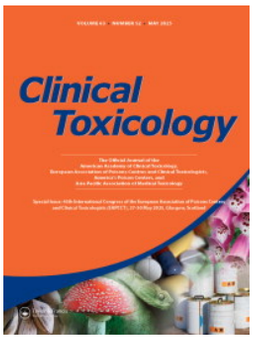

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POISON CENTRE RESEARCH

Mortality risk factors for patients with cardiotoxic exposures treated with high-dose insulin: analysis of the National Poison Data System®

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ABSTRACT

Introduction: High-dose insulin/glucose is an inotrope, vasodilator, and standard therapy for beta-adrenoceptor and calcium channel blocker poisoning, yet no large database studies have examined its use. This study sought to describe high-dose insulin use in the United States using the National Poison Data System®. Determining mortality risk factors was the primary aim.

Methods: We identified all National Poison Data System® cases in which "High dose insulin/glucose" therapy was Recommended or Performed from 2019 to 2021, the first three years National Poison Data System® allowed specific coding for high-dose insulin. We developed logistic regression models to determine clinical factors associated with death in patients receiving high-dose insulin. We also evaluated methylthioninium chloride (methylene blue) use as a refractory vasoplegia marker.

Results: High-dose insulin was used in 1,856 patients, primarily for exposures to calcium channel blockers ($n=1,116$ [60%]) and beta-adrenoceptor blockers ($n=985$ [53%]), with the most common drugs being amlodipine ($n=677$ [61%]) and metoprolol ($n=371$ [38%]). Death occurred in 431 [23%] patients; amlodipine was the most common cardiotoxicant in fatal exposures ($n=202$ [47%]). Calcium channel blocker exposure was significantly associated with death compared to beta-adrenoceptor blockers (odds ratio 2.2; 95% CI: 1.6–3.8). Exposure to verapamil, compared to amlodipine or diltiazem, was associated with death (odds ratio 1.7; 95% CI: 1.0–2.7). Increasing age, hyperglycemia, heart block, and concomitant treatment with mechanical ventilation or vasopressors were all associated with death. Methylthioninium chloride was more commonly used in patients with amlodipine exposures (110/677 [16%]) than with verapamil or diltiazem (7/325 [2%]; $P<0.001$).

Discussion: Among patients treated with high-dose insulin, amlodipine-exposed patients were more commonly treated with methylthioninium chloride, suggesting they experienced more refractory vasoplegia. As high-dose insulin is a vasodilator, more data are needed to better define the role for high-dose insulin in amlodipine poisoning.

Conclusion: In this study of patients treated with high-dose insulin, exposure to calcium channel blockers was more lethal than beta-adrenoceptor blocker poisoning. Amlodipine was the most common cardiotoxicant in patients who lived or died, while verapamil was the most lethal cardiotoxicant.

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Amlodipine; antidotes; beta-adrenoceptor blockers; calcium channel blockers; cardiotoxic agents; insulin; shock; poisoning; sotalol; verapamil

Introduction

Cardiovascular drugs are a common cause of poisoning in the United States (US). In 2023, they represented the fifth most common reason for calls to US poison centers, and calls continue to increase [1]. Cardiovascular drugs also commonly cause fatal poisonings in the US. In 2023, they were the third most common cause of fatal poisonings reported to US poison centers after analgesics and stimulants [1]. The majority of these fatalities were attributed to calcium channel blockers and beta-adrenoceptor blockers [1].

While many therapies are recommended for cardiotoxic poisoning, high-dose insulin has become a

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standard treatment for both calcium channel blocker and beta-adrenoceptor blocker poisoning [2–4]. At high doses (typically a regular insulin bolus of 1 U/kg, followed by an infusion of ≥1 U/kg/hour), insulin acts as an inotrope and vasodilator, increasing cardiac output in a dose-dependent fashion primarily via enhanced cardiac contractility [5,6]. While high-dose insulin is recommended by clinical/medical toxicologists [2,3] and consensus guidelines [7,8], clinical evidence is confined to a single randomized trial evaluating its use in aluminum phosphide poisoning [9], case reports, small series, and single poison center studies, most of which are descriptive in nature and do not identify risk factors for poor outcomes [10–12]. The use of high-dose insulin as a therapy for cardiotoxic poisoning has not been examined using larger, multicenter datasets.

Based on the existing human case experience, the use of high-dose insulin has expanded beyond the drugs for which it was studied [10,12–15]. This raises the possibility of unexamined drug-drug interactions between high-dose insulin and unstudied cardiotoxicants. Two such cardiac drugs of interest are amlodipine and sotalol.

Amlodipine and high-dose insulin both cause vasodilation via stimulation of endothelial nitric oxide synthase [16,17] leading some to posit that high-dose insulin may lead to synergistic vasodilation in amlodipine poisoning [18]. Methylthioninium chloride (methylene blue) is a nitric oxide scavenger and directly counteracts endothelial nitric oxide synthase to cause vasoconstriction [19]. Methylthioninium chloride is commonly used in amlodipine poisoning as rescue therapy for refractory vasoplegia [18,20,21].

Sotalol is unique among beta-adrenoceptor blockers in that it also possesses Vaughan Williams class III (potassium channel blockade) antidysrhythmic activity, which may cause ventricular dysrhythmias, including torsade de pointes [7,22]. High-dose insulin, via intracellular shifting of potassium, frequently causes hypokalemia, which can exacerbate QT interval prolongation and theoretically worsen the risk of ventricular dysrhythmias. To our knowledge, no studies have examined if patients with sotalol poisoning have a higher incidence of ventricular dysrhythmias in the setting of high-dose insulin therapy.

In 2019, America's Poison Centers® modified the National Poison Data System® (NPDS®) to allow high-dose insulin to be coded as a specific therapy ("High dose insulin/glucose") [23]. As such, the purpose of the present study is to describe the use of high-dose insulin for poisoning throughout the US. Our primary objective was to determine mortality risk factors for patients treated with high-dose insulin. Secondary outcomes included mortality by drug class and specific cardiotoxic drug, the use of methylthioninium chloride in amlodipine poisoning as a marker for refractory vasoplegia, and the incidence of ventricular dysrhythmias in sotalol poisoning. This study [24] has been published in abstract.

