DOI: 10.7860/JCDR/2015/15562.6883

Case Series

Pharmacology Section

Valproate Induced Hyperammonemic Delirium

ANUPAMA MURALEEDHARAN[1], DHANYA SASIDHARAN PALAPPALLIL[2], RENEEGA GANGADHAR[3], SOUMITRA DAS[4]

ABSTRACT

Sodium valproate induced hyperammonaemic delirium with normal liver function tests is a relatively uncommon adverse effect. It may be mistaken for psychosis or worsening of mania leading to wrong diagnosis and improper management. Plasma ammonia levels should be monitored in all patients developing altered mental status after receiving valproate therapy. This is a case series of hyperammonaemic delirium due to valproate reported to the Department of Pharmacology from Department of Psychiatry over a period of one year.

Keywords: Plasma ammonia, Valproate therapy

CASE SERIES

This is a case series of three patients with Bipolar Affective Disorder (BPAD) who developed Valproate Induced Hyperammonaemic Delirium (VIHD) in the psychiatry department of a tertiary care hospital. All the patients were on irregular treatment with sodium valproate for several years before occurrence of the adverse drug reaction (ADR). Before restarting valproate for the current episode of mania the baseline Liver Function Tests (LFT) were done to rule out any evidence of hepatic impairment and impending danger of hepatotoxicity.

Case 1

A 46-year-old male developed features of BPAD following an accident 20 years back. He was on irregular therapy with valproate. He developed decreased sleep and excessive talk following which he was admitted to the Psychiatry department and started on Sodium valproate 500 mg twice daily along with Lorazepam 2mg once daily. Eighteen days later the patient developed confusion and lack of orientation in place and time. The drug was continued for six more days following which the patient's condition progressively deteriorated. The arterial ammonia was investigated and found to be 81 micromoles/L (Normal-11-32 micromoles/L). His random blood sugar, renal function tests and LFT were normal. Valproate was stopped following which there was drastic improvement in the clinical condition of the patient. The arterial ammonia level fell to 46micromoles/L three days after stopping the drug. The patient was started on Lithium 600mg thrice daily.

Case 2

A 53-year-old male with BPAD was admitted to the psychiatry ward. He was on valproate therapy since 12 years but often defaulted. For his current episode of mania he was re-started on valproate 500 mg orally twice daily along with Olanzapine 10 mg twice daily and Lorazepam 2 mg at night. Two days later the patient developed confusion, lack of orientation to time, place, or person; his memory was impaired and he had decreased concentration and attention. His arterial ammonia was estimated four days later and was found to be 130micromoles/L and Spacing error hence the drug was stopped on the next day. LFT was repeated and found to be normal during the period. The patient showed good clinical improvement in the symptoms after stopping valproate. The arterial ammonia was found to be falling and was 50micromoles/L three days after stopping the drug. The patient was started on Lithium 600mg thrice daily.

Case 3

A 36-year-old female with BPAD since the age of 17 years had episodic attacks of mania and was using sodium valproate for the last two years. Default of the medications resulted in reappearance of maniac attacks and she was admitted in psychiatric ward and started on sodium valproate 200 mg thrice daily orally along with Lithium 600 mg thrice daily and Lorazepam 2 mg at night. Two days later the patient was found to be drowsy and later fell unconscious. The arterial ammonia estimated was 68micromoles/L and valproate was stopped on the same day and dose of Lithium was escalated. As in the previous case LFT were normal in this patient also. Three days later the patient had clinically improved from the symptoms and the arterial ammonia was 34 micromoles/L.

DISCUSSION

Sodium valproate is an antiepileptic drug used as a mood stabilizer in acute mania and BPAD. The occurrence of VIHD in persons with normal LFT is not a common ADR. The first case of hyperammonaemic encephalopathy due to valproate was published in the 1990s [1]. A prospective study screening for hyperammonaemia in patients receiving valproate in psychiatry setting found that a positive correlation exists between the serum concentration of valproate and ammonia levels [2].

Hyperammonaemia can be either asymptomatic or symptomatic. It may occur with both therapeutic and supratherapeutic concentrations of valproic acid, indicating influence of other factors. Patients who have been on valproate for several years without developing any complications can suddenly develop symptoms of encephalopathy [3].

Delirium or acute confusional state is a serious neuropsychiatric syndrome frequently seen in the elderly. Rapid and fluctuating in course it presents with inattention, global changes in cognition and generalized severe disorganization of behaviour [4].

Patients monitored in our hospital were middle aged and had symptoms suggestive of delirium. All the three patients were on sodium valproate for several years and often defaulted. In the current episode of mania they received the drug in therapeutic concentration. The causality assessment with Naranjo Score was 5 indicating a Probable causality for the ADR. World Health Organisation scale also showed it was a probable ADR. Re-challenge was not done in any of the patients. Since the ADR increased the length of stay it was of moderate severity.

