Case Report

Approach to Acute Valproic Acid Intoxication: A Case Presentation

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ABSTRACT

Valproic acid (VA) is a broad spectrum antiepileptic that is commonly used in epilepsy, mood disorders and migraine prophylaxis. Although it is not encountered frequently, VA intoxication can be seen during childhood. In VA intoxication, mainly the central nervous system and also liver, heart, kidneys, lungs and hematological system are affected. Since acute VA intoxication can lead to serious complications, and also it may be fatal; the clinical and laboratory follow-up together with early treatment are essential. In this case presentation, we aimed to examine the approach to acute VA intoxication in a case that occurred after ingestion of high dose of VA for suicidal purpose.

Key-Words: Valproic acid, intoxication, mortality, management, L-carnitine

Introduction:

Drug intoxications are common during childhood. Intoxications due to antiepileptics however, are rare. Nonetheless, they may have fatal consequences. According to the 2007 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS), valproic acid (VA) was responsible for 8,461 exposures with 1,835 (22%) requiring treatment in a health-care facility.1

Valproic acid is used in partial and generalized epilepsies, in some childhood age epileptic syndromes (e.g. West, Lennox Gastaut syndrome), and other than epilepsy, in some other neurological diseases like migraine 23.

Following its oral intake, VA is rapidly and almost completely absorbed. Its oral bioavailability is high. Plasma peak concentration is reached after nearly 2 hours. It binds to the plasma proteins in a rate of 90%. It has a half-life of 8–12 hours. It is mainly metabolized in the liver, and the major route of elimination involves glucuronidation. The therapeutic range is 50-100 mg/L. Intoxication signs appear when levels exceed this range.4 5

Symptoms that involve various organ systems may be observed in VA intoxication. Central nervous system suppression, increased frequency of seizures, confusion, lethargy and coma due to brain edema, pancytopenia due to bone marrow suppression, pancreatitis, hepatotoxicity, electrolyte disturbances, metabolic acidosis and hyperammonemia can be seen. 4 7

In this case presentation, we aimed to discuss the current approach to acute VA intoxication by examining a case that ingested high dose of VA for suicidal purpose.

Case Report:

Seventeen years old male case with a bodyweight of 66 kg had ingested 5 boxes (approximately 150 tablets) of a drug with the active ingredient as sodium valproate for the purpose of suicide. One hour after ingestion of the drugs, he developed drowsiness and loss of consciousness. He was taken to emergency service in an external center. On his admission, his Glasgow coma score (GCS) was 8, and he was intubated; gastric lavage and activated charcoal were applied, and he was referred to our hospital for advanced follow-up and treatment. Following his initial examination, the case was admitted to the intensive care unit. In his initial examination, his body temperature was 37°C, arterial blood pressure was 133/77 mmHg, heart rate was 113/min, peripheral oxygen saturation (SpO2) was 96%. In his physical examination, his overall condition was poor, he was unconscious, intubated, and had mydriatic pupils. Cardiac sounds were rhythmic, lung sounds were natural on auscultation and he did not have organomegaly. GCS was 6, pediatric risk of mortality (PRISM II) score was 21(39.3%), pediatric index of mortality (PIM) score was 0.3%. His laboratory results were as follows: hemoglobin: 14.5 g/dL, white blood cell count: 8410/mm3, platelet count: 203000/mm3, glucose: 100

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mg/dL, urea: 45 mg/dL, creatinine: 113 mg/dL, Na: 154 mEq/L, K: 5 mEq/L, Ca: 6.12 mg/dL, AST: 90 U/L, ALT: 33 U/L, LDH: 432 U/L, creatine kinase: 11267 U/L, total bilirubin: 1.3 mg/dL, direct bilirubin: 0.6 mg/dL, troponin: 0.12 ng/ml, ammonia: 735 μg/dL, VA level: 1194 μg/mL, INR: 1.6, PTT: 20.1 sec., aPTT: 74 sec. Chest X-ray, computed tomography of the head, electrocardiogram and arterial blood gases were evaluated as normal.

