CASE REPORT

Valproate induced hyperammonemic encephalopathy treated by haemodialysis

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ABSTRACT

Valproate (VPA)-induced hyperammonemic encephalopathy is an unusual, but serious, adverse effect of divalproex sodium (DVPX) treatment and if untreated can lead to raised intracranial pressure, seizures, coma, and eventually death. It can, however, be reversed if an early diagnosis is made. It is therefore extremely important to recognize it and discontinue DVPX treatment. Our patient developed sudden deterioration of sensorium, drowsiness, lethargy, and later severe comatose state after few days of starting DVPX with high levels of serum ammonia despite therapeutic levels of VPA and normal liver function test. He responded to hemodialysis, cerebral decongestants, and other intensive supportive measures.

KEYWORDS: Divalproex sodium, encephalopathy, hyperammonemia

Divalproex sodium (DVPX) is a stable coordination compound comprising sodium valproate (VPA) and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. DVPX is an antiepileptic drug that is approved for the treatment of several types of seizures. It is also an effective treatment option for bipolar affective disorder, schizoaffective disorder, neuropathic pain, and for the prophylaxis and treatment of migraine headaches. Valproate-induced hyperammonemic encephalopathy (VHE)/delirium with normal liver function tests (LFTs) is a relatively uncommon adverse effect. It may be mistaken for psychosis or worsening of mania leading to wrong diagnosis and improper management. It may be confused with delirious mania and may result in further increased dose of DVPX. Serum ammonia levels should be monitored in all patients developing altered mental status after receiving VPA therapy.

CASE REPORT

A 25-year-old male was referred for psychiatric evaluation with a 1-week history of abnormal behavior in the form of hyperactivity, restlessness, speaking excessively in domineering manner, and displaying disruptive tendencies. History revealed that he had two manic episodes in the past 2 years which were managed with tablet olanzapine (15 mg/day in divided doses) and tablet DVPX (1000 mg/day in divided doses). He had a history of noncompliance with maintenance medication for the past 5 months. There were no developmental issues. Physical examination was within normal limits, and there was no focal neurological deficit. Psychiatric evaluation and ward observation revealed persistent elevated mood, disinhibition, pressure of speech, increased psychomotor activity, inflated self-esteem, impaired judgment, insight with reduced need for sleep, increased energy, and appetite.

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in the absence of delusions or perceptual disturbances in a setting of clear sensorium. Young’s Mania Rating Scale score was 47 (cutoff of 20 for hypomania and 25 for mania). Relevant investigations at the time of admission including complete blood count, LFT, renal function test, blood sugar, thyroid profile, electrocardiogram, serum electrolytes, and computed tomography (CT) scan brain were within normal limits. Urine for drug screen for Cannabis, opioids, cocaine, amphetamines, benzodiazepines, and barbiturates was negative. He was diagnosed as a case of bipolar affective disorder, current episode manic without psychotic symptoms (International Classification of Diseases, 10th Edition [ICD 10] – F31.1) as per the diagnostic criteria of ICD-10, and started on injection haloperidol (5 mg) + injection phenergan (25 mg) intramuscular SOS, tablet DVPX (1500 mg/day in divided doses), tablet risperidone (4 mg/day in divided doses), and tablet clonazepam (4 mg/day in divided doses). The patient continued to be irritable, hyperactive, overtalkative, displaying disruptive behavior over the next 1 week despite ensuring regular compliance to psychotropics. On day 10 of the hospitalization, he was noted to be drowsy but able to carry out his routine activities; hence, all his medications were withheld. On day 11 of hospitalization, drowsiness further worsened Glasgow coma scale (GCS 12/15) score, and he had irrelevant speech and disorientation. Clinical examination revealed the following: temperature - 98.6°F, pulse - 74/min, regular blood pressure (BP) - 120/70 mmHg, pupils - normal in size and normally reacting to light, no rigidity, and plantars were flexor. All medications were withdrawn. Relevant urgent investigations revealed - creatine phosphokinase - 113.5 IU/L (0–170 IU/L), normal LFT, and repeat CT scan brain. He was shifted to intensive care unit (ICU). By evening, his drowsiness further worsened (GCS-E1V1M3), temperature - 98.6°F, Pulse rate (80–90/min), and BP (systolic 110–120 mmHg and diastolic 70–84 mmHg). His urgent serum ammonia level was 396 μmol/L (normal - 11–32 μmol/L), serum VPA level was 67 (50–100 μg/ml), and other findings were pH – 7.53, PO₂ – 86, Na⁺ – 139 meq/L, and K⁺ – 3.6 meq/L. He was diagnosed as a case of nonhepatic hyperammonemic encephalopathy caused by VPA. He was promptly managed with hemodialysis, injection mannitol 100 mg intravenous (IV) 8 hourly, and ICU supportive care. On day 12, he was conscious but drowsy and partially oriented, tablet L-carnitine 1000 mg for every 12 h was also added while being continued on hemodialysis and injection mannitol. On day 14, he was conscious, obeying commands, but restless. His repeat serum ammonia levels showed a declining trend (44 μmol/L) and his hemodialysis was discontinued. His restlessness was subsequently managed with tablet lorazepam. He was started on tablet oxcarbazepine as a mood stabilizer, which was well tolerated and later discharged on maintenance oxcarbazepine (900 mg/day in divided doses).

