Amlodipine overdose

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We describe the case of a 24-year-old woman who intentionally ingested between 400 and 600 mg of amlodipine along with a large number of simvastatin and trazodone tablets.

CASE HISTORY

A 24-year-old white woman with a past history of depression being treated with sertraline presented to the emergency department with nausea, vomiting, and diarrhea after ingesting 400 to 600 mg of amlodipine and unknown quantities of simvastatin and trazodone. The quantities ingested were deduced based on the last refill date and contacting the pharmacy. The patient had one previous suicide attempt while in high school. She reported a recent altercation with her estranged husband and a history of alcohol abuse and rehabilitation. She was sober until the night of the overdose, when she had a beer. She smoked 30 cigarettes each day and denied the use of any illicit drugs.

In the emergency department, she was euthermic with a heart rate of 99 beats/minute, in no distress, but with a blood pressure of 72/34 mm Hg. Her skin was cold and clammy. Her laboratory results at presentation are shown in *Table 1*. She received 3 L of normal saline and 1 L of 5% dextrose in normal saline in the emergency department. Because the hypotension remained refractory, vasopressor agents were initiated with dopamine and norepinephrine followed by vasopressin and phenylephrine. The patient was intubated for airway protection. Glucagon was started with a 10 mg bolus followed by a continuous infusion at 10 mg/h. A 20% fat emulsion (Intralipid) was started with a 1.5 mg/kg bolus over 10 minutes followed by 0.25 mL/kg/h. A calcium gluconate drip was started at a rate of 1 g/h. In addition, an intravenous insulin infusion was started at a rate of 70 units/h along with 10% dextrose. The patient started developing metabolic acidosis in spite of an intravenous isotonic bicarbonate infusion. Continuous venovenous hemodialysis without any ultrafiltration was started for the worsening metabolic acidosis and the anuria. Intravenous hydrocortisone was administered at a dose of 50 mg every 8 hours.

On the second day of hospitalization, a chest radiograph showed worsening bilateral pulmonary infiltrates. With numerous catecholamines, the heart rate was up to 140 beats per minute and the respiratory rate increased to 35 breaths per minute. A fractional inspired oxygen concentration (FiO_2) at 100% was instituted. Ultrafiltration was started with continuous venovenous hemodialysis. Dopamine and lipid emulsion infusions were discontinued as hemodynamic stability improved.

By the third hospital day, the patient's heart rate had slowed, but leukocytosis developed. Meropenem and levofloxacin were added. Phenylephrine was tapered, and albumin 25 g every 8 hours was started to aid in vasopressor tapering.

By the fourth day of hospitalization, the FiO_2 was reduced to 60% with maintenance of good oxygen saturation. A chest radiograph showed improvement in the pulmonary infiltrates. The high-dose insulin drip was discontinued and the calcium gluconate drip was decreased to 0.5 g/hour. Vancomycin was started for methicillin-resistant *Staphylococcus aureus* coverage and the intravenous bicarbonate was stopped. The following day, vasopressin and norepinephrine were tapered off.

Two days later, glucagon and calcium gluconate were discontinued. The patient was extubated on the ninth day of admission and transitioned to intermittent hemodialysis. The patient's continued kidney failure was attributed to acute tubular necrosis from hypotension and rhabdomyolysis. The rhabdomyolysis reached a peak creatine phosphokinase of 5035 U/L 50 hours after ingestion. This eventually resolved without the need for continued hemodialysis 17 days after continuous venovenous hemodialysis was first initiated. Her creatinine at the time of discharge was 1.7 mg/dL. She was discharged home 23 days after admission.

