Valproic acid-induced hyperammonemic encephalopathy

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Mrs. C, age 75, is transferred to our inpatient medical/surgical hospital from a psychiatric hospital after presenting with shortness of breath and altered mental status.

Eight days earlier, Mrs. C had been admitted to the psychiatric hospital for bipolar mania with psychotic features. While there, Mrs. C received quetiapine, 400 mg nightly, and an initial valproic acid (VPA) dosage of 500 mg 2 times daily. While receiving VPA 500 mg 2 times daily, her VPA total level was 62 µg/mL, which is on the lower end of the therapeutic range (50 to 125 µg/mL). This prompted the team at the psychiatric hospital to increase her VPA dosage to 500 mg 3 times daily the day before she was transferred to our hospital.

At our hospital, she is found to be in hypoxic respiratory failure secondary to pneumonia. Upon admission, her laboratory data show evidence of infection and anemia and she also has an albumin level of 3.0 g/dL (normal range: 3.5 to 5.5 g/dL). All other laboratory values, including liver enzymes, are unremarkable. She is started on IV levofloxacin. Her previous medications—quetiapine and VPA—are continued at their same dosages and frequencies from her inpatient psychiatric stay.

From hospital Day 3 to Day 6, Mrs. C experiences gradual improvement in her respiratory and mental status. However, on hospital Day 7, she has extreme somnolence and altered mental status without respiratory involvement. Our team suspects VPA toxicity and/or VPA-induced hyperammonemic encephalopathy (VHE).

VPA-induced hyperammonemia

Hyperammonemia can occur in individuals receiving VPA and is most often asymptomatic. However, elevations in ammonia may lead to VHE, which is a rare but serious adverse effect. VHE has been reported early in treatment, in acute VPA overdose, and in chronic VPA use despite normal doses and levels.[1] It also can occur in the absence of

Practice Points

- **VPA-induced hyperammonemic encephalopathy (VHE) is a relatively rare but serious adverse effect.** VHE has been reported with acute and chronic use and can occur with therapeutic VPA levels and in the absence of hepatotoxicity.
- **To decrease the risk of VHE, avoid polypharmacy for patients receiving VPA,** and consider using an alternative agent in patients with urea cycle disorders. Enzyme-inducing antiepileptics, topiramate, and second-generation antipsychotics may increase the risk of VHE.
- **It is important to check ammonia levels in patients who develop altered mental status while receiving VPA,** or those who have had a VPA overdose. If the ammonia level is high, stop the VPA and consider prescribing lactulose or levocarnitine.

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Table

Potential interventions for valproic acid-induced hyperammonemic encephalopathy

Intervention	Rationale	Dosing
Stop valproic acid	Removal of the offending agent. Consistent evidence supports this as an effective first-line intervention	
Lactulose	Enhances removal of ammonia from the blood to the gut, where it is converted to ammonium. This creates an osmotic effect in the colon and promotes removal from the body	20 to 30 g, 3 to 4 times daily
Levocarnitine	Valproic acid can deplete carnitine stores, which is associated with elevated ammonia levels	Start 330 mg 3 times daily Doses up to 1,980 to 2,500 mg, divided 2 to 3 times a day, have been reported in the literature

Source: References 1-3

clinical and laboratory evidence of hepatotoxicity. VHE is associated with significant morbidity and CNS damage. Symptoms of VHE include vomiting, lethargy, and confusion. If left untreated, VHE can lead to coma and death.

Mechanism of VHE. The exact mechanism of VHE is unknown.[1-3] Ammonia is a toxic base produced by deamination of amino acids. The liver eliminates ammonia via the urea cycle.[2] Valproic acid metabolites, propionate and 4-en-VPA, can directly inhibit *N*-acetyl glutamate, which can disrupt the urea cycle, leading to elevated ammonia levels.[3] Long-term or high-dose VPA can lead to carnitine deficiency, primarily by inhibiting its biosynthesis and depleting stores.[4] Carnitine deficiency leads to disturbances in mitochondrial function, causing inhibition of the urea cycle and increasing ammonia. CNS toxicity due to hyperammonemia is thought to be due to activation of glutamate receptors.[3]

Risk factors. Co-administration of other antiepileptic drugs (AEDs) with VPA is a risk factor for VHE.[1,5] This happens because enzyme-inducing AEDs such as phenytoin, phenobarbital, and carbamazepine can increase toxic metabolites of VPA, which can lead to hyperammonemia. Topiramate can also inhibit the urea cycle, leading to increased ammonia levels. Additionally, co-administration of VPA with quetiapine, paliperidone, risperidone, or aripiprazole has been reported to increase the risk of VHE.[1,5] Intellectual disability, carnitine deficiency, low albumin, and abnormal liver function have also been reported to increase the risk of VHE.[1,5]

Diagnosis and management. If a patient receiving VPA is experiencing nausea, fatigue, or somnolence, it is important to check the patient's ammonia level (normal range: 11 to 32 µmol/L) and VPA total levels (therapeutic range: 50 to 125 µg/mL). Consider checking a VPA free level, especially in geriatric patients or patients who have low albumin; the therapeutic range of VPA free is 6 to 22 µg/mL.[3] If the ammonia level is elevated, discontinue VPA immediately (***Table***).[1-3] Clinicians may also elect to prescribe lactulose until ammonia levels return to normal range. Adding levocarnitine may also help, although evidence is limited to small case series or retrospective studies.[3] Currently, there is no known advantage in combining lactulose and levocarnitine to address VHE. Severe cases of

Clinical Point

Check ammonia levels in patients who have nausea, fatigue, or somnolence while taking VPA

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VHE (ammonia levels >400 µmol/L) may require hemodialysis.[1]

Prevention. Strategies to prevent VHE include avoiding polypharmacy, especially concurrent use of enzyme-inducing AEDs and possibly second-generation antipsychotics. Additionally, VPA should not be used in individuals with urea cycle disorders. It is unknown if levocarnitine supplementation is preventive, but this approach has been suggested.[3]

Clinical Point

To prevent VHE, avoid polypharmacy in patients receiving valproic acid

CASE CONTINUED

Mrs. C has several possible risk factors for VHE, including co-administration of quetiapine and VPA, and a low albumin level. A further laboratory workup for Mrs. C reveals a VPA free level of 19 µg/mL (21.1% free), a VPA total level of 90 µg/mL, and an ammonia level of 79 µmol/L, confirming our suspicions regarding VHE. We determine that Mrs. C's altered mental status is likely due her elevated ammonia levels, because the infection had been improving in the days leading up to the sudden, extreme somnolence.

VPA is immediately stopped and Mrs. C receives 1 dose of lactulose. The following day, Mrs. C's mental status improves, and her ammonia levels return to normal. On hospital Day 9, she is transferred back to the psychiatric facility for management of manic and psychotic symptoms.

Related Resources

- Brown LM, Cupples N, Moore TA. Levocarnitine for valproate-induced hyperammonemia in the psychiatric setting: a case series and literature review. Ment Health Clin. 2018;8(3):148-154.
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Drug Brand Names

Aripiprazole • Abilify
Carbamazepine • Tegretol
Lactulose • Enulose
Levocarnitine • Carnitine, Carnitor
Levofloxacin • Levaquin IV
Paliperidone • Invega
Phenobarbital • Luminal
Phenytoin • Dilantin
Quetiapine • Seroquel
Risperidone • Risperdal
Topiramate • Topamax
Valproic acid • Depakene

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