Valproate induced hyperammonemia in patients with bipolar affective disorder - Case Study

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ABSTRACT

Valproic acid (VPA, valproate), is an acidic chemical compound, has found clinical use as an anti-convulsant and mood stabilising drug, primarily in the treatment of epilepsy, bipolar disorder and prevention of migraine. Hyperammonemia is an idiosyncratic side effect in patients on valproate. Serum ammonemia levels were estimated in 20 patients with bipolar affective disorder who were on valproate for atleast 6 months and presented with drowsiness. The results showed that most of the patients were males, with nicotine dependence & above 40yrs. Hyperammonemia could be due to chronic use of valproate.

Key words: Valproate, bipolar affective disorder, Serum ammonia

Introduction:

Valproate (2-propyl pentanoic acid) is effective in the treatment of bipolar affective disorder, seizure disorder, migraine, behavioral agitation in dementia, impulse control disorders, borderline personality disorders, panic disorder, alcohol withdrawal & relapse prevention, schizophrenia, schizoaffective disorder, prophylaxis against seizure in clozapine therapy & chronic pain syndromes. (1,4,5,6,12,13,16-18) In psychiatry it is most commonly used in the treatment of acute mania & prophylaxis in bipolar affective disorder. The therapeutic dose ranges from 500mg to 2000mg/day.

In 1980, Coulter and Allen reported the first case of hyperammonemia, in a child with epilepsy treated with valproic acid(2). Since that time, there have been several additional case reports and studies within the neurology literature that have established hyperammonemia with otherwise normal hepatic function as a potential side effect of valproic acid, especially in children and adolescents. Settle published the first case of
hyperammonemia in a psychiatric setting in 1995. Several additional cases have followed it, but there are a few prospective studies published in the psychiatric literature. (3,20-22)

Although the incidence of valproate related hyperammonemic encephalopathy is unknown, mild and reversible elevations in ammonia have been described in 16%—52% of patients receiving valproate therapy. In a case series, asymptomatic hyperammonemia was observed in 52% of patients receiving valproate monotherapy, 55% of those treated with valproate in combination with other anticonvulsants and 8% of patients receiving anticonvulsant regimens that did not include valproate(7,8,20,21).

There remains controversy as to whether these symptoms have any relationship to daily dose or plasma concentration of valproic acid. Multiple studies, a few randomized but most of them cohort studies, have searched for a correlation between dose of valproic acid or plasma valproic acid concentration and serum ammonia levels. The results are mixed. Hyperammonemia occurs at both therapeutic and supratherapeutic concentrations of valproic acid, implying that other factors often influence the development of symptomatic hyperammonemia. (3)

Hyperammonemia is a rare side effect seen in patients on valproate, most commonly seen in patients with liver dysfunction or Krebs-Henseliet urea cycle disorders. Other risk factors include: concomitant treatment with carbamazepine, phenobarbital, topiramate &lorazepam, high initial dose, long-term valproate therapy, co-medication with drugs like salicylates, strict vegetarianism, diabetes, uretersigmoidostomy, and disorders associated with reduced albumin synthesis (7,8,10,11,14,15,20,22,26).

The clinical presentation of hyperammonemic encephalopathy can be varied and includes irritability, agitation, drowsiness, coma and occasionally these patients may have paradoxical seizures. The other symptoms include loss of appetite, nausea and vomiting(3-6,9,10,22,25,26). Electroencephalography (EEG) is characterized by signs of severe encephalopathy with continuous generalized slowing, a predominance of theta and delta activity, occasional bursts of frontal intermittent rhythmic delta activity, and triphasic waves(3,5,22,25). MRI shows bilateral T2-hyperintense lesions located in the cerebellar white matter and globus pallidus. Proton MR spectroscopy (MRS) showed a severe depletion of myoinositol and choline with glutamine excess, and a moderate decrease of N-acetyl aspartate. (5,22)

We studied the frequency of hyperammonemia in patients who were receiving treatment with valproate for bipolar affective disorder & its association with dosage, duration and associated co-morbidities.