Methods

Study design

This was a retrospective cohort study of patients reported to the NPDS® from 1 January 2019 to 31 December 2021, for which "High dose insulin/glucose" was coded as a Recommended or Performed therapy. This study was approved by our institutional review board.

Data source and patient population

The NPDS® is managed and owned by America's Poison Centers®, the organization that accredits and supports all 53 accredited US poison centers. The NPDS® contains over 81 million exposure cases and dates back to 1983. Pharmacists, nurses, physicians, and doctors of philosophy with specialty toxicology training collect all NPDS® data in real time and use a systematic tool to prospectively track therapies, and assign predefined clinical effects, reasons for exposure, and adjudicate clinical outcomes on a five-point ordinal scale ("No effect," "Minor effect," "Moderate effect," "Major effect," "Death"). Definitions of each outcome are provided in Supplemental Table 1. Therapies, after discussion with the treating clinicians, are coded as "Recommended," "Performed," "Recommended and performed," or "Recommended/known not performed." Narrative case notes from individual case records were not reviewed as part of this study.

Inclusion and exclusion criteria

We identified all cases reported to the NPDS® from 2019 to 2021 in which "High dose insulin/glucose" was coded. Patients were excluded if "High dose insulin/glucose" was coded as "Recommended/known not performed" or "Recommended" only. Patients were included if "High dose insulin/glucose" was coded as "Recommended and performed" or "Performed" only.

Outcomes

In addition to the five-point ordinal NPDS® clinical outcomes noted previously, standard NPDS® outcomes are also reported. Specific, pre-existing definitions of all

outcomes, reasons for exposure, clinical effects, and therapies are available in the NPDS® coding manual and are provided in Supplemental Tables 1–4 [25]. The primary outcome of interest, death, was defined as occurring as a direct result of the exposure, or a complication directly related to the exposure. Secondary outcomes included mortality by drug class and specific cardiotoxic drug, including sub-analyses of single-substance cases. Last, sub-analyses were planned to examine potential drug-drug interactions between high-dose insulin and two unique cardiotoxicants, amlodipine and sotalol, given their unique pharmacodynamic and toxicodynamic effects compared to other common calcium channel and beta-adrenoceptor blockers.

Data analysis

Descriptive statistics are reported. Medians, interquartile ranges, ranges, and confidence intervals were calculated and reported when appropriate. Comparisons were made using Fisher's exact and Chi-squared tests as appropriate.

Two logistic regression models were developed, one to evaluate the association of xenobiotic class (beta-adrenoceptor blocker or calcium channel blockers) with death, and the other to evaluate the association of common calcium channel blockers (diltiazem, verapamil, and amlodipine) with death. In each model we also included independent variables associated with mortality in the setting of overdose, including age, the use of vasopressors, the presence of hyperglycemia or heart block (NPDS® code "Heart block (2nd, 3rd degree)"), the ingestion of additional xenobiotics (i.e., the ingestion of any additional substance other than a beta-adrenoceptor or calcium channel blocker), endotracheal intubation and mechanical ventilation (NPDS® code "Ventilator"), and the intentionality of the exposure [26–30]. Polysubstance exposure was defined as exposure to two or more substances as coded in NPDS®. Exposures were defined as "Intentional" if coded within NPDS® as "Intentional – abuse," "Intentional – misuse," "Intentional – suspected suicide," "Intentional – unknown," or "Other – malicious." Exposures coded within NPDS® as "Unintentional – general," "Unintentional – misuse," "Unintentional – occupational," "Unintentional – therapeutic error," or "Unintentional – unknown" were defined as "Unintentional;" those coded as "Unknown" were excluded [8]. In both models we excluded those cases in which the reason was coded as "Unknown." In the second model (diltiazem versus verapamil versus amlodipine), we excluded cases in which exposure was to multiple calcium channel blockers or in which there was exposure to both calcium channel and beta-adrenoceptor blockers to avoid lack of clarity related to the relative contributions of multiple exposures; other substances were included and accounted for in the model.

Data were analyzed utilizing Microsoft Excel (Microsoft, Redmond, WA) and Stata/BE 17 (StataCorp. 2021. Stata statistical software: Release 17. College Station, TX: StataCorp LLC).

Sub-analyses of unique cardiotoxic drugs

Two unique drugs were identified for pre-specified sub-analyses: amlodipine and sotalol. We sought to determine if patients exposed to amlodipine more commonly received methylthioninium chloride compared to other calcium channel blockers, which could be a marker for the presence of refractory vasoplegia. We also sought to determine if patients exposed to sotalol more commonly suffered ventricular dysrhythmias (NPDS® codes "V. tachycardia/V. fibrillation" or "Torsade de pointes") than patients exposed to other beta-adrenoceptor blockers.

Results

We identified 2,556 patients in the NPDS® on our initial data query; 700 patients were excluded as high-dose insulin was coded as "Recommended only" or "Recommended but not performed" leaving 1,856 patients with high-dose insulin coded as "Performed" for final analysis. Death was more common in patients with high-dose insulin coded as "Performed" (431/1,856 [23%]) compared to cases in which high-dose insulin was recommended but not performed (86/700 [12%]; $P<0.001$). Study enrollment is outlined in Figure 1.

Characteristics of study subjects receiving high-dose insulin

High-dose insulin therapy was performed in all 50 United States. Of the 1,856 poisonings treated with high-dose insulin, 579 occurred in 2019, 633 occurred in 2020, and 644 occurred in 2021. The median age was 53 years; 55% were female. Only 10 cases occurred in children under 13 years of age, two of whom died. One child, aged 14 months, died after a reported "adverse drug reaction" to diltiazem and sotalol, while a second child, aged 2 years, died after a reported "Unintentional-general exposure" to nifedipine and

