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Evaluation of Liver Enzymes Rising in Patients Treated with Sodium Valproate (VPA)

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Abstract

Introduction

Valproic acid (VPA, Valproate) is an eight-branch fatty acid and varies from other antiepileptic drugs. VPA use might lead to mild to severe hepatotoxicity. The aim of this study was to investigate valproic acid impact on liver transaminases at the beginning of VPA treatment and after three and six months of it.

Materials and Methods

This study was designed as a cross sectional project in Pediatrics Neurology ward of a Tertiary Academic Hospital (Ghaem Hospital, Mashhad-Northeastern Iran). All children who needed valproic acid therapy alone were selected for study. Liver function test was performed for them at the beginning of VPA administration, three and six months after VPA, respectively. Data was analyzed by SPSS version 16.

Results

60 children with mean age of 49±28.6 months were entered the study. 37 of them were male and 23 were female. 5% (3 children) were mental retard and 11.7% (7 patients) had neurologic or developmental deficit. Mean value of Aspartate transaminase (AST), Alanine aminotransferase (ALT) and Alkaline phosphatase (ALP) were 27, 30.8 and 30.4 and 17.4, 20.7 and 22.8 and 425, 426 and 441 at the beginning of VPA administration, three and six months after VPA, respectively. In six months of our follow up, only one child (1.7%) had elevated liver transaminases.

Conclusion

Regard to our findings and its agreement with previous researches, it is important to control adverse drug events by measuring liver transaminases during antiepileptic treatment.

***Keywords*:** Liver failure, Liver transaminases, Valproic acid.

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Introduction

Valproic acid (VPA, VA) is a mood stabilizing and anticonvulsant agent. Its salt forms also have been used (1). Various side effects have been reported for VPA such as gastrointestinal complaints, vision disturbance, hormonal impairments, hair loss and etc. One of the most important adverse effects of VA is mild to severe hepatotoxicity (2). Aminotransferases rises rapidly in 11% of patients. Hepatic macrosteatosis is the main pathology feature in patients whom use VA, cellular necrosis could be occur in some cases. Mitochondria are prominent in hepatocytes and cell become granular and eosinophilic (3).

Behavioral disorders caused by VA are rare. Small portion of users develop lethargy and coma, ammonium serum level raise in these patients, and serum carnitine level decreases. There are some evidences about the role of VA in blocking carnitine metabolism. VA treatment discontinuation improve patients' consciousness level in few days (4-6).

VA has two hepatotoxic component; 1- Hypoglycin which leads to Jamaican vomiting sickness and micro-vesicular liver steatosis; 2- Pantoic acid which inhibits beta oxidation and causes micro-vesicular liver steatosis, this process could be controlled by dose reduction. In rare cases, severe hepatic failure like ray syndrome can be happened (2).

It has been proposed at least 4 months VA regular usage is needed for Hepatic Injury (HI), this duration becomes longer in some cases. Predisposing factor for HI include: infancy, multi antiepileptic drugs administration, mental retardation, developmental delay and congenital anomalies (7).

Valproate severe hepatotoxicity manifest with hepatitis like symptoms such as malaise, anorexia, nausea and vomiting. Some cases might presented by fever, coagulopathy and icter. In chronic forms, hepatic failure features like ascites and hypoglycemia are the predominant signs and symptoms. These cases have a poor prognosis and death happen due to hepatic failure and infections (8).

Some patients, particularly young infants with neurologic syndromes need more than one anticonvulsant drugs, so these children are at more risk (1/800) to develop idiosyncratic and mortal hepatic failure. These cases are characterized by abdominal pain, anorexia, weight loss and retch after few weeks or months of VA treatment. Sustained and significant gastrointestinal symptoms should be determined as more important in these children (9-11).

Screening Liver Function Test (LFT) should be considered in children who are candidate for long term VA therapy, particularly in infancy and other neurologic syndromes existence. The aim of this study was to perform serial LFT in children using VA in regular intervals.

Materials and Methods

This study was conducted under the supervision of Mashhad University of Medical Sciences. Our study was designed as a cross sectional project in Pediatrics Neurology Clinic of a Tertiary Academic Hospital (Ghaem Hospital, Mashhad-Northeast of Iran). All children needed VA administration were enrolled the study after obtaining written constant from their parents. Patients' characteristics and comorbid diseases were recorded in a checklist. Then 5 cc venous blood samples were obtained from each patient and liver function tests were performed. This sampling was conducted at the beginning of the study and every 3 months for 6 months.

Data were coded and entered Statistical Package for the Social Sciences (SPSS) version 16. Descriptive statistics expressed as frequency and mean and standard deviation (SD). Chi-square test was used to compare qualitative data and Mann Whitney and independent t-test were performed to assess enzymes level changes during the study. This cross sectional study was approved by ethical committee of Mashhad University of Medical Sciences. Significance level was considered as P <0.05.

