

Critical Care Management of Verapamil and Diltiazem Overdose With a Focus on Vasopressors: A 25-Year Experience at a Single Center

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Study objective: Verapamil or diltiazem overdose can cause severe morbidity and death, and there exist limited human data describing management and outcome of a large number of such patients. This article describes the management and outcome of patients with nondihydropyridine calcium-channel blocker overdose, with an emphasis on vasopressor dosing, at a single center.

Methods: This study is a retrospective chart review of patients older than 14 years and admitted to the inpatient toxicology service of a single tertiary care medical center for treatment of verapamil or diltiazem overdose from 1987 through 2012, and who had the presence of either drug confirmed by urine drug screening. Patients were identified by review of patient encounter logs. Data abstracted from medical records included demographics, laboratory results, drugs used to support blood pressure, complications, and outcomes. A second group included patients with a reported calcium channel blocker ingestion but for whom results of the urine drug testing were no longer available. In an effort to assess selection bias, this group was included to determine whether patients who were excluded from the primary group only because of unavailability of urine drug screen results had different outcomes.

Results: During the study period, 48 patients met inclusion criteria. The median age was 45 years, with a range of 15 to 76 years, and 52% were male patients. Verapamil accounted for 24 of 48 (50%) ingestions. Vasopressors were administered to 33 of 48 (69%) patients. Maximal vasopressor infusion doses were epinephrine 150 $\mu\text{g}/\text{minute}$, dopamine 100 $\mu\text{g}/\text{kg}$ per minute, dobutamine 245 $\mu\text{g}/\text{kg}$ per minute, isoproterenol 60 $\mu\text{g}/\text{minute}$, phenylephrine 250 $\mu\text{g}/\text{minute}$, and norepinephrine 100 $\mu\text{g}/\text{minute}$. The use of multiple vasopressors was common. Hyperinsulinemic euglycemia was used in 3 patients who also received multiple vasopressors. Eight probable or possible ischemic complications were noted in 5 of 48 (10%) patients. Gastrointestinal bleeding occurred in 3 of 48 (6%) patients; a brain magnetic resonance imaging in 1 patient suggested mild ischemia, without clinical evidence of infarction; 1 patient had ischemic bowel; and 3 patients developed renal failure from acute tubular necrosis, which resolved in each case. Six of the 8 ischemic complications were evident before use of vasopressor therapy. Three patients sustained in-hospital cardiac arrest before admission and were successfully resuscitated. Each of these arrests occurred before instituting vasopressor infusions. One patient experienced a late cardiac arrest from primary respiratory arrest from administration of sedatives, and multiple organ system failure followed resuscitation, with death occurring during manipulation of a pulmonary artery catheter. The remaining 47 patients recovered. There were 12 patients in the group of additional poisoned patients for whom results of urine drug screening were unavailable. Four patients were treated with vasopressors, 2 experienced acute tubular necrosis that was present before vasopressor use, and all recovered.

Conclusion: In our series of patients admitted with verapamil or diltiazem overdose, hypotension was common and managed with the use of multiple vasopressors and without hyperinsulinemic euglycemia in all but 3 cases. Despite high doses of vasopressors, ischemic complications were the exception and were usually present before use of vasopressors. Death occurred in a single patient whose death was not attributed directly to calcium-channel blocker toxicity. Vasopressor use after verapamil or diltiazem overdose was associated with good clinical outcomes without permanent sequelae. [Ann Emerg Med. 2013;62:252-258.]

Please see page 253 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Overdose of calcium-channel blockers can result in substantial toxicity. According to the American Association of Poison Control

Centers, 2,300 patients were treated in health care facilities for overdose of these drugs in 2010.¹ Because many cases are likely never reported to poison centers, the true incidence is higher.

Three general classes of calcium-channel blockers are used in the United States: phenylalkylamines (verapamil),

Editor's Capsule Summary*What is already known on this topic*

High-dose insulin and glucose have become popular treatments for calcium-channel blocker toxicity.

What question this study addressed

Does the use of vasopressors without insulin and glucose result in good outcomes in patients with severe verapamil or diltiazem poisoning?

What this study adds to our knowledge

The use of vasopressors, often multiple vasopressors in high doses, was associated with good responses and few ischemic complications.

