

INTRAVENOUS LIPID EMULSION THERAPY FOR SUSTAINED RELEASE DILTIAZEM POISONING: A CASE REPORT

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ABSTRACT

We present a case of refractory cardiogenic shock secondary to sustained release diltiazem poisoning. Intravenous lipid emulsion therapy was initiated approximately 13 hours after ingestion. Vasopressors were weaned off hours after initiation of intravenous lipid emulsion therapy and the patient went on to make a full recovery. This report adds to the paucity of data on intravenous lipid emulsion rescue therapy in sustained release diltiazem poisoning. We hypothesize that the intravenous lipid emulsion may have mediated its favorable hemodynamic effects via increases in myocardial calcium concentration with resultant increased inotropy.

Key Words: *Diltiazem, poisoning, calcium channel blockers, fat emulsion, overdose*

Intravenous lipid emulsion (ILE) therapy has been used as a rescue agent in a number of medication overdoses. Calcium channel blocker (CCB) overdose is one such scenario in which ILE therapy has been used successfully. ILE may increase blood pressure through increased myocyte calcium concentration, disinhibition of transmembrane fatty acid transport, and via 'lipid sink' mechanisms. The effectiveness of ILE in the setting of sustained release (SR) diltiazem is unknown. Traditionally, therapy for CCB overdose has consisted of gastric decontamination and hemodynamic support. These supportive measures have resulted in variable hemodynamic responses and outcomes. Recently, the first reports of ILE therapy for SR diltiazem overdose were published. In these cases, ILE therapy produced disparate hemodynamic effects. We present a case in which ILE rescue therapy contributed to hemodynamic improvement and eventual recovery in a patient with a SR diltiazem overdose.

Case Report

A 57-year-old female with a past medical history of hypertension, peripheral vascular disease, smoking, ethanol abuse and depression with prior suicide attempts, with normal baseline kidney function, was brought to the emergency department (ED) by ambulance after her roommate found her with deep lacerations to her wrists. She admitted to ingesting an unknown amount of sustained release (SR) diltiazem 360 mg, bisoprolol 5 mg, candesartan/hydrochlorothiazide 16/12.5 mg, acetaminophen/caffeine/codeine, dimenhydrinate, and ethanol.

On arrival to the ED, her vital signs were: temperature 37.3° C, blood pressure 65/40 mmHg, heart rate of 55/min, respiratory rate 22/min, and oxygen saturation 97% on 5L/min nasal cannula. She was alert and oriented with a Glasgow coma scale score of 15. The remainder of the physical examination was unremarkable. Initial laboratory investigations were remarkable for a hemoglobin of 115 g/L, creatinine of 170 umol/L, sodium of 139 mmol/L, potassium of 3.4 mmol/L, chloride

of 110 mmol/L, and a blood glucose of 6.4 mmol/L. A venous blood gas demonstrated a pH of 7.33, pCO₂ 35, pO₂ 60, and HC03 19. Serum salicylate, acetaminophen, methanol, ethylene glycol, isopropyl alcohol, and acetone were negative. Initial EKG showed sinus bradycardia with no evidence of atrioventricular block, wide QRS, or prolonged QT. Troponin T was elevated at 0.14 mcg/L. Comprehensive urine drug screen by gas chromatography-mass spectrometry was positive for codeine, norcodeine, hydrocodone, morphine, diltiazem, and dimenhydrinate.

In the ED, the patient was given 4 liters of normal saline, 3 g of calcium chloride, and two 5 mg doses of glucagon. The poison centre was consulted and gastrointestinal decontamination with whole bowel irrigation was discussed but not performed at the discretion of the attending emergency physician. To continue treatment for suspected bisoprolol toxicity, additional glucagon was administered in the form of an infusion at 5 mg/hr. The patient was admitted to the intensive care unit.