**DISCUSSION**

Ammonia is a normal constituent of all body fluids. At physiologic pH, it exists mainly as ammonium ion. Reference serum levels are <35 μmol/L. Excess ammonia is excreted as urea, which is synthesized in the liver through the urea cycle. Various causes of hyperammonemia include congenital deficiencies of urea cycle enzymes, hepatic encephalopathies, renal or hepatic failure, congenital lactic acidosis, organic acidemias, drug induced (VPA, 5-fluorouracil, and salicylates), and Reye's syndrome. Although VHE is rare, VPA frequently causes a rise in serum ammonia levels, usually resulting in asymptomatic hyperammonemia. Murphy and Marquardt studied the frequency of hyperammonemia in asymptomatic patients receiving valproic acid; plasma ammonia concentrations were measured in 55 patients receiving this drug and in 12 patients receiving other anticonvulsants. Twenty-nine of the 55 patients receiving valproic acid and none of the control patients had plasma ammonia levels above the normal range. Hyperammonemia can have varied presentation from 4 days to 4 years after valproic acid therapy initiation. The mechanism of valproic acid and its derivatives causing hyperammonemia is multifactorial. VHE pathogenesis is related to urea cycle defect mostly in the form of carbamoyl phosphate synthetase-1 inhibition leading to decreased utilization of ammonia followed by a hyperammonemic state. VPA also reduces the hepatic synthesis of carnitine and increases its renal excretion, thereby precipitating hyperammonemia. Hyperammonemic encephalopathy can lead to edema of astrocytes through glutamate uptake inhibition, which may lead to cerebral edema and neuronal injury. There is apparently no link between the development of VHE and serum levels and doses of valproic acid. A relationship between daily doses of VPA and the appearance and severity of VHE has not been found. Serum VPA levels are within normal range in most VHE cases.

The Naranjo Adverse Drug Reaction Probability Scale of this case scored 9 (definite adverse drug reaction). Risk factors for the development of hyperammonemia are high initial dose (probably slightly higher in our case), long-term VPA therapy, concomitant medicines such as antipsychotics (as in our case) or anticonvulsants (topiramate, phenobarbitone, phenytoin, and carbamazepine) added to VPA, urea cycle disorders, low plasma carnitine levels, rich protein diet, and fasting. Some of the unusual features of the present case are sudden deterioration to severe comatose state (GCS-5/15), absence of seizures, DVPX...
Table 1: Comparison of the present case series with similar reports in literature

| Patient details | Patient details | Disease for which VPA initiated | Age and sex | Total VPA dose (mg/day) | Duration of VPA use | Concomitant drugs | Serum ammonia levels (µmol/L) | Rechallenge | Management | Naranjo’s casualty assessment |
|-----------------|----------------|-------------------------------|-------------|------------------------|--------------------|--------------------|-----------------------------|------------|------------|-----------------------------|
| Present case report | Case VHE | BPAD | 25, male | 1500 | 1 year with default. VPA started for mania | Risperidone Clonazepam | 396 | 46 | Not done | VPA stopped | Hemodialysis Carnitine | 9 definite |
| Muraleedharan et al. | Case 1 VHD | BPAD | 46, male | 1000 | Several years with default VPA started for mania | Lorazepam | 81 | 46 | Not done | VPA stopped | Not available | 5 probable |
| | Case 2 VHD | BPAD | 53, male | 1000 | 1 month | | | | | | | |
| | Case 3 VHD | BPAD | 36, female | 600 | 3 years | | | | | | | |
| Pradeep | Case 1 VHD | BPAD | 53, male | 1000 | Dose increased 2 days before VHD | NIL | 95 | 25 | Done | VPA stopped | Not available | |
| | Case 2 VHD | BPAD | 60, male | 1000 | 1 month | | | | | | | |
| | Case 3 VHD | SEIZURE | 20, male | 750 | 7 days | Topiramate Quetiapine | 232 | 56 | Not done | VPA stopped | Carnitine | Not available |
| Wadzinski | Case 1 VHE | PTSD | 51, female | 1000 | 7 days | Topiramate Quetiapine | 98 | 30 | Not done | VPA stopped | Not available | |
| | Case 2 VHE | BPAD | 29, female | 1500 | 5 months | Fluvoxamine | 182 | 41 | Not done | VPA stopped | | |
| | Case 1 VHD | Mania | 31, male | 1000 | Escalated to 1500 | Topiramate olanzapine | 98 | 30 | Not done | VPA stopped | | 9 definite |

First - Ammonia level checked first after suspecting hyperammonemia; Second - 2 or 3 days after stopping VPA. VHD – Valproate-induced hyperammonemic delirium; VHE – Valproate-induced hyperammonemic encephalopathy; BPAD – Bipolar affective disorder; PTSD – Posttraumatic stress disorder; OCD – Obsessive-compulsive disorder; VPA – Valproate
with no concurrent anticonvulsants, absence of medical comorbidity, and life-threatening condition requiring hemodialysis, cerebral decongestants, and L-carnitine. Our patient did not have seizures as documented in other case reports of VHE[22-25] in which there was rapid neurological deterioration which responded to hemodialysis [Table 1].

Principles of management include correction of the biochemical abnormalities; ensuring adequate nutritional intake and compounds that increase the removal of nitrogen waste. Treatment involves withdrawal of VPA, cessation of protein and/or nitrogen intake, hemodialysis, and supportive care with parenteral intake of calories. Complete recovery generally occurs over a period of 24 h to a few days. L-carnitine supplementation has been shown to improve the symptoms of VPA-related toxicities. L-carnitine has also been shown to be effective in reducing ammonia levels and in improving the symptoms of hyperammonemia. It is generally safe and may be given orally or IV at a dose of 50–100 mg/kg/day.[19] There are currently no specific recommendations for screening people for asymptomatic hyperammonemia. This case report purports to caution the psychiatrist that there should be a high index of suspicion for VPA-induced hyperammonemia in case a patient shows deterioration in clinical recovery or develops deliriumencephalopathy while on treatment with VPA as hyperammonemia is a potentially reversible condition.

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Conflicts of interest
There are no conflicts of interest.

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