ORIGINAL ARTICLE

PREVENTION OF HEPATOTOXICITY OF VALPROIC ACID WITH CONCOMITANT SUPPLEMENT OF CARNITINE: AN EXPERIMENTAL STUDY IN ALBINO RATS

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ABSTRACT

Background: Valproic acid is an antiepileptic drug which may cause carnitine deficiency and subsequently hepatotoxicity in the form of necrosis and steatosis. The objective of this study was to observe the protective role of carnitine against valproic acid induced hepatotoxicity in albino rats.

Material & Methods: This was an experimental study of concurrent parallel design in albino rats, carried out in Department of Pathology, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, Karachi. Thirty adult and apparently healthy albino rats were selected. The animals were divided into five equal groups; Group A control, kept on the diet of animal house only, Group B treated with therapeutic doses of valproic acid + carnitine supplement, group C treated with toxic doses of valproic acid + carnitine supplement, Th group treated with therapeutic doses of valproic acid and Tx group treated with toxic doses of valproic acid. All the animals were fed on routine diet of animal house and sacrificed after 3 weeks of treatment. The liver of each animal was properly fixed, sectioned, processed, stained with H & E stain and seen under light microscope.

Results: No significant changes in the livers were seen in group A. Focal necrosis was be seen in the liver of one out of six animals (16.66%) of group B, foci of steatosis were seen in one (16.66%) and necrosis in 3(50%) animals of group C whereas in Th group steatosis was seen in 5(83.33%) and necrosis in one (16.66%) and in Tx group steatosis in 5(83.33%) and necrosis in 2(33.33%).

Conclusion: Valproic acid induced hepatotoxicity in the form of steatosis can be prevented by carnitine supplement in albino rats.

KEY WORDS: Valproic acid; Carnitine; Hepatic steatosis.

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INTRODUCTION

Valproic acid (VPA) is a broad-spectrum antiepileptic drug and is effective in the treatment of many types of partial and generalized epileptic seizures. VPA is an eight carbon branched chain fatty acid having a broad spectrum of anticonvulsant activity, thus indicated in the treatment of epilepsy. Its chemical structure resembles to that of short chain fatty acids. The formula of VPA is $C_8H_{16}O_2$.[1] Its mechanism of action includes enhanced neurotransmission of gamma amino-butyric acid. However, several other mechanisms of action in neuropsychiatric disorders have been proposed for VPA.[2] Despite the pharmacological importance and effectiveness of VPA, its potential hepatotoxicity is a major concern.[3]

Acute VPA intoxication may occur as a consequence of intentional or accidental overdose. It usually results in mild and self-limited central nervous system depression. However, serious toxicity and even deaths have been reported.[4] Severe VPA induced hepatotoxicity (VHT) in association with hepatic failure is rare, but it may develop an idiosyncratic reaction that is often fatal. Histological changes are similar to those observed in the Reye's syndrome, with early production of microvesicular

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steatosis followed by the development of centrilobular necrosis.[5,6]

VPA depletes carnitine stores, especially during long-term or high-dose therapy, through various synergistic mechanisms.[7,8] A reduction in tubular reabsorption of both free carnitine and acylcarnitine has been reported during VPA treatment. Also the mitochondrial depletion of CoA-SH impairs β-oxidation of fatty acids (and VPA) and ATP production. ATP depletion further impairs the function of the ATP-dependent membrane carnitine transporter.[9]

Raskind & El-Chaar extensively reviewed the pathophysiology and significance of VPA-induced carnitine deficiency and recommended carnitine supplementation during VPA therapy.[10-12] Some experimental and clinical data suggest that early intravenous supplementation with L-carnitine could improve survival in severe VPA-induced hepatotoxicity.[13] The objective of this study was to observe the protective role of carnitine against the valproic acid induced hepatotoxicity in albino rats.

MATERIAL AND METHODS

This experimental study was undertaken in Department of Pathology, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, Karachi.

We selected 30 adult and apparently healthy albino rats of Sprague–Dwaley strain. The animals were divided into five equal groups; group A (control, kept on the diet of animal house only, Group B treated with therapeutic doses of VPA i.e. 35 mg/Kg/day, increased by 5-10 mg /kg/week and the supplement of carnitine in a dose of 60 mg/Kg/day and group C treated with toxic doses of VPA i.e. 85 mg/Kg/day, increased by 10-20 mg /kg/week and the supplement of carnitine in a dose of 100 mg/Kg/day. Th group animals were treated with therapeutic doses of VPA i.e. 35 mg/Kg/day, increased by 5-10 mg/kg/week and Tx group were treated with toxic doses of VPA i.e. 85 mg/Kg/day, increased by 10-20 mg / kg/week. The animals were sacrificed after 3 weeks of treatment. The liver of each animal was properly fixed, sectioned, processed, stained with H&E and seen under the light microscope.