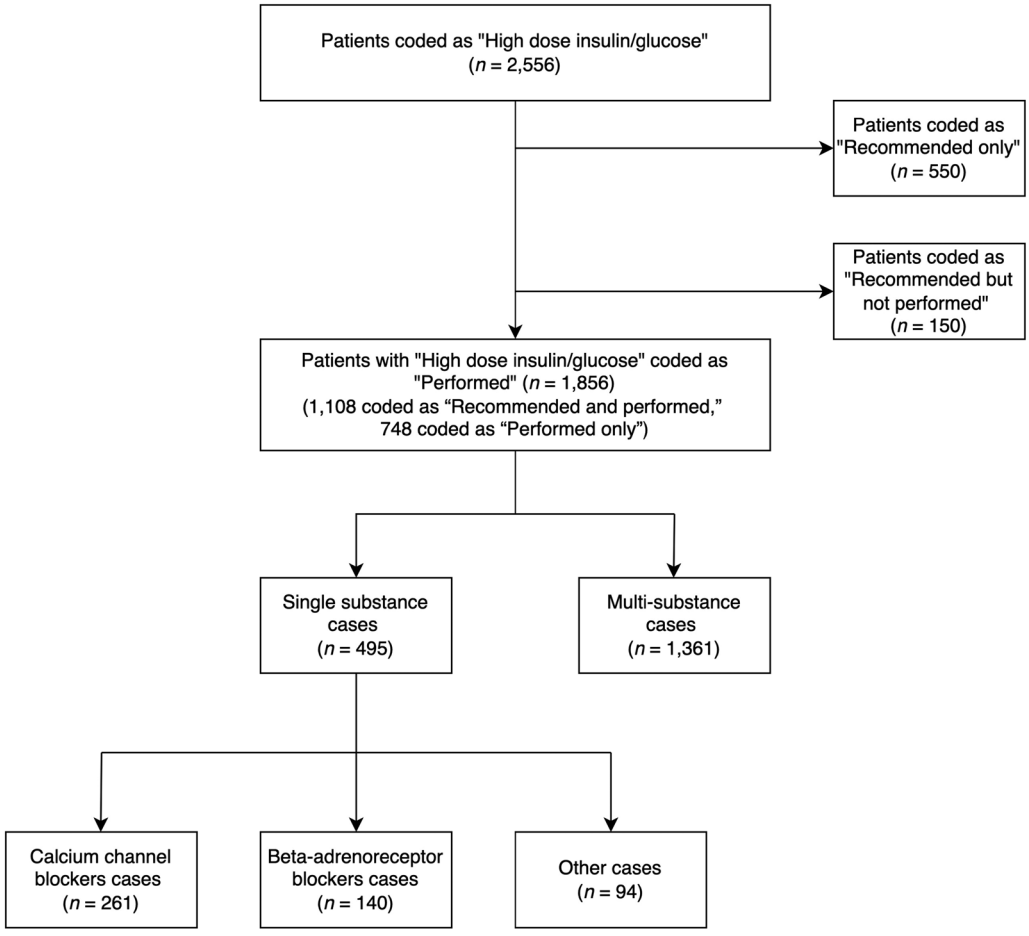

Figure 1. Study flow diagram.

labetalol. For the entire cohort, amlodipine was the most common cardiotoxicant associated with death ($n = 202$ [47%]), followed by verapamil ($n = 49$ [11%]).

High-dose insulin was used primarily for calcium channel blockers ($n = 1,116$ [60%]) and beta-adrenoceptor blockers ($n = 985$ [53%]), with the most common drugs being amlodipine ($n = 677$ [61%]) and metoprolol ($n = 371$ [38%]). Outcomes, clinical effects, and additional concomitant therapies are displayed in Table 1. Reasons for exposure are outlined in granular detail in Supplemental Table 5.

Mortality risk factors for all patients exposed to beta-adrenoceptor or calcium channel blockers

The results of regression model one, evaluating mortality associated with calcium channel and beta-adrenoceptor blocker exposure in 1,636 patients receiving high-dose insulin therapy, are presented in Table 2. Two hundred and twenty cases were excluded due to incomplete intentionality data, exposure to other than calcium channel or beta-adrenoceptor blockers, or due to exposure of more than one calcium channel or beta-adrenoceptor blocker. Goodness-of-fit testing demonstrated acceptable model fit (Hosmer-Lemeshow $X^2 = 3.29$; $P = 0.92$). A sensitivity analysis performed on model one, removing all exclusions save a substance other than calcium channel or beta-adrenoceptor blockers, did not change the results of the presented analysis.

Calcium channel blocker exposure was significantly associated with death compared to beta-adrenoceptor blocker exposure (OR 2.2; 95% CI: 1.6–3.8), as was co-ingestion of both drug classes (OR 1.6; 95% CI: 1.1–2.4). Increasing age, hyperglycemia, heart block, and concomitant treatment with mechanical ventilation or vasopressors were all associated with death (Table 2). Goodness-of-fit testing demonstrated acceptable model fit (Hosmer-Lemeshow $X^2 = 4.84$; $P = 0.77$)

Mortality risk factors for all patients exposed to calcium channel blockers

The results of regression model two, comparing mortality associated with amlodipine, diltiazem, and verapamil in 933 patients treated with high-dose insulin,

Table 1. Outcomes, clinical effects and concomitant therapies for patients in whom high-dose insulin was administered.

