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Clinical Review

VALPROIC ACID OVERDOSE REVIEW OF A CASE WITH ELECTROCARDIOGRAPHIC CHANGES

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☐ **Abstract—Background: Valproic acid (VPA) is increasingly used to treat a variety of medical disorders, such as seizures, psychiatric disorders, and headaches. Therefore, accidental and intentional ingestions with valproic acid are increasing. Objectives: A case is presented in an adolescent with ischemic electrocardiographic changes after an acute overdose with VPA. Discussion: Major features of a valproic acid overdose include respiratory depression, progressive coma, hepatotoxicity, thrombocytopenia, and hemodynamic instability. Electrocardiographic abnormalities usually consist of tachycardia and nonspecific changes. Supportive care is indicated in most overdoses and involves the monitoring and correction of electrolyte abnormalities, coagulopathies, and acid-base imbalances. Treatment may include activated charcoal, naloxone, L-carnitine, and extracorporeal detoxification. Conclusions: Valproic acid overdose is a relatively rare and electrocardiographic changes usually consist of tachycardia and nonspecific changes, but ischemic changes may occur and usually transient and require only recognition.** © 2017 Elsevier Inc. All rights reserved.

☐ **Keywords—valproic acid; overdose; electrocardiogram; ischemic changes**

INTRODUCTION

Valproic acid (VPA) has been used to treat a myriad of medical diseases. It has been used to treat a variety of seizures, ranging from simple and complex absence seizures to complex partial, tonic clonic, and myoclonic seizures (1). It is also used as a mood stabilizer in the treatment of bipolar disorders, schizoaffective disorders, schizophrenia, social phobias, borderline personality disorder, and impulse disorders (2). In addition, off-label uses for this drug are many, and include the management of aggression and agitation in elderly patients with dementia, alcohol withdrawal, personality disorders, catatonia, chorea, cluster headache, prophylaxis and treatment of migraines, neuropathic pain, myelodysplastic disorders, and social phobias (3–6).

According to the Toxic Exposure Surveillance System of the American Association of Poison Control Centers, there were 8,456 human ingestions of VPA reported to the poison centers in the United States in 2009 (7). Children younger than 6 years of age accounted for 776 cases, with only 1 reported death, and it is rarely associated with electrocardiographic (ECG) changes (7). The major manifestation of a VPA overdose includes central nervous system depression, hypotension, respiratory depression, electrolyte and acid–base disturbances (eg, hypoglycemia, hypocalcemia, hypernatremia, hypophosphatemia, and anion gap metabolic acidosis), and hyperammonemia (8–10).

A case is presented of an adolescent with ischemic ECG changes after an acute overdose of VPA with review of the current medical literature.

CASE REPORT

A 16-year-old female presented to the emergency department with an intentional overdose of 20 VPA (250 mg) pills. She denied fever, chest pains, dyspnea, or vomiting.

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Her medical history included bipolar disease. Her medications were VPA, nefazodone, and olanzapine; she had no allergies. She denied cigarette smoking, alcohol, or illicit drug use.

She had a temperature of 37.7°C, blood pressure was 144/82 mm Hg, heart rate was 86 beats/min, and respiratory rate was 18 breaths/min. Her physical examination was unremarkable.

Her white blood cell count was 5,200/mm^3 with 49% neutrophils, hemoglobin 13.0 g/dL, and platelets 345,000/mm^3. Her electrolytes, blood urea nitrogen, creatinine, calcium, glucose, liver function tests, prothrombin time, and activated partial thromboplastin time were normal. Her urine toxicologic and blood alcohol were negative. Her VPA level was 294 μg/mL (therapeutic level 50–100 μg/mL). Her cardiac enzymes were normal. Her 12-lead ECG showed a normal sinus rhythm with ST-segment depression in leads V_4–V_6 and T-wave inversion in V_4–V_6, I, and aVL. Her corrected QT-interval and QRS complex were normal (Figure 1).

Initial treatment included activated charcoal 50 g orally. Over the next few hours, she became less responsive, but easily aroused. Her dextrose stick showed a glucose level of 88 mg/dL. She was hospitalized and monitored closely with no further symptoms. Her ECG findings normalized. She did well and was transferred to a psychiatric facility for further treatment on the following day.

