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TOXICOLOGY OBSERVATION

L-Carnitine for the Treatment of a Calcium Channel Blocker and Metformin Poisoning

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Abstract
Introduction The object of the current communication is to discuss the theory and the evidence for the use of L-carnitine in calcium channel blocker and metformin poisonings.
Case Report A 68-year-old male known for hypertension and type II diabetes was admitted to the critical care unit of a community hospital following an overdose of amlodipine and metformin. The patient was intubated, ventilated, and hemodynamically supported with vasopressors. Despite calcium, glucagon, high-dose insulin (HDI), and lipid emulsion for calcium channel blocker and bicarbonate for metabolic acidosis, the patient remained hemodynamically unstable. The patient was considered too unstable to initiate continuous renal replacement therapy; and without access to extracorporeal life support, the administration of L-carnitine was administered as a last resort. One hour after L-carnitine, the norepinephrine requirements started to decrease, the patient began to improve and was subsequently extubated successfully without apparent sequelae in less than 4 days.
Discussion L-Carnitine combined with HDI may have helped with the calcium channel blocker (CCB) poisoning by decreasing insulin resistance, promoting intracellular glucose transport, facilitating the metabolism of free fatty acids, and increasing calcium channel sensitivity. It may have also stimulated oxidative utilization of glucose instead of converting pyruvate into lactate and contributed to decrease lactate production with metformin poisoning.

Keywords Carnitine · Calcium channel blocker · Amlodipine · Metformin · Poisoning

Introduction

One of the proposed mechanisms of calcium channel blocker (CCB) toxicity that has been raised by studying verapamil toxicity in dogs involves the shifting of cardiac metabolism from free fatty acids to carbohydrate [1]. It is hypothesized that L-carnitine can reverse this metabolism back to free fatty acids [2], increase uptake of and hepatic oxidation of free fatty acids [3, 4], in addition to decrease insulin resistance [5, 6]. In an animal study, the use of L-carnitine in CCB poisoning increased survival and mean arterial pressure [2]. In vitro, palmitoylcarnitine, an ester derivative of carnitine, also increases the calcium channel sensitivity in a concentration-dependent relationship [7].

Case Report

We report the first case of successful treatment of CCB and metformin poisoning with high-dose insulin (HDI) and L-carnitine. The patient was a 68-year-old man (80 kg) who presented to the emergency department of a community hospital following a suicide attempt with the co-ingestions of 30 tablets of 10 mg amlodipine, 7 tablets of 500 mg metformin, and ethanol. His past medical history included hypertension, type II diabetes, benign prostate hypertrophy, and chronic anemia. His medications included acetylsalicylic acid, amlodipine, clonazepam, glyburide, irbesartan, metformin, tamsulosin, and vitamin B12. He had

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no known drug allergies, or previous history of substance and alcohol abuse.

Upon arrival, the patient was pale, diaphoretic, and hemodynamically unstable (blood pressure of 56/42 mmHg, heart rate of 77 beats per minute (bpm), normal sinus rhythm, blood glucose level of 13 mmol/L, oxygen saturation of 96 % on room air). The toxic alcohol screen was negative, the acetaminophen and the salicylate levels were undetectable. The ethanol level was 25.6 mmol/L. The complete blood count, the coagulation, cardiac, and liver profiles were within normal limits; creatinine was increased to 103 umol/L (normal, 50–100 umol/L) and the CK to 871 mmol/L. The electrolytes were normal except for a serum sodium level of 126 mmol/L. The ECG and the pulmonary radiography were normal. An hour after arrival, the arterial blood gas revealed a pH of 7.0, pCO2 of 42, BIC of 10 mmol/L, and lactate of 14.1 mmol/L (anion-gap of 22).

Initial resuscitation was with 2 l of normal saline given intravenously, along with glucagon 5 mg and three ampoules of calcium gluconate. The patient remained hypotensive, and an infusion of norepinephrine was started and titrated up to 13 μg/min. After 2 h of ongoing resuscitation, the patient remained in shock with a blood pressure of 55/27 mmHg and a heart rate of 62 bpm. Subsequently, a bolus of 80 units of insulin was given along with 80 ml of dextrose 50 %, and a transient increase of blood pressure was seen (blood pressure of 73/42 mmHg and heart rate of 62 bpm). The patient then underwent rapid sequence intubation with etomidate and succinylcholine, and mechanical ventilation was initiated. After intubation, the patient received activated charcoal by nasogastric tube. Approximately 45 min after the bolus, an insulin infusion was started at 12 units/h quickly titrated to 80 units/h over the next 2 h. Overnight, the patient continued to be in refractory shock, received another two ampoules of sodium bicarbonate and two ampoules of calcium chloride. The norepinephrine infusion was increased to 48 μg/min. A sodium bicarbonate infusion (three ampoules of sodium bicarbonates/850 ml of dextrose 5 %) was also started at 100 ml/h to correct the metabolic acidosis and increase to 250 ml/h later on. Also, two 120-ml bolus of 20 % intravenous lipid emulsion (Intralipid) were administered without benefit at 2:50 and 7:50 AM (3:50 and 8:50 AM after ED arrival).