Variables	High-dose insulin administered ($n = 1,856$)
Age (years)	
0–5, *n* (%)	4 (0.2)
6–12, *n* (%)	6 (0.3)
13–19, *n* (%)	121 (6.5)
≥20, *n* (%)	1,725 (93)
Reason for exposure	
Intentional, *n* (%)	1,607 (87)
Unintentional, *n* (%)	114 (6)
Adverse reaction, *n* (%)	52 (3)
Other, *n* (%)	1 (0.1)
Unknown, *n*	82
Beta-adrenoreceptor blockers, *n* (%)	985
Metoprolol, *n* (%)	371 (38)
Atenolol, *n* (%)	75 (8)
Propranolol, *n* (%)	196 (20)
Carvedilol, *n* (%)	207 (21)
Labetalol, *n* (%)	33 (3)
Sotalol, *n* (%)	11 (1)
Other beta-adrenoreceptor blockers, *n* (%)	92 (9)
Calcium channel blockers, *n* (%)	1,116
Non-dihydropyridines, *n* (%)	325 (29)
Diltiazem, *n* (%)	189 (17)
Verapamil, *n* (%)	136 (12)
Dihydropyridines, *n* (%)	729 (65)
Amlodipine, *n* (%)	677 (61)
Nifedipine, *n* (%)	49 (4)
Nicardipine, *n* (%)	2 (0.2)
Nimodipine, *n* (%)	1 (0.1)
Felodipine, *n* (%)	0
Other calcium channel blockers, *n* (%)	62 (6)
Selected clinical effects	
Asystole, *n* (%)	367 (20)
Bradycardia, *n* (%)	1,010 (54)
ECG change-QTc interval prolongation, *n* (%)	288 (16)
Electrolyte abnormality, *n* (%)	683 (37)
Heart block (2nd, 3rd degree), *n* (%)	67 (4)
Hyperglycemia, *n* (%)	360 (19)
Hypoglycemia, *n* (%)	237 (13)
Hypotension, *n* (%)	1,652 (89)
Pulseless electrical activity, *n* (%)	90 (5)
Kidney failure, *n* (%)	118 (6)
Torsade de pointes, *n* (%)	5 (0.3)
Troponin concentration increase, *n* (%)	33 (2)
Ventricular tachycardia/ventricular fibrillation, *n* (%)	34 (2)
Selected other therapies	
Activated charcoal (any), *n* (%)	320 (17)
Alkalinization – systemic, *n* (%)	379 (20)
Antidysrhythmic, *n* (%)	62 (3)
Calcium, *n* (%)	1,206 (65)
Cardiopulmonary resuscitation, *n* (%)	210 (11)
Dextrose, >5%, *n* (%)	862 (46)
Extracorporeal membrane oxygenation, *n* (%)	98 (5)
Gastric lavage, *n* (%)	22 (1)
Glucagon, *n* (%)	1,008 (54)
Hemodialysis, *n* (%)	145 (8)
Lipid emulsion therapy, *n* (%)	378 (20)
Mechanical ventilation, *n* (%)	1,062 (57)
Methylthioninium chloride, *n* (%)	154 (8)
Pacemaker, *n* (%)	172 (9)
Potassium, *n* (%)	647 (35)
Vasopressors, *n* (%)	1,612 (87)
Whole bowel irrigation, *n* (%)	39 (2)
National Poison Data System® outcome	
Moderate, *n* (%)	480 (26)
Major, *n* (%)	884 (48)
Death, *n* (%)	431 (23)
Other, *n* (%)	61 (3)

are presented in Table 3. Fifty cases were excluded due to exposure to multiple calcium channel blockers, to a calcium channel blocker with a beta-adrenoceptor blocker, or due to incomplete data regarding intentionality of exposure. Sensitivity analysis of the model removing all exclusions save a substance other than

calcium channel blockers eliminated the significant difference in odds of death between verapamil and amlodipine.

Exposure to verapamil, compared to amlodipine as the reference cardiotoxicant, was associated with death (OR 1.7; 95% CI: 1.0–2.7). Increasing age, hyperglycemia, heart block, and concomitant treatment with mechanical ventilation or vasopressors were all associated with death.

Single substance cases

There were 495 cases with a single substance coded; 261 involving calcium channel blockers, and 140 involving beta-adrenoceptor blockers. Among single substance cases, mortality was higher among patients exposed to calcium channel blockers ($n = 65$ [25%]) than with beta-adrenoceptor blockers ($n = 13$ [9%]; $P < 0.001$). The most common cardiotoxicants in single substance cases were amlodipine and verapamil. Amlodipine was the most common cause of death among single substance cases (Figure 2). Mortality data for individual single substance calcium channel or beta-adrenoceptor blocker cases are additionally stratified by age in Supplemental Table 6. Single substance cases are further characterized by concomitant clinical effects in Table 4 and concomitant therapies in Table 5. Supplemental Table 7 displays single substance cases treated with high-dose insulin not involving calcium channel or beta-adrenoceptor blockers; the most common substance was digoxin ($n = 9$).

Table 2. Risk factors for death among calcium channel and beta-adrenoceptor blocker exposures treated with high-dose insulin therapy ($n = 1{,}636$).

Variable	Odds ratio	95% confidence interval	*P* value
Xenobiotic			
Beta-adrenoceptor blocker (reference)	1		
Calcium channel blocker	2.25	1.64–3.09	<0.001
Both calcium channel and beta-adrenoceptor blockers	1.63	1.12–2.37	0.011
Age (years)			
<18 years (reference)	1		
18–29	2.14	0.88–5.2	0.093
30–49	3.19	1.49–6.83	0.003
50–69	4.17	1.98–8.75	<0.001
>70	7.81	3.56–17.14	<0.001
Vasopressors used	4.43	1.9–10.33	0.001
Hyperglycemia present	2.02	1.54–2.64	<0.001
Heart block present	2.14	1.23–3.7	0.007
Polysubstance exposure	1.23	0.91–1.67	0.18
Mechanically ventilated	3.64	2.67–4.96	<0.001
Intentional exposure	1.32	0.77–2.23	0.311

Amlodipine subgroup

Among patients exposed to calcium channel blockers treated with high-dose insulin, the use of methylthioninium chloride was more common in patients exposed to amlodipine (110/677 [16%]) than those exposed to verapamil or diltiazem (7/325 [2%]; $P < 0.001$). This finding persisted when examining single substance cases (24/113 [21%] for amlodipine versus 4/120 [3%] for verapamil or diltiazem; $P < 0.05$).

Sotalol subgroup

Among patients exposed to beta-adrenoceptor blockers and treated with high-dose insulin, we found ventricular tachycardia or fibrillation were more common in patients exposed to sotalol (4/11 [35%]) than all other beta-adrenoceptor blockers (16/974 [1.6%]; $P < 0.05$). Similarly, we found torsade de pointes to be more common in patients exposed to sotalol (2/11 [18%]) than those exposed to other beta-adrenoceptor blockers (2/974 [0.2%]; $P < 0.05$). Three single-substance sotalol cases were treated with high-dose insulin: two experienced ventricular tachycardia or ventricular fibrillation, two experienced torsade de pointes, and two experienced ventricular tachycardia or ventricular fibrillation and torsade de pointes.