How this is relevant to clinical practice

The most appropriate treatment of severe calcium-channel blocker overdose has not been established. Vasopressors are reasonable agents for use in verapamil or diltiazem poisoning.

benzothiazepines (diltiazem), and dihydropyridines (eg, amlodipine, nifedipine). Although these classes are structurally different, they share similar pharmacologic properties in that they all antagonize L-type voltage-gated calcium channels.^{2,3} At therapeutic doses, however, the dihydropyridines tend to produce more peripheral vasodilation (and less negative inotropy) than verapamil or diltiazem and as a result commonly cause hypotension with reflex tachycardia after overdose.^{4,5} In contrast, serious overdose of verapamil or diltiazem typically presents with hypotension and bradycardia, sometimes with atrioventricular conduction blocks.^{5,6}

Traditional treatment of symptomatic patients after verapamil and diltiazem ingestions has included administration of intravenous calcium, vasopressors, and occasionally glucagon.^{4,7} High doses of vasopressors may be required.⁷ In recent years, hyperinsulinemia euglycemia therapy has emerged as a suggested option for managing patients with hemodynamic instability,⁷⁻⁹ but the effectiveness and exact timing of when to institute it are controversial, with some advocating its use as an adjunctive therapy for cases refractory to standard doses of vasopressors^{10,11} and others advocating it as one of the first medications to be administered.^{12,13} More recently, despite lack of human trials comparing insulin with vasopressors, it has been claimed that hyperinsulinemic euglycemia therapy is not only responsible for a decrease in mortality in the treatment of calcium-channel blocker overdose⁵ but also is superior to vasopressors.^{5,12,13}

Since the 1980s at our institution, the approach by medical toxicologists to managing shock resulting from verapamil or diltiazem toxicity has centered on fluid challenges to correct hypovolemia and use of vasopressors, sometimes administered

in high doses. During this period, there has been increased use of ultrasonography and echocardiography and decreased reliance on pulmonary artery catheters in monitoring these patients. Pharmacologic treatment has remained relatively constant, however, with an emphasis on the use of high-dose, direct-acting vasopressors. In the past 5 years, high-dose insulin therapy has also been used in occasional cases. Whenever possible, comprehensive urine drug screens are obtained for all patients with suspected calcium-channel blocker toxicity to confirm exposure to the implicated agent.

It is our impression that vasopressors are effective and that even the sickest of patients respond to this therapy. This study sought to determine whether these impressions were accurate because, to our knowledge, the medical literature contains no large series that describes both detailed vasopressor doses and outcomes in such patients. The primary purpose of this study was to describe the clinical characteristics and treatment modalities, including vasopressor dosing, of patients with verapamil and diltiazem overdose at a single center by a single medical toxicology practice. A secondary purpose was to report the short-term outcome of these patients, including ischemia and death.

MATERIALS AND METHODS

This retrospective case series was performed at a tertiary care medical center in Phoenix, AZ, which serves as a regional referral center for poisoned patients. This study was approved by the institutional review board.

The standard practice pattern at this center is for patients with suspected drug toxicity to be admitted to the toxicology service, which is staffed by physician toxicologists. Patients were identified by review of a patient log maintained by the Department of Medical Toxicology. The logbook is a consecutive record of all patient encounters by toxicologists in the medical center. Inclusion criteria for the primary group of patients in this study were admission to the inpatient toxicology service after a verapamil or diltiazem overdose between January 1, 1987, and September 15, 2012, age greater than or equal to 14 years, availability of medical records, and documentation of verapamil or diltiazem in urine by gas chromatography/mass spectrometry.

To ensure that the review did not exclude verapamil or diltiazem overdose patients who may have had different outcomes, complications, or treatments, a separate second group of patients who met all of the aforementioned inclusion criteria, except that results of urine drug screening were no longer available in medical records, was also reviewed.

Data Collection and Processing

Data abstracted from medical records included demographics, ingested drug, presence of coingestants, results of urine drug screening, initial and peak recorded serum creatinine concentration, presenting and nadir recorded values for pulse rate and blood pressure, whether a pacemaker was placed, use of

mechanical ventilation, the presence of ischemic complications, and outcome. A detailed collection of treatment strategies to support blood pressure was recorded that included vasopressor dosing, along with maximal dose of each vasopressor, through review of the entire medical record (eg, paramedic run sheets, emergency department [ED] records, nursing notes, progress notes, intensive care flow sheets, respiratory therapy notes).

