CLINICAL VIGNETTE

Acute Valproic Acid Toxicity

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Case Report

A 45-year-old male with a history of bipolar disorder and hypertension was brought to the Emergency Department after being found acutely altered at home by his wife. The patient was last seen (normal) 4 to 5 hours before by his wife who discovered the patient laying face down in bed with an empty bottle of divalproex sodium (Depakote®) nearby. His wife reported the patient had been depressed but had not voiced any suicidal ideation.

On ED arrival, the patient was somnolent, but arousable with an intact gag reflex. He was able to state his name and reported taking 20-25 500mg pills of divalproex sodium 3 hours prior to admission, to commit suicide. He denied any complaints other than feeling tired and slightly nauseated. Vital signs included a temperature of 99.3°F, pulse of 79, blood pressure of 118/68, respirations of 14 and a pulse oximetry of 97% on room air. His Glasgow Coma Scale was 4-6-4 (one point subtracted for slightly slurred speech). His pupils were 2mm bilaterally and minimally reactive to light. The remainder of the physical exam was unrevealing including a non-focal neurological exam. ECG was normal.

Bedside glucose was 108 mg/dL and the patient did not respond to nalaxone 0.4 mg and thiamine 100 mg. Head CT revealed no acute pathology. On laboratory evaluation, the patient was found to have a slight metabolic acidosis, AST and ALT of 56 and 68 IU/L, lactate of 2.8 mmol/L, ammonia of 98 mg/dL and a critically high valproic acid level of 212 mg/mL.

A presumptive diagnosis of valproate toxicity was made and the patient was started on parenteral carnitine. Serial ammonia and valproic acid levels were followed. The psychiatry service placed the patient on a hold. The patient's mental status gradually improved back to baseline over 48 hours, accompanied by decreasing valproic acid and ammonia levels. The patient was subsequently transferred to the inpatient psychiatric service and suffered no long-term sequelae from the valproic acid overdose.

Discussion

Valproic acid (VPA), valproate sodium and divalproex sodium are used in the treatment of various seizure disorders, the manic phase of bipolar disorder as well as in the treatment and prophylaxis of migraine headaches. Although the mechanisms through which VPA exerts its therapeutic benefits is not well understood, it is thought that VPA inhibits the degradation and increases the synthesis of g-aminobutyric acid (GABA), an inhibitory central nervous system neurotransmitter[1]. It is this increase in GABA that is thought to account for the anti-epileptic effect of VPA.

Valproic acid is commercially available in immediate-release and delayed-release enteric-coated oral preparations as well as an intravenous preparation. The immediate-release preparations are readily absorbed via the gastric lining and reach a peak plasma concentration within 1 to 4 hours. In contrast, the delayed-release preparations are largely absorbed in the jejunum and take 3 to 5 hours to reach peak plasma levels[2].

VPA has a relatively low volume of distribution (0.1 to 0.4 L/kg) making it amenable to dialysis[3]. However, at therapeutic levels (generally in the range of 50 to 100 mg/mL), 80 to 90% of VPA is highly protein-bound, making it more difficult to remove by dialysis. Fortunately, at supratherapeutic plasma concentrations, the protein-binding sites become saturated and VPA circulates as a largely "free" drug more amenable to removal via dialysis[4].

VPA is metabolized by the liver, largely via glucuronic acid conjugation as well as CYP450 beta- and omega-oxidation, with only 3% of VPA being excreted unchanged in the urine. CYP450 omega-oxidation may become more relevant in the setting of overdose when other pathways are overwhelmed, leading to the formation of numerous metabolites, some of which are biologically active and responsible for the hepatic and neurologic effects seen in VPA overdose. For instance, 2-propyl-2-pentenoic acid (2-EN-VPA) may lead to cerebral edema while 2-propyl-4-pentenoic acid (4-EN-VPA) and propionic acid metabolites may be responsible for hepatotoxicity and hyperammonemia[2].

Valproic acid toxicity may occur both from acute overdose as well as with chronic therapy. Unfortunately, serum levels of valproate correlate poorly with the degree of clinical severity and there is much individual variation in clinical presentation even with similar amounts of ingestion. However, it is generally accepted that ingestions of more than 200 mg/kg and serum levels above 180 mg/mL represent a high risk of toxicity[5].