Ten hours into his initial course, the patient remained in refractory shock (BP 110/50 mmHg, norepinephrine running

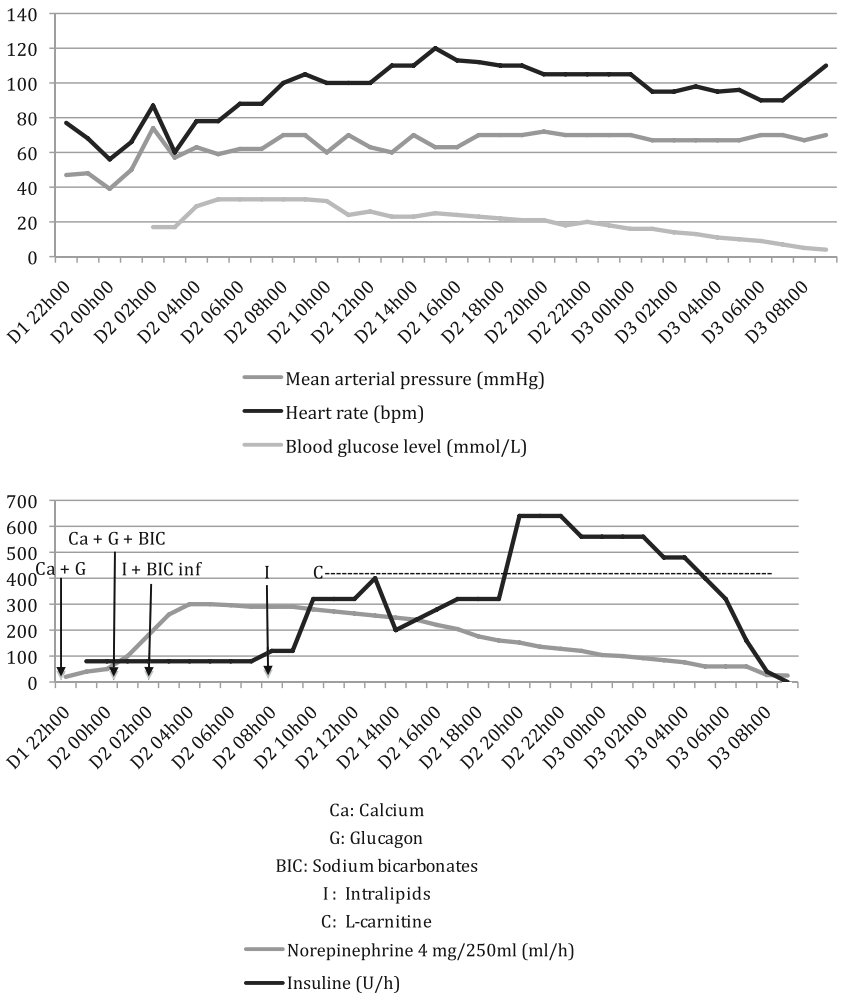

Fig. 1 Clinical evolution

at 80 μg/min), hyperglycemic (33 mmol/L), oliguric, and acidotic (pH 6.95, pCO2 43 mmHg, BIC 8 mmol/L, lactate 28 mmol/L). The insulin infusion was gradually increased in attempt to improve the patient hemodynamics. A bedside echo was performed and showed normal systolic function. His heart rate was 110 bpm at the time with a central venous saturation of 75 %. The patient was still not improving after more than 1 h of insulin infusion at 320 units/h, was considered too unstable to start continuous renal replacement therapy, and extracorporeal life support was not available. Based on the limited options left, the potential benefits of L-carnitine and its low side effect profile, 6 g of IV L-carnitine followed by 1 g IV every 4 h was administered at 11 h into the patient's initial presentation and the insulin infusion was further increased.

Thirty minutes after the end of the L-carnitine loading dose, the blood pressure was 110/50 mmHg, the heart rate 100 bpm, the norepinephrine requirement decreased from 80 to 68 μg/min, the metabolic acidosis gradually resolved (pH 7.22, pCO2 35 mmHg, BIC 14 mmol/L, lactate 25 mmol/L), and diuresis began to occur. The patient was weaned from the vasopressors within 36 h of his initial presentation. Figure 1 illustrates the clinical evolution.