Before data abstraction, each reviewer received brief training on the data abstraction sheet, and 3 “practice charts” were abstracted for the purpose of ensuring uniform data abstraction. Data were collected on predesigned data abstraction sheets, independently, by 2 investigators (M.L., A.P.-J.) and subsequently entered into a spreadsheet (Excel 2007; Microsoft, Redmond, WA). A third investigator (S.C.C.) then reviewed results, and any discrepancies were resolved by a joint review of medical records by all 3 authors, with unanimous agreement on final parameters. Because all recorded parameters were objective data from printed or computer records (eg, vasopressor dose, blood pressure, survival), agreement was easily achieved.

Any agent that augmented blood pressure through either α or β adrenoceptor agonism was considered a vasopressor for the purposes of this study. As such, epinephrine, norepinephrine, isoproterenol, dopamine, dobutamine, and phenylephrine were considered vasopressors, whereas insulin, glucagon, and calcium were not, though their use was recorded and is reported. Hyperinsulinemia euglycemia was defined as the intravenous infusion of at least 0.5 units/kg per hour of insulin, with or without an insulin bolus, in an attempt to increase blood pressure.

Patients with serum creatinine values greater than 1.5 mg/dL were considered to have had acute tubular necrosis if the serum creatinine concentration remained above 1.5 mg/dL for at least 2 days and either urine sodium was greater than 40 mEq/L (in the absence of diuretics) or a written diagnosis of acute tubular necrosis was made by an attending nephrologist. Patients whose creatinine level normalized within 2 days were assumed by nephrologists and authors to have had prerenal azotemia. Ischemic complications were defined as digital or extremity necrosis, acute tubular necrosis, stroke, myocardial infarction by elevated cardiac biomarkers and regional wall motion abnormality on echocardiography, intestinal ischemia, or gastrointestinal bleeding.

Primary Data Analysis

Descriptive statistics were used to report ordinal and proportional data. Data were analyzed with Stata 2007 (StataCorp, College Station, TX).

RESULTS

A total of 69 potential patients were identified (Figure). Six patients were excluded because of unavailability of older medical records. Of the 63 remaining patients, results of comprehensive urine drug screening were available for 51 patients, and 3 patients were excluded because urine drug screen showed the

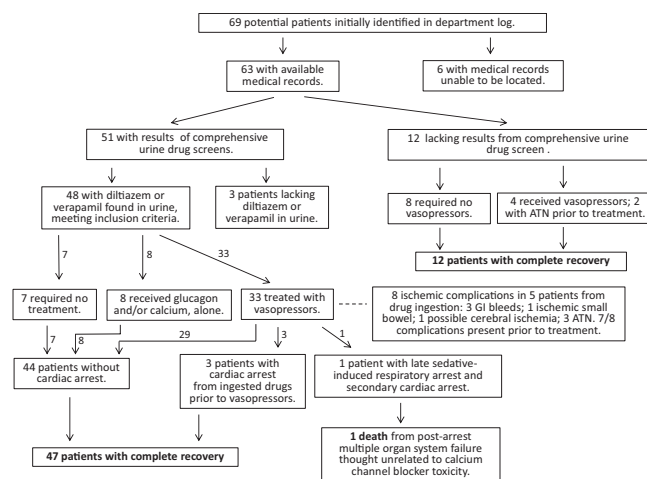


Figure. Final study population.

absence of verapamil or diltiazem, leaving 48 patients in the primary group who met all inclusion criteria (Figure). There were 12 patients in the second group composed of patients meeting inclusion criteria but for whom results of urine drug screening were unavailable.

Of the 48 patients with verapamil or diltiazem in urine, the median age was 45 years (range 15 to 76 years; interquartile range 34 to 53 years). Men accounted for 25 of 48 patients (52%), and verapamil accounted for 24 of 48 ingestions (50%). Coingestions were common, with 38 of 48 patients (79%) having taken at least 1 additional medication as part of their overdose. Eight patients had coingested a β -blocker.

Blood pressure, pulse rate, and serum creatinine values are summarized in Table 1. Mechanical ventilation was performed in 20 of 48 patients (41%). On presentation, 20 of 48 patients (41%) presented with a serum creatinine level greater than 1.5 mg/dL, but as described below, only 3 patients developed acute tubular necrosis, and 2 of these patients required transient hemodialysis.