His treatment consisted of repetitive doses of 0.5 gr/kg activated charcoal administered through nasogastric tube, L-carnitine, vitamin K and calcium gluconate. Hydration was provided with intravenous 0.9% NaCl solution. Due to his unconscious state, high VA level and hyperammonemia, hemodialysis was applied in two sessions each lasting 4 hours. After hemodialysis, his VA level decreased to 139 μg/ml, ammonia level decreased to 72 μg/dl, GCS was 13, and the patient was extubated. On his third day of follow-up, hemoglobin level was 13.2 g/dL, white blood cell count was 2370/mm³, and platelet count was 59000/mm³. Absolute granulocyte count was 800/mm³, therefore granulocyte colony stimulating factor (G-CSF) was administered with a dose of 0.5 mIU/kg. He did not develop any complications in his clinical follow-up, and also his hemogram and biochemical test results returned to normal on the 6th day of hospital stay. The patient was discharged upon complete recovery on the 7th day of his follow-up.

Discussion:

Valproic acid consists of an eight carbon fatty acid that is called dipropylacetate. It reduces reuptake of gamma amino butyric acid (GABA) from the synaptic cleft by inhibiting GABA transaminase, and shows its action by increasing GABA concentration in the synaptic gap. Additionally, it shows antiepileptic effect by blocking voltage-activated Na channels and altering thalamic Ca circuits⁴,⁵. It is mainly metabolized in the liver, and major elimination route is glucuronidation. Carnitine is used during oxidation of VA. The enzyme carbamoyl synthetase 1 is responsible of addition of ammonia into the urea cycle. Carnitine is the activator of carbamoyl phosphate synthetase 1 whereas VA is the inhibitor of this enzyme. If there is no adequate carnitine, activation of carbamoyl synthetase 1 stops, and ammonia cannot be incorporated into the urea cycle. This results in accumulation of ammonia in plasma (10). Our case had a blood VA level of 1194 μg/mL, and blood ammonia level of 735 μg/dL. His unconsciousness was associated with hyperammonemia and high VA levels.

Symptoms that involve various organ systems may be observed in VA intoxication. Central nervous system suppression, increased frequency of seizures, confusion, lethargy and coma due to brain edema, pancytopenia due to bone marrow suppression, pancreatitis, hepatotoxicity, electrolyte disturbances, metabolic acidosis and hyperammonemia can be observed⁶. At the time of his presentation, our case had rhabdomyolysis, central nervous system suppression, hyperammonemia, hypocalcemia, and on his 4th day of follow-up he had bicytopenia. Decreased intestinal calcium absorption due to VA is thought to be responsible for pathogenesis of hypocalcemia⁷. Hypocalcemia that is thought to arise due to drug action was corrected by fluid and electrolyte replacement.

Supportive treatment is the primary option in VA intoxication. Airway should be maintained, and patients should be monitored to avoid fluid, electrolyte and acid-base disturbances and coagulation disorders, and treatment should be initiated as required. Benzodiazepines should be preferred in cases that develop seizures. Gastric lavage and repetitive activated charcoal administration performed at the first hour following oral VA intake can help to reduce blood VA levels by decreasing absorption of the drug⁸,⁹. Our case had central nervous system suppression; therefore he was intubated, and gastric lavage and repetitive doses of activated charcoal were applied.

Valproic acid is a low molecular weight, hydrophilic drug that can be bound to plasma proteins to a great extent¹⁰. However, as its blood levels increase, its protein binding rate decreases¹¹. Hemodialysis has been shown to increase VA elimination, and improve mental state and cardiac functions¹². For this reason, hemodialysis can be useful in acute intoxications and particularly in patients with high blood VA levels. Besides hemodialysis, hemoperfusion and hemofiltration among other extracorporeal methods are used for treatment purposes in VA intoxication. These methods are particularly recommended in cases with rapidly
deteriorating clinical conditions, disturbed hepatic functions, still ongoing drug absorption and blood VA levels exceeding 1000 mg/L. Our case had a blood VA level of 1194 mg/L, and ammonia level was 735 μg/dl. Since his clinical condition deteriorated rapidly, one session of 4 hour-hemodialysis was performed. After hemodialysis, his mental state improved, and blood VA and ammonia levels decreased.

In conclusion, since acute VA intoxication can lead to severe complications, clinical and laboratory follow-up together with early treatment is essential. In addition to supportive treatment in VA intoxication, extracorporeal methods and L-carnitine administration may be used as a supportive treatment approach in cases with rapidly deteriorating clinical condition, hyperammonemia and still ongoing drug absorption.

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