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The status of blood ammonia level in valproic acid monotherapy for epileptic patients: a prospective study

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Abstract:

Valproic acid is a first line and widely used drug in epilepsy. Many patients' experiences mild to intolerable toxicities and some biochemical changes occur in course of valproic therapy in epileptic patients. This prospective study was carried out in Pediatric Neurology unit, Bangabandhu Sheikh Mujib Medical University from June 2011

to January 2012. After taking informed written consent from patient and or their legal guardians patients who fulfilled inclusion and exclusion criteria were selected for the study. Patient's history, clinical findings and blood ammonia level estimation was done before and after treatment with valproate. Among 26 epileptic patients 77% were male and 23% were female, male to female ratio was 3.3: 1. Mean age of male patients were 5.47±3.74 years and that of female were 6.41±4.36 years. 60% male and 83% female presented as generalized and idiopathic seizure. Baseline mean serum ammonia level was 19.25±5.8 µmol/L and after treatment with valproate it was 48.18±21.33µmol/L whereas upper normal reference value was 30µmol/L. This change was highly significant (p value was 0.000). Higher value than normal range was found in 77% cases. Adverse effects of drug were listed at every follow up. Nausea abdominal pain and dyspepsia were found common side effects. 77% patients experienced nausea and 61.5% complaints of abdominal pain. Chronic consumption of valproate can altered blood ammonia level but does not cause encephalopathy.

Key words: valproic acid monotherapy, blood ammonia level, epileptic patients

INTRODUCTION:

Valproic acid is a commonly used antiepileptic drug in children. Hyperammonemia is a complication of valproic acid therapy. It may lead to hyperammonemic encephalopathy which is associated with significant morbidity. Valproic acid has become a widely used antiepileptic drug in treating seizure disorder. It is also used as a mood stabilizer in bipolar disease and other psychiatric disorders. The most common toxic effects are gastrointestinal – including nausea, vomiting, anorexia, and hepatitis. Nervous system toxicities have been documented in numerous reports since 1973 a spectrum of symptoms from drowsiness to stupor and coma. One of the earliest reports of

valproate associated hyperammonaemia appeared in 1980 in a case report by Caulter and Allen.[1]

Hyperammonaemia is an uncommon and under recognized serious adverse effect of valproate therapy. The reported incidence of asymptomatic hyperammonaemia in children was 20%, and of symptomatic hyperammonaemia was 5%.[2] Hyperammonaemia should be suspected in any patient taking valproate and presenting with altered sensorium. The clinical presentation can be varied – including irritability, agitation, drowsiness, coma and occasionally paradoxical seizures.

Hyperammonaemia has been described even with therapeutic levels of serum valproate and there is no direct correlation between serum valproate level and hyperammonaemia.[3,4] However, high serum valproate level and serum ammonia may have synergistic effects.[5] Valproate-induced hyperammonaemic encephalopathy is often seen in association with hepatic dysfunction but may also rarely occur with normal liver function.[6] It is necessary to emphasize that previous satisfactory tolerance to valproate does not preclude the occurrence of hyperammonaemia encephalopathy.[7] Most of the cases occur at initiation of valproate therapy or after an increase in dose. The highest level of serum ammonia reported till date in the setting of valproate therapy is 377 µg/dl.[6] Highest level of ammonia was 366 µg/dl in one of our cases and mean ammonia level was 262.6 µg/dl.Of the 3 patients, co-AED medication included carbamazepine in 1st patient, phenytoin and clobazam in 2nd patient, and phenytoin in 3rd patient. In all the patients valproate was added before the present illness. The mean duration of valproate therapy was 12 days before onset of symptoms and 17.33 days before presentation to us and the mean dose of valproate was933.33mg/day range (800 - 1,000 mg/day).The cause of hyperammonaemia without hepatic dysfunction appears to be multifactorial and not well elucidated. Propionate, a metabolite of valproate reduces

hepatic N-acetylglutamate concentration, which is an obligatory activator of carbamoyl phosphate synthetase-1 (CPS-1), the first enzyme of the urea cycle. Decline inCPS-1 activity results in defective ammonia utilisation and accumulation of ammonia. Reduction of hepatic carnitine levels by valproate causes reduced beta-oxidation of fatty acids, resulting in reduced levels of acetyl coA. Decreasein acetyl coA disrupts the urea cycle resulting in hyperammonaemia. This may be one of the mechanisms in which carnitine therapy helps to lower ammonia level in these patients.[6, 7, 8] Less common mechanism is an increment in the mitochondrial glutamine transport, resulting in increased glutamine uptake by kidney and release of ammonia, but renal contribution is minor8,9.Risk factors for valproate-induced hyperammonaemia includes urea cycle enzyme deficiencies, underlying liver disease, high initial dose of valproate, long-term valproate therapy, co-medication with drugs like topiramate, salicylates, strict vegetarianism, uretero sigmoidostomy, and disorders associated with decreased albumin synthesis8. In patients with valproate-induced hyperammonaemia, there is good correlation between the fall in serum ammonia level and clinical improvement8. Along with discontinuation of valproate, haemodialysis and haemoperfusion, symptomatic and supportive measures are the mainstay of treatment.[9]

There is no literature on blood ammonia levels in Bangladeshi children on valproic acid therapy. Furthermore, the correlation between the dose and serum levels of valproic acid with blood ammonia levels is not clear in previous study. It is uncertain whether patients on a high dose of valproic acid are more susceptible to develop hyperammonemia. Therefore this study was designed to evaluate the blood ammonia levels in epileptic children on valproic acid monotherapy.