In no instances were vasopressors, calcium salts, glucagon, or insulin begun before onset of hypotension. Seven of 48 patients (14%) never developed hypotension or significant bradycardia and did not require treatment (Figure). Eight of 48 patients (17%) developed hypotension, sometimes with accompanying bradycardia, in the outlying ED where they were treated, before transfer, with fluid challenges along with glucagon or calcium salts and without vasopressors or hyperinsulinemic euglycemia, with good response. After transfer, 5 of these 8 patients received no continuation of therapy and remained hemodynamically stable. Two of these 8 patients were maintained on a glucagon infusion alone with good results; 1 of these patients had coingested a β -blocker. None developed ischemic complications. Calcium and glucagon dosing is described in more detail below.

Vasopressors were administered to 33 of 48 patients (69%) (Figure). Among those patients who received vasopressors, the median number of vasopressors used was 2 (range 1 to 5).

Table 1. Measured selected parameters in the primary group (N=48).

Parameter Measured	Initial Measurement Median (Range; IQR)	Nadir Recorded Value During Hospitalization Median (Range; IQR)	Peak Recorded Value During Hospitalization Median (Range)
SBP, mm Hg	82 (32–149; 69–105)	70 (0–105; 60–80)	
DBP, mm Hg	50 (13–112; 38–59)	37 (0–70; 35–56)	
Pulse rate	60 (20–118; 50–81)	50 (0–80; 41–59)	
Serum creatinine, mg/dL	1.3 (0.5–4.2)		1.6 (0.7–7.2)

IQR, Interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2. Doses of vasopressors, insulin, and glucagon in the primary group (N=33).

Drug	Number of Patients	Median (IQR) Infusion Rate	Maximal Infusion Rate
Norepinephrine	25	15 (8.4–24.5) $\mu\text{g}/\text{min}$	100 $\mu\text{g}/\text{min}$
Dopamine	19	19 (12–20) $\mu\text{g}/\text{kg per min}$	100 $\mu\text{g}/\text{kg per min}$
Epinephrine	13	20 (10–26) $\mu\text{g}/\text{min}$	150 $\mu\text{g}/\text{min}$
Isoproterenol	13	11 (5–25) $\mu\text{g}/\text{min}$	60 $\mu\text{g}/\text{min}$
Dobutamine	7	10 (7–15) $\mu\text{g}/\text{kg per min}$	245 $\mu\text{g}/\text{kg per min}$
Phenylephrine	3	100 (100–175) $\mu\text{g}/\text{min}$	250 $\mu\text{g}/\text{min}$
Insulin	3	1 (0.9–1) units/kg per h	2 unit/kg per h
Glucagon*	26	16 (5–46) mg	390 mg

*Listed as total dose, not infusion rate, because many patients had received intermittent boluses with or without a continuous infusion.

Detailed descriptions of vasopressor dosing are in Table 2. Among patients treated with vasopressors, 25 of 48 (52%) received norepinephrine; 19 of 48 (40%), dopamine; 13 of 48 (27%), epinephrine; 13 of 48 (27%), isoproterenol; 7 of 48 (15%), dobutamine; and 3 of 48 (6.25%), phenylephrine.

Intravenous calcium salts in the form of calcium chloride or calcium gluconate were administered to 38 of 48 patients (79%). In most cases, the calcium was administered as a combination of intermittent boluses and infusions. The median total dose of elemental calcium was 2 g, whether administered as chloride or gluconate.

Twenty-six of 48 patients received glucagon. Of these 26 patients, 7 were receiving or had also ingested β -blockers (atenolol in 4 and metoprolol in 3 patients). The median total dose of glucagon administered throughout the stay (including boluses and infusions) was 26 mg (range 1 to 390 mg; interquartile range 5 to 46 mg).

Hyperinsulinemic euglycemia was administered to 3 patients, each of whom also required treatment with multiple vasopressors. Two patients received intravenous 1 unit/kg regular insulin as a bolus, followed by 1 unit/kg per hour, whereas 1 patient received intravenous 0.87 units/kg regular insulin as a bolus, followed by 0.87 units/kg per hour. One of the 2 patients who began receiving 1 unit/kg per hour had the insulin increased to a maximal infusion rate of 2 units/kg per hour. The patients who received hyperinsulinemic euglycemia therapy presented later in the series, reflecting the recent changing national trends in management.

In this series, the median nadir recorded pulse rate was 50 beats/min (range 0 to 80 beats/min; interquartile range 41 to 59 beats/min). Of the 48 patients in the primary group, 31 developed bradycardia ranging from sinus bradycardia to various degrees of atrioventricular blocks. With one exception,

these bradycardic rhythms responded to vasopressors or glucagon.