Discussion

In this analysis of the first three years in which high-dose insulin was a codable therapy in NPDS®, we found that high-dose insulin was most commonly used for amlodipine exposure. High-dose insulin appears to have gained widespread acceptance as a therapy for

Table 3. Risk factors for death among specific calcium channel blocker exposures treated with high-dose insulin therapy ($n = 933$).

Variable	Odds ratio	95% confidence interval	*P* value
Xenobiotic			
Amlodipine (reference)	1		
Diltiazem	0.89	0.57–1.39	0.605
Verapamil	1.66	1.04–2.66	0.034
Age			
<18 years (reference)	1		
18–29	1.90	0.63–5.79	0.257
30–49	4.66	1.86–11.67	0.001
50–69	5.65	2.31–13.83	<0.001
>70	10.97	4.26–28.27	<0.001
Vasopressors used	5.04	1.52–16.70	0.008
Hyperglycemia present	2.13	1.56–2.92	<0.001
Heart block present	2.14	1.12–4.09	0.022
Polysubstance exposure	1.29	0.89–1.87	0.182
Mechanically ventilated	3.27	2.25–4.76	<0.001
Intentional exposure	1.82	0.95–3.5	0.074

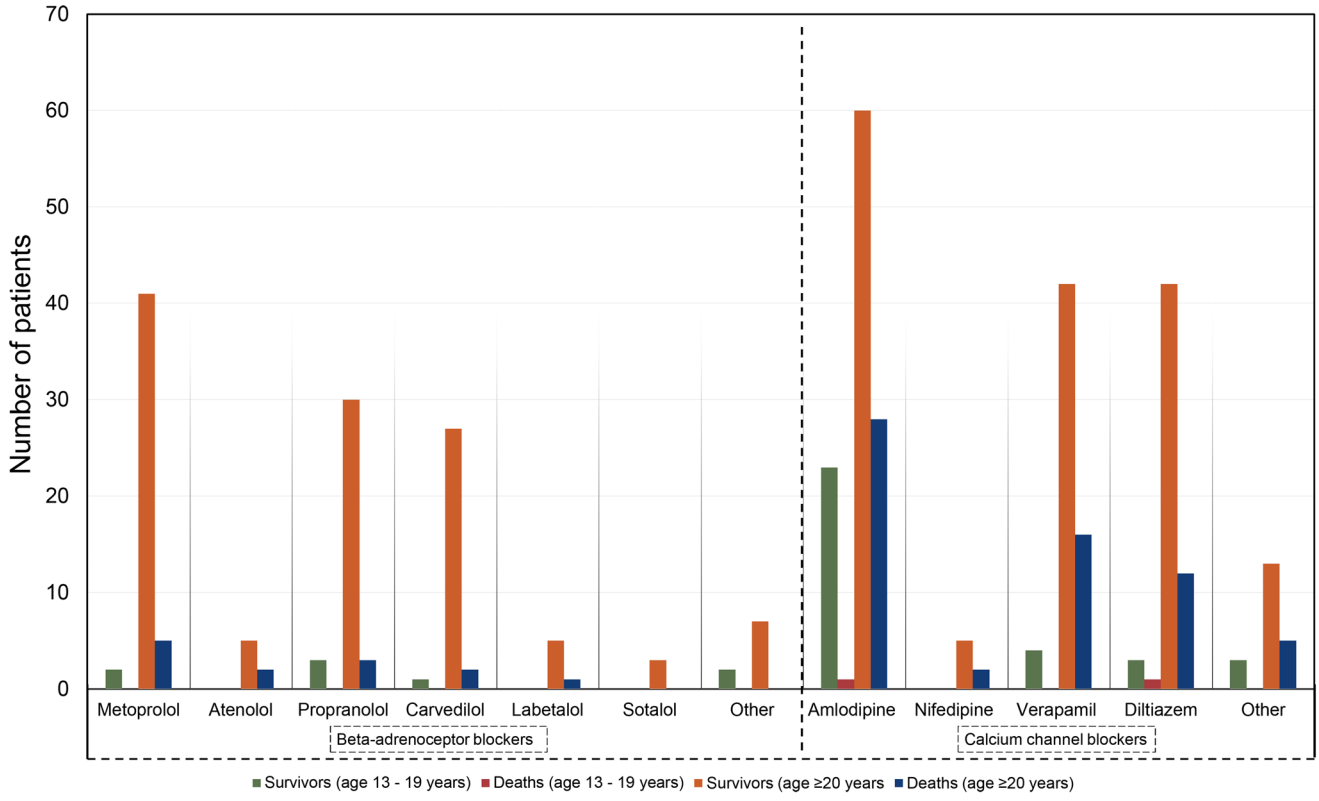

Figure 2. Mortality for single-product beta-adrenoceptor blocker or calcium channel blocker ingestion cases. *for ages <13 years, there were two survivors (one other beta-adrenoceptor blocker, and one amlodipine) and no deaths.

Table 4. Clinical effects for common single substance cases.

