*Case Report*

# Valproate-Associated Hyperammonaemic Encephalopathy

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## Abstract

We present the case of a 55 year old who presented multiple times with altered conscious levels. He was often treated as being post-ictal, when in fact, he had Sodium Valproate induced hyperammonaemic encephalopathy. Sodium Valproate can frequently increase ammonia levels, and in some patient lead to hyperammonaemic encephalopathy.



## Keywords

Sodium Valproate, Valproate, Ammonia, encephalopathy


## Case History

A 55 year old male presented to the medical team after having been found less responsive by his carers. His Glasgow Coma Scale (GCS) was initially recorded as 8/15 in the emergency department, but had spontaneously improved to 12/15 on the medical ward (Eyes 4 Verbal 3 Motor 5).

He had a background of longstanding seizure disorder and learning disabilities. 14 months earlier he had suffered from a traumatic subdural haemorrhage (managed conservatively). He had had a history of alcohol excess, but had been abstinent for the last 5 years.

In the preceding five months he had attended hospital four times with a similar history of increasing drowsiness, or altered behaviour.He was usually observed for 48-72 hours, and discharged when it was felt his confusion had improved. He was often diagnosed as being post-ictal, though no preceding seizures were ever documented. There were no obvious precipitating factors such as infection, poor compliance to medications, or alcohol excess.

He was on four long term anti-epileptic medications: phenytoin (100mg TDS), sodium valproate (800mg OM, 1600mg ON), lamotrigine (150mg BD) and levetiracetam (1.5g BD). He was also taking thiamine, vitamin B supplements, and folic acid. On one prior admission his sodium valproate (SVPA) was increased from 1600mg once a day to 1600mg (morning) and 800mg (evening). On a prior admission his serum drug levels were requested; revealing elevated phenytoin levels at *30.2mg/L (n*ormal 5.0-20.0 mg/L). Lamotrigine and levetiracatem levels were within normal range.

Admission bloods were unremarkable (Table 1):

His venous blood gas also showed normal parameters: pH 7.36, pC02 6.5, Lactate 1.8, BE 1.4, HCO3 27.7, glucose 4.7

Computed tomography (CT) imaging of the brain showed no acute abnormal findings. Neurological exam did not elicit any focal neurological deficits, and tone, power and reflexes were documented as normal.

In view of his frequent attendances and lack of obvious precipitating causes, the decision was made to monitor him and to maintain a seizure chart. Over the next 4 days, it was noted that his GCS could fluctuate between 13 and 15; mainly differences were in motor and verbal components. He was often unable to maintain conversations, and had poor recall of events and discussions from the previous day.

No obvious overt seizure activity was documented. At the multidisciplinary team meeting, social workers established that though he was drinking heavily in the past, there was no recent history of alcohol consumption. Collateral from carers revealed that his compliance to medication was good.

A neurology review advised checking his phenytoin and ammonia levels, looking for phenytoin toxicity and SVPA-induced hyperammonaemic encephalopathy. Phenytoin level was *25.6mg/L* (Normal 5.0-20.0 mg/L) and the serum ammonia level was *160umol/L* (Normal range 11.2 – 60.0

**Table 1.**

| | |
|---|---|
| Full Blood Count | Hb 140g/l, PLT 180x 109/l MCV 96 Fl, Neutrophils 2.7x109/l |
| Urea and Electrolytes | Na 141mmol/L, K+ 4.1mmol/L, Urea 4.6mmol/L, Creatinine 45µmol/L, eGFR>90, Adjusted Calcium 2.29mmol/L, Phosphate 1.25mmol/L |
| Clotting | INR 1.2, Prothrombin time 16.2 |
| Liver Function: | Bilirubin: 3µmol/l, Alp:9iu/l, Alt : 93iu/l |
| CRP | 6mg/L |