Two patients underwent placement of temporary intravenous pacemakers for refractory bradycardia associated with hypotension. First, a 69-year-old woman who ingested diltiazem experienced progressive bradycardia and hypotension despite rapid escalation of intravenous isoproterenol, norepinephrine, calcium, and glucagon infusion rates. After pacing to a rate of 75 beats/min, blood pressure increased to 120/90 mm Hg, and pacing was able to be discontinued after a few hours. All vasopressors were discontinued during the next 24 hours. Second, a 19-year-old woman had a pacemaker placed for unclear reasons at an outside facility before transfer to us, and the pacemaker was discontinued on arrival at our center without a change in pulse rate (60 beats/min) or blood pressure. Isoproterenol was used to increase pulse rate and blood pressure and she rapidly improved and recovered.

Four patients sustained in-hospital cardiac arrests. In 3 of these cases, the patient experienced a single in-hospital cardiac arrest in the ED before vasopressor dosing. All 3 patients stabilized after resuscitation with implementation of vasopressor therapy. Hyperinsulinemic euglycemic therapy was not used in any of these patients. A fourth patient experienced severe alcohol withdrawal late during hospital day 2. For treatment of alcohol withdrawal, he received repeated doses of benzodiazepines, became lethargic, and then aspirated, leading to a primary respiratory arrest followed by pulseless electrical activity. Multisystem organ failure and severe shock followed resuscitation (which included emergency bronchoscopy to remove large amounts of aspirated material). Nonetheless, during manipulation of a pulmonary artery catheter, the patient experienced a sudden bradysystolic arrest 5 hours after the first arrest and was not able to be resuscitated. Before the first cardiac

Table 3. Characteristics of patients in the primary group with probable or possible ischemic complications.

Pt #	Sex	Age, Year	Cr ₁ , mg/dL	Cr ₂ , mg/dL	No. of Vasopressors	Use of HIE	Ischemic Complications	Evidence of Ischemia on Presentation
1	M	51	1.8	1.8	3	Yes	Possible cerebral ischemia, GIB	No Yes
2	M	45	4.2	7.2	2	No	Ischemic bowel, ATN	Yes Yes
3	M	62	2	2.8	4	No	ATN GIB	Yes No
4	M	64	1.4	4.9	2	Yes	GIB	Yes
5	M	32	2.7	2.7	4	No	ATN	Yes

Pt, Patient; Cr₁, Initial serum creatinine; Cr₂, maximal serum creatinine; HIE, hyperinsulinemic euglycemia; GIB, gastrointestinal bleeding; ATN, acute tubular necrosis. Patient 1 developed evidence of a possible stroke (see text) in the presence of a pulmonary embolism and a patent foramen ovale; recovery was complete without neurologic deficit.

arrest, the patient was improving from a hemodynamic standpoint, and the infusions of calcium and isoproterenol were being titrated down.

Eight probable or possible ischemic complications were noted in 5 patients (Figure, Table 3). Gastrointestinal bleeding occurred in 3 of 48 patients (6%), and 2 of these patients presented with bleeding before start of vasopressors. One patient experienced small bowel infarction, which was suspected before vasopressor therapy. This patient presented with hypotension, abdominal pain, and a venous plasma lactic acid concentration of 9.3 mmol/L. Three patients met the case definition of acute tubular necrosis, and renal failure was evident on presentation before vasopressor use in each instance. Two of these patients experienced other ischemic complications (gastrointestinal bleeding in one, ischemic bowel in the other). One patient treated with vasopressors and hyperinsulinemic euglycemia therapy was slow to completely awaken after weaning from mechanical ventilation and sedatives. This patient had also experienced gastrointestinal hemorrhage on admission. A magnetic resonance imaging study of the brain, performed because of concern for cerebral ischemia, revealed findings consistent with chronic hypertensive vascular disease and a suggestion of a small area of ischemia without a clear infarct. On awakening, however, the patient was neurologically intact without any clinical evidence of stroke. No patient displayed ischemic complications involving digits or an extremity.

With the exception of the aforementioned death, all patients survived and recovered completely, without documented neurologic deficits. Three patients were discharged to short-term rehabilitation as a result of deconditioning during prolonged hospital stays. The median length of stay for all patients was 3.5 days (range 1 to 30 days; interquartile range 2 to 7.4 days).