	Most common calcium channel blockers			Most common beta-adrenoceptor blockers		
Clinical effects	Amlodipine (*n* = 113)	Verapamil (*n* = 62)	Diltiazem (*n* = 58)	Metoprolol (*n* = 48)	Propranolol (*n* = 36)	Carvedilol (*n* = 30)
Acidosis, *n* (%)	44 (39)	22 (36)	23 (40)	7 (15)	6 (17)	3 (10)
Aspartate and alanine aminotransferase activity >1,000 U/L, *n* (%)	1 (1)	2 (3)	1 (2)	0	0	2 (7)
Asystole, n (%)	23 (20)	15 (24)	13 (22)	6 (13)	7 (19)	2 (7)
Bradycardia, *n* (%)	27 (23)	48 (77)	39 (67)	27 (56)	20 (56)	15 (50)
Central nervous system depression (major), *n* (%)	17 (15)	17 (27)	13 (22)	8 (17)	10 (28)	3 (10)
Creatinine concentration increased, *n* (%)	33 (29)	18 (29)	13 (22)	3 (6)	2 (6)	1 (3)
Disseminate intravascular coagulation, *n* (%)	0	1 (2)	0	0	0	0
ECG change – QRS interval prolongation, *n* (%)	6 (5)	8 (13)	4 (7)	1 (2)	7 (19)	2 (7)
ECG change – QTc interval prolongation, *n* (%)	9 (8)	5 (8)	4 (7)	1 (2)	7 (19)	4 (13)
Electrolyte abnormality, *n* (%)	43 (38)	21 (34)	17 (29)	8 (17)	9 (25)	7 (23)
Heart block (2nd, 3rd degree), *n* (%)	4 (4)	7 (11)	5 (9)	0	0	1 (3)
Hyperglycemia, *n* (%)	35 (31)	28 (45)	21 (36)	2 (4)	1 (3)	2 (7)
Hypoglycemia, *n* (%)	6 (5)	8 (13)	6 (10)	7 (15)	5 (14)	6 (20)
Hypotension, *n* (%)	105 (93)	58 (94)	52 (80)	41 (85)	30 (83)	26 (87)
Hypoxic brain injury, *n* (%)	1 (1)	0	0	1 (2)	0	0
Oliguria/anuria, *n* (%)	17 (15)	7 (11)	10 (17)	1 (2)	0	2 (7)
Pulmonary edema, *n* (%)	13 (11)	2 (3)	4 (7)	0	0	0
Pulseless electrical activity, *n* (%)	3 (3)	4 (7)	6 (10)	5 (10)	1 (3)	1 (3)
Kidney failure, *n* (%)	12 (11)	4 (7)	2 (3)	0	1 (3)	0
Seizures (any)[a], *n* (%)	2 (2)	2 (3)	2 (3)	0	5 (14)	1 (3)
Tachycardia, *n* (%)	42 (37)	5 (8)	8 (14)	1 (1)	5 (14)	0
Torsade de pointes, *n* (%)	0	0	0	0	0	0
Troponin concentration increased, *n* (%)	3 (3)	3 (5)	2 (3)	0	0	1 (3)
Ventricular tachycardia/ventricular fibrillation, *n* (%)	1 (1)	1 (2)	1 (2)	0	0	0

[a]Seizures (any) includes any of the following NPDS codes: "seizure (single)," "seizures (multi/discrete)," and "seizures (status)."

both calcium channel and beta-adrenoceptor blocker exposures, as it was used in all 50 states and was implemented over 500 times per year. Patients treated with high-dose insulin after exposure to calcium channel blockers were at greater odds of death compared to those exposed to beta-adrenoceptor blockers.

Table 5. Concomitant therapies for common single substance cases.

	Most common calcium channel blockers			Most common beta-adrenoceptor blockers		
Concomitant therapies	Amlodipine (*n* = 113)	Verapamil (*n* = 62)	Diltiazem (*n* = 58)	Metoprolol (*n* = 48)	Propranolol (*n* = 36)	Carvedilol (*n* = 30)
Activated charcoal (any)[a], *n* (%)	25 (22)	13 (21)	12 (21)	7 (15)	10 (28)	2 (7)
Alkalinization – systemic, *n* (%)	21 (19)	10 (16)	10 (17)	2 (4)	7 (19)	2 (7)
Antidysrhythmic, *n* (%)	5 (4)	4 (7)	2 (3)	0	2 (6)	0
Calcium, *n* (%)	95 (84)	51 (82)	50 (86)	15 (31)	14 (39)	15 (50)
Cardioversion, *n* (%)	1 (1)	2 (3)	0	0	0	0
Continuous kidney replacement therapy, *n* (%)	18 (16)	4 (7)	7 (12)	1 (2)	1 (3)	1 (3)
Cardiopulmonary resuscitation, *n* (%)	7 (6)	5 (8)	8 (14)	3 (6)	5 (14)	3 (10)
Dextrose, >5%, *n* (%)	47 (42)	30 (48)	30 (52)	18 (38)	16 (44)	14 (47)
Extracorporeal membrane oxygenation, *n* (%)	19 (17)	2 (3)	2 (3)	0	0	0
Gastric lavage, *n* (%)	0	0	1 (2)	0	0	0
Glucagon, *n* (%)	35 (31)	24 (39)	26 (45)	32 (67)	23 (64)	20 (67)
Hemodialysis, *n* (%)	14 (12)	3 (5)	3 (5)	3 (6)	2 (6)	1 (3)
Hydroxocobalamin, *n* (%)	4 (4)	1 (2)	0	0	0	0
Lipid emulsion therapy, *n* (%)	28 (25)	16 (26)	10 (17)	3 (6)	8 (22)	5 (17)
Magnesium, *n* (%)	15 (13)	11 (18)	8 (14)	5 (10)	7 (19)	3 (10)
Mechanical ventilation, *n* (%)	61 (54)	32 (52)	27 (47)	18 (38)	21 (58)	8 (27)
Methylthioninium chloride, *n* (%)	24 (21)	2 (3)	2 (3)	0	0	2 (7)
Octreotide, *n* (%)	0	0	0	0	0	0
Pacemaker, *n* (%)	4 (4)	10 (16)	12 (21)	3 (6)	4 (11)	4 (13)
Potassium, *n* (%)	51 (45)	24 (39)	16 (28)	9 (19)	15 (42)	12 (40)
Vasopressors, *n* (%)	101 (90)	57 (92)	48 (83)	33 (69)	27 (75)	24 (80)
Whole bowel irrigation, *n* (%)	3 (2)	2 (3)	4 (7)	0	2 (6)	0

[a]Activated charcoal includes either of the following NPDS® codes: "charcoal, single dose" or "charcoal, multiple doses."

Among patients exposed to calcium channel blockers, though amlodipine was associated with the greatest number of fatalities, patients exposed to verapamil had the highest odds of death. Similar to other studies, we found increasing age, hyperglycemia, heart block, and concomitant treatment with mechanical ventilation or vasopressors were all associated with death [26,27,29,30].

Unlike the vast majority of toxicologic studies [26,31], intentional ingestion was not associated with death in our study. The cause for this is uncertain. The vast majority of our cases (*n* = 1,542; Supplemental Table 5) involved intentional exposures with suspected suicide; 24% of whom died. While unintentional-general cases were far less common (*n* = 22), eight of these patients died, making for a similar case-fatality rate. This result may be a reflection of the narrow therapeutic index of many cardiovascular drugs. For instance, nifedipine has been described to cause fatal poisoning in a child after ingestion of a single pill [32]. Coding errors may also have clouded the data, given the relatively small number of unintentional cases. Another explanation is that once a patient is ill enough that high-dose insulin is employed, the reason for the exposure simply is no longer associated with survival.

