Case Report
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L-Carnitine Treatment in a Child With Valproic Acid Intoxication

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Abstract

With its growing application in neurological and psychiatric diseases, valproic acid overdose due to acute and chronic use has been causing emergency admission. Asymptomatic cases of hyperammonemia may be found in valproic acid poisoning ranging from central nervous system depression to coma. While supportive therapy is adequate, in most cases active charcoal, levocarnitine supplementation, and treatment with naloxane and hemodialysis, when needed, can also be used. In the case study reported in this paper, we aimed to focus at bringing awareness to the use of levocarnitine in asymptomatic patients with valproic acid poisoning accompanied by hyperammonemia.

Keywords: hyperammonemia, intoxication, L-carnitine, valproic acid

Introduction

Valproic acid (VPA) is an antiepileptic drug frequently used for pediatric epilepsy. Due to its narrow therapeutic range, its use might result in intoxication or overdose. The clinical feature of acute and chronic VPA intoxication is usually idiosyncratic; most cases have hyperammonemia without hepatic failure, leucopenia, pancreatitis, alopecia, and thrombocytopenia[1]. The most common symptom of acute poisoning is central nervous system depression, which can progress to loss of consciousness. Mild cases might present with coma, hemodynamic instability, cerebral swelling, bone marrow depression, multiple organ dysfunction, and death [1-3]. Levocarnitine (L-carnitine) can decrease the production of the toxic metabolites of VPA, and early infusion of L-carnitine may prevent severe complications related to VPA intoxication[4-5]. In this paper, we discuss a case report of a child with VPA intoxication, presenting with asymptomatic hyperammonemia at admission and treated with L-carnitine.

Case Report

A 3-year-old boy with a 2-year history of epilepsy was admitted to our pediatric emergency department due to accidental exposure to VPA suspension (approximately 100 cc). During the initial evaluation, his vital signs were normal, his blood gas analysis pH was 7.35, pCO2 was 35.6 mm/Hg, pO2 was 32.5 mm/Hg, HCO3 was 19.2 mEq/L, and lactate level was 2.4 mmol/L. The biochemistry and complete blood count results were within the normal limits six hours after admission to the emergency department. The patient was lethargic and his Glasgow Coma Scale (GCS) was 13. Activated charcoal was given at a dose of 0.5 mg/kg through the nasogastric tube. The patient was transferred to the pediatric intensive care unit. The serum VPA level was 235.1 mcg/mL (50–100 mcg/mL), which is a toxic level. The serum ammonia level was 103 mcg/dL. Intravenous L-carnitine infusion was started at a dose of 100 mg/kg/ day until the patient was conscious. We observed that the serum level of VPA ammonia started to decrease after 48 hours of L-carnitine treatment. Six hours after starting the L-carnitine infusion, the patient's GCS was 15 and the ammonia level decreased to 93.4 mcg/dL. However, 12 hours after the first infusion of L-carnitine, the ammonia level increased from 93.4 mcg/dL to 151 mcg/d. Thus, we continued the L-carnitine treatment, which was terminated 60 hours later when the ammonia level was normal. On the 3rd day of hospitalization, the patient was discharged from the intensive care unit and discharged form the hospital on the 5th day of hospitalization.

Discussion

VPA is an antiepileptic drug that is widely used to treat a variety of neurological and psychological conditions. The