Twelve patients met all inclusion criteria, except that results of urine drug screening were unavailable, and their courses were reviewed to assess whether their exclusion from the primary group omitted reported therapies or outcomes (Figure). Two of 12 patients received fluids and calcium alone, and 6 patients required no therapy. Four of these 12 patients (33%) were treated with vasopressors and none with hyperinsulinemic euglycemia. Two patients experienced acute tubular necrosis

that was evident on presentation and before vasopressor therapy. All patients recovered completely and were discharged.

LIMITATIONS

A limitation to this study is its retrospective nature. Consequently, the conclusions are limited by the quality and completeness of data recorded in the medical record. To minimize some problems inherent to retrospective chart review, only dichotomous variables (eg, use of vasopressors or not, documented ischemic hand or not) and continuous variables (eg, epinephrine dose) were abstracted. These choices for data collection likely minimized some of the limitations inherent in a retrospective review.¹⁴ Although the included patients who ingested multiple medications were similar to the patient population encountered in practice, it is possible that hypotension or shock requiring vasopressor use was not always primarily due to verapamil or diltiazem toxicity, despite the presence of these drugs in the urine in the primary group. Another limitation of this study is the use of a single institution, which limits the external validity of the results. The single center with similar practice pattern, however, increases the internal validity of the study.

DISCUSSION

When calcium-channel blocking agents are received in overdose, bradycardia and hypotension leading to shock and death may occur. Of patients in our primary group, 69% were treated with vasopressors, 41% presented with azotemia from prerenal failure or acute tubular necrosis, 41% required mechanical ventilation, 4 patients experienced cardiac arrest, and complications included ischemic bowel requiring resection and possible cerebral ischemia.

Considering the frequency of calcium-channel blocker overdose, the literature contains surprisingly few case series involving verapamil or diltiazem toxicity,^{6,15-17} and only occasionally do series describe any details of vasopressor therapy.¹⁷ No randomized controlled human trials evaluating different therapeutic modalities for managing these patients have been reported, to our knowledge.

Deters et al¹⁵ reported poison center data on a series of patients with calcium-channel blocker overdose but did not report information on vasopressor dosing. Their series of verapamil, diltiazem, and dihydropyridine ingestions included many asymptomatic or minimally symptomatic patients. Verapamil accounted for 25% and diltiazem for 3% of ingestions. Mortality was 2.8% for all patients who ingested verapamil or diltiazem (6/207) (personal communication, Michael Deters, Poisons Information Centre-PIC, Erfurt, Germany. March 2013). Ingestions were not confirmed with drug screening.

Levine et al⁶ described 40 patients admitted to one of 5 ICUs for verapamil or diltiazem ingestions. Twelve patients received vasopressors for hypotension or developed bradycardia, and 1 patient died. No detailed information on vasopressor dosing was provided and confirmation of drug in urine was not provided.

Greene et al¹⁷ described 4 patients who ingested diltiazem or verapamil, required treatment with vasopressors, and were also treated with insulin infusions. Vasopressor dosing was epinephrine less than or equal to 1 $\mu\text{g}/\text{kg}$ per minute ($N=3$), norepinephrine less than or equal to 1.5 $\mu\text{g}/\text{kg}$ per minute ($N=3$), and dobutamine 10 $\mu\text{g}/\text{kg}$ per minute ($N=2$).

Megarbane et al¹⁶ reviewed records of 65 symptomatic patients with verapamil poisoning during 8 years who were admitted to 2 ICUs in Paris. Similar to our results, 62% developed shock, 11% experienced cardiac arrest, 43% received mechanical ventilation, 3% were treated with hemodialysis, and 3% underwent temporary cardiac pacing. Unlike our series and that by Deters et al,¹⁵ 8% of their patients died. Although calcium, epinephrine, norepinephrine, dobutamine, dopamine, isoproterenol, insulin, and glucagon were used, detailed dosing was not provided. Many patients had ingestions confirmed with serum verapamil concentrations.

The current case series is one of the largest describing nondihydropyridine calcium-channel blocker toxicity to date and also reports detailed information on vasopressor dosing. Because of the potential for late onset of toxicity after ingestion of extended-release formulations of calcium-channel blocking agents, a few patients in this study were hospitalized despite the absence of clinical toxicity and never developed hypotension requiring intervention. However, the majority of patients in the primary group did develop hypotension, which was treated with vasopressors. The high rate of hypotension likely reflects referral bias in that many patients were transferred to our toxicology service because they had already become ill.