**Methodology:**

This study was conducted in a Medical College Hospital in Mangalore, Karnataka. We followed up both in-patients & out-patients diagnosed to have Bipolar affective disorder, who were treated with valproate for at least 6 months. The study was conducted from July 1st 2011 to July 1st 2012. Diagnosis was made using the ICD-10 criteria, which included both acutely symptomatic & those in remission. We conducted a baseline hemogram, glycemic scores, renal & liver function tests & thyroid function tests. We estimated the serum
ammonia levels using the enzymatic method in patients who were noticed to be drowsy. Serum ammonia was calculated using the enzymatic method with glutamate dehydrogenase (GLDH).

\[
\text{GLDH} \\
\text{NH}_4^+ + 2\text{-Oxoglutarate} + \text{NADPH} \\
\xrightarrow{\text{L-Grutamate + NADP}^+ + \text{HO}_2}
\]

The concentration of NADP formed is directly proportional to the ammonia concentration. It is determined by measuring the decrease in absorbance. The normal range in males is 16-60 mmol/L & females is 11-51 mmol/L. We also studied the duration and dose of valproate treatment & associated co-morbidities in each of these patients.

**Table-1: ADS- Alcohol Dependence Syndrome; NDS-Nicotine Dependence Syndrome; CDS-Cannabis Dependence Syndrome.**

<table>
<thead>
<tr>
<th>Sl.No.</th>
<th>Age/Sex</th>
<th>Dosage of valproate &amp; duration</th>
<th>Comorbidity</th>
<th>Duration of illness</th>
<th>Serum ammonia (mmol/L)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>56yrs/Male</td>
<td>1000mg X 7yrs</td>
<td>Bronchial asthma (on beta 2 agonists), NDS</td>
<td>8 yrs</td>
<td>169</td>
<td>Stoppage of valproate &amp; carnitine supplementation</td>
</tr>
<tr>
<td>2.</td>
<td>44yrs/Male</td>
<td>500mg X 12yrs 750mg X 1wk</td>
<td>ADS, NDS</td>
<td>12yrs</td>
<td>60.6</td>
<td>Tapering of valproate dosage.</td>
</tr>
<tr>
<td>3.</td>
<td>40yrs/Male</td>
<td>750mg X 13yrs 1000mg X 2months</td>
<td>NDS</td>
<td>14yrs</td>
<td>82.4</td>
<td>Tapered &amp; stopped valproate</td>
</tr>
<tr>
<td>4.</td>
<td>41yrs/Fema</td>
<td>1000mg X 12yrs</td>
<td>Hypothyroidism</td>
<td>15yrs</td>
<td>60</td>
<td>Tapered valproate</td>
</tr>
<tr>
<td>5.</td>
<td>43yrs/Male</td>
<td>1000mg X 5yrs 1500mg X 2days</td>
<td>Diabetes mellitus</td>
<td>6yrs</td>
<td>135</td>
<td>Tapered &amp; stopped valproate; Carnitine supplementation</td>
</tr>
<tr>
<td>6.</td>
<td>45yrs/Male</td>
<td>1000mg X 11yrs</td>
<td>NDS</td>
<td>12yrs</td>
<td>118.7</td>
<td>Tapered &amp; stopped valproate</td>
</tr>
<tr>
<td>7.</td>
<td>26yrs/Male</td>
<td>1500mg X 3yrs</td>
<td>NDS</td>
<td>3yrs</td>
<td>34.1</td>
<td>-</td>
</tr>
<tr>
<td>8.</td>
<td>40yrs/Male</td>
<td>1500mg X 12yrs</td>
<td>Diabetes mellitus</td>
<td>13yrs</td>
<td>77.1</td>
<td>Tapered &amp; stopped valproate</td>
</tr>
<tr>
<td>9.</td>
<td>20yrs/Male</td>
<td>1000mg X 2yrs</td>
<td>CDS &amp; NDS</td>
<td>2yrs</td>
<td>117.7</td>
<td>Tapered &amp; stopped valproate</td>
</tr>
<tr>
<td>10.</td>
<td>30yrs/Male</td>
<td>1000mg X 4yrs</td>
<td>NDS</td>
<td>5yrs</td>
<td>331</td>
<td>Tapered &amp; stopped valproate. Carnitine supplementation</td>
</tr>
</tbody>
</table>
### Results:

We followed up patients who were diagnosed to have bipolar affective disorder & were on valproate for at least 6months. The duration of illness in these patients varied from 1yr to 20yrs, and most of them were maintaining well on valproate. We studied 20 patients with Bipolar affective disorder, who were treated with valproate, and who presented with drowsiness. Serum ammonia estimation were done in these patients & 19 out of 20(95%) patients were found to have elevated ammonia levels. Most of these patients were 40yrs &above (11/19,57.89%), were males (15/19,78.94%), had nicotine dependence (11/19,57.89%) & were on a dose of 1000mg (13/19,68.42%). Three patients were dependent on alcohol, one on cannabis & two on both alcohol & nicotine, among the 20 patients. Seven had medical illnesses, most common been diabetes mellitus (3/7, 42.8%) followed by seizure disorder (2/7, 28.5%), 2 of them had other systemic illness.

