. Treatment with VPA may produce long-term effects as reduction of the bone mass, with increased risk of fractures, an effect associated with high levels of plasma ALP.[22]

This study found no any elevation in hepatic enzyme activities, such as ALT, AST and ALP in the patients who were treated with Levetiracetam (LEV). LEV is a pyrrolidine derivative of anticonvulsant medication which is believed to act by preventing secondary spread of focal seizure activity and to decrease simultaneous neuronal firing.[23] LEV has minimal hepatic metabolism and its metabolism is not dependent on the liver cytochrome P450 enzyme system, epoxide hydrolase, or UDP-glucuronyltransferase and is mainly excreted unchanged through the kidney. The major metabolic pathway is enzymatic hydrolysis of the acetamide group, producing the inactive carboxylic acid metabolite in the blood.[24] Prospective studies reported that LEV therapy was not accompanied by significant elevations in serum aminotransferase levels and clinically apparent liver injury was not observed.[23] In this study when liver enzyme activity were compared with different AEDs, the serum ALT activity was not affected in patients treated with LEV (Mean ±SD= 21.87±2.68IU/L),but increased activity was observed in patient treated with VPA (Mean ±SD= 34.72±6.20 IU/L), followed by CBZ (Mean ±SD= 32.11±5.57 IU/L).Similarly, serum AST activity was not affected in patient treated with LEV (Mean ±SD= 23.90±2.50 IU/L), but was increased in patient treated with VPA (Mean ±SD= 31.03±4.81 IU/L), followed by CBZ (Mean ±SD= 28.43±4.95 IU/L) as shown in Fig 1 and 2. Aminotransferase levels are sensitive indicators of liver-cell injury. ALT is a cytosolic enzyme which is liver specific, its raised activity on plasma suggests liver injury.[25] Likewise, serum ALP activity was increased in patient treated with CBZ (Mean ±SD= 217.54±50.19), followed by VPA (Mean ±SD= 210.54±40.10) as shown in Fig 3. An elevation of serum ALP activity depends on duration of drug administration.[26]

There are some limitations in this study such as inability to follow up the patient for longer duration and limited number of sample size. Further studies are required to be conducted on a larger population and need to follow up for longer duration to reveal the hepatotoxic effect of the drugs.

CONCLUSION

Anticonvulsant drugs used during the treatment of seizure disorder have an adverse effect of mild to moderate hepatotoxicity. From our study, results showed that levetiracetam has minimal hepatic metabolism, while sodium valproate are more hepatotoxic than carbamazepine. Routine screening of hepatic enzymes level during the treatment with antiepileptic drugs is recommended. The need for obtaining baseline liver function tests is essential before starting antiepileptic therapy and regular monitoring should be done for any of the risk factors for liver damage during antiepileptic therapy. Precautions should be taken when using antiepileptic drugs in epileptic patients due to pre-existing hepatic disorders, or inpatients using potentially hepatotoxic drugs, if signs or symptoms of hepatic impairment appear.

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REFERENCES:

