Original Research Paper Medical Science

Assessing the effects of Sodium Valproate on Liver Function test in patients of Bipolar disorder

* Dr.Dharmesh N. Gamit	Assistant professor, Department of Biochemistrty, GMERS Medical College, Valsad * Corresponding Author
Dr.Dharmesh K. Patel	Assistant Professor, Department of Physiology, GMERS Medical college, Valsad
Dr. Avanish Mishra	Professor & Head, Department of Biochemistry, GMERS Medical College, Valsad
Dr.Hariom Sharma	Professor & Head, Department of Biochemistry, Govt. Medical College, Bhavnagar
Dr.Kalpana Gamit	Tutor, Departement of Physiology GMERS Medical College, Valsad.

ABSTRACT *The study comprised effects of sodium valproate on liver in patients of bipolar disorder. In the present study 75 known patients of Bipolar disorder were enrolled and subjected to various biochemical investigations initially and after 3 months of treatment with Sodium Valproate. Venous blood samples (5ml) were collected from all the patients and analyzed for Bilirubin, Alanine aminotransferase ,Aspartate aminotransferase , Alkaline phosphatase and pseudocholinesterase . The levels of ALT and AST ($p<0.001$) were significantly increased and Pseudocholinesterase levels were significantly decreased , but there were no stastical significant changes in the levels of Alkaline Phosphtase and Bilirubin. In the Present study Alterations in the levels of Alanine aminotransferase and Aspartate aminotransferase show positive indication that treatment with Sodium Valproate affect the liver function, which suggest periodic monitoring of liver function test in the patients receiving long term sodium Valproate therapy.*

KEYWORDS : Sodium Valproate, Bipolar disorder, Liver function test

INTRODUCTION: -

Bipolar disorder is one of the most disabling mental disorders. It is associated with reduced emotional and social functioning, increased suicidal behaviour, increased utilization of mental health services, and more days of bed rest and absenteeism compared to other mental disorders. (1) Bipolar disorder affects approximately 1% of world poulation.(2)

Sodium Valproate is the most useful and effective drug in epilepsy and in bipolar disorder for long term therapy. Valproate is used in the treatment of Epilepsy, to control the fits (seizures or blackouts) and to stabilize the mood, in the patient is suffering from Bipolar disorder. (3)

When initiating Valproate as long-term treatment, patients should have their height and weight measurement, a full blood count and liver function tests. Valproate should not be prescribed routinely for women of child-bearing potential. If there is no effective alternative to Valproate, than adequate contraception should be used, and the risks of taking valproate during pregnancy should be explained. (4)

Keeping in view the different outcomes of the previous researchers, the present study was designed to evaluate significance of liver function test in patients of Bipolar disorder treated with Sodium Valproate.

AIMS & OBJECTIVE:-

1. To study the alterations in Liver function after the administration of Sodium Valproate in patients of Bipolar Disorder.
2. To evaluate which parameter of Liver function test including Serum Pseudocholinesterase is a better indicator of hepatic dysfunction.

MATERIALS AND METHODS:-

The present study was conducted at Department of Biochemistry , Govt. medical college & Sit Takhtsinhji General Hospital, Bhavnagar Gujarat, in which 75 known cases of Bipolar disorder were included. Patients with acute abdominal or hepatic disease (confirmed by USG abdomen) , renal disease, alcohol abuse, organophosphate poisoning and those receiving medications which could alter liver function tests are excluded from the study. All the patients were subjected initial physical examination and various biochemical investigations initially and after 3 months of continuous treatment with Sodium Valproate. Doses of Sodium Valproate administered from 600-1200 mg/day. The study was approved by the Institutional Review Board (Human Ethics committee), Govt. medical college , Bhavnagar and informed consent was obtained from all subjects.

Venous blood was collected from all the patients and analyzed for various biochemical parameters like Bilirubin (DMSO Dimethylsulfoxide Colorimetric method), alanine aminotransferase (ALT) , aspartate aminotransferase (AST) through IFCC method (International federation of clinical chemistry),, alkaline phosphatase(ALP) through DGKC (Deutsche gesellschaft fur klinische chemie) recommended p-Nitrophenylphosphate kinetic method and Pseudocholinesterase by new DGKC Kinetic method on fully auto analyzer- Miura A1005 (Logotech) Italy at NABL Accreditated Clinical Biochemistry Section, Laboratory Services , Sir Takhtsinhji General Hospital, Bhavnagar.(5)

Enzymes activities were expressed as IU/l and Bilirubin in mg/dl. Graph pad instat 3 demo version software was used for statistical analysis. Descriptive statistics are shown as mean ± standard deviation. Mean enzymes levels of pre- and post- treatment periods were compared by paired t-test. Normal distribution was tested and data was not found to follow normal distribution. Hence, non-parametric wilcoxan matched –pairs signed ranks test was applied to compare each parameter. P value less than 0.05 was considered significant.

