

# STUDY OF HISTOPATHOLOGIC CHANGES IN THE LIVER OF ALBINO RATS, INDUCED BY TOXIC DOSES OF VALPROIC ACID

Syed Khanzada Khan,\* Kazi Abdul Shakoor,\*\* Muhammad Amin Jan,\*  
Aziz Marjan Khattak,\* Syed Humayun Shah\*

\*Department of Pathology, Gomal Medical College, D.I. Khan and \*\*Department of Pathology, Frontier Medical College, Abbottabad.

## ABSTRACT

**Background:** This study was conducted to see the histopathologic changes in the liver of albino rats, induced by the toxic doses of valproic acid.

**Material & Methods:** The study was carried out in the Department of Pathology, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, Karachi, from September 1996 to March 1997. Twenty-four adult & apparently healthy albino rats were selected. The animals were divided into two equal groups; Group Tx and Group C. "Group Tx" was treated with oral toxic regimen of Valproic acid and "Group C" (Control) was kept on the routine diet of animal house. All the animals were fed at libitum and sacrificed after three weeks of treatment. The liver of each animal was properly fixed, sectioned, processed and stained by H&E stain and other stains where needed. The slides were examined under the light microscope, with reference to the architecture, portal area and parenchyma.

**Results:** No significant changes were seen in the "Group C." Foci of steatosis were seen in the livers of 10 out of 12 animals (88.33%) and necrosis in 4 out of 12 animals (33.33%) of the "Group Tx."

**Conclusion:** The results of our experimental study support the evidence that steatosis and necrosis are the main histopathologic changes, induced by Valproic acid, if given as monotherapy in toxic doses to albino rats.

**Key words:** Valproic acid, Liver, Steatosis, Necrosis, Albino rats.

## INTRODUCTION

Valproic acid (VPA) is a simple branched carboxylic acid,<sup>1</sup> which offers a novel approach to the treatment of epilepsy.<sup>2</sup> VPA was first introduced as anti-epileptic drug in France in the early 1960s, while metabolism of the drug was studied in the late 1970s.<sup>3</sup> VPA is generally regarded an agent of first choice for most forms of idiopathic and symptomatic generalized epilepsies.<sup>4</sup> VPA is closely related to the network of fatty acid metabolism, bearing important implications in VPA associated hepatotoxicity.<sup>4</sup>

It has some other serious side effects including teratogenicity, bronchopneumonia, hyperammonemia, pancreatitis and anti-folate activity.<sup>5,6</sup> Young age, polytherapy, developmental anomalies<sup>7</sup> and coincidental medical disorders<sup>2</sup> are the risk factors.

VPA toxicity has been reviewed<sup>2</sup> & discussed by various authors.<sup>5</sup> The histopathological features were noted as micro-vesicular steatosis usually with necrosis, which were the most frequent findings, es-

pecially in the high risk group.<sup>7</sup> The ultra structural changes observed were characterized by myeloid bodies, lipid vacuoles & mitochondrial abnormalities.<sup>8</sup>

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<sup>9</sup> or mediation of lipid per-oxidation<sup>10</sup> 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.<sup>11</sup> Hypocarnitinemia has been reported with some antiepileptic drugs (AED), principally VPA as monotherapy or polytherapy.<sup>12</sup> Supplementation of carnitine &/melatonin<sup>13</sup> on valproate therapy may improve the quality of life in epileptic children..

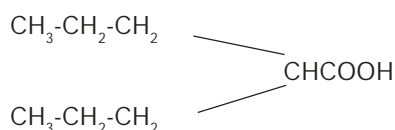
## MATERIAL AND METHODS

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:



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,<sup>14</sup> in a single dose of 85 mg/kg/day,<sup>15</sup> increased by 10-20 mg/kg/week.<sup>16</sup> 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<sup>17</sup> and with special stains, PAS

and Trichrome, where indicated.<sup>18</sup> 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.**

Group		Lobular architecture	
		Intact	Distorted
Control (C ) (n = 12)	No. of animals	10	2
	%age	83.33%	16.66%
Toxic (Tx) (n = 12)	No. of animals	10	2
	% age	83.33%	16.66%

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

Group		Histopathologic Changes		
		Infiltration	Ductal proliferation	Congestion
Control (C ) (n=12)	No. of animals	8	4	0
	%age	66.67	33.33%	0
Toxic (Tx) (n=12)	No. of animals	4	6	2
	% age	33.33	50.00%	16.67%

**Table 3: Histopathologic changes affecting the parenchyma of livers of albino rats.**

Group		Histopathologic Changes		
		Steatosis	Necrosis	Infiltration
Control (C ) (n=12)	No. of animals	0	0	0
	%age	-	-	-
Toxic (Tx) (n=12)	No. of animals	10	4	0
	% age	(83.33%)	(33.33%)	-