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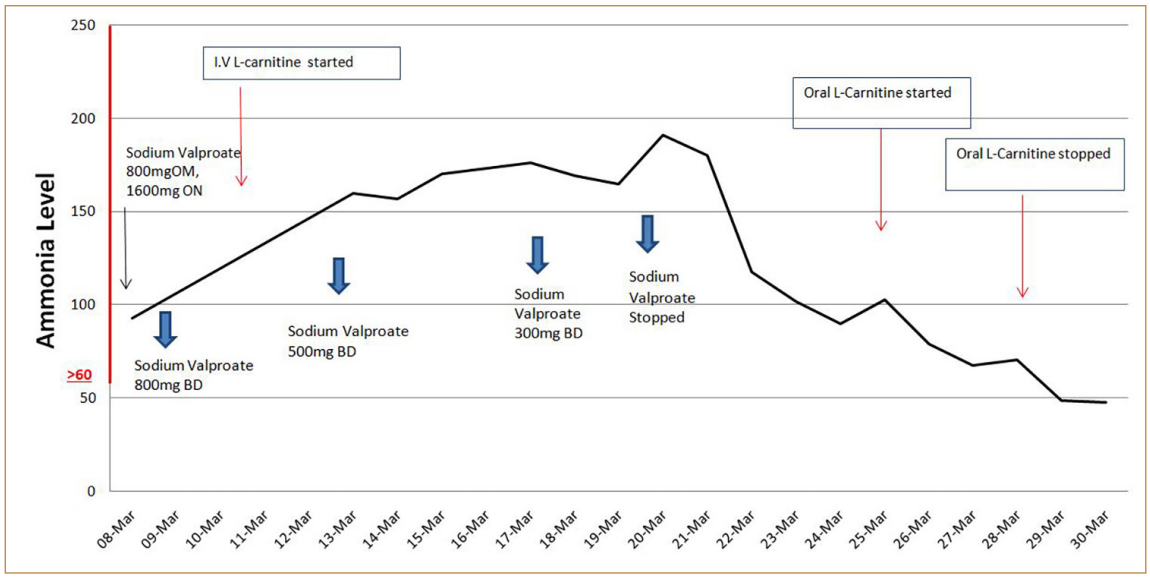


**Figure 1.** Ammonia levels throughout admission, with corresponding changes to medication

umol/L). SVPA level was low at 38 mg/L (normal 50 – 100 mg/L). He was discussed with neurology and pharmacy, and his phenytoin dosing was reduced to 125mg morning and 150mg at night, and SVPA was reduced to 800mg Bd. His ammonia levels still remained elevated, and the patient remained drowsy with a GCS of 13/15.

With the history of alcohol excess, a possible hepatic cause of the raised ammonia was considered. An ultrasound of the liver was normal, and the patients INR and albumin were within normal range, indicating normal liver function. The gastroenterology team reviewed the patient and subsequently felt that liver disease was an unlikely cause. An electroencephalogram (EEG) was consistent with diffuse encephalopathy, and suggested a metabolic cause or possibly relating to his learning difficulties.

After further consultation with neurology and the pharmacy team, he was started on L-carnitine intravenous infusion (6 grams over 24 hours, in 4 hourly infusions of 1gram) for sodium valproate-induced hyperammonaemic encephalopathy. This did not decrease his elevated ammonia levels.

His sodium valproate was reduced to 500mg twice daily, then 300mg twice daily, and eventually completely stopped, resulting in a significant drop in his ammonia levels. This was also clinically reflected in improved cognition and GCS.

He was subsequently switched to an oral maintenance dose of L-carnitine once Ammonia levels were below 100umol/L; this continued for four days and was stopped when the ammonia levels normalised. The patient was now able to have more coherent and appropriate conversations, and had better recall of prior events.

The changes to his medications, with the introduction of L-carnitine, are summarized in Figure 1:

With the SVPA completely withdrawn, he started to have generalised seizures again. He was then started on lacosamide 100mg twice daily, with the dose subsequently increased to 100mg OM and 150mg ON. His lamotrigine was also increased to 175mg twice daily).

Since discharge, he has not required any further admissions. (At the time of writing this had been 7 months)

## Discussion

SVPA is a widely used anti-epileptic medication. It is sometimes as an adjunct in treating mental health disorders, and sometimes also migraines. The potential toxic effects of SVPA have been known for some time, but this is often under-appreciated and described.[1]

The incidence of asymptomatic valproate-associated hyperammonaemia in the general population of patients taking SVPA is not well established but is thought to be common; cross sectional studies suggest a prevalence of 16% to 100%.[2] Elevated ammonia levels are not always associated with symptoms in patients.There is a scarcity of literature regarding the incidence of symptomatic SVPA-associated hyperammonaemia (ie. hyperammonaemic encephalopathy). It is rare, but has been well described in case reports and medical literature.

Patients with hyperammonaemic encephalopathy may present with increased seizure frequency, altered behaviour, vomiting, confusion, erratic behaviour and in rare cases, even death. This can

occur even if liver functions tests are normal and plasma concentrations of valproate are within the normal range. Symptomatic SVPA associated hyperammonaemic encephalopathy has also been described in patients with sub-therapeutic levels of SVPA,[3] as was the case with our patient.

Diagnosis is based on elevated ammonia levels, with typical symptoms. Neuro-imaging is often not helpful, though there are case reports on non-specific MRI findings in some cases.[4,5] EEG is not diagnostic, but may show patterns consistent with generalised encephalopathy.

