L-Carnitine Treatment In Acute Valproic Acid Intoxication: Case Report

Akut Valproik Asit İntoksikasyonunda L-Karnitin Tedavisi: Olgu Sunumu

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ABSTRACT

Valproic acid (VPA) is a widely used drug with various indications (psychiatric disorders, epilepsy, migraine etc.) and it has been used in many cases of suicide attempts. VPA intoxication may cause electrolyte imbalances, hepatotoxicity, pancreatitis, bone marrow suppression, and brain edema. The most common finding in VPA intoxication is coma and respiratory depression as a result of central nervous system suppression. Case reports emphasize that the efficacy of L-carnitine and various extracorporeal elimination techniques like intermittent hemodialysis or continuous renal replacement therapies in the treatment of VPA intoxication. In this report we present the case of a 34 year old female with VPA intoxication who was successfully treated with L-carnitine.

Keywords: valproic acid, L-carnitine, hemodialysis, drug abuse

Introduction

VPA is a drug that is frequently used for reasons such as psychiatric disorders, epilepsy and migraine, and the incidence of intoxication increases as its use becomes widespread (1). It may reach toxic blood levels even at treatment doses (2). The VPA therapeutic serum level is between 50 - 100 mcg / mL. It has toxic effects at daily doses above 1800 mg and serum levels above 100 mcg / mL (3). The most common finding of intoxication is central nervous system depression and may range from mild dizziness to coma. In addition; acute respiratory distress syndrome, acute renal failure, heart block, pancreatitis, thrombocytopenia, anemia, leukocytopenia, elevation in liver enzymes, hyperammonemia, metabolic acidosis, hypernatremia and hypocalcemia may occur (4).

VPA is metabolized mainly via glucuronic acid conjugation, mitochondrial beta-oxidation and cytosolic omega-oxidation by the liver (5). L-carnitine also contributes during VPA oxidation. Carbamoyl synthetase 1 is the enzyme responsible for adding ammonia to the urea cycle. L-carnitine is a carbamoyl phosphate synthetase 1 activator and VPA is an inhibitor of the same enzyme. It causes ammonia accumulation in plasma (6). The neurotoxic effects of the metabolite due to oxidation of the drug in the liver and the direct toxic effect of hyperammonemia on neurons have been reported to occur in 48-72 hours after the...
drug intake. The presence of hyperammonemia is also responsible for the development of stupor, coma and seizures (7-9). Spiller et al. reported that coma developed in all patients with serum VPA levels of 850 mcg / mL (10).

There is no specific antidote for VPA. While supportive treatment is the main goal, extracorporeal methods and L-carnitine can be used to accelerate the healing process. L-carnitine treatment has an important role in protection from hepatotoxicity and the reversal of coma due to VPA intoxication (11). As a result, L-carnitine has been considered as a potential antidote to restore mitochondrial function, reduce the production of toxic metabolites, and counter or reverse the toxic effects of VPA (12).

In this case report, we wanted to share our experience of L-carnitine treatment in our patient who received VPA for suicidal purpose.

Case Report

A 34-year-old woman, with a prior medical history of epilepsy was found unconscious after taking 90 tablets of VPA 500 mg for suicidal purpose and brought to the emergency department. During the initial evaluation in the emergency department, her blood pressure 113/71 mmHg, respiratory rate 18 / min, heart rate 97 / min, fever 36.3°C, oxygen saturation 93% were recorded. In the arterial blood gas analysis pH: 7.38, pCO2: 40 mmHg, pO2: 84 mmHg, HCO3: 16.9 mEq / L, lactate level: 4 mmol / L were recorded. The patient’s complete blood count and biochemistry panel had no abnormal value except mild anemia. The patient was somnolent and Glasgow Coma Scale (GCS) was 13 (E3M6V4). Contrast-free brain tomography was normal. A nasogastric tube was inserted, and gastric lavage was performed. Then activated charcoal was given at a dose of 1 mg / kg through the nasogastric tube. The patient was intubated due to regression GKS score from 13 to 8 and occurrence of respiratory depression during follow-up and admitted to intensive care unit. The serum VPA level was reported 386 mcg / mL which is a toxic level. Since the patient’s measured ammonia serum level was 151 mcg/mL (reference level is 18,7 - 86,9 mcg/ dl), intravenous (IV) L-carnitine infusion was started at a dose of 100 mg / kg 30 min IV loading dose and 15 mg / kg 6x1 maintenance treatment was applied until the patient was conscious. We saw that the serum level of VPA and ammonia were started to decrease fourth hour of L-carnitine treatment. With this treatment, serum VPA and ammonia levels were decreased to 50 mcg / mL and 61 mcg / dl respectively at the end of the first day. L-carnitine administration was terminated after normalization of the ammonia level. The patient regained consciousness on the 16th hour of hospitalization and was extubated. On the second day of follow-up, electrolyte imbalance occurred. Serum calcium and potassium levels were respectively 6,43 mg/dl, 2,77 mg/dl. Serum electrolyte levels were monitored at regular intervals. The patient was given calcium gluconate and potassium chloride replacement until the Ca++ and K+ reference value were reached. The patient’s vital signs were stable on the 3rd day of hospitalization, she did not have any problem in the blood count and biochemistry panel and she was discharged with psychiatric outpatient follow-up suggestion.

