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ORIGINAL ARTICLE

HYPERAMMONEMIA AND HEPATIC STATUS DURING VALPROATE THERAPY

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ABSTRACT

The present study was conducted to assess correlation of ammonia levels with valproate levels in epileptic patients presenting with valproate toxicity and also whether liver enzymes and ammonia levels could serve as biochemical marker of valproate toxicity. 100 patients with epilepsy who had received valproate therapy for more than 12 months and had presented with valproate toxicity and 100 controls were included in the study. The serum valproate, ammonia and liver enzymes were measured in these subjects. In patients with valproate toxicity, the mean level of serum valproate was 110.91 ± 28.68 mg/dL (therapeutic range 50- 100 mg/dL). Serum ammonia was higher (86.37 ± 39.90 μg/dL) in patients with valproate toxicity compared to controls (68.73 ± 30.07 μg/dL). Out of 100 patients, only 37 patients had serum valproate level > 120 mg/dL and 22 patients had raised levels of valproate as well as ammonia. Age < 30 years and serum ammonia > 69 μg/dL is risk factors for valproate toxicity. Serum ammonia, liver enzymes should be regularly investigated in patients on valproate therapy for early diagnosis of valproate toxicity.

KEY WORDS

Hyperammonemia, VHE, Valproate toxicity, Hepatic Status, Epilepsy.

INTRODUCTION

Valproic acid (VPA) is an effective and commonly used first line anti-epileptic drug used in a number of other neuropsychiatric diseases like migraine prophylaxis and as mood stabilizer. Although well tolerated, it has been associated with many neurological and systemic side effects (1). One of the most important complications is valproate induced hyperammonemic encephalopathy (VHE). It may be fatal if drug is not withdrawn (2, 3).

Valproate induced encephalopathy is commonly associated with hepatic failure in children less than 2 years, urea cycle defects or carnitine deficiency. VHE is more common in patients on valproate in adjunct with phenobarbital, phenytoin or cabamezepine (3, 4).

The pathophysiological mechanism that leads to VHE is raised serum ammonia levels. It has been suggested that hyperammonemia inhibits glutamate uptake by astrocytes which may lead to potential neuronal injury and thus cerebral oedema and possibly seizures (5). Ammonia conjugates with α-keto glutarate to form glutamate thereby depleting α-keto glutarate and blocking the Kreb's cycle. Hence, serum ammonia determination has special significance in the diagnosis and monitoring of liver disease and valproate toxicity.

In view of the above, the study was undertaken to determine the levels of ammonia and liver enzymes in epileptic patients presenting with valproate toxicity. The correlation of ammonia with valproate levels was also studied in the same. Further the attempt has been made to observe the most common presentation during valproate toxicity.

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MATERIALS & METHODS

A retrospective study was undertaken in 100 epileptic patients who were on sodium valproate therapy for more than 12 months and had presented with signs and symptoms of valproate toxicity. Dose of sodium valproate was 20- 30 mg/kg/day. A control group consisting of 100 subjects attending the OPD for treatment other than epilepsy was taken. All the patients in the study group underwent routine biochemical investigations including liver enzymes along with serum ammonia and valproate assay.

Patients in the age group of 10- 50 years of either sex receiving antiepileptic drugs like sodium valproate, phenytoin, carbamezepine and phenobarbitone for at least 12 months were included in the study. Patients with history of chronic illness like cancer, severe renal disease, hepatic disease etc. or receiving anti-epileptic drugs other than valproate for less than 12 months were excluded.

Sodium valproate concentration in the serum was measured by immunoassay method using using CEDIA Valproic acid II assay kits from Microgenics Corporation,USA. For ammonia levels, Blood was collected in a vial containing EDTA and was transferred to the laboratory within 15 minutes on ice pack. Ammonia in the sample was assayed by Berthelot- Indophenol method using kit from WAKO Chemicals, USA. The plasma was separated within 30 minutes of sample collection to avoid high results. Alanine transaminase (ALT) and aspartate transaminase (AST) were measured in serum by Kinetic method using the kit from ERBA Diagnostics Mannheim Gmbh, Germany. All the assays were performed on Autoanalyser XL-300 from Transasia Biomedical Limited.

Descriptive statistics (mean ± SD) were calculated for all the considered variables (age, valproate, ammonia, ALT and AST). Data was dichotomized and χ^2- test was applied to explore association between serum valproate & variables- age, sex, ammonia, ALT and AST. Crude Odds Ratio and their confidence interval were calculated to estimate the risk of serum ammonia, ALT and AST towards higher value of serum valproate level. SPSS 17 was used for the data analysis.

RESULTS

100 patients (58 males & 42 females), taking treatment for epilepsy at Institute of Human Behaviour and Allied Sciences (IHBAS), Delhi, India were taken in the study. All the patients had symptom or signs of drug related complications like aggressive behaviour (38 patients), sudden jerky movements (30), anorexia, nausea and vomiting (26 patients), postictal psychosis and unconsciousness (6). Out of hundred patients only ten were on monotherapy. The details of the patient's characteristics are given in Table1.

Table 1: Patient Characteristics

	Characteristics	No. of patients (n = 100)
Seizure type	GTCS	65
	Focal seizure	7
	Seizure disorder	28
Presenting signs	Aggressive and violent behavior	38
& symptoms	Anorexia, nausea and vomiting	26
	Repeated seizure	30
	Unconsciousness	6

Distribution of data for most of the variables- serum valproate, ammonia, ALT and AST was skewed and range was very wide for all the variables, so non-parametric analysis was done. The data was dichotomised for all the variables, considering the mean value of controls as cut off value except in valproate. The cut off was taken as more than 120 mg/dL for valproate. Mean serum valproate, ammonia and liver enzymes levels in cases and controls are summarized in Table 2. When data was examined individually, it was observed that 22 subjects had both serum valproate and ammonia levels raised and 6 patients had liver enzymes also elevated along with valproate and ammonia levels.