We also did not find polysubstance exposures to be associated with fatal outcomes. In polysubstance exposures, this likely was due to our a priori definition, as we defined ingestion of any additional substances as polysubstance exposures. Minimally toxic co-exposures may have biased our results toward the null. Results demonstrated, however, that for patients exposed to beta-adrenoreceptor blockers, concomitant exposure to a calcium channel blocker was associated with increased odds of death (OR = 2.25; 95% CI: 1.64–3.09), suggesting the toxicity of the co-exposed drug plays an important role. This finding was consistent with prior literature on beta-adrenoreceptor blocker poisoning [28].

Similar to other studies, we found amlodipine to be the most common cause of fatal cardiotoxic poisoning [33,34]. This finding, however, likely reflects an overall increase in amlodipine prescriptions [35] rather than a proclivity for amlodipine to cause more severe poisoning, as we found verapamil to be more strongly associated with death. Our findings align with historical and recent data suggesting verapamil is a more potent cardiotoxicant after overdose than dihydropyridines such as amlodipine [34,36,37]. We also found hyperglycemia to be associated with death. In overdose, verapamil blocks pancreatic calcium channels, leading to insulin resistance and hyperglycemia [38], and in patients exposed to diltiazem or verapamil, higher serum glucose concentrations correlate with more severe toxicity [27], though a similar correlation was not seen in amlodipine poisoning [39]. Though we found hyperglycemia correlated with death regardless of drug class, the diabetogenic effects of verapamil may have accounted solely for this finding in our analysis. Though the existing high-dose insulin literature is

stronger for verapamil than any other cardiotoxic medication [6,13,38,40,42], our findings suggest high-dose insulin is not a panacea in verapamil poisoning, highlighting the need for multi-modal treatment or mechanical circulatory support, such as veno-arterial extracorporeal membrane oxygenation [43,44], in profound shock from verapamil.

Calcium channel blockers functionally belong to two categories: dihydropyridines, such as amlodipine, and non-dihydropyridines, like diltiazem and verapamil. Verapamil and diltiazem tend to have more central myocardial effects, resulting in reduced cardiac contractility, depressed sinoatrial node activity, and slowed atrioventricular node activity, while dihydropyridines tend to result primarily in vasodilation and reflex tachycardia, though in severe poisoning reduced cardiac contractility also occurs [15,45]. Review articles and consensus guidelines, however, generally make recommendations on calcium channel blocker poisoning as if toxicity is homogenous, with the notion that class specificity is lost in overdose [2,3,8,46]. We found, however, that patients exposed to amlodipine treated with high-dose insulin more commonly received methylthioninium chloride, suggesting refractory vasoplegia may have been more common in this group. While it has been suggested that such vasoplegia may be owing to synergism between amlodipine and high-dose insulin, this remains theoretical [18]. Regardless of its cause, clinicians will likely need to manage severe vasoplegia in amlodipine overdose, and current literature is unclear as to the optimal use of high-dose insulin in this setting.

Though these data suggest that amlodipine is now the most common cardiotoxic drug exposure treated with high-dose insulin reported to US poison centers, comparative effectiveness data supporting the use of high-dose insulin for amlodipine poisoning remain sparse. To our knowledge, large animal experiments supporting the use of high-dose insulin to treat calcium channel blocker poisoning are confined to a series of experiments on dogs exposed to verapamil [6,13,38,40,42] and a single swine study examining nifedipine poisoning [15]. Existing large animal models of dihydropyridine poisoning demonstrate there is a cardiogenic component of severe shock [15,45], suggesting high-dose insulin may be beneficial in some cases. Large animal models of amlodipine poisoning exist but have not examined high-dose insulin [47,48]. More data are needed to better define the role of high-dose insulin in amlodipine poisoning.

We found that patients treated with high-dose insulin for beta-adrenoceptor blocker exposure had better outcomes than those exposed to calcium channel blockers. To our knowledge, large animal data on beta-adrenoceptor blocker poisoning is limited to models of propranolol toxicity [5,14,49,51]. We found clinicians used high-dose insulin for exposures to numerous beta-adrenoceptor blockers, all of which had similar mortality outcomes (Figure 2; Supplemental Table 5). Notably, patients exposed to sotalol more commonly experienced ventricular dysrhythmias than those exposed to other beta-adrenoceptor blockers. As high-dose insulin causes hypokalemia which may exacerbate QT interval prolongation and ventricular dysrhythmia risk, other therapies, such as chronotropes, pacemakers, and hemodialysis may be preferred in sotalol poisoning [22,52]. Given the limitations of our data, however, it is impossible to know for certain if these patients would have experienced ventricular dysrhythmias without exposure to high-dose insulin as sotalol poisoning so commonly causes dysrhythmias in and of itself [53].

While the vast majority of cases involved calcium channel and beta-adrenoceptor blocker poisoning, we identified 94 additional single substance cases involving other xenobiotics. On occasion, clinicians have used high-dose insulin to treat shock from cardiotoxicants other than calcium channel and beta-adrenoreceptor blockers, such as aluminum phosphide [9], bupropion [54], citalopram [55], venlafaxine [56], and caffeine [57], as well as stress cardiomyopathy from funnel web spider envenomation [12]. The mechanisms of action of high-dose insulin are not unique to calcium channel or beta-adrenoceptor blockers [55]. Future work should examine the use of high-dose insulin for other common cardiotoxicants known to cause cardiogenic shock, particularly those commonly treated with invasive therapies like veno-arterial extracorporeal membrane oxygenation, such as bupropion [44,58,59]. While there are substantial risks to high-dose insulin, such as volume overload [60], electrolyte derangements [12], and prolonged hypoglycemia [61,62], these are all likely preferable to the complications associated with veno-arterial extracorporeal membrane oxygenation [63].