<table>
<thead>
<tr>
<th></th>
<th>Age/Gender</th>
<th>Dose</th>
<th>Diagnosis</th>
<th>Duration</th>
<th>Serum ammonia (umol/l)</th>
<th>Treatment &amp; Other Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.</td>
<td>28/Female</td>
<td>1000mg X 8yrs</td>
<td>NDS, Seizure disorder (on phenytoin 300mg/d)</td>
<td>10yrs</td>
<td>224.4</td>
<td>Tapered &amp; stopped valproate. Carnitine supplementation.</td>
</tr>
<tr>
<td>12.</td>
<td>24yrs/Male</td>
<td>1000mg X 6yrs</td>
<td>Diabetes mellitus</td>
<td>7yrs</td>
<td>72.1</td>
<td>Tapered &amp; stopped valproate</td>
</tr>
<tr>
<td>13.</td>
<td>28yrs/Male</td>
<td>1500mg X 5yrs</td>
<td>NDS</td>
<td>5yrs</td>
<td>108</td>
<td>Tapered &amp; stopped valproate. Carnitine supplementation</td>
</tr>
<tr>
<td>14.</td>
<td>42yrs/Male</td>
<td>1500mg X 12yrs</td>
<td>-</td>
<td>15yrs</td>
<td>66</td>
<td>Tapered &amp; stopped valproate.</td>
</tr>
<tr>
<td>15.</td>
<td>40yrs/Male</td>
<td>1000mg X 13yrs</td>
<td>ADS(on topiramate)</td>
<td>20yrs</td>
<td>120</td>
<td>Tapered &amp; stopped valproate. Carnitine supplementation</td>
</tr>
<tr>
<td>16.</td>
<td>29yrs/Female</td>
<td>1000mg X 9yrs</td>
<td>Seizure disorder (on phenytoin 300mg/d)</td>
<td>10yrs</td>
<td>180</td>
<td>Tapered &amp; stopped valproate.</td>
</tr>
<tr>
<td>17.</td>
<td>20yrs/Male</td>
<td>1500mg X 9months</td>
<td>-</td>
<td>1yr</td>
<td>303</td>
<td>Tapered &amp; stopped valproate. Carnitine supplementation</td>
</tr>
<tr>
<td>18.</td>
<td>40yrs/ Female</td>
<td>1000mg X 12yrs</td>
<td>-</td>
<td>16yrs</td>
<td>89</td>
<td>Tapered &amp; stopped valproate.</td>
</tr>
<tr>
<td>19.</td>
<td>28yrs/Male</td>
<td>1500mg X 8yrs</td>
<td>NDS</td>
<td>10yrs</td>
<td>108</td>
<td>Tapered &amp; stopped valproate</td>
</tr>
<tr>
<td>20.</td>
<td>43yrs/Male</td>
<td>1000mg X 15yrs</td>
<td>ADS, NDS</td>
<td>18yrs</td>
<td>82</td>
<td>Tapered &amp; stopped valproate</td>
</tr>
</tbody>
</table>

* ADS (Alcohol Dependence Syndrome) * NDS (Nicotine Dependence Syndrome) * CDS (Cannabis Dependence Syndrome)
(hypothyroidism & bronchial asthma). Three patients were on anticonvulsants, two of them were on phenytoin 300mg for seizure control & one was on topiramate, as a anti-craving agent in a patient with alcohol dependence. All our patients had normal liver & renal function tests.

**Discussion:**

The findings obtained in this study is similar to that in other studies, done in psychiatric setting. The increased frequency in males could be because 80% of the sample consisted of males. Most of the cases were found at a supratherapeutic dose of 1000mg/day, which is similar to previous studies. The higher frequency of nicotine dependence could be because valproate was our first preferred drug as a mood stabilizer in bipolar patients with substance use.

