JPPT | Case Report

Valproate-Induced Hyperammonemic Encephalopathy Following Accidental Ingestion in a Toddler

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Clinical manifestations of valproic acid (VPA) toxicity can range from just mild confusion and drowsiness to serious encephalopathy, leading to depressed sensorium and even coma and death. The exact cause(s) of how VPA influences the integrity of brain function remains unknown. Nevertheless, several mechanisms have been postulated including a surge in the blood ammonia concentration. Valproic acid–induced hyperammonemic encephalopathy is a rare yet serious sequalae and that can lead to grave outcomes. We report a case of hyperammonemic encephalopathy with preserved liver function following a moderate VPA intoxication in a toddler, who was successfully managed conservatively. Additionally, we briefly discuss mechanistic basis of VPA toxicity and highlight some of the available potential therapies.

ABBREVIATIONS CNS, central nervous system; IV, intravenous; VPA, valproic acid

KEYWORDS accidental ingestion; adverse effect; case report; encephalopathy; hyperammonemia; infant; valproic acid

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Introduction

Valproic acid (VPA) is a commonly prescribed antiepileptic therapy with broad-spectrum efficacy.[1] Certainly, VPA is widely used in controlling multiple types of seizures, most notably in treating patients with idiopathic generalized epilepsy,[2] and in managing schizoaffective disorders.[3] Further, VPA is considered a relatively safe therapy because the commonly reported adverse effects are usually mild and transient.[4] Serious adverse reactions are fortunately rare and usually include CNS toxicity.[4] VPA-induced hyperammonemic encephalopathy is a rare variant of CNS adverse effect and has been reported following both early initiation of treatment and in the case of acute overdose, more commonly in patients receiving chronic VPA therapy.[5–7] We present a case of hyperammonemic encephalopathy with preserved liver function in a toddler following an accidental ingestion of VPA. Additional aims are to briefly review the mechanistic basis of VPA toxicity and outline some of the available treatment modalities.

Case

A previously healthy toddler aged 20 months and weighing 14 kg was brought by his mother to the emergency department with a history of slow deterioration in his level of consciousness with poor interaction following an accidental ingestion of 1500 mg of VPA (Depakote 500-mg tablet; SANOFI, Earley, Reading, United Kingdom) 10 hours earlier. The child was admitted where his initial assessment showed depressed sensorium with impaired level of consciousness. A CNS examination revealed areflexia with hypotonia and both pupils were constricted with sluggish reaction to light. The toddler's Glasgow Coma Scale was 9 out of 15. The remainder of his physical examination was unremarkable. Basic investigations including complete blood chemistry and renal parameters were unremarkable. His liver function tests were normal, with the exception of an elevated blood ammonia concentration (see Table). Further, his serum VPA concentration was 150 mg/L (therapeutic range, 30–100 mg/mL).[8] A diagnosis of hyperammonemic encephalopathy with preserved liver function was made. Following admission to the ICU, the child was managed conservatively (nil per mouth, oxygen by mask, vital sign monitoring, serial Glasgow Coma Scale assessment, routine IV fluids and input/output). The child showed a gradual improvement in the level of consciousness before he made full recovery scoring 15 on Glasgow Coma Scale after 36 hours from time of the admission. Serial blood measurements of the ammonia, VPA, and liver parameters were shown in the Table.

Discussion

Valproic acid is widely prescribed treatment for children with a seizure disorder. In relation to the drug's CNS toxicity, 3 forms of encephalopathy have been described in VPA intoxicated subjects.[6] Encephalopathy with a normal blood ammonia concentration, encephalopathy with derangements in liver parameters, and hyperammonemic encephalopathy with preserved liver function was observed in our case described in the

Table. Serial Blood Concentrations of VPA, Blood Ammonia, and Liver Function Tests As Well As Level of Consciousness in a Toddler Who Accidently Ingested VPA

Association With Ingestion	VPA, mg/L	Ammonia, mcg/dL	AST, U/L	ALT, U/L	Bilirubin, mg/dL	GCS, 15
Time of admission: 10 hr after VPA ingestion	150	170	15	29	0.20	9
Time of discharge: 46 hr after VPA ingestion	25	75	16	31	0.25	15
Time of follow-up: 94 hr after VPA ingestion	2	50	20	25	0.30	15

