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CASE REPORT

The Role of Levocarnitine in the Management of Valproic Acid Intoxication: A Case-Based Review

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ABSTRACT

The administration of L-carnitine to patients with VPA intoxication and CNS depression with normal ammonia concentrations has a rationale, on the grounds that it is a safe compound with no severe adverse effects reported. Herein, we present a case of valproate poisoning with normal ammonia levels and discuss about the therapeutic as well as the prophylactic potential of L-carnitine administration in such cases.

INTRODUCTION

Levocarnitine (L-carnitine) has been successfully administered in valproic acid (VPA) intoxication cases, especially to patients experiencing hepatotoxicity and/or hyperammonemic encephalopathy[1]. Herein, we present a case of a fifty-eight years old female patient with valproate poisoning, central nervous system (CNS) suppression, but normal serum levels of ammonia.

CASE PRESENTATION

A fifty-eight years old female patient was admitted to the hospital due to decreased level of consciousness. Suffering from bipolar disorder, she was treated with VPA as a mood stabilizer. The VPA serum concentration was high: 290 mg/L (normal range: 50-100 mg/L), but she had normal ammonia levels, i.e. 47,10 μmol/L. A steady decline of VPA levels was observed. In particular, four hours after admission, the VPA levels were 271 mg/L and twelve hours later 128 mg/L, respectively. Other abnormal laboratory findings were metabolic acidosis and hypernatremia. The patient's mental status rapidly progressed to coma with anisocoria due to cerebral edema, although no herniation was observed in computed tomography of the brain. Apart from the supportive care, such as the administration of intravenous fluids, gastric evacuation and activated charcoal, naloxone was administered to her, without any remarkable neurological improvement. Despite the fact that she hadn't had elevated liver enzymes or ammonia levels, L-carnitine was administered intravenously. Based on previous knowledge,

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TABLE 1. Evidence from human studies regarding the utility of L-carnitine supplementation in VPA toxicity.

Study, year	Human studies			
	Study Population	**Clinical Presentation**	**L-Carnitine supplementation**	**Remarks**
Bohles et al, 1996[15] PMID: 8740302	Sixty-nine children and young adults, among who, 24 had hyperammonaemia	Monitoring. As their clinical condition was not described	1g/d *per os* for 2 months	Reduction in serum ammonia levels. The authors conclude that they cannot be certain that L-Carnitine supplementation may lower the risk of developing a Reye-like syndrome
Ishikura et al, 1996[16] PMID: 8837953	A 16 months old male child	Coma	*Per os* for 4 days through gastrointestinal tube	The child improved and was discharged at day 8 after his admission. No neurological sequelae neither any hepatotoxicity
Murakami et al, 1996[17] PMID: 8681902	A child	Non-hypereammonaemic coma	For 3 days	The child was comatose for three days, but recovered thereafter. No liver dysfunction nor hypeammonaemia was reported
Borbath et al, 2000[18]	A 51 y.o. female patient	Hyperammonaemic coma	100mg/Kg/d *iv* for 4 days	Serum ammonia levels rapidly decreased and her clinical condition improved
Minville et al, 2004[19] PMID: 15120780	A 36 y.o. male patient	Coma	50mg/Kg/d iv for 4 days	The patient improved and recovered without any neurological sequelae. He also received haemodialysis
Hantson et al, 2005[20] PMID: 15647953	A 47 y.o. male patient	Hyperammonaemic coma	100mg/Kg/d iv for 4 days	The patient remained comatose for three weeks, even though the serum ammonia levels returned to normal within four days
Temel et al, 2013[11] PMID: 23762657	An 18 y.o. female patient	Coma	50mg/kg/d iv for 3 days	The patient recovered after two days. She also received haemodialysis
Maldonado et al, 2017[6] PMID:	A 42 y.o. female patient	Increased frequency of seizures and gastrointestinal disturbances	1g/d *per os* for 2 months	Reduction in serum ammonia levels. Continuation of VPA treatment with better control in the patients' seizures
Tichelbacker et al, 2018[10] PMID: 30148132	A 46 y.o. female patient	Hyperammonaemic coma. She was intubated	100mg/Kg iv as a loading dose and 500mg/Kg afterwards after 8 and 16 hours for one day	Her laboratory tests as well as her clinical condition improved and she was extubated 12 hours after the intubation. She also received haemodialysis
Venkata et al, 2021[21] PMID: 34336460	A 57 y.o. male patient	Hyperammonaemic coma. He was intubated	2g as a loading dose and afterwards 1,625mg every 4 hours for one day	Rapid improvement of the patients' clinical condition and laboratory tests. He was extubated on day three after admission. He also received haemodialysis

Abbreviations: d: daily; L-Carnitine: Levo-Carnitine; VPA: Valproic Acid; y.o.: years old.