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range for a VPA therapeutic dose is narrow and the drug is commonly used for epilepsy treatment in children; however, some metabolic diseases can increase the efficacy of VPA doses worsening a patient's clinical symptoms[2]. In the case reported in this paper, the patient's medical history showed that he had been followed up for 2 years with a diagnosis of epilepsy, although he did not have a metabolic disease. VPA produces metabolites by mitochondrial B oxidation and cytosolic omega oxidation[3]. Some side effects of VPA are not dose-dependent; toxic effects can be observed at a daily VPA dose >1800 mg and blood levels >100 µg/mL[6]. VPA is metabolized in the liver via beta-oxidation, omega oxidation, and glucuronic acid conjugation[4]. VPA inhibits carbamoyl synthetase 1 enzyme, which impacts the ammonia urea cycle; in contrast, L-carnitine activates this enzyme. It decreases the ammonia level in plasma[5]. In the case presented in this paper, after admission to the emergency department clinic, the patient was asymptomatic but had a high serial serum VPA and hyperammonemia. Six hours later, the patient's lethargy and Glasgow Coma Scale (GCS) had decreased. Even if a patient is asymptomatic, the serial serum VPA level should be obtained. Ingels et al.[7] reported that 15% of patients who eventually developed toxic levels of VPA had a normal VPA level upon hospital admission. We used an L-carnitine infusion early on in the treatment process. The patient's ammonia concentration decreased to a normal level 60 hours later. These early treatments may prevent hepatotoxicity and VPA-induced hyperammonemia. If a significant VPA serum level is observed, L-carnitine may also be given to patients with asymptomatic hyperammonemia, since no randomized studies have evaluated the L-carnitine treatment dose, especially children. In this patient, 100 mg/kg L-carnitine infusion was administered until the ammonia levels were normal.

According to some clinical studies reporting cases of VPA-related severe hepatotoxicity, survival increased with early intravenous L-carnitine supplementation[4-5]. In the literature, L-carnitine supplementation has been reported to be effective in returning metabolic abnormalities and lowering hyperammonemia[6]. Although most VPA intoxication cases progress asymptomatically, it can result in multiorgan involvement, especially cerebral edema and central nervous system and respiratory depression, which can advance to coma. VPA intoxication can also result hypotension, tachycardia, and hyperthermia, and laboratory changes, such as hyperammonemia, high anion aperture metabolic acidosis, hypernatremia, and hypocalcemia. In our case, ammonia was 103.1 µg/dL (27.2–102 µg/dL) and VPA level 235.1 µg/ml (50–100 µg/ml); no abnormalities were detected in other laboratory tests.

Serum VPA level is not always correlated with toxicity. Cases of coma with normal serum VPA levels have been reported, possibly due to hyperammonemia or VPA metabolites that cannot be measured in serum[3]. In our case, the patient was evaluated asymptomatically and after a six-hour follow-up lethargy was observed; thus, we started an L-carnitine infusion. Complications due to L-carnitine treatment were prevented, as no similar symptoms were observed during follow-up. The majority of VPA is taken orally and absorbed from the gastrointestinal tract, reaching the plasma peak concentration within six hours. Although VPA is highly bound to plasma proteins, this rate decreases as the blood level exceeds 300mg/L[2]. Ghannoum et al.[8] reported high plasma VPA levels, shock table, cerebral edema, and respiratory depression development, and high gas anion gap metabolic acidosis was indicated as a hemodialysis indication VPA intoxication. in Since we did not observe these in our case, hemodialysis was not performed. In symptomatic cases, L-carnitine can be loaded in 30 minutes with a maximum dose of 6 mg at a dose of 100 mg/kg intravenously. After loading, maintenance therapy should be started at15 mg/kg, 4–6 times/day. Oral L-carnitine is administered in asymptomatic cases[9]. In our case, although the patient was initially asymptomatic, after six hours, lethargy developed so intravenous L-carnitine treatment was given due to the increase in ammonia values, and consciousness was restored with the L-carnitine treatment. The patient's VPA and ammonia levels tended to decrease. While high ammonia values were detected again 12 hours after starting L-carnitine treatment, they were in the normal range 60 hours later. If hyperammonemia is observed in pediatric patients who are asymptomatic upon admission and showing mild clinical symptoms of VPA intoxication, serious complications can be prevented by early L-carnitine infusion. Although VPA intoxications are usually asymptomatic, serious clinical results may occur. Early intervention reduces mortality and morbidity and protects against the need for interventional procedures, such as hemodialysis. Although hemodialysis is a successful treatment option, L-carnitine may be an alternative or supportive treatment approach in these patients.

Conclusion

Hyperammonemia is observed in pediatric patients who are asymptomatic upon admission and showing mild clinical symptoms of VPA intoxication. Serious complications can be prevented using an early treatment of L-carnitine infusion.

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