Patient details		Disease for which valproate initiated	Age and Sex	Total Valproate dose (mg/day)	Duration of valproate use	Concomitant drugs	Serum ammonia levels		Rechallenge	Management	Naranjo's Causality Assessment
							1st*	2nd**			
Present case series	Case 1 VIHD	BPAD	46 M	1000	Several years with default. Valproate restarted for mania	Lorazepam	81	46	Not done	Valproate stopped	5-Probable
	Case 2 VIHD	BPAD	53 M	1000		Olanzepine Lorazepam	130	50			
	Case 3 VIHD	BPAD	36 F	600		Lithium Lorazepam	68	34			
Pradeep et al., [5]	Case 1 VIHD	BPAD	53 M	1000	Dose increased 2 days before VIHD	Nil	95	25	Done	Valproate stopped	Not available
	Case 2 VIHD	BPAD	60 M	1000	1 month		150	80	Not done		
	Case 3 VIHD	Seizure	20 M	750	3 years		366	-			
Wadzinski et al., [6]	Case 1 VIHE	PTSD	51 F	1000	7 days	Topiramate, Quetiapine	232	56	Not done	Valproate stopped Carnitine	Not available
	Case 2 VIHE	BPAD OCD	29 F	1500	5 months	Fluvoxamine Clonazepam	182	41	Not done	Valproate stopped	
Dixit et al., [7]	Case 1 VIHD	Mania	31 M	1000 escalated to 1500	15 days	Topiramate Olanzepine	98	30	Not done	Valproate stopped	9-Definite

[Table/Fig-1]: Comparison of present case series with similar reports in literature.
*Ammonia level checked first after suspecting hyperammonaemia **2 or 3 days after stopping valproate
VIHD-Valproate Induced Hyperammonaemic delirium; VIHE- Valproate Induced Hyperammonaemic Encephalopathy
BPAD-Bipolar Affective Disorder, PTSD-post traumatic stress disorder; OCD-Obsessive Compulsive Disorder

Despite the co-administration of other drugs, the temporal relation of termination of valproate and symptomatic improvement of patients suggest that the offending drug is valproate. The elevation of ammonia levels in the absence of deranged LFT supports the occurrence of VIHD. The positive correlation between stoppage of the valproate and quick reversal of clinical symptoms with fall in arterial ammonia levels in all the three patients is also suggestive of VIHD. [Table/Fig-1] compares the present case series with those published in the literature.

Valproate induced hyperammonaemia is a transient phenomenon but can become chronic and complicated and lead to VIHD if undetected. It could manifest as drowsiness, disorientation, and reversible cognitive deficits, which may progress to marked sedation, coma, and even death. Rashkind et al., states that valproate induced delirium occurs more commonly in the paediatric population [8].

Risk Factors for development of hyperammonaemia are high initial dose, long term valproate therapy, concomitant medicines such as antipsychotics or anticonvulsants added to valproate [9]. A well-established risk factor for hyperammonaemia in the neurological literature is the combination of valproic acid with other antiepileptic medications like phenobarbitone, phenytoin and topiramate [10].

The causes of valproate induced hyperammonaemia are many. As proposed by Panda et al., a reduction in hepatic N-Acetyl glutamate, an obligatory activator of Carbamoyl phosphate synthetase I (CPS I) by valproate metabolite propionate is one among them. Decline in CPS I activity disrupts the urea cycle thus resulting in defective ammonia utilization and accumulation [11].

Another mechanism proposed is reduction in hepatic carnitine levels by valproate. This results in decreased beta oxidation of fatty acids, which decreases Acetyl CoA leading to disruption of the urea cycle, resulting in hyperammonaemia [12]. Other mechanisms like induction of mitochondrial glutamine transport by valproate causing increased glutamate uptake by kidney and release of ammonia; inhibition of glutamate uptake by astrocytes, leading to neuronal injury and cerebral edema have also been proposed [13,14]. Deficiency of Ornithine transcarbamylase enzyme is the most common inherited cause of hyperammonaemia and valproate therapy can worsen the pre-existing hyperammonaemia [15].

Several drugs cause hyperammonaemia by disrupting the urea cycle. Glycine which is used in transurethral resection of prostate stimulates ammonia production [16]. Salicylates can reduce mitochondrial function in the liver as suggested by the Reye syndrome [17]. Although the mechanisms are unclear there have been a few reported case of hyperammonaemia due to carbamazepine, ribavirin and Sulfadoxine/Pyrimethamine [18-20]. Discontinuation of valproate helps in dramatic clinical improvement. The role of carnitine (2-4g/day) for prevention and treatment of VIHD has been established [10].

CONCLUSION

Hyperammonaemic delirium can be missed because of its close similarity with symptoms suggestive of worsening of psychosis. Hence it could be suggested that plasma ammonia levels should be monitored promptly in all patient developing altered mental status after receiving valproate therapy. There is also need of systematic evaluation of safety and efficacy for longer term use of valproate.