Our findings are consistent with those of Megarbane et al¹⁶ with regard to the severity of hypotension, vasopressor requirements, and the rate of mechanical ventilation and cardiac arrest. Therefore, the predicted mortality of our patient population might be expected to be high. However, no deaths were directly attributable to calcium-channel blocker toxicity. The frequency of hypotension and end-organ dysfunction suggests that the overwhelming good outcome is not simply because the patients were not seriously poisoned, but rather because the patients responded to aggressive treatment. Despite

high doses of vasopressors, no patient experienced any digital or limb ischemia. Ischemic complications that were found were usually present before the start of vasopressors (Table 3) and were likely due to hypoperfusion resulting from the calcium-channel blocker toxicity before treatment.

One of the strengths of this study was inclusion of patients treated at a single center by a single group of physician toxicologists with generally similar practice patterns. Patients were not treated according to a specific protocol, but aggressive use of high-dose vasopressors, when necessary, was uniform among medical toxicologists at our center. The specific vasopressors chosen and the order in which they are applied may vary among clinicians.

A second strength of this study was confirmation of the presence of verapamil or diltiazem in the urine, which does not necessarily mean that the drug is present in toxic concentrations, but the exclusion of patients from the primary series in whom the calcium-channel blockers were absent strengthens the study. In some circumstances, histories may be inaccurate, and without confirmatory drug testing, incorrect conclusions may be made. In this study, 3 patients who presented after a reported verapamil or diltiazem ingestion were excluded because drug testing failed to identify either drug in their urine. One of the excluded patients was a critically ill 47-year-old man who reportedly ingested extended-release diltiazem, along with several other agents. However, his urine contained no diltiazem or verapamil but only a large amount of metoprolol. This case highlights the importance of confirming the history provided by the patient through drug testing.

Patients with coingestants were included, which decreases the homogeneity of the sample but more likely represents what is clinically observed in practice, thereby increasing the external validity of this study.

After publication of animal studies in which large insulin infusions were reported to be beneficial in the treatment of verapamil toxicity,¹⁸⁻²⁰ hyperinsulinemic euglycemia therapy has been advocated in the treatment of humans for calcium-channel blocker poisoning. There has been suggestion that vasopressor therapy is inferior to insulin and that vasopressor therapy may even be harmful.^{5,12-13} However, it is our impression that patients seriously poisoned with verapamil and diltiazem almost always respond well to vasopressors and that death or permanent disability after such therapy is rare, even in the sickest patients. We reviewed a single center's experience during the past 25 years to determine whether these impressions were accurate.

Of those patients who received vasopressors, many received doses that were much higher than typically recommended in standard references. For example, one critical care text recommends maximal infusions of epinephrine of 10 $\mu\text{g}/\text{minute}$, norepinephrine of 30 $\mu\text{g}/\text{minute}$, isoproterenol of 1 to 10 $\mu\text{g}/\text{minute}$, and dopamine of 20 $\mu\text{g}/\text{kg}$ per minute,²¹ whereas another text lists the maximal recommended dose of dopamine at 30 $\mu\text{g}/\text{kg}$ per minute and of norepinephrine at 80 $\mu\text{g}/\text{minute}$.²² It has long been recognized that some critically ill patients require high-dose vasopressors and sometimes multiple vasopressors.²³ The

patients in our study did not appear to experience untoward complications of high-dose β - and α -adrenoreceptor agonists. All ischemic complications, with 2 possible exceptions, occurred before vasopressors were administered.

We conclude that management with high-dose vasopressors without hyperinsulinemic euglycemia is not detrimental, given complete recovery in all but 1 patient. The 3 cardiac arrests in our series occurred before administration of vasopressors. Once vasopressor infusions began, calcium-channel blocker–induced cardiac arrest did not recur. The single patient who died did so as a consequence of complications after a primary respiratory arrest from pulmonary aspiration.

Considering our results, the lack of human trials comparing hyperinsulinemic euglycemia therapy with vasopressors, and the limited evidence from case reports and unblinded animal studies, we recommend the use of initial fluid challenges and vasopressors as first choices in supporting blood pressure and treating shock caused by verapamil and diltiazem toxicity.