Levels sent a posteriori confirmed an amlodipine (83 ng/ml at arrival, peaked at 160 ng/ml at 12:37; therapeutic, 3–11 ng/ml) and a metformin (24 μg/ml at 8:35; therapeutic, 1–2 μg/ml) poisoning. When able to consent, the patient was informed of the treatment he received and agreed with the publication.

Discussion

In calcium channel blocker poisoning, supportive treatment and calcium IV often fail to improve hemodynamic status in severely poisoned patients. HDI, when started, early can increase inotropy, facilitate intracellular glucose transport, enhance endothelial nitric oxide synthase activity, and microvascular perfusion [8]. Since cases of HDI failure have been reported, Engerbretsen et al. [6] mentioned that this could have been due to inadequate dosing, delayed administration, inadequate duration, or underlying pathophysiology unresponsive to inotropic therapy. In the case of our patient, the appropriate HDI (1 U/kg/h) was only started 4 h after presentation when the patient was already on escalating doses of vasopressors. In those refractory cases, some institutions advocate for higher doses of HDI (up to 10 U/kg/h) in the aim to limit the high dosages of vasopressors in order to avoid adverse effects of vasoconstriction and decreased cardiac output [8]. However, our patient did not seem to respond even using HDI of 320 units/h for an hour.

Despite the use of multiple therapies in this critically ill patient, L-carnitine in combination with HDI may have

