Valproic Acid Poisoning

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CE Earn Up to 7.5 Hours. See page 108.

A 4-year-old girl was brought to the emergency department after her mother had difficulty waking her that morning. In the emergency department, the patient was completely unresponsive, with a blood pressure of 92/60 mm Hg and a heart rate of 82 beats per minute. The patient's mother reported that the child had opened a bottle of valproic acid (VPA) 500-mg tablets the night before and was caught with a tablet in her mouth; she was unclear about how many tablets the child may have swallowed.

VPA is a commonly prescribed broad-spectrum anticonvulsant drug used to treat and prevent various types of seizures. It is also prescribed for migraine prophylaxis and as a mood stabilizer for mania associated with bipolar disorder. VPA intoxication is fairly common. In 2016, close to 8000 cases involving VPA were reported to US Poison Control Centers, with 2305 exposures resulting in moderate to major adverse outcomes and 18 deaths (including cases involving multiple substances).[1]

Pharmacology and Toxicology

VPA is available in different forms, dosages, and formulations, and under different brand names. Although VPA is well absorbed from the gastrointestinal tract, peak concentrations may be delayed for up to 24 hours in the setting of overdose, especially with extended or delayed-release and enteric-coated tablets.[2,3] The exact pharmacologic mechanisms of VPA have not been fully established. Its therapeutic effect is thought to be primarily related to its ability to increase the main inhibitory neurotransmitter γ-aminobutyric acid in the brain.[4]

Toxicity can result from overdose or from chronic, especially supratherapeutic, doses. VPA exerts its toxicity through several mechanisms. First is the extension of its therapeutic effect on γ-aminobutyric acid, leading to excessive sedation.[4] Second, during metabolism, VPA depletes carnitine stores in the liver, leading to carnitine deficiency. Carnitine is needed to metabolize fatty acids.[2,4] This disruption in fatty acid metabolism leads to liver injury and hyperammonemia. Third, VPA also depletes an important coenzyme in the liver.[2,4] This coenzyme is needed for incorporating ammonia into the urea cycle. Its depletion leads to excessive buildup of ammonia, also contributing to hyperammonemia.[2,4]

Clinical Manifestations

The 2 primary effects of VPA toxicity are central nervous system (CNS) depression and metabolic derangements. Patients with a VPA overdose typically present with CNS depression of varying degrees, from lethargy to coma and seizures.[2] Significant CNS depression can lead to respiratory depression and hypoventilation requiring intubation and mechanical ventilation.[2,5] Severe cases may present with hemodynamic instability, namely hypotension, tachycardia, and prolonged QT interval.[2,5]

Metabolic derangements seen in persons with severe toxicity can include anion gap metabolic acidosis, hypernatremia, and/or hypocalcemia.[2,3,5] Hyperammonemia with encephalopathy can occur from an overdose or from chronic therapeutic use of VPA.[2-5] Rare end-organ effects associated with severe toxicity include cerebral edema, pancreatitis, and acute kidney injury.[2] Delayed onset of bone marrow suppression with thrombocytopenia, anemia, and leukopenia, occurring 3 to 5 days after large overdoses, also have been described.[2]

Diagnostic Testing

Serum VPA concentrations are readily available in hospital laboratories and should be obtained for all confirmed or suspected VPA exposures.[2] Because peak concentrations can be delayed in cases of overdose, serial VPA levels should be obtained every 4 to 6 hours until peak and downward trend is established. Therapeutic VPA

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concentrations are 50 to 100 mg/L. VPA-induced hyperammonemia is common in persons who have overdosed as well as with chronic therapeutic use, and thus serum ammonia and liver function should be monitored in all patients. In patients with significant toxicity, blood gases, electrolytes, lactic acid, renal function, and ECGs also should be monitored. For all intentional and/or suicidal cases, common coingestants should always be ruled out initially in the emergency department by obtaining serum acetaminophen, aspirin, and blood alcohol concentrations as well as a urine drug screen.

Management

In the ED setting, the 2 priority management principles for VPA are gastrointestinal decontamination and supportive care. Once the patient is stabilized, antidotal therapy and mechanisms to enhance the elimination of VPA can be considered.

GASTROINTESTINAL DECONTAMINATION

If the patient presents to the emergency department within 2 hours of the ingestion, activated charcoal (AC) can be administered, given that there are no contraindications for its use (eg, the patient is fully awake and alert and there is minimal risk of aspiration). Multiple-dose AC should be considered in overdose cases involving large numbers of enteric-coated or extended-release formulations. AC, whether single or multiple dose, should never be given to patients who have any one of the several contraindications to its use. Contraindications to AC include decreased level of consciousness, compromised airway, ingestion of corrosive substances, and nonintact gastrointestinal tract (eg, suspected obstruction, perforation, or hemorrhage).

SUPPORTIVE CARE

Management of a patient with VPA poisoning is largely symptomatic and supportive.[2,5] Supportive care may be all that is needed to ensure patient safety and recovery. An adequate airway, breathing and circulation must be maintained, and one should treat the patient, not the poison. Patients with a severe case of poisoning who experience significant CNS depression, coma, respiratory depression, or hypotension will require intubation and mechanical ventilation, fluid resuscitation, and/or vasopressors.

ANTIDOTAL THERAPY: L-CARNITINE

Because VPA depletes carnitine stores in the liver, leading to impaired fatty acid metabolism and, in turn, liver injury and hyperammonemia, it is reasonable to consider L-carnitine (levocarnitine) as an antidote for VPA.[2,6] Levocarnitine is an amino acid that plays a vital role in the utilization of fatty acids in the mitochondria. Unfortunately, strong evidence to support its efficacy and routine use in VPA overdose and that substantiates its effect on improved patient outcomes is lacking.[2,6] However, based on the available evidence and because of the known mechanism of VPA-induced hyperammonemia and liver toxicity, it should be considered in patients with hyperammonemia, metabolic abnormalities, hepatic dysfunction, and significantly elevated VPA concentrations (>450 mg/L).[2]

ENHANCED ELIMINATION

In cases of overdose, much of the VPA remains unbound to protein and therefore can be removed by hemodialysis or hemoperfusion.[2,7] Hemodialysis typically is used because it is easier to perform and readily available. Such an invasive procedure should only be performed in the most severely poisoned patients, such as those with marked acidosis and hemodynamic instability refractory to supportive care and antidotal therapy.[2,7]

Case Outcome

The child's initial serum VPA concentration was an impressive 681 mg/L. She was profoundly symptomatic—comatose, hypotensive, and acidemic with an arterial pH of 7.21. She required intubation with mechanical ventilation and a norepinephrine drip. Intravenous L-carnitine was initiated for mild hyperammonemia (peak of 45 mmol/L). Transient transaminitis developed, with aspartate aminotransferase and alanine aminotransferase levels in the range of the 60s (U/L), an elevated creatinine kinase level peaking at 2400 U/L, and electrolyte disturbances (hypocalcemia and hypernatremia). Gastrointestinal decontamination and hemodialysis were not performed. The patient was treated supportively until VPA concentrations declined gradually to 98 mg/L on hospital day 4 (5 days after exposure), at which time she was extubated. The patient made a full recovery and was discharged home on hospital day 7.

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