INTRODUCTION

Valproic acid (VPA) is a simple branched carboxylic acid, which offers a novel approach to the treatment of epilepsy. VPA was first introduced as an anti-epileptic drug in France in the early 1960s, while metabolism of the drug was studied in the late 1970s. VPA is generally regarded an agent of first choice for most forms of idiopathic and symptomatic generalized epilepsies. VPA is closely related to the network of fatty acid metabolism, bearing important implications in VPA associated hepatotoxicity.

It has some other serious side effects including teratogenicity, bronchopneumonia, hyperammonemia, pancreatitis, and anti-folate activity. Young age, polytherapy, developmental anomalies and coincidental medical disorders are the risk factors.

VPA toxicity has been reviewed and discussed by various authors. The histopathological features were noted as micro-vesicular steatosis usually with necrosis, which were the most frequent findings, especially in the high risk group. The ultra structural changes observed were characterized by myeloid bodies, lipid vacuoles & mitochondrial abnormalities.

The mechanism of hepatic injury has been studied extensively but is still unclear. Some authors postulated that VPA aberrant metabolism with the formation of toxic metabolites or mediation of lipid per-oxidation might be the underlying mechanism of serious hepatic reactions. Similarities between carnitine deficiency & VPA toxicity were noted and it was suggested that VPA could produce reduction of carnitine. Hypocarnitinemia has been reported with some antiepileptic drugs (AED), particularly VPA as monotherapy or polytherapy. Supplementation of carnitine & melatonin on valproate therapy may improve the quality of life in epileptic children.

MATERIAL AND METHODS

This experimental study was undertaken in the Department of Pathology, Jinnah Postgraduate Medical Center, Karachi, during September 1996 to March 1997.
The animals selected for the study were 24 adult & apparently healthy albino rats of Sprague-Dawley strain. The animals were divided into two equal groups; Tx (toxic) and control, each comprising 12 animals.

The animals of Group C (Control) were fed ad libitum, i.e. they were given the normal routine diet of animal house. While those of “Group Tx” were given VPA in toxic regimen, along with the routine animal diet at the animal house.

**Drug:** Valproic acid is a simple branched chain carboxylic acid. Its structural formula is as follows:

$$\text{CH}_3\text{CH}_2\text{CH}_2\text{CHCOOH}$$

It is an anti-epileptic drug available in the market with the name of Epilim or Epival. It is available in syrup form as well. It was given orally, in a single dose of 85 mg/kg/day, increased by 10-20 mg/kg/week. All the animals were sacrificed after three weeks of treatment. The liver of each animal was removed in toto. The suitable sections of liver were properly fixed, sectioned, processed and stained with H&E stain and with special stains, PAS and Trichrome, where indicated. The slides were examined under the light microscope, with reference to the lobular architecture, portal area and parenchyma.

**RESULTS**

The observations were noted as below:

**Group C (Control):** The lobular architecture of the liver of animals was intact in 10 out of 12 animals (83.33%) & partly distorted in 2 out of 12 animals (16.66%) due to parasitic cysts. However no other significant changes were seen. Table-1

**Group Tx (Toxic):** The lobular architecture of liver was partly distorted in 2 out of 12 animals (16.66%). Table-1

Drug induced changes were noted as focal steatosis in 10 out of 12 animals (83.33%) and focal necrosis in 4 out of 12 animals (33.33%). Table-2,3 and Fig-1,2

In addition we also noted some minor changes like foci of inflammatory cell infiltrates, proliferation of bile ductules and congestion in the portal areas.

Parasitic cysts were seen even in the control group ‘C’.

### Table 1: Histopathologic changes affecting the lobular architecture of livers of albino rats.

<table>
<thead>
<tr>
<th>Group</th>
<th>Lobular architecture</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Intact</td>
<td>Distorted</td>
</tr>
<tr>
<td>Control (C)</td>
<td>No. of animals 10</td>
<td>2</td>
</tr>
<tr>
<td>(n = 12)</td>
<td>% age 83.33%</td>
<td>16.66%</td>
</tr>
<tr>
<td>Toxic (Tx)</td>
<td>No. of animals 10</td>
<td>2</td>
</tr>
<tr>
<td>(n = 12)</td>
<td>% age 83.33%</td>
<td>16.66%</td>
</tr>
</tbody>
</table>

### Table 2: Histopathologic changes affecting the portal area of livers of albino rats.

<table>
<thead>
<tr>
<th>Group</th>
<th>Histopathologic Changes</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Infiltration</td>
<td>Ductal proliferation</td>
</tr>
<tr>
<td>Control (C)</td>
<td>No. of animals 8</td>
<td>4</td>
</tr>
<tr>
<td>(n=12)</td>
<td>%age 66.67</td>
<td>33.33%</td>
</tr>
<tr>
<td>Toxic (Tx)</td>
<td>No. of animals 4</td>
<td>6</td>
</tr>
<tr>
<td>(n=12)</td>
<td>%age 33.33</td>
<td>50.00%</td>
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Table 3: Histopathologic changes affecting the parenchyma of livers of albino rats.

<table>
<thead>
<tr>
<th>Group</th>
<th>Histopathologic Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Steatosis</td>
</tr>
<tr>
<td>Control (C)</td>
<td>0</td>
</tr>
<tr>
<td>(n=12)</td>
<td>%age</td>
</tr>
<tr>
<td>Toxic (Tx)</td>
<td>10</td>
</tr>
<tr>
<td>(n=12)</td>
<td>%age</td>
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</tbody>
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Fig. 1: Photomicrograph of liver showing area of steatosis (arrows) in Tx group animal. The animal was kept on toxic doses of VPA. (H&E x500)

Fig. 2: Photomicrograph of liver, showing extensive necrosis and inflammatory cell infiltrate (arrow) in “Tx group” animal. The animal was kept on toxic doses of VPA. (H&E x500)
DISCUSSION

VPA is a commonly used anti-epileptic drug but it has serious side effects, when given with other anti-epileptic drugs, especially in the high risk group.6,20

During our study we carried out the microscopic examination of the livers of all animals. Some of the minor findings like inflammatory cell infiltrates, proliferation of bile ductules & congestion which could also be seen even in control group, were presumed as non-significant changes. We noted no other significant changes in group ‘C’. The major changes seen in Group ‘Tx’ (Toxic) were steatosis (83.33%) and necrosis (33.33%). Our results support the studies conducted by several other authors,5,6,8,18,19,20 who observed steatosis & necrosis as the most frequent histopathological findings.

Like VPA hepatotoxicity reported in the high risk patients,5,20 i.e. polypharmacy, young age, medical & metabolic disorders, we also observed VPA hepatotoxicity in adult and apparently healthy animals, when VPA was given as monotherapy in toxic doses.

The reasons of hepatotoxicity in our study might be:
(a) Change of the model as albino rat
(b) Coincidental diseases like parasitic cysts, etc.
(c) VPA monotherapy in toxic regimen.
(d) Any other unknown reason.

CONCLUSION

Valproic acid is hepatotoxic and causes steatosis and necrosis if given in toxic doses to albino rats. While administering to human beings the therapeutic levels should be carefully monitored.

REFERENCES


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