REFERENCES

[1] Settle EC. Valproic acid-associated encephalopathy with coma. *Am J Psychiatry.* 1995;152(8):1236–37.
[2] Raja M, Azzoni A. Valproate-induced hyperammonaemia. *J Clin Psychopharmacol.* 2002;22(6):631–33.
[3] Carr RB, Shrewsbury K. Hyperammonaemia Due to Valproic Acid in the Psychiatric Setting. *Am J Psychiatry.* 2007;164(7):1020–27.
[4] Davis DH, Barnes LE, Stephan BC, MacLullich AM, Meagher D, Copeland J, et al. The descriptive epidemiology of delirium symptoms in a large population-based cohort study: results from the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). *BMC Geriatrics.* 2014;14(1):87.
[5] Pradeep RJ. Valproate monotherapy induced-delirium due to hyperammonaemia: A report of three adult cases with different types of presentation. *Indian J Psychiatry*. 2008;50(2):121–23.
[6] Wadzinski J, Franks R, Roane D, Bayard M. Valproate-associated hyperammonaemic encephalopathy. *J Am Board Fam Med.* 2007;20(5):499-502.
[7] Dixit S, Namdeo M, Azad S. Valproate Induced Delirium due to Hyperammonaemia in a Case of Acute Mania: A Diagnostic Dilemma. *J Clin Diagn Res.* 2015;9(4):VD01-2.
[8] Raskind JY, El-Chaar GM. The Role of Carnitine Supplementation During Valproic Acid Therapy. *Ann Pharmacother.* 2000;34(5):630–38.
[9] Panda S, Radhakrishnan K. Two cases of valproate-induced hyperammonaemic encephalopathy without hepatic failure. *J Assoc Physicians India.* 2004;52:746–48.

[10] Clay AS, Hainline BE. Hyperammonaemia In The ICU. *Chest.* 2007;132(4):1368-78.
[11] Raby WN. Carnitine for valproic acid-induced hyperammonaemia. *Am J Psychiatry.*1997;154(8):1168–69.
[12] Murakami K, Sugimoto T, Nishida N, Kobayashi Y, Kuhara T, Matsumoto I. Abnormal metabolism of carnitine and valproate in a case of acute encephalopathy during chronic valproate therapy. *Brain Dev.* 1992;14(3):178–81.
[13] Marini AM, Zaret BS, Beckner RR. Hepatic and renal contributions to valproate-induced hyperammonaemia. *Neurology.* 1998;38(3):365–71.
[14] Verrotti A, Trotta D, Morgese G, Chiarelli F. Valproate-induced hyperammonaemic encephalopathy. *Metab Brain Dis.* 2002;17(4):367–73.
[15] Oechsner M, Steen C, Sturenburg H, Kohlschutter A. Hyperammonaemic encephalopathy after initiation of valproate therapy in unrecognised ornithine transcarbamylase deficiency. *J Neurol Neurosurg Psychiatry.* 1998;64(5):680-82.
[16] Ryder KW, Olson JF, Kahnoski RJ, Karn RC, Oei TO. Hyperammonaemia after transurethral resection of the prostate: a report of 2 cases. *J Urol.*1984;132(5):995-97.
[17] Makela AL, Lang H, Korpela P. Toxic encephalopathy with hyperammonaemia during high-dose salicylate therapy. *Acta Neurol Scand.* 1980;61(3):146-56.
[18] Rivelli M, el-Mallakh RS, Nelson WH. Carbamazepine-associated asterixis and hyperammonaemia. *Am J Psychiatry.* 1988;145(2):269-70.
[19] Bertrand P, Faro A, Cantwell P, Tzakis A. Intravenous ribavirin and hyperammonaemia in an immunocompromised patient infected with adenovirus. *Pharmacotherapy.* 2000;20(10):1216-20.
[20] Sekas G, Paul HS. Hyperammonaemia and carnitine deficiency in a patient receiving sulfadiazine and pyrimethamine. *Am J Med.* 1993;95(1):112-13.

PARTICULARS OF CONTRIBUTORS:
1. Junior Resident, Department of Pharmacology, Government TDMC, Alappuzha, Kerala, India.
2. Assistant Professor, Department of Pharmacology, Government TDMC, Alappuzha, Kerala, India.
3. Professor, Department of Pharmacology, Sree Mookambika Institute of Medical Science, Kulasekharam, Tamil Nadu, India.
4. Junior Resident, Department of Psychiatry, Government TDMC, Alappuzha, Kerala, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Dhanya Sasidharan Palappallil,
Assistant Professor, Department of Pharmacology, Government TDMCA, Kerala-688005, India.
E-mail: drspdhanya@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Jul 05, 2015**
Date of Peer Review: **Sep 16, 2015**
Date of Acceptance: **Oct 16, 2015**
Date of Publishing: **Dec 01, 2015**