Most of the cases were patients who were on valproate for more than 6 months had reported of excessive drowsiness and very non-compliant. Non-compliance led to frequent relapses in these cases which had to be managed not only with antipsychotics & benzodiazepines. The reason of relapse is questionable as to whether they stopped the medication as they lost insight which heralded the onset of new episode, or they stopped it because they were excessively drowsy. Most of our patients reported drowsiness, interfering with their activities as the main reason to stop the medication. The drowsiness could have been because of hyperammonemia which resolved on discontinuation of valproate earlier. This may indicate that history of drowsiness on valproate could be a risk factor for subsequent development of hyperammonemia within a short period, as noted in this study. Chronic treatment with valproate can decrease the carnitine levels which might have predisposed these individuals, indicating that though these cases presented in a short duration on valproate, the underlying cause would have been present much before the re-initiation of valproate.

Animal studies have shown that L-carnitine improves IGF & IGF related proteins. Abnormality in carnitine metabolism has been found in diabetic patients & this could have increased the risk of hyperammonemia in our patients. Concomitant use of phenytoin & topiramate may increase ammonia levels further. Topiramate inhibits glutamine synthetase in the CNS, inhibits carbonic anhydrase (increases ammonia due to decrease in mitochondrial urea synthesis in liver) & depletes L-carnitine.

**Proposed mechanism of action:**

Several possible mechanisms have been explored for hyperammonemia in patients on valproate, but none of them have been completely understood.

(i) In hepatic mitochondria, valproic acid is believed to cause an accumulation of ammonia by reducing free carnitine and co-enzyme A. Loss of co-enzyme A prevents the beta-oxidation of fatty acids into acetyl-co-enzyme A, which is a substrate of N-acetylglutamate, the required activator of the initial enzyme in the urea cycle. The relationship between VPA and carnitine and the subsequent development of hyperammonemia is not completely understood. VPA reduces levels of carnitine by 2 methods. Structurally, VPA is a short, branched-chain fatty acid. Carnitine is a carrier-type molecule required for the transport and beta oxidation of fatty acids in the mitochondria. VPA is believed to complex with carnitine in such
a manner that the renal excretion of carnitine is enhanced.

In addition, VPA, carnitine, and coenzyme A form poorly productive intracellular complexes that have 2 negative effects. The first is a reduction in fatty acid use for energy needs. Because cellular energy demands remain constant there is likely an increase in compensatory amino acid oxidation and a subsequent increase in the production of nitrogenous waste. The second effect is caused by the binding of VPA to coenzyme A, which is required for the formation of N-acetylglutamate, a powerful allosteric activator of carbamoyl phosphate synthetase I and critical to the regulation of nitrogen flux toward its appropriate metabolism (4,5,15).

Figure-1: 1-N-acetyl glutamate synthetase; 2-Carbomyl phosphate synthetase 1;3- Ornithine carbamylase; 4-Arginosuccinate synthetase; 5- Arginosuccinate lyase 6- Arginase

(ii) An association between encephalopathy induced by valproic acid and genetic impairment in the urea cycle was described in the pediatric neurology literature, the age when most of these genetic disorders are first recognized.(23) Most common been the heterozygous deficiency of ornithine transcarbamoylase, an enzyme in the urea cycle. This X-linked disorder occurs in approximately 1 of 30,000 women. Laboratory findings suggestive of ornithine transcarbamoylase deficiency include elevated urine levels of orotic acid; elevated blood levels of ammonia, glutamine, and alanine; and low levels of citrulline. Most cases of VPA-induced hyperammonemia, however,
occur in people without a known enzyme deficiency.\(^4,5\)

(iii) 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. Decrease in CPS-1 activity results in defective ammonia utilization and accumulation of ammonia\(^4,6,25-27\).

(iv) The less common mechanism is the stimulation of the renal (cortex) mitochondrial glutaminase by valproate & its metabolites (sodium 2-propyl-4-pentenoate (4-en-VPA) resulting in increased glutamine uptake by kidneys and release of ammonia\(^9,17,22,27\).

The CNS toxicity due to hyperammonemia is mediated by the excessive activation of the NMDA type of glutamate receptors, mainly in the acute hyperammonemia phase.\(^5,22\) The mental status change associated with hyperammonemia is not fully understood, but Brusilow, in a narrative review on hyperammonemia, summarized how ammonia is thought to cause encephalopathy. Within the CNS, increased ammonia increases glutamine synthetase activity, causing increased production and accumulation of glutamine within astrocytes. This increased intracellular glutamine leads to cerebral edema and astrocyte dysfunction. The mechanisms by which the brain is thought to compensate for astrocyte swelling in chronic hyperammonemia include decreased osmolarity and thus edema by down-regulation of myo-inositol, increased brain tissue compliance, and mild to moderate brain atrophy.\(^30\)

**Treatment:**

Various treatments for hyperammonemia induced by valproic acid have been tried, including those derived from the treatment of hepatic encephalopathy, such as withdrawal of valproate, lactulose, naloxone, neomycin & hemodialysis\(^3,12\). Because one way that valproic acid is thought to cause hyperammonemia is by depleting hepatic carnitine, its replenishment might be a treatment specific for encephalopathy induced by valproic acid.

