Case Report

Severe valproate induced hyperammonemic encephalopathy successfully managed with peritoneal dialysis

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Abstract

Valproic acid (VPA) is a commonly used drug for epilepsy, psychiatric disorders and migraine and is frequently used in neurosurgical intensive care units. Though most of its side-effects are mild and transient, certain idiosyncratic side-effects have been attributed to VPA. Valproate induced hyperammonemia (VIH) is one such side-effect. VIH can produce symptoms of encephalopathy known as valproate induced hyperammonemic encephalopathy (VHE). VIH and VHE usually respond to withdrawal of VPA. However, in some cases VHE can be unresponsive to supportive measures and severe enough to be life-threatening. In such cases, dialysis can be used to rapidly reverse hyperammonemia and VHE and can prove to be a lifesaving measure. We report such a case of VIH and life-threatening VHE in a postoperative neurosurgical patient that was managed successfully with peritoneal dialysis.

Keywords: Dialysis, valproate induce hyperammonemia, valproate induced hyperammonemic encephalopathy, valproic acid

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Introduction

Valproic acid (VPA) is a commonly used drug for epilepsy, psychiatric disorders and migraine and is frequently used in neurosurgical intensive care units. Most of its side-effects are mild/transient and well-tolerated. However, certain idiosyncratic side-effects, unrelated to serum valproate levels, have been attributed to VPA.[1] Valproate induced hyperammonemia (VIH) without associated liver dysfunction is one such side-effect.[1]

Though asymptomatic in most,[1] VIH can present as valproate induced hyperammonemic encephalopathy (VHE) that can be life-threatening. We describe one such case of VHE that was unresponsive to supportive measures, but was successfully managed with peritoneal dialysis (PD). The case is being reported to stress the importance of dialysis as a lifesaving adjunctive measure in such cases.

Case Report

A 35-year-old female patient underwent excision of parietal convexity meningioma. Intraoperative and immediate postoperative periods were uneventful. Patient was on oral VPA (500 mg TDS) preoperatively for past 6 months that was continued postoperatively. Two days after surgery, patient started deteriorating neurologically. Within 24 h, her Glasgow coma score fell from E4V5M6 to E1VtM5 and she required ventilator support. There were no witnessed seizures. Noncontrast computed tomography showed mild edema around operative cavity with no midline shift, mass effect or residual tumor. Electroencephalogram done with a suspicion of nonconvulsive status epilepticus revealed generalized slowing suggestive of metabolic encephalopathy. Biochemical profile revealed normal liver functions, normal serum VPA (90 μg/ml; normal range: 50-100 μg/ml) and very high serum ammonia levels (200 μmol/L; normal range: <33 μmol/L). VPA was stopped and patient started on levetiracetam.

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However, ammonia levels did not fall even 48 h after stopping VPA and she continued to deteriorate neurologically (E1VtM2) and hemodynamically, requiring inotropic support. At this stage, decision to dialyze was taken and PD was started, as the patient was hemodynamically unstable, on two inotropes and unfit to undergo hemodialysis. After 10 cycles of PD, patient started showing signs of improvement and became fully conscious, oriented and off inotropic and ventilatory support after 30 cycles. Serum ammonia levels normalized (10 μmol/L) within 48 h and the patient was finally discharged home without any deficits.

Discussion

Valproate induced hyperammonemia is quite common and its incidence has been reported to be as high as 75% in patients on VPA.[1] VHE, however, is rare though its exact incidence is unknown. In VHE, liver functions are normal unlike hepatic encephalopathy, indicating different mechanisms involved in its pathogenesis.

Pathophysiology

Valproic acid affects both renal and hepatic metabolism of ammonia. In liver, ω-oxidation of VPA produces sodium 2-propyl 4-panteonate (4-en-VPA) and propionic acid. 4-en-VPA stimulates renal glutaminase and increases glutamine uptake and ammonia release. Propionic acid and 4-en-VPA suppress N-acetylglutamate production, which in turn leads to decreased activity of CPS, which consequently affects urea cycle.[2]

Raised ammonia levels in brain inhibit glutamate uptake thereby raising its extracellular levels. Glutamate activates N-methyl-D-aspartate receptors with consequent decreased seizure threshold. There is also increased production and accumulation of glutamine inside astrocytes leading to astrocyte swelling and cerebral edema. Ammonia also conjugates with α-ketoglutarate and depletes it causing a block in Kreb's cycle, thereby damaging the neurons.[3]

Risk factors

Urea cycle disorders, malnutrition, liver disease, chronic VPA intake, concomitant use of other antiepileptic drugs[1,4] particularly, topiramate are certain factors that predispose to VIH and VHE. Though, a positive relation between VPA and ammonia levels has been reported in some studies, others did not find such correlation.[2]

Clinical manifestations

Valproate induced hyperammonemic encephalopathy can manifest as malaise, lethargy, vomiting, cognitive impairment, focal neurological deficits and altered sensorium ranging from drowsiness to coma.[2] The onset of VHE van be acute with rapid neurological deterioration as happened in the present case or subacute. The focal neurological deficits may be unilateral or bilateral and patients may develop seizures.