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REFERENCES

- Bronstein AC, Spyker DA, Cantilena LR Jr, et al. 2010 Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 28th Annual Report. *Clin Toxicol*. 2011;49:910-941.
- Abernethy DR, Schwartz JB. Calcium antagonist drugs. *N Engl J Med*. 1999;341:1447-1457.
- Brunton LL, Lazo JS, Parker KL, et al, eds. *Goodman & Gilman's the Pharmacological Basis of Therapeutics*. 11th ed. New York, NY: McGraw Hill; 2005.
- Arroyo AM, Kao LW. Calcium channel blocker toxicity. *Pediatr Emerg Care*. 2009;25:532-538.
- Marraffa JM, Cohen V, Howland MA. Antidotes for toxicological emergencies: a practical review. *Am J Health Syst Pharm*. 2012;69:199-212.
- Levine M, Boyer EW, Pozner CN, et al. Assessment of hyperglycemia after calcium channel blocker overdoses involving diltiazem or verapamil. *Crit Care Med*. 2007;35:2071-2075.
- Kems W 2nd. Management of beta-adrenergic and calcium channel antagonist toxicity. *Emerg Med Clin North Am*. 2007;25:309–331.
- Yuan TH, Kearns WP 2nd, Tomaszewski CA, et al. Insulin-glucose as adjunctive therapy for severe calcium channel antagonist poisoning. *J Toxicol Clin Toxicol*. 1999;37:463-474.
- Patel NP, Pugh ME, Goldberg S, et al. Hyperinsulinemic euglycemia therapy for verapamil poisoning: a review. *Am J Crit Care*. 2007;16:498-503.
- Shepherd G. Treatment of poisoning caused by beta-adrenergic and calcium-channel blockers. *Am J Health Syst Pharm*. 2006;63:1828-1835.
- Levine M, Brooks DE, Truitt CA, et al. Toxicology in the ICU: part 1: general overview and approach to treatment. *Chest*. 2011;140:795-806.
- Engelbrechtsen KM, Kaczmarek KM, Morgan J, et al. High-dose insulin therapy in beta-blocker and calcium channel-blocker poisoning. *Clin Toxicol*. 2011;49:277-283.
- Holger JS, Stellpflug SJ, Cole JB, et al. High-dose insulin: a consecutive case series in toxin-induced cardiogenic shock. *Clin Toxicol*. 2011;49:653-658.
- Gilbert EH, Lowenstein SR, Koziol-McLain J, et al. Chart reviews in emergency medicine research: what are the methods? *Ann Emerg Med*. 1996;27:305-308.
- Deters M, Bergmann I, Enden G, et al. Calcium channel antagonist exposures reported to the poison information center Erfurt. *Eur J Intern Med*. 2011;22:616-620.
- Megarbane B, Karyo S, Abidi K, et al. Predictors of mortality in verapamil overdose: usefulness of serum verapamil concentrations. *Basic Clin Pharmacol Toxicol*. 2011;108:385-389.
- Greene SL, Gawarammana I, Wood DM, et al. Relative safety of hyperinsulinaemia/euglycaemia therapy in the management of calcium channel blocker overdose: a prospective observational study. *Intensive Care Med*. 2007;33:2019-2024.
- Kline J, Raymond R, Leonova E, et al. Insulin improves heart function and metabolism during non-ischemic cardiogenic shock in awake canines. *Cardiovasc Res*. 1997;34:289-298.
- Kline J, Leonova E, Raymond R. Beneficial myocardial metabolic effects of insulin during verapamil toxicity in the anesthetized canine. *Crit Care Med*. 1995;23:1251-1263.
- Kline J, Tomaszewski C, Schroeder J, et al. Insulin is a superior antidote for cardiovascular toxicity induced by verapamil in the anesthetized canine. *J Pharmacol Exp Ther*. 1993;267:744-750.
- Givertz MM, Fang JC. Approach to the patient with hypotension and hemodynamic instability. In: Irwin RS, Rippe MJ, eds. *Irwin and Rippe's Intensive Care Medicine*. 7th ed. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins; 2012:307-317.
- Todd SR, Turner KL, Moore FA. Shock: general. In: Gabrielli A, Layon AL, Yu M, eds. *Civetta, Taylor, and Kirby's Critical Care*. 4th ed. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins; 2009:813-834.
- Dewitt CR. Calcium channel antagonist poisoning. In: Irwin RS, Rippe MJ, eds. *Irwin and Rippe's Intensive Care Medicine*. 7th ed. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins; 2012:1403-1409.