Valproic acid rechallenge after valproate-induced hyperammonemic encephalopathy

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ABSTRACT

A 24-year-old man with a past medical history of behavioral disturbances and spastic tetraplegia secondary to traumatic brain injury presented to the psychiatry consult service with acute exacerbation of agitation and aggression. The patient's behavioral disturbances were previously reduced with 1500 mg daily of valproic acid (VPA). Prior to admission, VPA was discontinued due to elevated serum ammonia levels of 96 $\mu\text{mol/L}$ and clinical findings consistent with valproate-induced hyperammonemic encephalopathy (VIHE), such as lethargy, confusion, frank delirium, and ataxia. Current guidelines for treating VIHE suggest either a complete discontinuation of the drug or a drug rechallenge with the addition of levocarnitine or carnitine supplementation. In this case, VPA was rechallenged without supplementation to decrease the risk of noncompliance. The patient received a lower dose of VPA with subsequent up-titration. His ammonia level decreased to an acceptable level. This case report discusses the challenges of managing VIHE in patients requiring VPA and discusses opportunities for further research in preventing VIHE.

KEYWORDS Ammonia; carnitine; hyperammonemia; levocarnitine; valproate-induced hyperammonemic encephalopathy; valproic acid

Valproic acid (VPA) is an anticonvulsant and mood stabilizer that is known to cause a host of side effects, including gastrointestinal distress, increased appetite and weight gain, tremor, pancreatitis, neural tube defects, and valproate-induced hyperammonemic encephalopathy (VIHE).¹ VIHE, presenting with lethargy, confusion, frank delirium, blurred vision, seizures, or coma, is most commonly treated by discontinuing the drug and adding a substance to diminish ammonia levels, including lactulose or rifaximin/neomycin; however, current research has proposed mechanisms of prevention, treatment, and maintenance therapy to allow for the continuation of VPA using supplementation of levocarnitine or carnitine.^{2–5} Studies have shown that individuals with a past medical history of VIHE may continue VPA with the addition of supplementation, but continuation of VPA without supplementation in a patient with a past medical history of VIHE has not previously been reported.

CASE DESCRIPTION

A 24-year-old man with a past medical history of behavioral disturbances, spastic tetraplegia, and seizures secondary

to traumatic brain injury was admitted to the hospital for agitation and aggressive behavior. At baseline, the patient was nonverbal, was able to communicate only via an assisted electronic device, and required 24-hour care. The patient also had a history of self-harm and violence toward others. His care had been managed at behavioral health facilities, rehabilitation hospitals for brain injury, and several inpatient admissions for acute, unmanageable exacerbations in behavior. The patient's aggressive behavior was well controlled with VPA 1500 mg orally twice a day.

The patient continued VPA therapy for 2 years until developing clinical symptoms of drowsiness, lethargy, and ataxia consistent with VIHE. His serum ammonia level was 96 $\mu\text{mol/L}$. Liver-associated enzymes were normal at this time. VPA was discontinued and lactulose was added. The patient's unmanageable behavioral disturbances returned after discontinuing VPA. To prevent a resurgence of VIHE, other medications were implemented sequentially, including lamotrigine 100 mg twice a day and quetiapine 100 mg twice a day; risperidone 1 mg twice a day; propofol 40 mg daily and clonazepam 0.5 mg daily; olanzapine 5 mg intramuscularly every 8 h; and lamotrigine 100 mg twice a day and olanzapine 5 mg twice a day. However, no medication

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Received April 1, 2020; Revised May 1, 2020; Accepted May 7, 2020.

Table 1. Serum ammonia levels associated with dosage of valproic acid following previous discontinuation of valproic acid secondary to hyperammonemia

Day after rechallenge	Dosage of valproic acid (mg)	Serum ammonia level (reference, 16-60 mol/L)
Baseline	None	53
1	125 intravenously twice a day	26
2	125 intravenously twice a day	46
3	125 intravenously twice a day	65
4	250 intravenously twice a day	46
5	500 intravenously twice a day	36
6	500 intravenously twice a day	46
62	500 orally twice a day	34

produced the equivalent effects of VPA, and the decision was made to rechallenge the patient with close monitoring.

The patient was initially started on 125 mg VPA intravenously twice a day for 4 days, with up-titration based on clinical symptoms and serum ammonia levels. The patient received 250 mg intravenously twice a day for 1 day and 500 mg intravenously twice a day for 2 days and was discharged on 500 mg orally twice a day. Frequent lab monitoring during this rechallenge showed ammonia levels within normal limits (Table 1). The patient did not show any clinical symptoms of VIHE or complications associated with VPA use. Three months after VPA rechallenge, during a hospitalization for medical complications of spastic tetraplegia, serum ammonia and VPA levels were within normal limits (34 $\mu\text{mol/L}$ and 56.6 $\mu\text{g/mL}$, respectively). The original dosing of 1500 mg orally twice a day, the level at which the patient previously experienced an episode of VIHE, was not considered considering the patient's behavioral disturbances were, once again, well controlled with the current dose of VPA.

DISCUSSION

The traditional model of managing a patient with a history of VIHE includes discontinuing VPA or restarting VPA using supplementation. Previous studies have suggested discontinuation as the primary treatment unless a risk-benefit analysis concludes continuation is warranted with supplementation.^{6,7} However, at present, there have been no cases of a successful retreatment without supplementation. Despite literature suggesting that hyperammonemia would resurface and the patient's risk factor of intellectual disability, his primary caregiver and guardian requested a rechallenge while the patient was hospitalized and could be closely monitored given the excellent response to the medication.^{6,8} On VPA, the patient could communicate reasonably well and ambulate with a walker; he was alert and did not exhibit aggression.

The dosing regimen used on rechallenge is conservative and may have contributed to the outcome (Table 1). Review of the literature suggests a variety of rechallenge regimens, including 200 mg two times a day titrated up to 500 mg two times a day, 1000 mg daily titrated up to 750 mg two times a day, and a 2750 mg divided dose (1250 mg in the morning, 1500 mg at bedtime).^{3,9} While hospitalized, the patient's ammonia level fluctuated moderately (with one notable elevation outside our institution's normal range of 60 $\mu\text{mol/L}$ on day 3 of rechallenge), but thereafter decreased to an acceptable level. The patient completed an additional 3 months of treatment without further elevation outside the normal range and remained asymptomatic.

This successful trial warrants further work on the necessity of levocarnitine or carglumic acid supplementation with VPA rechallenge. Additionally, the dosing strategy of this rechallenge must be considered. This report suggests that if close monitoring of ammonia levels is available, clinicians may consider reinstating VPA without supplementation.

ACKNOWLEDGMENTS

We would like to acknowledge the patient in this study and the network of family members and caregivers who support the patient's treatment. We would also like to thank all of the nurses, counselors, doctors, and clinic staff who worked with this patient.

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