Table 2: Serum valproate, ammonia & liver enzymes in controls and patients with valproate toxicity

Variables	Controls (n= 100) Mean ± SD	Cases (n = 100) Mean ± SD
Age (Years)	29.75 ± 17.11	22.27 ± 12.76
Valproate (mg/dL)	-	110.91 ± 28.68
Ammonia (µg/dL)	68.73 ± 30.07	86.37 ± 39.90
Alanine transaminase (U/L)	39.26 ± 57.81	45.02 ± 40.44
Aspartate transaminase (U/L)	46.34 ± 32.16	60.04 ± 38.56

Table 3 shows the chi-square analysis to explore the association of variables- serum valproate, ammonia, ALT and AST in cases and controls and crude odds ratios were calculated to estimate the risk of valproate toxicity. All the variables except gender showed higher risk towards valproate toxicity.

Table 3: Crude Odds Ratio & Confidence Interval of risk factors in valproate toxicity

Variables	Case (n=100)	Control (n=100)	χ^2 –value	P-value	COR	95% CI
Sex						
Male	58	67	1.73	0.19	0.68	0.38-1.21
Female	42	33				
Age (in years)						
<30	71	56	4.85	0.03*	1.92	1.07-3.45
≥30	29	44				
Ammonia (µg/dL)						
≥69	62	42	8.01	0.01*	2.25	1.28-3.97
<69	38	58				
AST (IU/L)						
≥47	68	44	11.69	0.00**	2.71	1.52-4.81
<47	32	56				
ALT (IU/L)						
≥40	38	18	9.92	0.00**	2.79	1.46-5.35
<40	62	82				

*Significant; **Highly significant

Age (χ^2: 4.85, P-value: 0.03) and serum ammonia (χ^2: 8.01, P-value: 0.01) were significantly associated with valproate toxicity. Patients with age < 30 years had two times higher risk (COR: 1.92, CI: 1.07-3.45) towards valproate toxicity. Similarly, serum ammonia level ≥ 69 µg/dL showed two times more risk of developing valproate toxicity. Liver enzymes ALT (χ^2: 11.69, P-value: 0.01) and AST (χ^2: 9.92, P-value: 0.00) were significantly associated with valproate toxicity and showed three times higher risk (COR: 2.79 & 2.71; CI: 1.40-7.28 & 1.31-5.09) of having valproate toxicity.

DISCUSSION

Valproate therapy may show rare but serious adverse effect-valproate-induced hyperammonemic encephalopathy (VHE) which can lead to death. However, if detected on time, discontinuation of valproate reverses the complication. Hence it is important to detect the presenting features of VHE in patients on valproate therapy as early as possible along with the predisposing causes of VHE. The present study was undertaken to detect the most common clinical features patients present with in suspected cases of valproate toxicity and to study whether raised serum ammonia level and liver enzymes can be taken as the mandatory biochemical markers which can detect valproate toxicity in patient on valproate therapy at the early stage.

Valproate toxicity is clinically associated with varied and wider presentation and includes irritability, agitation, drowsiness, coma and paradoxical seizures (7). Rarely, patient may present with loss of appetite, nausea and vomiting (8). In our study, aggressive and violent behaviour and repeated seizures were the most common presentation and was observed in 38% and 30% patients respectively presenting with valproate toxicity. In the present study, 62% patients showed raised ammonia levels. However, only 22% patients had both serum valproate and ammonia levels raised. Earlier studies (9) have reported 53 % patients on valproate having raised serum ammonia. The present study also shows that only 6% patients had abnormal liver functions associated with raised ammonia and valproate levels. This finding supports the reports that increased renal production of ammonia may also be one of the causes of hyperammonemia in valproate toxicity in addition to hepatic involvement (10, 11). Though it is well known that the clinical measurement of serum ammonia levels can be helpful in diagnosis of valproate toxicity, the correlation between serum ammonia and valproate during valproate toxicity is not clear. Studies done to find out the correlation between serum ammonia and AEDs had contradictory reports (12, 13). Ettora et al found a significant correlation between serum ammonia and AEDs, mostly valproate, which was in contrast to the findings of Laub et al who found no such correlation. Also a good correlation has been found in clinical improvement with the fall in serum ammonia level on valproate withdrawal in patients with valproate toxicity (14). It can be concluded from this study that high serum valproate and ammonia levels may have a synergistic effect.

In our best knowledge, no study has been undertaken so far where odds ratios are calculated to assess the risk of variables like age, serum ammonia, liver enzymes ALT and AST towards valproate toxicity. In the present study it was found that age < 30 years and serum ammonia level ≥ 69 µg/dl had two times higher risk of having valproate toxicity. Also ALT ≥ 40 U/L and AST ≥ 47 U/L had almost three times higher risk towards valproate toxicity. The present study also showed that valproate therapy, alone or in combination, is associated with elevated serum ammonia levels. The other significant finding is that raised levels of serum ammonia and liver enzymes are risk factors for the valproate toxicity.

It can be concluded from the present study that serum ammonia along with liver enzymes and serum valproate levels should be measured regularly in epileptic patients on valproate therapy and in patients presenting with early signs and symptoms of valproate toxicity.

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