GROSS HEPATIC CHANGES IN DEVELOPING ALBINO RATS EXPOSED TO VALPROIC ACID

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INTRODUCTION

Epilepsy being an important problem from a medical, social and legal point of view is the third most common serious neurologic disorder following Stroke and Alzheimer’s disease. It affects approximately 0.5–1% of pregnant women. In most women seizures are well controlled during pregnancy but if fit frequency changes, it is usually for the worse. It is generally agreed that the avoidance of generalised seizures during pregnancy is paramount and the avoidance of all seizure types is desirable for psychosocial and socioeconomic reasons as well as for the physical well-being of the mother and fetus.

Valproic acid (VPA) is a branched carboxylic acid and is an established broad spectrum antiepileptic drug. It is the only drug capable of controlling all types of seizures associated with the idiopathic generalised epilepsies. VPA undergoes extensive placental transfer in animals as well as humans. It crosses the placenta and may reach pharmacologically toxic concentration. VPA plasma protein binding is significantly decreased in pregnant women with increase in free fraction. VPA undergoes extensive placental transfer in animals as well as humans. It crosses the placenta and may reach pharmacologically toxic concentration. VPA plasma protein binding is significantly decreased in pregnant women with increase in free fraction. It undergoes extensive placental transfer in animals as well as humans. It crosses the placenta and may reach pharmacologically toxic concentration.

RESULTS

In group D (Control), the external surface of the foetal liver was smooth and shiny and its colour was reddish brown. The gross appearance of the foetal liver in group A, B and C was found to be similar to that of foetal liver in group D and therefore no abnormality was noted. The mean weight of foetal liver for the control group D was found to be 0.45±0.00 gm, 0.40±0.09 gm for group A, 0.24±0.00 gm for group B and 0.28±0.00 gm for group C (Table-1). The mean weights of the foetal liver in experimental groups A, B and C were significantly reduced as compared with the control group D (p<0.01). The reduction in the weight of the foetal liver in group A versus B, A versus C and C versus B was also statistically significant (p<0.01) (Table-2).

The mean relative tissue weight index for group D (control) foetuses was calculated to be
8.21±0.00, 6.07±0.07 for group A, 6.54±0.15 for group B and 7.50±0.05 for group C foetuses (Table-1). The mean relative tissue weight indices of the groups A, B and C showed statistically significant reduction when compared with the control group D (p<0.01). The reduction in RTWI of the group C versus A, C versus B and B versus A was also statistically significant (p<0.01) (Table-3).

### Table-1: Effects of VPA on weight of liver and relative tissue weight index (RTWI) of the rat foetuses

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Groups</th>
<th>A (n=28)</th>
<th>B (n=37)</th>
<th>C (n=42)</th>
<th>D (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver weight (gm)</td>
<td></td>
<td>0.40±0.09</td>
<td>0.24±0.00</td>
<td>0.28±0.00</td>
<td>0.45±0.00</td>
</tr>
<tr>
<td>RTWI</td>
<td></td>
<td>6.07±0.07</td>
<td>6.34±0.15</td>
<td>7.50±0.05</td>
<td>8.21±0.00</td>
</tr>
</tbody>
</table>

All values are expressed as Mean±SD, n= Number of foetuses

### Table-2: Effects of VPA on the weights of the foetal liver

<table>
<thead>
<tr>
<th>Source of variation</th>
<th>Sum of square (SS)</th>
<th>Degree of freedom (DF)</th>
<th>Mean square (MS)</th>
<th>Variation ratio (F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A vs B</td>
<td>0.05</td>
<td>1</td>
<td>0.05</td>
<td>22.31**</td>
</tr>
<tr>
<td>A vs C</td>
<td>0.00</td>
<td>1</td>
<td>0.00</td>
<td>5.08*</td>
</tr>
<tr>
<td>A vs D</td>
<td>0.45</td>
<td>1</td>
<td>0.45</td>
<td>492.17***</td>
</tr>
<tr>
<td>B vs C</td>
<td>0.03</td>
<td>1</td>
<td>0.03</td>
<td>31.31***</td>
</tr>
<tr>
<td>B vs D</td>
<td>0.98</td>
<td>1</td>
<td>0.98</td>
<td>1069.17***</td>
</tr>
<tr>
<td>C vs D</td>
<td>0.71</td>
<td>1</td>
<td>0.71</td>
<td>771.95**</td>
</tr>
<tr>
<td>Between groups</td>
<td>1.24</td>
<td>3</td>
<td>0.41</td>
<td>451.33***</td>
</tr>
<tr>
<td>Within groups</td>
<td>0.14</td>
<td>157</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.39</td>
<td>160</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VPA=Valproic Acid, D=Control Group, A, B, C=Experimental Groups, **p<0.01, *p<0.05, Based on one way ANOVA

### Table-3: Effect of VPA on relative tissue weight indices (RTWI)

<table>
<thead>
<tr>
<th>Source of variation</th>
<th>Sum of square (SS)</th>
<th>Degree of freedom (DF)</th>
<th>Mean square (MS)</th>
<th>Variation ratio (F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A vs B</td>
<td>3.54</td>
<td>1</td>
<td>3.54</td>
<td>12.88**</td>
</tr>
<tr>
<td>A vs C</td>
<td>34.65</td>
<td>1</td>
<td>34.65</td>
<td>126.23**</td>
</tr>
<tr>
<td>A vs D</td>
<td>84.37</td>
<td>1</td>
<td>84.37</td>
<td>307.35**</td>
</tr>
<tr>
<td>B vs C</td>
<td>18.33</td>
<td>1</td>
<td>18.33</td>
<td>66.75**</td>
</tr>
<tr>
<td>B vs D</td>
<td>61.10</td>
<td>1</td>
<td>61.10</td>
<td>222.55**</td>
</tr>
<tr>
<td>C vs D</td>
<td>11.67</td>
<td>1</td>
<td>11.67</td>
<td>42.52**</td>
</tr>
<tr>
<td>Between Group</td>
<td>109.95</td>
<td>3</td>
<td>36.65</td>
<td>133.51**</td>
</tr>
<tr>
<td>With in Groups</td>
<td>43.10</td>
<td>157</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>153.05</td>
<td>160</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VPA=Valproic Acid, D=Control Group, A, B, C=Experimental Groups, **p<0.01, Based on one way ANOVA

### DISCUSSION

There are reports of VPA induced hepatotoxicity in adult liver. However very little data is available on the effects of VPA on the foetal liver. The present study was designed to assess the effects of VPA on the gross structure of the foetal liver in albino rats exposed to the drug during various trimesters of pregnancy. VPA is an anticonvulsant agent used in the management of various forms of epilepsy including absence, myoclonic and tonic clonic seizures.

The mechanism by which VPA induces liver injury remains unknown. It is hypothesised to involve the generation of toxic metabolites and/or reactive oxygen species. The reaction of toxic metabolites with glutathione in mitochondria produces a localised depletion of glutathione that would result in oxidation stress. Oxidative stress precedes the onset of steatosis and necrosis in liver.

The current study showed that VPA induces liver injury in all the three experimental groups. Though gross appearance of the foetal liver was normal in all the groups, foetal liver of the experimental groups showed significant decrease in weight as well as RTWI as compared to their control. The reason may be the loss of hepatic parenchyma due to necrosis and also due to incomplete formation of the trabeculae during hepatic development.

### REFERENCES


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