Results

60 children aged 49±28.6 months were enrolled the study. 37 (61.7%) were male and 23 (38.3) were female. Mental retardation and developmental delay frequency were 5% (3 children) and 11.7% (7 children), respectively (Figure.1) Aspartate transaminase (AST) levels were 27, 30.8 and 30.4 UI/L at the beginning, after three and six months respectively. Average of Alanine aminotransferase (ALT) levels was 17.4, 20.7 and 22.8 UI/L, respectively. Alkaline phosphatase (ALP) levels were 425, 426 and 441 IU/L, also. Only one child (1.7%) had abnormal Liver Function Tests (LFTs) (AST, ALT and ALP).

Table.1 shows LFT results during the study in both genders. Although ALT and AST levels did not differ significantly between male and female patients, ALP was significantly higher in girls.

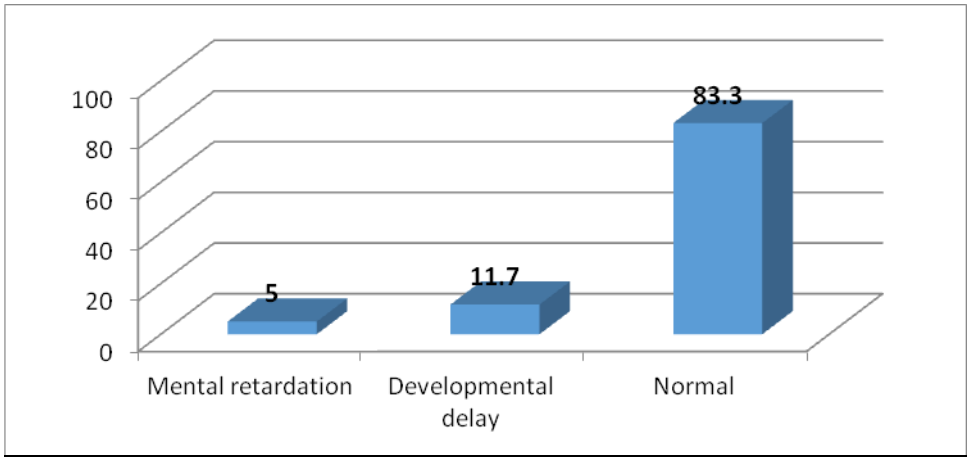

Fig 1: Mental retardation and developmental delay frequency in children

Table-1: Comparing LFT results in male and female

TIME	LFT (UI/L)	Male	Female	P- value
Beginning	AST	27±6.5	27±7.4	**0.892
	ALT	17±4.5	17±5	**0.859
	ALKP	385±104	489±163	*0.945
After 3 months	AST	31±5.1	30±6.8	**0.667
	ALT	20.2±3.2	21.5±5.6	**0.267
	ALKP	386±95	490±116	*<0.001
After 6 months	AST	31.3±1.5	30.4±3.6	**0.674
	ALT	22.3±8	22±5	**0.867
	ALKP	414±98	494±101	*0.004

*Mann Whitney test; ** Independent t-test

Discussion

VA toxicity might appear as a mild to severe syndrome. These patients experience hyperammonemia, hepatitis feature such as malaise, anorexia and nausea and vomiting(12).

There are evidences about higher incidence of VA toxicity in children with neurologic deficit, but this theory did not confirm in our study and children with mental retardation and developmental delay had not have higher rate of impaired LFT in comparison with other children. This might happen due to shorter follow up period in our study (6 months). On the other hand we evaluated children with single drug therapy (only VA).

Antoniuk et al. reported 3 patients develop VA hepatotoxicity (2 cases after 6 months and 1 case after 12 months) (13). In our study only one child (1.7%) had abnormal LFT (AST, ALT and ALP) after 3 and 6 months of VA therapy. This child was male and aged younger than 1 year, aminotransferases raised two times higher than the beginning of the study in the 6 months follow up.

Binek et al. showed that VA hepatic adverse effects are more common in children younger than 10 years, hepatic failure occurs in 10% of patients after 5 months. Male gender, neurologic deficit and poly therapy are the main risk factors for developing hepatotoxicity (14). Although our study was longer than Binek's study, none of our study participants developed hepatic failure(15).

In Callaghan, VA leads to raise 4% in ALT level and AST did not change (16). In our study AST and ALT levels increased lightly in children and this difference was not significant. Shayegan results were same as our study, and aminotransferases did not significantly increase 6 months after VA and carbamazepine administration (17).

It is important to consider hepatotoxicity in all patients receive VA. Some studies showed that VA hepatotoxicity is an idiosyncratic reaction (18). VA metabolism changes in younger age, poly therapy and high dose of drugs (19, 20). So, low dose VA and serial VA serum level evaluation could not predict idiosyncratic reaction.

One of important limitation in our study was short term follow up. We did not investigate interactions between valproate and other antiepileptic drugs.

Conclusion

Regard to our findings and its agreement with previous researches, it is important to control adverse drug events by measuring liver transaminases during antiepileptic treatment.

Conflict of interest: None.

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