Infusions of norepinephrine, vasopressin, and dopamine were administered for ongoing hypotension. These agents were titrated up to 0.6 mcg/kg/min, 0.04 U/min, and 20 mcg/kg/min, respectively. After nine hours of vasopressor therapy, the patient experienced chest pain with ischemic EKG changes. Her repeat blood gas showed a pH of 7.22, pCO₂ of 46 mmHg, pO₂ of 43 mmHg, and HC03 of 18 meq/L. Her mean arterial pressure (MAP) was 60 mmHg and her urine output was 10-20 ml/hr. She was subsequently intubated and the decision was made to initiate ILE therapy. Hyperinsulinemia-euglycemia therapy (HIE) was considered at this point; however, given the patient's hemodynamic instability and failure to respond to other therapies, ILE was preferentially selected because of its potential for rapid effect. Further, the use of HIE could be re-evaluated after ILE was completed. 20% ILE was administered with a loading dose of 1.5 ml/kg then an infusion of 0.25 ml/kg/min for a total of 8 ml/kg. After completion of ILE therapy her MAP was 68 mm Hg. Dopamine was discontinued 4 hours post ILE, glucagon at 5 hours, vasopressin at 20 hours, and norepinephrine at 45 hours. The patient was extubated six days post-admission and was transferred to psychiatry. She made a full recovery

and was discharged after a 16-day hospital stay. A 4-hour post-ingestion serum diltiazem level (9 hours prior to ILE therapy) was 1891 ng/ml (reference range 50-200 ng/ml), and a repeat concentration at 19 hours postingestion was 1944 ng/ml (6 hours after ILE therapy).

DISCUSSION

We present a case of ILE therapy in a case of intentional SR diltiazem overdose. There have been two reports of ILE therapy for diltiazem overdose; one in which the ingestion was with diltiazem alone and the formulation was clearly SR¹ and a second in which diltiazem was part of a polydrug overdose and the formulation was unknown.² Aside from these two recent reports, previous descriptions of ILE therapy in CCB overdose have been restricted to verapamil.³⁻⁵

Prior to recent initiatives with ILE, management of patients with SR diltiazem has consisted of hemodynamic support and expediting gastric decontamination during hepatic elimination of diltiazem to subtoxic levels.^{1,6-12} Whole bowel irrigation with polyethylene glycol solution has also been employed. A review of the literature has demonstrated a wide range of reported therapies, including aggressive crystalloid infusions, calcium, glucagon, extracorporeal membrane oxygenation¹⁰, to, most recently, extracorporeal albumin dialysis.¹³ As was also the case in the present report, vasopressin, dopamine, and norepinephrine have been used as adjuncts to overcome profound hypotension, and not for any CCB-specific antagonism. The reported effectiveness of individual agents within this supportive regimen has varied widely.

There is also emerging evidence for HIE as an adjunct in the management of CCB toxicity.¹⁴ HIE is thought to improve hemodynamics by minimizing CCB-induced insulin insufficiency, which increases myocardial glucose influx, ultimately improving cardiac output. Hypoinsulinemia and peripheral insulin resistance are mediated by inhibition of L-type calcium channels in pancreatic beta cells and peripheral tissues, respectively.¹⁴ As a result, glucose influx into cardiomyocytes is limited, precluding optimal anaerobic myocardial metabolism, exacerbating CCB-mediated decreases in inotropy and

chronotropy. Insulin infusion, with rates ranging from 0.5 to 1.0 U/kg/hr, have yielded variable hemodynamic improvements, with reported effects ranging from equivocal^{1,2}, to rapid and marked.¹⁴ Part of this variability may result from disparate times to administration, with earlier administration times being associated with greater hemodynamic improvement.¹⁴

Case reports of SR diltiazem toxicity have included patients with ingestions ranging from 0.7⁸ to 12¹⁰ g. Elimination half-lives have ranged from 13.3⁷ to 40¹⁰ hours, far longer than the 4 to 12 hour half-lives reported in immediate-release diltiazem overdoses.¹⁵ Authors have hypothesized that multiple effects work in concert to increase the half-life of SR diltiazem in overdose: CCB-induced ileus and inadequate gastric decontamination may lead to a gastrointestinal diltiazem depot, leading to a prolonged absorption and half life.⁶ Indeed, the case report describing the shortest half-life in SR diltiazem overdose also administered the most aggressive gastric decontamination regime.⁷

Recently, the first case reports of ILE therapy for SR diltiazem overdose have been described. In the first report¹, an 18-year-old woman ingested 3.6 g of SR diltiazem with a corresponding peak serum level of 7893 ng/ml and a half-life of 30.9 hours. ILE was started 24 hours post-ingestion for hypotension refractory to calcium salts, aggressive fluid resuscitation, norepinephrine infusion, and HIE. Hemodynamic parameters did not improve following the ILE. The authors postulate that late ILE administration and concomitant severe sepsis may have mitigated any observable hemodynamic effect.