Discussion

In this report we present a case of VPA intoxication with neurological involvement after VPA overdose. Valproic acid overdose is usually well tolerated. Intoxication generally results in mild central nervous system (CNS) depression, but serious toxicity and death have been reported (5). The patients who ingest more than 200mg/kg VPA and/or have plasma concentrations greater than 180 μg/mL usually develop severe CNS depression (4). In our case, the patient took 90 tablets of VPA 500 mg and serum levels taken 2 and 10 hours after ingestion were very high (resp., 386 mcg / mL and 368 μg/mL). At the time of admission to the emergency room her GCS was 13 and regressed to 8 in two hours. Other clinical manifestations of severe VPA intoxication include hypotension, respiratory depression, bone marrow failure (thrombocytopenia and leukocytopenia), tachycardia, tremors, myoclonus, hypoglycaemia, seizures, hyperammonemia and electrolyte imbalance (4). Spiller et al. (10) demonstrated that thrombocytopenia occurred with valproate concentrations >450 μg/mL. Our patient showed, tachycardia, hypoglycaemia, hypokalemia, hyperammonemia, leukocytopenia (2,3 103 / ul) and thrombocytopenia (134 103 / ul) in the intensive care follow-up period compatible with VPA intoxication.

Management of acute VPA intoxication is mainly supportive; early charcoal application, serum electrolytes, blood gas and haemodynamic monitoring. Interventions may involve blood pressure support with intravenous fluids and vasopressors, as well as correction of electrolyte abnormalities or acid-base disorders. Mechanical ventilation may be necessary in patients who require airway protection or who develop cerebral oedema or respiratory depression (10). Hemodialysis can be considered in cases with deep coma, acidosis, severe renal failure, and VPA serum level > 1000 mcg / mL (13). VPA is highly protein bound, and saturation of available binding sites usually occurs when blood levels reach 90–100 μg/mL. Therefore, there can be very high serum levels of free VPA and its metabolites circulating in the blood stream that can be easily removed by hemodialysis with resultant reversal of the severe metabolic abnormalities seen in VPA toxicity (14,15). In addition, L-carnitine treatment can be used in selected patients with hemodialysis (16). In our patient, we preferred to use L-carnitine because VPA serum level was less than 1000 mcg / mL and control serum level after L-carnitine treatment was decreased compared to the previous value. Various extracorporeal techniques for managing VPA toxicity have been described, but none has prevailed as standard therapy (15).

L-carnitine treatment has been shown to be effective in protecting hepatotoxicity, reversing coma, and effectively reducing ammonia levels (5,10,11). Published evidence of the efficacy and safety of L-carnitine as an antidote for acute VPA intoxication is limited. L-carnitine has been shown to be generally safe and effective in retrospective trials and case reports (5,12,17-19). The safety of L-carnitine administration in VPA overdoses, was evaluated in a retrospective study. The authors concluded that L-carnitine can be safely administered in patients with VPA toxicity who have hyperammonemia (13). Borbath et al. described the successful use of L-carnitine in a 51-year-old woman who developed VPA...
induced hyperammonemic encephalopathy after receiving VPA 10 mg/kg i.v. daily to prevent seizures after neurosurgery (20). Perrott J et al. reported that based on the available evidence, it is reasonable to consider L-carnitine for patients with acute overdose of VPA who demonstrate decreased level of consciousness. They recommend intravenous administration of L-carnitine by infusion thereafter, continuing until ammonia levels are decreasing and the patient demonstrates signs of clinical improvement or until adverse events associated with L-carnitine occur (17).

In our case, liver enzymes were normal, coma and respiratory depression were occurred. Cerebral edema findings like shift, loss of cerebral sulcus ect. were not detected in brain tomography. The patient’s somnolent was thought to be due to hyperammonemia and high VPA serum level. Then intravenous L-carnitine infusion was applied until normalization of ammonia level and consciousness. Although there is no definitive application in the treatment protocol, there are also patients who are administered 50 mg/kg/day (16). In our case, consciousness was opened with L-carnitine treatment. VPA and ammonia levels had a tendency to decrease and there was no need for dialysis.

**Conclusion**

In this case, VPA intoxication was treated with L-carnitine and supportive treatment. The patient recovered rapidly from coma. L-carnitine administration may be an alternative or supportive treatment choice in patients with hyperammonemia and high serum VPA levels.

**References**