We found high-dose insulin was rarely used in children, highlighting a gap in the pediatric toxicologic literature. Of the 131 pediatric patients receiving high-dose insulin in the present study, 121 were ages 13–19 years, demonstrating pediatric intensivists most commonly used high-dose insulin in children sized closer to adults. A recent analysis of 13 years of data from poisoned children treated in 40 unique intensive care units revealed only 17 cases in which high-dose insulin was used, consistent with our findings [64]. The fact that high-dose insulin was used primarily in

teenagers is likely because children under 13 years of age typically present with relatively small unintentional exposures and are not ill enough to warrant high-dose insulin, though we did identify one such fatal case. The true reason for the low frequency use of high-dose insulin in children is unknown. For example, we do not know if adoption of high-dose insulin was similar between adult and pediatric intensivists during the study period. Complicating matters, small children have unique anatomic and physiologic differences relevant to the use of high-dose insulin. They have small veins, which may preclude the use of concentrated dextrose solutions. They are also more prone to hypoglycemia than adults. Further study on the use of high-dose insulin in children is warranted, particularly since these data may not represent current approaches to these poisonings in children.

Limitations

This study has several limitations, including the usual limitations of observational poison center studies such as inaccurate clinical data [65]. For example, we were unable to view individual medical records to confirm high-dose insulin was actually administered. Cases may have been coded incorrectly in the categorical field for high-dose insulin in the NPDS®. We believe the large number of cases in our study helps mitigate this limitation, however. The majority of our cases involved cardiotoxicants, treatments, and clinical effects that were similar to studies examining hospital-level data, suggesting our study has face validity [12,34,66]. Confirmatory blood or urine testing is also frequently lacking in poison center data, nor is there a standardized way to request such data from NPDS®. Cases severe enough to be treated with high-dose insulin, however, were likely diagnosed clinically rather than with the aid of laboratory testing, as confirmatory testing is frequently unavailable in a timely manner for such cases. Furthermore, the observational nature of our study makes inferring causality impossible. We can only make associations. High-dose insulin was used in tandem with numerous other treatments, many of which are often used as salvage therapies. High-dose insulin may have merely been a marker of severity of illness.

The NPDS® also does not allow for an assessment of comorbidities. For example, inotropes, including high-dose insulin, often have limited utility in patients with underlying heart disease, and prior cardiac disease is a risk factor for in-hospital cardiovascular adverse events after drug overdose [10,29,67]. Other underlying conditions, such as liver or kidney disease, may have also contributed to poorer outcomes. While we observed the risk of death to increase with age, which may be a reflection of increasing comorbidities that often accumulate as patients age, comorbidities are not recorded in NPDS®. Hospital-level data are needed to address the roles comorbidities play in cardiotoxicant poisoning.

An additional limitation of using NPDS® for studying any therapy is it does not allow for determining sequencing or dosing of therapies; NPDS® only demonstrates if two or more therapies were administered to the same patient for the same poisoning. An area of controversy regarding high-dose insulin is whether to initiate the treatment as a rescue therapy after vasopressors or other inotropes [68] or if it should be the first-line therapy after simple, supportive treatments such as intravenous crystalloid fluids, atropine, and calcium [69]. Animal data show high-dose insulin to be clearly superior to vasopressors [13,14,49,51]; hence, some recommend using it before vasopressors [69]. Others note the side effects of high-dose insulin and high demands on nursing, including frequent glucose measurements, the need to manage multiple infusions, as well as the general paucity of experience in human poisonings compared with vasopressors; as such, they recommend vasopressors be tried first [68]. We also were unable to determine doses of therapies, including both high-dose insulin and vasopressors. While most agree that high-dose insulin should be started as a 1 U/kg/hr infusion after a 1 U/kg intravenous loading dose [2,3,8,66], it remains controversial if high-dose insulin should be titrated higher. Evidence for a dose-response effect of high-dose insulin is limited to one swine model of propranolol poisoning and case reports, including doses as high as 22 U/kg/hr [5,70]. Future studies should examine sequencing and dosing of therapies to optimize outcomes and minimize side effects.

Last, NPDS® is limited in its ability to assess safety outcomes related to high-dose insulin. For example, in the present study, hypoglycemia was coded in only 13% of cases, while studies with more granular data show hypoglycemia is more common, ranging from 31 to 73% of cases [10,12]. As such, NPDS® likely underreports adverse effects related to high-dose insulin. Electrolyte derangements are another challenge when using NPDS®. First, there is only one generic NPDS® code encompassing all electrolyte derangements, making it impossible to determine the number of patients with, for example, hypokalemia. Similar to hypoglycemia, electrolyte derangements are likely underreported in NPDS®. In the present study, we found electrolyte abnormalities occurred in 37% of cases, while other studies of high-dose insulin report hypokalemia occurs

more than 80% of the time [12]. Hospital-level data are likely a superior data source when assessing the adverse effects of high-dose insulin.

Conclusions

In this study of patients reported to US poison centers who were treated with high-dose insulin for cardiotoxic exposures, calcium channel blockers were more lethal than beta-adrenoreceptor blockers. Increasing age, hyperglycemia, heart block, and concomitant treatment with mechanical ventilation or vasopressors were all associated with death. Amlodipine was the most common cardiotoxicant treated with high-dose insulin, and patients exposed to amlodipine were more commonly treated with methylthioninium chloride, suggesting they had more evidence of refractory vasodilation. Among patients exposed to calcium channel blockers, though amlodipine was associated with the greatest number of fatalities, patients exposed to verapamil were at the greatest risk of death. Further study is needed to understand the optimal sequencing of therapies in cardiotoxic poisoning and if high-dose insulin should be employed differently based on the class of calcium channel blocker.

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America's Poison Centers® maintains the National Poison Data System®, which houses de-identified case records of self-reported information collected from callers during exposure management and poison information calls managed by the country's poison centers. National Poison Data System® data do not reflect the entire universe of exposures to a particular substance as additional exposures may go unreported to poison centers; accordingly, National Poison Data System® data should not be construed to represent the complete incidence of US exposures to any substance(s). Exposures do not necessarily represent a poisoning or overdose and America's Poison Centers® is not able to completely verify the accuracy of every report. Findings based on National Poison Data System® data do not necessarily reflect the opinions of America's Poison Centers®.

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Data availability statement

Data available on request due to privacy/ethical restrictions.

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