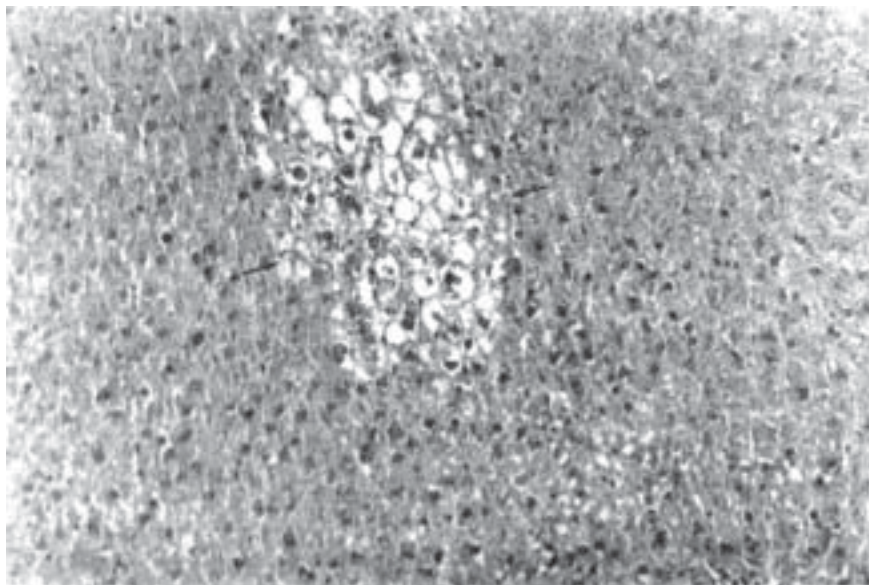


Fig. 1: Photomicrograph of liver showing area of steatosis (arrows) in Tx group animal. The animal was kept on toxic doses of VPA. (H&E x500)

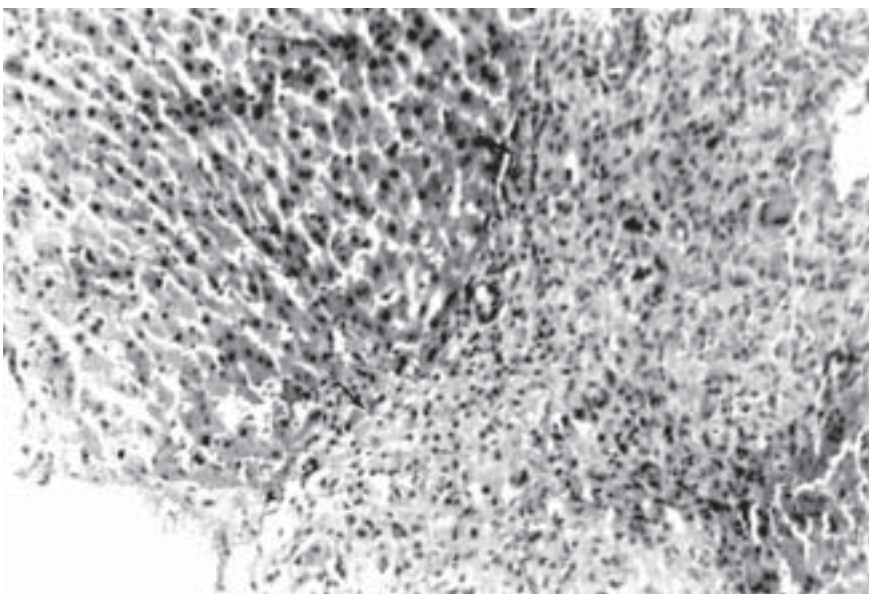


Fig. 2: Photomicrograph of liver, showing extensive necrosis and inflammatory cell infiltrate (arrow) in "Tx group" animal. The animal was kept on toxic doses of VPA. (H&E x500)

## DISCUSSION

VPA is a commonly used anti-epileptic drug but it has serious side effects, when given with other anti-epileptic drugs,<sup>2,6</sup> for long duration,<sup>19</sup> especially in the high risk group.<sup>6,20</sup>

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,<sup>6,8,18,19,20</sup> who observed steatosis & necrosis as the most frequent histopathological findings.

Like VPA hepatotoxicity reported in the high risk patients,<sup>5,7</sup> 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.

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### Address for Correspondence:

Dr. Syed Khanzada Khan  
Assistant Professor  
Department of Pathology  
Gomal Medical College  
D.I.Khan