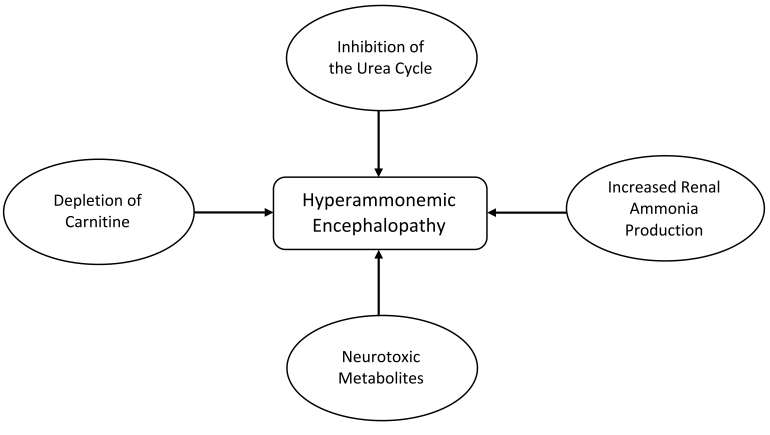
ALT, alanine amino transferase; AST, aspartate amino transferase; GCS, Glasgow Coma Scale; VPA, valproic acid

current report.[9–11] Interestingly, our toddler developed hyperammonemic encephalopathy with almost 100 mg/kg of VPA, which might support the suggestion that children appear more prone for VPA toxicity than adults.[12] Indeed, 1 observation has documented cerebral edema secondary to hyperammonemic encephalopathy with blood ammonia concentration of 279 mcg/dL, in a female newborn aged 28 days who was accidently given 75 mg/kg of VPA.[13] In contrast, adults ingesting more than 200 mg/kg of VPA has been reported to be associated with CNS depression,[14,15] and if more than 400 mg/kg is consumed, can ultimately lead to hyperammonemia and coma.[16]

To date the exact molecular basis for how VPA might increase the blood ammonia concentration with subsequent development of encephalopathy remains unknown, although there are several proposed mechanisms (see Figure). Firstly, VPA reduces the activity of mitochondrial carbamoyl phosphate synthetase-1, the first enzyme in the urea cycle, and thereby interrupting the ammonia detoxification process.[14] VPA also enhances renal production of ammonia by stimulating the activity of renal glutaminase.[3] Further, high doses of VPA can shift the metabolism from β-oxidation to omega-2 oxidation and thereby increase production of several neurotoxic metabolites, particularly 2-propyl-2-pentenoic acid, and that posing detrimental effects on the brain functioning.[14] Additionally, VPA reduces carnitine body stores by decreasing its synthesis and inhibiting its reabsorption by renal tubules.[3]

Although there is no consensus guideline concerning the management of the VPA intoxicated patient, immediate discontinuation of the drug and may be all that is necessary for a positive resolution for most mild to moderate pediatric exposures.[17] This is what we observed in our patient who responded promptly with only supportive interventions. For more severe exposures, repeat dose activated charcoal should be used, when possible, to enhance drug elimination[18] where a number of other treatment options have been described including lactulose, rifaximin, neomycin, and protein restriction for alleviating symptoms of hyperammonemic encephalopathy.[3] Moreover, given the role of carnitine depletion in the pathogenesis of hyperammonemic encephalopathy, levocarnitine supplementation may promote body store repletion augmenting normal VPA metabolism (β-oxidation), and fostering decreases in the blood ammonia concentration.[17–19] Indeed, in a recent case series of VPA intoxicated pediatric patients, it was noted that a dose of 100 mg/kg a day of levocarnitine is a safe and effective regimen in the management of hyperammonemic encephalopathy in

Figure. Mechanistic basis of valproate induced hyperammonemic encephalopathy.[16]



children.[20] Additionally, for very severe cases of VPA toxicity, multiple therapies have been promoted in conjunction with multidose or continuous nasogastric infusion of activated charcoal and that includes diuretics[3] and most importantly use of extracorporeal removal strategies, particularly hemodialysis.[21]

Conclusion

We present a case of acute VPA toxicity in a toddler who developed hyperammonemic encephalopathy with preserved liver function. Routine supportive treatment, including discontinuation of the drug, seems like a key step in treatment of mildly to moderately intoxicated patients; however, continued research is warranted to define improved approaches for the management of pediatric VPA intoxications.

Article Information

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