Toxicity primarily affects the CNS, though hepatic, gastrointestinal and metabolic complications are also seen. CNS symptoms can range from mild drowsiness and confusion to significant encephalopathy and coma resulting from cerebral edema. At toxic levels, the seizure threshold may actually be decreased, myoclonic jerks may be observed and patients may exhibit pupillary meiosis[6].

Gastrointestinal toxicity includes nausea, vomiting and diarrhea. More rarely, acute pancreatitis may be induced. Hepatotoxicity is also noted in both acute ingestion as well as an idiosyncratic response to chronic therapy. This results in minor increases in aminotransferase levels that resolve upon discontinuation of the drug[7].

Since valproic acid is a weak organic acid, significant ingestions may lead to a primary anion gap metabolic acidosis with the gap resulting from unmeasured valproate anions. Other metabolic consequences of valproate toxicity include hypernatremia and hypocalcemia[1].

Hyperammonemia, is often associated with significant ingestions as toxic metabolites of VPA inhibit carbamyl phosphate synthetase, which catalyzes the conversion of ammonia to carbamoyl phosphate in the first step of the urea cycle[8].

Hyperammonemia may contribute to the CNS effects of valproate toxicity and is known as valproate-associated hyperammonemic encephalopathy. Encephalopathy may occur with or without elevations in aminotransferase levels and should prompt the clinician to monitor serum ammonia levels carefully[2].

Fortunately, the complications of VPA-toxicity are largely self-limited and usually resolve with discontinuation of the drug. Mortality rates are exceedingly low and usually result from respiratory compromise in the setting of severe CNS encephalopathy. Therefore, in the vast majority of cases, only supportive care is indicated[9].

As with most ingestions, the first step in treatment should always be evaluation and stabilization of the airway and to assure adequate breathing and circulation by employing advanced cardiac life-support measures. Once these basic steps are completed, attention can be focused on

gastrointestinal decontamination. Since VPA is adsorbed by charcoal, activated charcoal may be given to patients presenting within one to two hours of a significant ingestion[10]. Induced emesis and gastric lavage are not usually employed due to a high complication rate (i.e. aspiration), but may be used if the patient manifests severe symptoms and presents within one hour of ingestion[5].

Due to the delayed absorption of some formulations of valproic acid, serial VPA levels should be drawn every four to six hours until a decline is noted to ensure that peak levels have passed[1].

Hemodialysis and hemoperfusion effectively remove VPA from the circulation[3]. However, given the invasive nature and inherent risks of these procedures, they are often reserved for severely ill patients with hemodynamic instability that has not been responsive to less invasive therapies[3].

L-carnitine may confer potential benefit in VPA-toxicity, especially in the setting of hepatotoxicity, hyperammonemia or significant CNS depression[11]. A small study of L-carnitine in patients with severe VPA-toxicity demonstrated a significant mortality benefit[12]. Moreover, L-carnitine is often used as a prophylactic supplement in those taking valproic acid on a chronic basis in order to prevent hepatotoxicity and hyperammonemia[13]. Although the mechanism of action is not well understood, it is known that VPA ingestion is associated with decreased intrinsic carnitine levels in a dose-dependent fashion[14]. Given the favorable safety profile of L-carnitine, it is currently recommended for patients exhibiting hepatotoxicity, hyperammonemia or significant CNS depression in a dose of 50mg/kg/day divided TID. It is available as either an oral or intravenous preparation[12,15].

In summary, most cases of VPA-toxicity are rather benign and resolve with supportive therapy. However, these patients should be observed carefully as toxicity can be delayed from the time of ingestion and co-ingestions are common. Treatment decisions should be based on clinical presentation rather than isolated VPA levels and may require advanced elimination techniques such as hemodialysis or specific therapies such as L-carnitine. Given the frequency and multiple uses of valproic acid, clinicians should be aware of the presenting signs and symptoms of valproate toxicity.

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Submitted on July 21, 2011