1. Zack MM, Kobau R. National and State Estimates of the Numbers of Adults and Children with Active Epilepsy — United States, 2015. MMWR. 2017;66(31):821–5. [DOI]
2. Stafstrom CE, Carmant L. Seizures and epilepsy: an overview for neuroscientists. Cold Spring Harb Perspect Med. 2015 Jun 1;5(6). [DOI]
3. Nikalje APG, Ghodke M, Girbane A. GABA Modulating Agents: A Brief Review. Asian Journal of Biological Sciences. 2011;4:201-20.[DOI]
4. Mohammad RS, Seyyed EH, Kordkheily MD. The effect of anticonvulsant drugs (phenobarbital and valproic Acid) on the serum level of cholesterol, triglyceride, lipoprotein And liver enzymes in convulsive children. Iran J Child Neurology. 2010;4(3):33-8. [DOI]
5. Demircioglu S, Soylu A, Dirik E. Carbamazepine and valproic acid: effects on the serum lipids and liver functions in children. Pediatr Neurol. 2000 Aug;23(2):142-6. [DOI]
6. Arroyo S, de la Morena A. Life-threatening adverse events of antiepileptic drugs. Epilepsy Res. 2001 Nov;47(1-2):155-74.[DOI]
7. Hoshino M, Heise CO, Puglia P, Almeida AB, Cukiert A. Hepatic enzymes' level during chronic use of anticonvulsant drugs. Arq Neuropsiquiatr. 1995 Dec;53(4):719-23.[DOI]
8. Ahmed SN, Siddiqi ZA. Antiepileptic drugs and liver disease. Seizure. 2006 Apr;15(3):156-64. [DOI]
9. Bjornsson E. Hepatotoxicity associated with antiepileptic drugs. Acta Neurol Scand. 2008 Nov;118(5):281-90. [DOI]
10. Lee WM. Drug-induced hepatotoxicity. N Engl J Med. 2003 Jul 31;349(5):474-85.[DOI]
11. Dewan P, Aggarwal A, Faridi MM. Effect of phenytoin and valproic acid therapy on serum lipid levels and liver function tests. Indian Pediatr. 2008 Oct;45(10):855-8. [PMID]
12. Aldenhovel HG. The influence of long-term anticonvulsant therapy with diphenylhydantoin and carbamazepine on serum gamma-glutamyltransferase, aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase. Eur Arch Psychiatry Neurol Sci. 1988;237(5):312-6.[DOI]
13. Hussein RRS, Soliman RH, Abdelhaleem AAM, Tawfeik MH, Abdelrahim MEA. Effect of antiepileptic drugs on liver enzymes. Beni-Suef University Journal of Basic and Applied Sciences. 2013;2(1):14-9. [DOI]
14. Vidaurre J, Gedela S, Yarosz S. Antiepileptic Drugs and Liver Disease. Pediatr Neurol. 2017 Dec;77:23-36.[DOI]
15. Hadzagic-Catibusic F, Hasanbegovic E, Melunovic M, Zubcevic S, Uzicanin S. Effects of Carbamazepine and Valproate on Serum Aspartate Aminotransferase, Alanine Aminotransferase and Gamma - Glutamyltransferase in Children. Med Arch. 2017 Aug;71(4):239-42. [DOI]
16. Fan HC, Lee HS, Chang KP, Lee YY, Lai HC, Hung PL, et al. The Impact of Anti-Epileptic Drugs on Growth and Bone Metabolism. Int J Mol Sci. 2016 Aug 1;17(8). [DOI]
17. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Carbamazepine. National Institute of Diabetes and Digestive and Kidney Diseases; 2017; Available from: https://www.ncbi.nlm.nih.gov/books/NBK548097/.[LINK]
18. Zhang X, Zhong R, Chen Q, Li M, Lin W, Cui L. Effect of carbamazepine on the bone health of people with epilepsy: a systematic review and meta-analysis. J Int Med Res. 2020 Mar;48(3):300060520902608.[DOI]
19. Willmore LJ, Wilder BJ, Bruni J, Villarreal HJ. Effect of valproic acid on hepatic function. Neurology. 1978 Sep;28(9 Pt 1):961-4. [DOI]
20. Felker BL, Sloan KL, Dominitz JA, Barnes RF. The safety of valproic acid use for patients with hepatitis C infection. Am J Psychiatry. 2003 Jan;160(1):174-8. [DOI]
21. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Valporate. National Institute of Diabetes and Digestive and Kidney Diseases; 2020; Available from: https://www.ncbi.nlm.nih.gov/books/NBK548284/. [LINK]
22. Pratico AD, Pavone P, Scuderi MG, Li Volti G, Bernardini R, Cantarella G, et al. Symptomatic hypocalcemia in an epileptic child treated with valproic acid plus lamotrigine: a case report. Cases J. 2009 Jun 17;2:7394.[DOI]
23. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Levetiracetam. National Institute of Diabetes and Digestive and Kidney Diseases; 2019; Available from: https://www.ncbi.nlm.nih.gov/books/NBK548785/.[LINK]
24. Radtke RA. Pharmacokinetics of levetiracetam. Epilepsia. 2001;42 Suppl 4:24-7. [DOI]
25. Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. N Engl J Med. 2000 Apr 27;342(17):1266-71. [DOI]
26. Tjellesen L, Christiansen C. Serum vitamin D metabolites in epileptic patients treated with 2 different anti-convulsants. Acta Neurol Scand. 1982 Sep;66(3):335-41.[DOI]