In contrast, Stellpflug and colleagues² describe a rapid and marked hemodynamic improvement with ILE in a 30-year-old woman with hypertrophic obstructive cardiomyopathy (HOCM) following a polydrug overdose, which included metoprolol, amiodarone, and an unreported formulation of diltiazem. This patient, who was initially normotensive, developed acute hypotension 3 hours after presentation to the ED. HIE monotherapy was subsequently started. As no response was seen after 85 minutes, ILE was administered. This resulted in normotension within 15 minutes. However, the atypical time course of the patient's hypotension, which is markedly disparate from that in other case

reports^{1,6,7}, the combination of ingested medications, close proximity to the initiation of HIE, and the patient's HOCM make it difficult to attribute the hypotension or its recovery to the diltiazem and the ILE, respectively.

Our case of ILE therapy in SR diltiazem overdose is unique in that it describes a hemodynamic response. Although not resulting in an immediate or dramatic response, ILE administration, 12-hours post ingestion, led to improvement in MAP. Dopamine and glucagon infusions were discontinued within 5 hours and vasopressin and norepinephrine at 20 and 45 hours, respectively. Given the delayed onset and prolonged duration of hypotension in previous case reports that did not use ILE, occurring at 17-18 hours post-ingestion^{9,11} and being sustained beyond 72 hours^{9,11}, vasopressor discontinuation within 48 hours is suggestive of an ILE-specific hemodynamic effect in the this case. As is the case with previous case reports, the causal effect of ILE on hemodynamic recovery is confounded by the use of multiple simultaneous vasoactive therapies.

In the absence of ILE, authors have attributed the prolonged duration of refractory hypotension to both the SR formulation of the diltiazem and to inadequate gastric decontamination.⁶ A case report describing rapid resolution of hypotension⁷, with weaning of vasopressors within 24 hours, occurred in the setting of aggressive gastric decontamination, occurring on day 1 and day 2. Therefore, considering the prolonged duration of refractory hypotension in previous SR diltiazem overdoses and the decision to not decontaminate the stomach in the present case, there is strong evidence for ILE-specific improvement in the present case. Although the demonstrated hemodynamic response was less dramatic than those described with non-CCB overdoses¹⁶, both in terms of magnitude and immediacy, it was clearly more significant than that reported in the previously reported case of confirmed SR diltiazem overdose.¹ This variation may be explained, in part, by the time to ILE administration, with those studies with the earliest ILE administration times demonstrating the most dramatic hemodynamic effect.

It is possible that ILE improved MAP through fatty-acid induced increases in myocardial calcium levels¹⁷ and subsequent

increases in inotropy. This myocardial calcium effect, together with disinhibition of transmembrane fatty acid transport and 'lipid sink' hypotheses¹⁸ represent the current understanding of the mechanisms of action of ILE. The 'lipid sink' mechanism is mediated by an increased plasma lipid phase, which effectively traps lipophilic substances, ultimately decreasing their free plasma concentration.¹⁸ This mechanism may have also attenuated the impact of the reported bisoprolol ingestion. Indeed, ILE has been described in at least 10 case reports of beta blocker toxicity¹⁹, and may offer particular benefit with bisoprolol as it is one of the more lipophilic beta blockers.²⁰ In addition, no side effects related to ILE administration were noted in this case. As opposed to reports^{16,21} in which ILE interfered with the analysis of a complete blood count and electrolytes, no such interference was noted.

As is the case with previous case reports, the simultaneous administration of multiple, potent, vasoactive agents confounds the individual impact of ILE in the clinical response in this case. Despite this difficulty, the present report is the first to demonstrate hemodynamic improvement with ILE in confirmed SR diltiazem overdose.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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