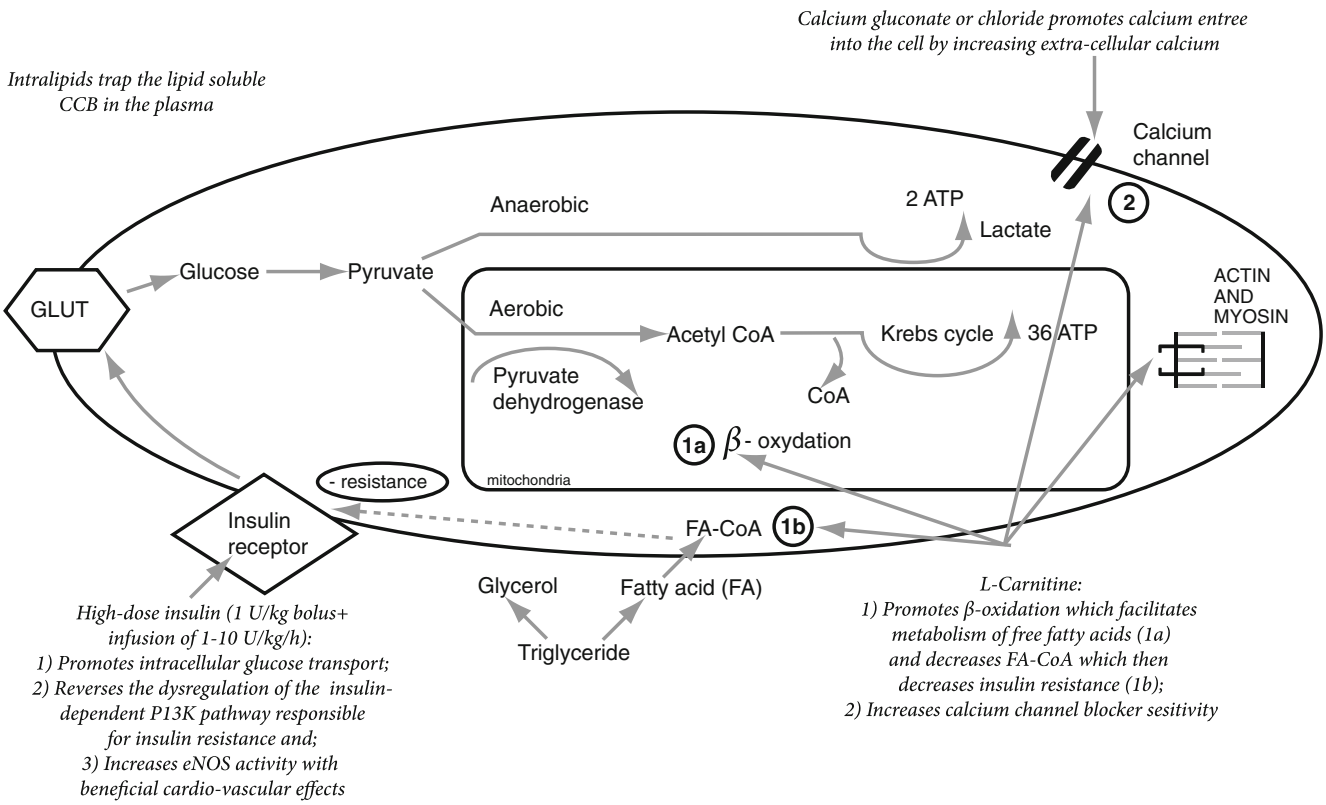

Fig. 2 Mechanism of action of antidotes used in CCB poisoning

contributed in the resolution of refractory shock in our patient. Although we feel that L-carnitine improved this patient's clinical status, we must also note that during this time he received an escalated dose of insulin as well. However, HDI even at 320 units/h alone did not seem to improve the patient condition even 1 h after reaching that level, which is normally the time by which the insulin would have demonstrated some efficacy. Despite the long half-life of amlodipine, all therapies except for ventilatory support were tapered off by 36 h postpresentation. The main proposed mechanisms are by decreasing insulin resistance, promoting intracellular glucose transport, increasing calcium channel sensitivity, and facilitating the metabolism of free fatty acids potentially even more so following intravenous fat emulsion. Figure 2 demonstrates the mechanism of action of antidotes used in CCB poisoning. The animal study done by Perez et al. [2] used L-carnitine in verapamil poisoning, but the effect on calcium channel sensitivity, insulin resistance, and fatty acid oxidation may also explain the potential endothelial benefit of L-carnitine in amlodipine poisoning [9].

Another possible explanation of the good outcome of this patient may be due to the effect of L-carnitine in negating the toxic effects of metformin, which was co-ingested by our patient although the reported ingested dose seemed to be modest. Metformin is a biguanide antihyperglycemic agent that increases lactic acid level by several mechanisms. It converts glucose to lactate in the splanchnic bed of the small intestines and inhibits hepatic gluconeogenesis from lactate, pyruvate, and alanine [10]. The effect of L-carnitine in metformin overdose is unknown. However, Mingrone et al. [5] suggests that L-carnitine normalizes pyruvate dehydrogenase (PDH) activity in type 2 insulin resistant diabetic patients in whom a defect of the PDH activity is present. It may stimulate oxidative utilization of glucose instead of converting pyruvate into lactate. In his study with 15 nonpoisoned type 2 diabetic patients, Mingrone et al. [5] observed a decrease in lactate level with L-carnitine infusion.

Conclusions

In summary, it is unclear if the positive effect observed with L-carnitine had to do with the reversal of the toxic effects of amlodipine, metformin, or if in fact the improvement noted was secondary to the increase of the HDI up to 640 units/h. Limitations to this case report are those common to cases such as this. The patient was on multiple therapies, including vasopressors and high-dose insulin. In this case, L-carnitine was used with no apparent adverse effects, which is consistent with its safety profile. Prospective studies comparing HDI to HDI combined with L-carnitine for CCB poisoning and animal studies using L-carnitine in metformin poisoning should be considered.

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Conflict of Interest The authors have no conflict of interest or financial disclosure. This case has never been presented at a meeting or never been submitted as an abstract.

References

1. Kline JA, Leonova E, Schroeder J, Williams T, Watts J (1996) Myocardial metabolism during graded intraportal verapamil infusion in awake dogs. J Cardiovasc Pharm 27:719–726
2. Perez E, Chu J, Bania T, Medljei K (2011) L-Carnitine increases survival in a murine model of severe verapamil toxicity. Acad Emerg Med 18:1135–1140
3. Gibault JP, Frey A, Guiraud M, Schirardin H, Bouletreau P, Bach AC (1988) Effects of L-carnitine infusion on intralipid clearance and utilization. Study carried out in septic patients of an intensive care unit. J Parenter Enter Nutr 12(1):29–34
4. Cederblad G (1984) Fat metabolism following an intravenous bolus dose of a fat emulsion and carnitine. Clin Physiol 4:159–168
5. Mingrone G, Greco AV, Capristo E, Benedetti G, Giancaterini A, DeGaetano A, Gasbarrini G (1999) L-Carnitine improves glucose disposal in type 2 diabetic patients. J Am Coll Nutr 18(1):77–82
6. Engebretsen KM, Kaczmarek KM, Morgan J, Holger JS (2011) High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning. Clin Toxicol 49:277–283
7. Spedding M, Mir AK (1987) Direct activation of Ca^{2+} channels by palmitoyl carnitine, a putative endogenous ligand. Br J Pharmacol 92(2):457–468
8. Holger JS, Engebretsen KM, Stellpflug SJ, Cole JB, Cooper AC, Harris CR (2010) A consecutive case series (abstract). Clin Toxicol 48:613
9. Du X, Edelstein D, Obici S, Higham N, Zou MH, Brownlee M (2006) Insulin resistance reduces arterial prostacyclin synthase and eNOS activities by increasing endothelial fatty acid oxidation. J Clin Investig 116(4):1071–1080
10. Nguyen HL, Concepcion L (2011) Metformin intoxication requiring dialysis. Hemodial Int 15:S68–S71