RESULTS

The histopathologic changes in the liver were observed as follows:

In group A (control), the lobular architecture was intact in 5 (83.33%) and focally altered in 1 (16.66%) due to parasitic cyst. No other significant changes such as focal necrosis or steatosis were observed. In group B (therapeutic regimen of VPA + carnitine), the lobular architecture was intact in 4 (66.66%) animals, however one animal showed parasitic cyst, while the other one revealed focal (midzonal) necrosis. No steatosis was observed. In group C (toxic regimen of VPA + carnitine), the lobular architecture was intact in 3 (50%) animals. However microvesicular steatosis was seen in one (16.66%) and focal necrosis in 3 (50%). In Th group (therapeutic regimen of VPA) steatosis was seen in 5 (83.33%) animals and necrosis in 1(16.66%). In Tx group (toxic regimen of VPA) steatosis was seen in 5 (83.33%) animals and necrosis in 2 (33.33%). (Table 1 & Fig 1).

Table 1: Comparison of histopathologic changes in the livers of albino rats induced by VPA alone and with supplement of carnitine.

Group	Percentage of steatosis	Percentage of necrosis
A (Control)	0	16.66
Th (Animals treated with therapeutic dosage of VPA only)	83.33	16.66
B (Animals treated with therapeutic dosage of VPA+ supplement of carnitine)	0	33.33
Tx (Animals treated with toxic dosage of VPA only)	83.33	33.33
C (Animals treated with toxic dosage of VPA+ supplement of carnitine)	16.66	50

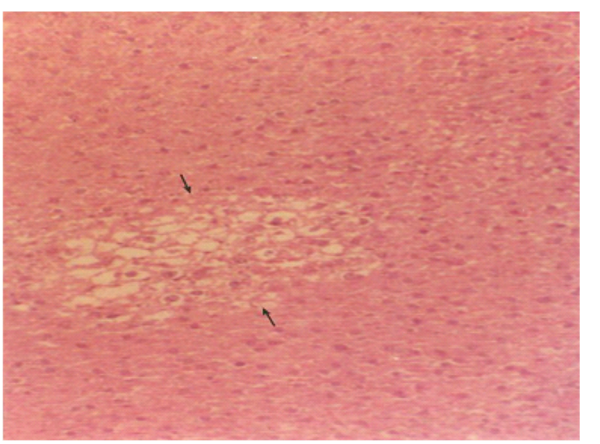

Figure 1: Photomicrograph of liver showing areas of steatosis (arrows) in the liver of animal kept on toxic doses of VPA. H & E x 500.

DISCUSSION

Several drugs including VPA are associated with decreased carnitine levels and occasionally with true carnitine deficiency.[14] VPA depletes carnitine

stores, especially during long-term or high-dose therapy, through various mechanisms.[15] VPA induced histological changes in the liver are in the form of microvesicular steatosis and centrilobular necrosis.[16] Among cases of severe hepatotoxicity occurring during VPA therapy, survival has been reported mainly in those patients treated with carnitine.[17-19]

In this study we supplemented carnitine with VPA in the therapeutic (group B) and toxic (group C) regimens of VPA. We observed no steatosis in group A & B and 16.66% in group C as compared to 83.33% of steatosis in animals treated with therapeutic and toxic regimens of VPA alone. Similarly, no focal necrosis was seen in controls. However, there was 16.66% of focal necrosis in group B (VPA + supplement of carnitine) equal to the effect of VPA alone (See Table 3), 50% in group C i.e. increased as compared to toxic regimen of VPA alone, which was 33.33% only. The protective role of carnitine in the form of necrosis was not significant.

Our findings in the form of steatosis are in agreement with the results reported by DeVivo et al15 and Nishida et al,18 that carnitine prevents VPA toxicity. Our findings regarding the necrosis are in accordance to the results of Fujimiya & Abbott[19] that carnitine deficiency cannot be the only reason for fatal VPA induced hepatotoxicity. VPA-induced lipid peroxidation and glutathione depletion could also contribute to hepatotoxicity.[20]

CONCLUSION

Valproic acid induced hepatotoxicity in the form of steatosis can be prevented by carnitine supplement in albino rats.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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None declared.