Carnitine, an important nutrient found in meat and dairy products, is a cofactor necessary for the oxidative metabolism of long-chain fatty acids. It is also necessary for the metabolism of valproic acid. Moreover, carnitine stores can be depleted by long-term treatment with valproic acid. Carnitine’s restoration of serum levels of ammonia to normal is accomplished most likely by removing valproic acid’s inhibition on carbamyl phosphate synthetase and urea synthesis\(^28,29\). The protective effect of carnitine (and probably other compounds with a trimethylamine group) against ammonium toxicity seems to be produced due to the action of glutamate against neurotoxicity, with an increase in the binding affinity of glutamate formetabotropic glutamate receptors.\(^22\) It is generally safe and may be given orally or intravenously at a dose of 50 to 100 mg/kg/day\(^4\).

Non-pharmacological interventions include initiation of a high calorie, protein-free diet and hydration.

**Limitations:**

The limitations of our study include: Nonrandom assignment of patients, lack of blinded
assessment, lack of standardized assessment & absence of control group. We assessed blood levels only one time. We have not investigated for any underlying urea cycle enzyme abnormalities in our patients. The study was hospital based & patients were hardly on regular follow-ups, & hence we would have missed many more cases. We studied patients who presented with drowsiness, but hyperammonemia presents with varying features like irritability, agitation, gastrointestinal symptoms etc. or maybe asymptomatic. Most of our patients were also on atypical antipsychotics & sedatives which would have also produced drowsiness. Hence hyperammonemia may have just been an incidental finding & indicate asymptomatic cases of hyperammonemia. We have not assessed the other risk factors for hyperammonemia.

Conclusion:

Valproate is the most common mood stabilizer used in the treatment of bipolar affective disorder, especially in those with psychotic symptoms & substance use disorders. This study highlights that hyperammonemia is a common complication even in the therapeutic range. The underlying pathology may be chronic, even though the presentation is acute.

Psychiatrists should consider this possible cause of changes in mental status in patients treated with VPA. Patients with VPA-induced hyperammonemia may be asymptomatic, may have behavioral changes, or may have marked deteriorations in their level of consciousness. Deaths have been reported.\(^{(4)}\)

The mental status changes due to valproic acid are difficult to distinguish from worsening psychosis or mania or even from a therapeutic response. Therefore we recommend monitoring both liver function and serum ammonia in patients taking valproic acid to assist in the early detection of adverse effects.

Screening for urea cycle disorders can be recommended in patients with:

(a) A known family history of OTC deficiency.

(b) Those patients who, after beginning treatment with VPA, develop unexplained episodes of confusion, especially in the setting of known stress factors (i.e., sepsis); aversion to protein (headache causing); and a family history of unexplained death in male children (especially males, because OTC is an X-linked disorder).

A provocative test such as allopurinol loading may also be carried out. This test consists of taking a single oral dose of allopurinol, which significantly increases the urinary excretion of orotic acid in OTC-deficient patients. Liver biopsy is useful for definitive diagnosis\(^{(22)}\).

Subclinical hyperammonemia is associated with decline in neuropsychological functioning. It may be useful to screen for hyperammonemia in otherwise asymptomatic patients on VPA treatment who are experiencing cognitive impairment. Neuropsychological testing is more sensitive than observational methods to assess subclinical VHE. Psychometric tests exploring motor speed, visual perception, construction, attention and concentration can be more specific.\(^{(5)}\)

Preventive measures may include, avoiding polypharmacy, observe for other causes for hyperammonemia & carnitine supplementation in patients on valproate.
Future Research:

Specific treatments have not been tested, making management of this adverse effect an important area for further research. L-carnitine has been used, but when to restore it is still controversial. Multiple areas such as risk factors, prevalence, & identification also need further studies. EEG studies might be helpful for identification, and further research is needed to characterize EEG findings in non-epileptic patients with hyperammonemic encephalopathy.

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