L-carnitine's loading dose is 100mg/kg iv (maximum dose 6g) followed by 50mg/kg given every 8 hours. The patient's level of consciousness gradually improved, and anisocoria was resolved. However, she was subsequently intubated due to severe aspiration pneumoniae and respiratory distress, but thereafter, she successfully recovered and remained well.

DISCUSSION

Over forty years of VPA's clinical use, many adverse effects have been reported. Some of them include bone marrow suppression, hepatotoxicity, hyperammonemia, hypoglycemia, hypotension, pancreatitis and neurological symptoms, such as myoclonus, tremors, miosis, agitation and seizures. The most important clinical manifestation of valproate overdose is encephalopathy and CNS depression[1]. The severity of such cases mainly depends on VPA plasma concentration. Levels higher than 450μg/ml usually lead to severe toxicity, CNS depression, coma and potentially death. Hyperammonaemic encephalopathy can be accompanied (or not) by liver dysfunction. However, VPA intoxicated patients with encephalopathy, but normal ammonia levels have been also reported, such as the case presented above.

L-carnitine, the active isomer of carnitine, is thought to be the optimal agent for VPA poisoning management. Indication for its use seems to be hyperammonaemic-induced encephalopathy[1,2]. Although, based on various reports, it may be helpful in cases of extremely high VPA total plasma concentration (>450μg/ml) or coma without hyperammonemia. Furthermore, it may be useful for hepatotoxicity associated with VPA use[1,2]. Based on previous case reports, the loading dose of L-carnitine is 100mg/kg, but not greater than 6 gr, followed by 50mg/kg iv given every 8 hours until clinical improvement occurs. It can be orally administered to patients with complications due to chronic use of VPA[1,2]. L-carnitine can be given to both adults and children with safety. No severe adverse reactions have been observed, as anaphylaxis is extremely rarely reported (Table 1).

The relationship between VPA and carnitine deficiency is well described. VPA is metabolized via glucuronic acid conjugation (50%) and beta oxidation (40%). Beyond L-carnitine administration and supportive care, such as intravenous fluids administration, gastrointestinal decontamination and use of activated charcoal, many other therapeutic measures have been proposed[1,2]. Naloxone has been suggested for patients with VPA poisoning and CNS depression. The optimal dose is 0.8-2mg. It seems to be effective mainly in patients with mild to moderate toxicity[3]. On the contrary, in cases with severe toxicity, extremely high VPA plasma concentrations and coma, extracorporeal removal may be beneficial[1,2,4]. Due to valproate´Ys low molecular weight, haemodialysis can remove the toxic drug from the body and, thus, improve the patient´Ys level of consciousness. Haemodialysis can be used when VPA serum concentrations are above 850μg/ml, and the amount of free drug is elevated due to the saturation of available binding proteins. Based on previous reports, haemoperfusion and haemodiafiltration seem to have positive outcomes, and they could be alternative therapeutic options in such cases[1,2,4]. Another potential intervention is the administration of carbapenems. There are numerous reports pointing out a reduction in VPA concentration in patients who are treated with carbapenems. These antibiotics can inhibit acylpeptide hydrolase, an essential enzyme for VPA absorption from the gastrointestinal tract. Another possible interaction seems to be the enhanced glucuronidation by UDP glucuronyl transferase. Hence, carbapenems could play a critical role in the management of patients with VPA intoxication[5].

CONCLUSION

The administration of L-carnitine to patients with VPA intoxication and CNS depression with normal ammonia concentrations has a rationale, on the grounds that it is a safe compound with no severe adverse effects reported. The efficacy of L-carnitine in cases of valproate poisoning and high levels of ammonia is well established. However, more trials should be performed to evaluate, not only the therapeutic, but also the prophylactic role of L-carnitine in cases of VPA intoxication.

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