Results & Discussion:-

Comparison of liver enzyme including bilirubin in the study group at interval of 3 months of treatment with Sodium Valproate (Table-1). The mean ages of groups were not significantly different. It was observed that out of 75 patients of Bipolar disorder 49 (65%) had significant increase in ALT level ($p<0.001$) & 67 (89%) in AST level ($p<0.001$).The Pseudocholinesterase levels was significantly decreased in 30 (40%) patients of Bipolar disorder($p<0.001$). There is slight elevation in Total Bilirubin level due to slightly increased in indirect bilirubin level.

Table-1: Comparison of Liver Function Test at interval of 3 months in Patients of Bipolar Disorder treated with Sodium Valproate

Parameter	Biological Reference Interval	Before treatment n=75			After treatment N=75			P value
		Mini.	Maxi.	Mean±SD	Mini.	Maxi.	Mean±SD	
ALT	Upto 45 IU/L	8	47	27±10	26	121	58±22	<0.001**
AST	Upto 35 IU/L	12	55	29±9	32	228	63±31	<0.001**
Pseudocholinesterase	4500-11000 IU/L	3986	8637	5676±1154	3568	6832	4734±758	<0.001**
Total Bilirubin	Upto 1.1 mg/dl	0.2	1.2	0.68±0.2	0.3	1.2	0.77±0.2	0.02*
Direct Bilirubin	Upto 0.3 mg/dl	0.1	0.6	0.36±0.1	0.1	0.7	0.39±0.1	0.06#
Indirect Bilirubin	Upto 0.8 mg/dl	0.1	0.6	0.32±0.1	0.1	0.6	0.37±0.1	0.02*
ALP	98-279IU/L	134	216	171±18	132	329	169±24	0.76#

*Significant,** Highly significant,#Non-significant

Sodium Valproate is commonly used first line drug in a number of neuropsychiatric diseases like Bipolar and drug of choice for mixed mania and rapid cycling. (6)

Sodium Valproate is usually well tolerated, but serious complications including hepatotoxicity and hyperammonemic encephalopathy may occur.(7) It is completely absorbed from the gastroinetestinal tract and extensively metabolized by the liver via glucuronic acid conjugation and partly because of beta- and omega- oxidation which produces multiple toxic metabolites. CYP (p450) mediated omega oxidation , which is normally responsible for a small component of Sodium Valproate metabolism , may generate toxic metabolites that have been implicated in the idiosyncratic hepatic, metabolic , and neurologic adverse effects of this drug. Sodium Valproate is particularly known to cause microvesicular steatosis , in which small fat droplets are present within the hepatocytes and do not displace the nucleus. Valproic Acid (VPA) induced hyper ammonemia and hepatotoxicity may be mediated in part by carnitine deficiency, therefore carnitine supplementation may prevent these adverse effects.(8) Gaetano Zaccara et al. concluded in his study that VPA-induced hepatotoxicity is direct cytotoxic effect of two metabolites, namely 4-en VPA and its ß-oxidation derivative 2, 4-dien VPA. The formation of 4-en VPA is largely catalyzed by CYP2C9(cytochrome P-2,C-9), whose activity is inducible and is higher in young children, which may explain why the risk of VPA-induced liver toxicity is highest in infants medicated with enzyme inducing antiepileptic drugs. 4-en VPA is further metabolized in mitochondria to 2, 4-dien VPA, which is a reactive species capable of causing inhibition of ß-oxidation and mitochondrial dysfunction. (9) N Buchnan reviewed in his study that the hepatic lesion is one of microvesicular steatosis and appears to be an idiosyncratic reaction, rather than being dose-related. It occurs predominantly in the first 6 months of treatment, mainly in children, especially those with epilepsy which is difficult to control. The condition predominately in the first 6 months of treatment , mainly in children. (10) Charlene LePane. et al. reported in his study that Fulminant hepatic failure can result from an idiosyncratic reaction to valproic acid in a patient with a previously healthy liver.(11) Raphale J Leo et al concluded that use of valproate is associated with possibility of elevation of enzymes and thrombocytopenia. Transient elevations in aspartate aminotransferase(AST) and alanine aminotransferase (ALT) have been reported in as many as 11% valproate treated patients.(12) In the present study significant increase in ALT and AST levels were observed but no significant change in ALP level was seen and this may be because of the difference in the doses of drug and duration of the study. It was also observed that the level of serum cholinesterase was significantly lower ($p<0.001$) in same patients after follow up of 3 months. Further there is slight elevation in Bilirubin level might be due to increased Indirect Bilirubin level ($p< 0.05$). This indicates altered liver function during treatment with Sodium Valproate. Long term studies are required to find out its diagnostic importance.