DISCUSSION

Amlodipine, a dihydropyridine calcium channel blocker, has a half-life of approximately 30 to 50 hours and a large volume of distribution (2 L/g). Its slower and longer (up to 72 hours) duration of action, relative lack of negative inotropy, and once-daily dosing has made it preferred over other calcium channel blockers (CCBs) such as verapamil or nifedipine. CCBs such as amlodipine reduce calcium flux through voltage-gated slow

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Table 1. Laboratory results obtained during the patient's early hospitalization for amlodipine overdose

		Hours after ingestion						
Test	Admit	12 h	24 h	36 h	50 h	80 h	110 h	140 h
Sodium (mEq/L)	140	139	141	138	140	137	135	138
Potassium (mEq/L)	4.2	4.1	3	3.4	3.9	4.3	5.5	4.5
Chloride (mEq/L)	107	113	111	104	107	105	102	103
Carbon dioxide (mEq/L)	17	13	17	25	23	21	24	26
Blood urea nitrogen (mg/dL)	15	17	18	9	5	3	14	20
Creatinine (mg/dL)	2.6	2.7	2.2	1.1	1.3	1.1	1.2	1
Glucose (mg/dL)	150	418	328	135	103	292	160	147
Calcium (mg/dL)	9.3	7.2	7.2	8.2	8.5	9.4	9.7	9.3
Protein (g/dL)	7.3	n/a	n/a	4.6	4	4.5	4.9	5.3
Phosphorus (mg/dL)	5.5	0.8	2.3	1.8	4.2	2.1	4.3	3.9
Magnesium (mg/dL)	1.6	1.4	1.7	1.9	1.6	1.6	1.9	1.8
Albumin (g/dL)	4.2	n/a	n/a	2.3	1.9	2.4	2.4	2.3
Bilirubin (mg/dL)	1.1	n/a	n/a	2.4	1.9	1.8	2.3	4.1
Alkaline phosphatase (U/L)	46	n/a	n/a	46	34	47	67	98
Aspartate aminotransferase (U/L)	11	n/a	n/a	180	184	108	94	88
Alanine aminotransferase (U/L)	18	n/a	n/a	44	52	40	41	49
pH	7.3	7.27	7.24	7.42	7.3	7.48	7.42	7.54
Partial pressure of oxygen (mm Hg)	124	149	84	79	47	154	180	93
Partial pressure of carbon dioxide (mm Hg)	26	21	43	41	50	31	41	32
Oxygen saturation (%)	98.1	98.9	94.6	99.3	77.2	99.4	99.3	98
White blood cells (K/uL)	14.3	n/a	24.7	n/a	33.8	26.5	27.4	23.4
Hemoglobin (g/dL)	13.4	n/a	11	11.5	10.5	9	8.5	8.8
Hematocrit (%)	39.4	n/a	33.4	34.1	31.2	26.6	24.8	25.4
Platelets (K/uL)	307	n/a	159	n/a	63	68	84	91
Creatine phosphokinase (U/L)	46	57	296	2547	5035	2189	1457	1191

(L-type) calcium channels. The major toxic effect of an overdose is refractory hypotension, due to both vasodilation and impaired cardiac metabolism and contractility. Tissue ischemia and lactic acidosis ensue. Blockade of calcium channels in other tissues, such as pancreatic beta cells, also has other important adverse consequences (i.e., reduced insulin release).

Intravenous volume expansion (using sodium bicarbonate–containing solutions to simultaneously attempt to correct the lactic acidosis) and multiple vasopressors are routinely initiated, but this treatment is often ineffective (1) because the primary mechanism of hypotension is arterial muscle relaxation and not hypovolemia. Calcium infusion provides a direct antidote and may be helpful; however, the response to calcium is also often inadequate (2). Given its relatively benign intervention, even in the presence of high serum concentrations acutely, calcium is still often utilized in these patients. Glucagon may be infused because it activates myocardial adenylate cyclase and thus increases cardiac cyclic adenosine monophosphate levels, which results in an inotropic effect. High-dose insulin infusion together with adequate glucose to maintain normal glucose levels—so-called "hyperinsulinemia/euglycemia therapy"—has been shown to be very effective in experimental models of CCB overdose (3, 4). Insulin has a direct positive cardiac inotropic action and may also improve myocardial carbohydrate oxidation, which is often impaired in these patients. Finally, intravenous lipid infusions have recently been used to treat lipid-soluble drug overdoses (5–8). Raising serum lipid levels can markedly increase the drug's volume of distribution and thereby reduce its effective plasma level. Furthermore, provision of triglycerides provides an alternative energy source for the myocardium.

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