METHODS:

It was a prospective type of study conducted on 26 purposively selected clinically and neurophysiologically diagnosed cases of epilepsy at Pediatric Neurology unit, Bangabandhu Sheikh Mujib Medical University, Dhaka from June 2012 to January 2013

RESULTS:

Table I: Socio-demographic information of participants.

Age group	Male		Female		Chi/ t-value	p value*
	Frequency	Percentage	Frequency	Percentage		
1-3	9	45	2	33		
4-6	3	15	1	17		
7-9	4	20	2	33	1.227	0.999^{ns}
10-12	3	15	0	0		
13-15	1	5	1	17		
Age range(Yrs)	Min. 1	Max.14	Min. 1	Max. 13		
Mean age(Yrs)	5.47		6.41		0.521	0.606^{ns}
SD	±3.74		±4.36			

Table II: Sex Distribution among the patients (n=26)

Sex	Male	Percentage	Female	Percentage	Ratio
	20	77%	6	23%	M:F = 3.3 : 1

Table III: Economic statusamong the patients (n=26)

Economic status	Male		Female		Chi/ t-value	p value*
	Frequency	Percentage	Frequency	Percentage		
Upper	1	5%	0	0%		
Middle	17	85%	5	83%	0.846	0.932
Lower	2	10%	1	17%		

Table IV: Type of seizure among the patients (n=26)

Type of seizureMale			Female		Chi/ t-value	p value*
	Frequency	Percentage	Frequency	Percentage		
Generalized idiopathic	12	60%	5	83%	1.893	0.388^{ns}
Generalized symptomatic	3	15%	1	17%		

Table V: Duration of drug intake before study among the patients (n=26).

	Minimum	Maximum	Mean	Std. Deviation
Duration of drug in months	3.0	60.0	6.85	±11.60

Table VI: Biochemical report among the patients (n=26).

Name of tests	Minimum	Maximum	Mean	Std. Deviation
Serum valproate level(µgm/ml)	33.81	150.00	70.50	±34.16
SGPT (U/L)	5.4	60.0	25.43	±11.33
Serum Creatinine level (mmole/L))	0.04	1.30	0.58	±0.22

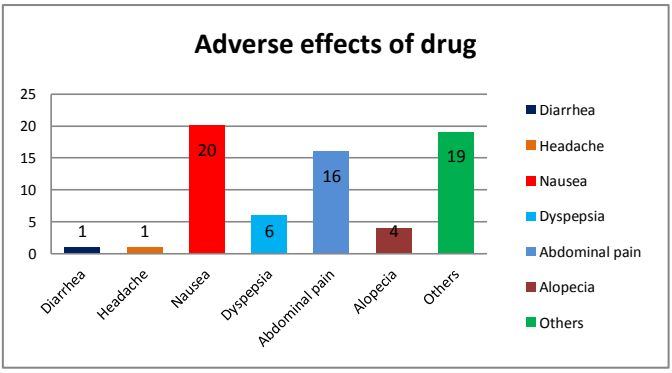
Table VII: Amonia level before and after treatment among the patients (n=26).

Amonia level	Mean	SD	t-value	p-value*
Baseline (**µmol/L**)	19.25	±5.8	-7.019	0.000**
Follow up (**µmol/L**)	48.18	±21.33		

Table VIII: Status of ammonia level after treatmentamong the patients (n=26).

Follow up amonia level	Frequency	Percentage
Normal	6	23
Higher than normal range	20	77

Figure I: Adverse effects of drug among the patients (n=26).



DISCUSSION:

A prospective interventional study was conducted on 26 patients of seizure disorder at the department of Paediatric Neurology, BSMMU, Dhaka, Bangladesh. Among the participants 77% patients was male and 23% was female. Male to female ratio was 3.3 : 1. Age range of patients was 1 to 14 in male and 1 to 13 in female. Mean age of participants was 5.74

±3.74 years in male and 6.41 ±4.36 years in female. Maximum patients were in 1-3 years age group.

Economic status of patients was classified into 3 classes upper, middle and lower. Maximum patients came from the middle economic class where male and female percentage was 85 and 83 respectively.

Both partial and generalized tonic clonic types of seizure presented by patients at the entry of study. In male patients 75% was generalized type and 25% was presented with partial type of seizure. Whereas in female 100% patients presented with generalized type of seizure.

Mean duration of course of valproate treatment at the entry of our study was 6.85 ±11.6 months.

Serum valproate level, liver function test and renal function test were within normal range in our study. Mean serum valproate level was 70.50 ±34.16(µgm/ml), serum ALT was 25.43 ±11.33 U/L and mean serum creatinine level was 0.58±0.22mmol/L.

Baseline blood ammonia level was 19.25 ±5.8 (µgm/ml) and after end of treatment with valproate it was 48.18 ±21.33 (µgm/ml) this difference was highly significant statistically. Blood ammonia level raised than upper normal limit in case of 77% patients after 12 weeks of valproate treatment. In a similar type of study researchers found raised level of blood in 25% cases. The reported incidence of asymptomatic hyperammonaemia in children was 20%, and of symptomatic hyperammonaemia was 5%. Their finding was similar but percentage was lower than our findings.

Adverse effects of drug were noted at every follow up in a preformed data collection sheet. Diarrhea, headache, nausea, Hyperactivity, abdominal pain, alopecia and other adverse effects was listed as per patients' complaints. Nausea was found in 77% cases, abdominal pain was found in 61.5% cases and Hyperactivity was found in 23% cases. But these symptoms

were minor and were relieved with symptomatic medications. Drug withdrawal was not required in any case.

CONCLUSION:

In the light of our study we found that treatment with valproate in epileptic children can be raised blood ammonia level which might have chance to progress in encephalopathy. A large scale and long course study is required to justify our findings.

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