ABSTRACT

OBJECTIVES: As aminotransferases are an accepted marker for liver injury, in this study, we investigated these enzymes levels along with alkaline phosphatase and Pseudocholinesterase in patients of Epilepsy treated with Sodium Valproate. MATERIALS AND METHODS: In the Present study 75 known patients of Epilepsy 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 Alanine aminotransferase, Aspartate aminotransferase, Alkaline phosphatase and Pseudocholinesterase on fully auto analyzer – Miura A 1005 (I.S.E.-Srl, Italy) at Clinical Biochemistry Section, Laboratory Services, Sir T General Hospital, Bhavnagar. RESULTS: The levels of ALT (27 ± 10 vs. 58 ± 22 IU/L, P <0.001) and AST (29 ± 9 vs. 63 ± 31IU/L, P < 0.001) were significantly increased in patients of epilepsy after administration of sodium Valproate for 3 months. Aminotransferases levels in Epilepsy patients significantly increased and Pseudocholinesterase levels were significantly decreased, but there were no statistical significant changes in the levels of other liver enzymes like Alkaline phosphatase. CONCLUSION: Present study concludes that patients of epilepsy treated with sodium valproate had significantly higher levels of aminotransferases, which suggest a need for monitoring of hepatic enzymes in patients receiving this drug.

Keywords: Alanine aminotransferase, Aspartate Aminotransferases, Epilepsy, Sodium Valproate

INTRODUCTION

Sodium Valproate is effective and commonly used first line anti-epileptic drug and also used in a number of other neuropsychiatric diseases like migraine prophylaxis and as mood stabilizer. Sodium Valproate is well tolerated at therapeutic doses. 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. The most common adverse effects are nausea, vomiting, anorexia, amenorrhoea, sedation, tremor, weight gain, alopecia, hyperammonemic encephalopathy, coagulation disorders, pancreatitis and hepatotoxicity which if, severe may lead to death. The investigators who have worked on epilepsy have used various chemicals for treating epilepsy, starting from a bromide which provides the first rational treatment for patients suffering from epilepsy to recent newer antiepileptics. In spite of the vast number of drugs introduced for the treatment of epilepsy, there is still a need for an ideal antiepileptic agent with properties like broad spectrum activity, rapid onset of action, least side effects, good oral bioavailability and low cost. Sodium Valproate is drug of choice and very well prescribed for a long term therapy in epilepsy patients. Regarding long-time treatment of epileptic patients, these treatment protocols may have side effects. Different studies on the effect of sodium valproate on liver profile have reported contradictory results. The present study was designed to evaluate significance of liver enzymes in patients of epilepsy when treated with long term sodium valproate therapy.
MATERIALS AND METHODS
The present study was conducted at Department of Biochemistry, Govt. medical college & Sir Takhtsinhji General Hospital, Bhavnagar Gujarat, in which 75 known cases of Epilepsy 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 were 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 sample (5ml) was collected from all the patients and analyzed for various biochemical parameters like Alanine aminotransferase, Aspartate aminotransferase, Alkaline phosphatase and Pseudocholinesterase on Fully Auto Analyzer – Miura A 1005 (Logotech) Italy at NABL Accreditated Clinical Biochemistry Section, Laboratory Services, Sir Takhtsinhji General Hospital, Bhavnagar.

Serum levels of Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) were evaluated 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 activity was measured by new DGKC Kinetic method. Enzymes activities were expressed as IU/L. Graph pad instat 3 demo version software was used for statistical analysis. Descriptive statistics are shown as mean ± standard deviation. Mean enzyme 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 wilcoxon matched –pairs signed ranks test was applied to compare each parameter. P value less than 0.05 was considered significant.

RESULTS
Comparison of liver Enzyme in the study group at interval of 3 months of treatment with Sodium Valproate was given in Table 1. The mean ages of the groups were not significantly different. It was observed that out of 75 patients (67%) of Epilepsy 50 had significant increase in ALT level (P <0.001) & 72 (96%) had significant increase in AST level (P <0.001). On other hand Pseudocholinesterase levels was significantly decreased in 33 patients (44%) of Epilepsy.

DISCUSSION
Sodium Valproate is highly effective in control of Epilepsy especially absence seizure, myoclonic and atonic seizure. Sodium Valproate is usually well tolerated, but serious complications including hepatotoxicity and hyperammonemnic encephalopathy may occur. It is almost completely absorbed from the gastrointestinal tract and is metabolized extensively by the liver via glucuronic acid conjugation, beta and omega oxidation to produce multiple 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 hyperammonemia and hepatotoxicity may be mediated in part by carnitine deficiency, therefore carnitine supplementation may prevent these adverse effects. Gaetano Zaccara et al. concluded in his study that mechanism involved in VPA-induced hepatotoxicity is due to direct cytotoxic effect of two metabolites, namely 4-en VPA and its β-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 co 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 β-oxidation and mitochondrial dysfunction. 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 is reversible if diagnosed earlier and the medication is withdrawn immediately.
Liver Enzymes Activity During Sodium Valproate Therapy

Table 1: Liver enzyme levels in Epilepsy patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean ± SD Pre-treatment (n=75)</th>
<th>Mean ± SD Post-treatment (n=75)</th>
<th>Biological Reference Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>27±10</td>
<td>59±23</td>
<td>&lt; 45</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>t=10.99</td>
</tr>
<tr>
<td>AST</td>
<td>32±11</td>
<td>59±23</td>
<td>&lt; 35</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>t=9.17</td>
</tr>
<tr>
<td>Pseudo cholinesterase</td>
<td>5612±1036</td>
<td>4887±921</td>
<td>4500-11000</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>t=4.52</td>
</tr>
<tr>
<td>ALP</td>
<td>169±36</td>
<td>164±17</td>
<td>98-279</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>t=1.08</td>
</tr>
</tbody>
</table>

* p < 0.05 – Stastically Significant, **p < 0.001 - Stastically Highly Significant. Figures in parentheses indicate the number of patients

Guerrini R. et al. reported in his study that liver damage occurred during the first 6 months of therapy with the period of maximum risk during Phenobarbital and Sodium Valproate monotherapy on serum lipid profile and liver function tests in epileptic children. There was a significant increase in levels of ALT, AST and ALP after treatment with Sodium Valproate. 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, 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 decreased 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. Previous studies have reported that levels of liver enzymes were affected when patients of Epilepsy were 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 Epilepsy. should be monitored periodically especially in those at most risk and those with a prior history of liver disease.

CONCLUSION

Alterations in the levels of Alanine aminotransferase and Aspartate aminotransferase show positive indication that treatment with Sodium Valproate adversely 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