DISCUSSION

VPA is an antiepileptic, antipsychotic, and anti-migraine drug that can cause serious toxicity when taken in higher than normal recommended doses. VPA seems to work by indirectly increasing brain concentrations of the putative neurotransmitter γ-aminobutyric acid (GABA) via several mechanisms, reduces release of γ-hydroxybutyrate, and blocks N-methyl-D-aspartate receptors (11–13). The exact mechanism of anti-seizure activity is unknown. In vitro, VPA enhances the activity of glutamic acid decarboxylase, an enzyme responsible for GABA synthesis (14). It inhibits GABA-transaminase and succinic semialdehyde dehydrogenase, enzymes involved in GABA breakdown. The end result is an elevation of GABA in the synaptic cleft (14,15). It is believed that GABA enhances inward chloride current flow in the postsynaptic neuron, which results in hyperpolarization with decreased responsiveness to epileptiform impulse transmission. In addition to its anticonvulsant properties, VPA has been shown to have morphine-like analgesic properties, which are also believed to be related to increased brain concentration of GABA, or may be a result from stimulation of the enkephalin system (12). This may be responsible in part for the opioid-like central nervous system depression observed in VPA overdoses, as well as mood stabilizing, anticonvulsant, and analgesic properties (16). Naloxone has been shown to reverse the VPA blockade of GABA uptake by cells, thereby, reversing VPA-mediated inhibition of neuronal firing, although the exact mechanism is unknown (17). Naloxone has been shown to displace GABA from its receptors, hence blocking its actions (18). Therefore naloxone may have a role in reversing VPA-induced GABA-mediated central nervous system depression after overdoses. Finally, VPA also alters dopaminergic and serotonergic functions (13).

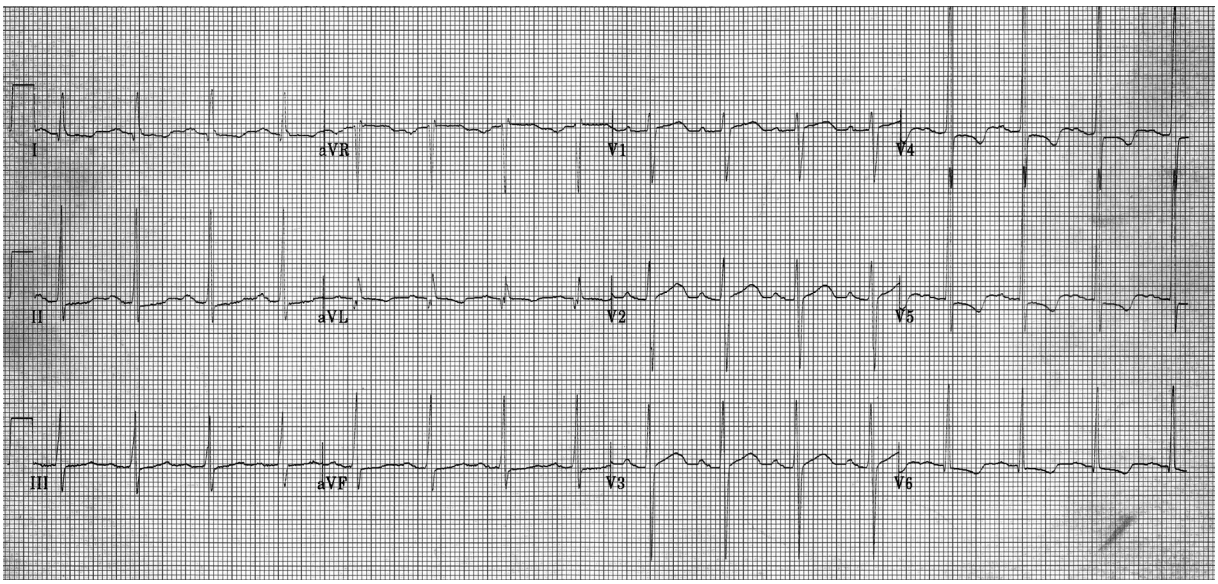

Figure 1. 12-lead electrocardiogram showing a normal sinus rhythm with ST-segment depression leads V4–V6 and T-wave inversions in V4–V6, I and aVL.