Ogunkeye et al. conducted a study on usefulness of serum cholinesterase activity in 20 liver disease patients and 20 non-liver disease patients. They found that serum Pseudocholinesterase activity was significantly lower in liver disease that is why an attempt was made in present study to find out usefulness of serum Pseudocholinesterase where hepatotoxicity need to be evaluated due to administration of Sodium Valproate.(13) Previous studies have reported that levels of liver enzymes are affected when patients of Bipolar disorder are treated with Sodium Valproate. The present study confirms the finding of previous studies and also observed that estimation of Alanine aminotransferase and Aspartate aminotransferase along with Serum Pseudocholinesterase helps in predicting hepatotoxicity due to administration of Sodium Valproate in patients of Bipolar disorder . Konig SA and siemes H concluded in their study that the risk of heaptoxicity is the highest early in the course of treatment, liver function tests should be conducted at monthly intervals during first 6 months of treatment, and less frequently thereafter. (14)

CONCLUSION: -

Alterations in the levels of Alanine aminotransferase and Aspartate aminotransferase show positive indication that treatment with Sodium Valproate affect the liver function. However, further studies in larger populations are needed to validate these data and to reveal the clinical usefulness of the enzyme, including in differential diagnosis between other liver Diseases. The early changes in liver profile suggest that periodic monitoring of liver function test would be in the better interest of the patients receiving long term sodium Valproate therapy and any future episode of liver dysfunctions can be prevented.

REFERENCES

1. Kessler RC. 2003.Tracing Bipolar Disorder to its Developmental Origin in the General Population.:pp 1-3.
2. Raphael j. Leo. 1999.Anticonvulsant use in the Treatment of bipolar disorder: A primer for primary care physician 1:3.,pp 74-84.
3. Pennine Care NHS Trust. Treatments for mood disorder. Jan/06 122AP/Central/CNST. pp-8-9.
4. Akiskal, H.S. 2006.The management of bipolar disorder in adults, children and adolescents, in primary and secondary care, The British Psychological Society & The Royal College of Psychiatrists, ,pp 76-77.
5. Tietz: Textbook of Clinical Chemistry & Molecular Diagnostics, 4th edition, 604-616, 1195-1198.
6. Straumann .: mitochondrial diseases represent a risk factor for valproate-induced fulminant liver failure.liver 200:20:346-348.(61)
7. Gugler R, Von Unruh GE. 1980 Clinical pharmacokinetics of valproic acid. Clinpharmacokinet: 5: 67-83
8. Ishikura H, Matsuo N, Matsubara M, Ishihara T, Takeyama N, Tanaka T. 1996. Valproic acid overdose and l-carnitine therapy. J anal Toxicol;20:55-58.
9. Zaccara G, Franciotta D, Perucca E, 2007. Idiosyncratic Adverse reactions to Antileptic drugs. Epilepsia. 48(7): 1223-1244.
10. Buchanan N, 1985. Use of Sodium Valproate , Indian J pediatr; 52 (6): 645-649.
11. Charlene Le Pane 2007.,Valproic Acid Induced Fulminant Hepatic Failure March.nd.
12. Raphael j. Leo. 1999. Anticonvulsant use in the Treatment of bipolar disorder: A primer for primary care physician 1:3.,pp 74-84.
13. O. O. Ogunkeye. 2006. Serum cholinesterase activity helps to distinguish between liver disease and non-liver disease aberration in liver function tests. Pathophysiology 13, 91–93.
14. S. A. Konig. 1999. Fatal Liver Failure Associated with Valproate Therapy in a Patient with Friedreich's Disease: Review of Valproate Hepatotoxicity in Adults. Epilepsia, Vol. 40, No. 7,.