SVPA has multiple and complex mechanisms of action when used in the treatment of epilepsy. One of its main effects is attributed to the potentiation of GABAergic neurotransmission in specific brain regions. The precise mechanisms remain unclear but sodium valproate has been shown to increase the concentration of GABA in the brain, leading to increased inhibition of the central nervous system.[6,7] This is augmented by SVPA also reducing excitatory neurotransmission via glutamate, via effects on N-metyl-D-aspartate (NMDA) receptors.[8] SVPA also inhibits neuronal voltage-gated ion channels resulting in a reduction in high frequency neuronal firing.[9] Modulation of dopaminergic and serotonergic neurotransmission pathways has also been demonstrated, which may explain the alternative use of Sodium Valproate as a mood stabiliser.[9]

Studies have shown a positive correlation between SVPA concentrations and Ammonia levels in the blood,[10] with carnitine concentrations being inversely related.[11]

Carnitine is an amino acid derivate, and is often sold as an over the counter dietary supplement, purported to have benefits for athletic performance, cognitive impairment, infertility, and cardiovascular disease. It is involved in the transport of fatty acids within the mitochondrial matrix, and also the transport of toxic metabolites out of the mitochondria.[12]

SVPA is hepatically metabolised predominantly via glucuronidation and beta-oxidation, but also to a lesser extent by omega-oxidation. Metabolism via omega-oxidation results in the formation of the toxic metabolite 4-en-valproic acid (4-en-VPA). This metabolite impairs the enzyme carbamoyl phosphate synthetase 1 (CPS1) which is involved in the breakdown of Ammonia in the urea cycle. It is impairment of CPS1 that is thought to lead to raised serum Ammonia levels. In addition, L-carnitine facilitates the transport of not only SVPA but also other fatty acids into the mitochondria for beta-oxidation. Impairment of fatty acid beta-oxidation can lead to a reduction in acetyl-CoA being produced. Acetyl-CoA is in turn involved in the activation of CPS1.[11,13]

High levels of SVPA, either from acute overdose, or chronic use, can lead to reduced L-carnitine concentrations.[11] This results in a reduction in the proportion of beta-oxidation metabolism of SVPA, instead shifting metabolism towards the omega-oxidation route, leading to increased production of 4-en-VPA.[13]

It has also been well documented that the concomitant use of phenytoin and other cytochrome P-450 (CYP-450) enzyme-inducing anti-epileptics, such as phenobarbital and carbamazepine, results in higher levels of Ammonia when taken with SVPA. The exact mechanism of this interaction remains unknown.[14,15]

SVPA is also thought to increase glutamine transportation in the renal mitochondria, which when metabolised to glutamate, produces Ammonia as a by-product, thus leading to hyperammonemia[9].

A potential treatment option for SVPA induced hyperammonaemic encephalopathy is supplementation of L-carnitine. An increase in available L-carnitine allows a metabolic shift back towards beta-oxidation, which reduces the proportion of omega-oxidation that occurs and therefore a decrease in production of 4-en-VPA.[11] In some case reports, L-carnitine supplementation has allowed patients to continue with SVPA.

Haemofiltration within the critical care setting can be used for life threatening situations.[18] Nitrogen scavenger agents such as sodium phenylacetate, benzoate or phenylbutyrate, can also be used,[18] though In practice they are seldom utilised.

Naloxone is another treatment option reported to have beneficial effects on central nervous system depression.[19] The theoretical mechanism of action of Naloxone is due to antagonism of the effects of GABA, and therefore, antagonism of SVPA itself. Whether naloxone also has these benefits in hyperammonaemic encephalopathy is yet to be proven.

There are no consensus guidelines regarding the management of raised ammonia in patients taking SVPA who are asymptomatic. One study has suggested that SVPA should be continued if clinically required, with careful ongoing monitoring of the patient's symptoms and ongoing review for the need to take SVPA.[20]

The most effective treatment for SVPA-induced hyperammonaemic encephalopathy ultimately remains cessation of SVPA as was demonstrated in our case.

In summary, we present a case of SVPA associated hyperammonaemic encephalopathy that was effectively treated by cessation of SVPA. Acute physicians should consider this reversible condition

in all clinical cases of altered consciousness or behavioir in patients taking SVPA, even if the dosage is small, or drug levels are sub-therapeutic. Physicians should also be mindful that hyperammonaemia is commonly associated with SVPA. In the absence of signs or symptoms of encephalopathy, SVPA should not necessarily be stopped.

## Declaration of competing interests

Nothing to declare.

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