Treatment

Withdrawal of VPA is primary treatment of VHE. Most patients recover over a period of 2-14 days.[5] Sodium benzoate and sodium phenyl acetate have also been shown to be of benefit.[6] L-carnitine can improve symptoms by decreasing ammonia levels.[7] However, L-carnititne is not universally available.

Dialysis has been shown to have a definite role in the management of acute VPA toxicity.[8] Ammonia is a small molecule (molecular weight of 17 daltons) that is not significantly protein bound, and these characteristics make ammonia easily dialysable. With dialysis, clearance of ammonia is hastened thereby normalization of ammonia levels and reversal of symptoms of encephalopathy can be achieved rapidly.[9] Thanacoody[8] reviewed 31 cases with VPA poisoning/VIH and concluded that hemodialysis should be considered in patients with severe VPA poisoning and severe cases of VIH. Eyer *et al*.[10] described four patients with severe VIH managed with hemodialysis. Tsai and Chen[9] described a case of VIH and VHE in which there was rapid neurological deterioration that responded to hemodialysis and patient recovered completely. Nasa *et al*.[11] in their study have reported a case of severe VPA toxicity and VIH/VHE, nonresponsive to supportive measures. They performed hemodialysis with rapid normalization of VPA and ammonia levels and complete recovery. In present case also, dialysis proved to be a lifesaving intervention as patient had shown rapid deterioration both neurologically and hemodynamically despite the supportive care given to patient. PD instead of hemodialysis was undertaken due to hemodynamic instability. Thus, in addition to supportive care, dialysis should be considered an adjunct in the management of severe VIH and VHE with rapid clinical deterioration, especially when supportive care alone proves insufficient.

Conclusion

Valproate induced hyperammonemia and VHE are potentially fatal consequences of VPA therapy. It should be considered in all patients on VPA who develop neurological symptoms/signs. Though reversible with withdrawal of VPA in most patients, dialysis must be

considered in severe refractory cases, especially those with rapid clinical deterioration that fail to respond to withdrawal of VPA and supportive measures.

References

1. Murphy JV, Marquardt K. Asymptomatic hyperammonemia in patients receiving valproic acid. Arch Neurol 1982;39:591-2.
2. Mehndiratta MM, Mehndiratta P, Phul P, Garg S. Valproate induced non hepatic hyperammonaemic encephalopathy : A study from tertiary care referral university hospital, north India. J Pak Med Assoc 2008;58:627-31.
3. Felipo V, Butterworth RF. Neurochemistry of ammonia. Neurochem Int 2002;41:79.
4. Sewell AC, Böhles HJ, Herwig J, Demirkol M. Neurological deterioration in patients with urea cycle disorders under valproate therapy: A cause for concern. Eur J Pediatr 1995;154:593-4.
5. Ott CA, Campbell N, Dworek EA. Valproic acid-induced hyperammonemia in a patient with schizoaffective disorder. J Pharm Pract 2007;20:82-92.
6. Prietsch V, Lindner M, Zschocke J, Nyhan WL, Hoffmann GF. Emergency management of inherited metabolic diseases. J Inherit Metab Dis 2002;25:531-46.
7. Bohan TP, Helton E, McDonald I, König S, Gazitt S, Sugimoto T, *et al*. Effect of L-carnitine treatment for valproate-induced hepatotoxicity. Neurology 2001;56:1405-9.
8. Thanacoody RH. Extracorporeal elimination in acute valproic acid poisoning. Clin Toxicol (Phila) 2009;47:609-16.
9. Tsai MF, Chen CY. Valproate-induced hyperammonemic encephalopathy treated by hemodialysis. Ren Fail 2008;30:822-4.
10. Eyer F, Felgenhauer N, Gempel K, Steimer W, Gerbitz KD, Zilker T. Acute valproate poisoning: Pharmacokinetics, alteration in fatty acid metabolism, and changes during therapy. J Clin Psychopharmacol 2005;25:376-80.
11. Nasa P, Sehrawat D, Kansal S, Chawla R. Effectiveness of hemodialysis in a case of severe valproate overdose. Indian J Crit Care Med 2011;15:120-2.

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