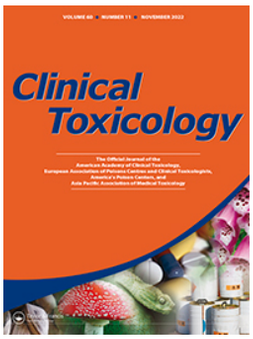

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CLINICAL RESEARCH

Vasodilation in patients with calcium channel blocker poisoning treated with high-dose insulin: a comparison of amlodipine versus non-dihydropyridines

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ABSTRACT

Background: High dose insulin (HDI), an inotrope and vasodilator, is a standard therapy for calcium channel blocker (CCB) poisoning. HDI causes vasodilation by stimulating endothelial nitric oxide synthase (eNOS). Most literature supporting HDI for CCB poisoning involves verapamil toxicity; however, amlodipine now causes more CCB poisonings. Unlike other CCBs, amlodipine stimulates eNOS and may cause synergistic vasodilation with HDI. The purpose of this study was to determine if amlodipine-poisoned patients treated with HDI had more evidence of vasodilation than similarly treated patients with non-dihydropyridine (non-DHP) poisoning.

Methods: This was a retrospective study from a single poison center. Cases were identified via the generic code "Calcium Antagonists" in which the therapy "High Dose Insulin/Glucose" was "performed, whether or not recommended" from 2019–2021. Evidence of vasodilation was assessed via maximum number of vasopressor infusions per case, vasopressor doses, and use of rescue methylene blue to treat refractory vasoplegia.

Results: Thirty-three patients were enrolled: 18 poisoned with amlodipine, 15 with non-DHPs (verapamil $n = 10$, diltiazem $n = 5$). The median number of maximum concomitant vasopressors in the amlodipine group was 3 (IQR: 2–5; range 0–6) and 2 in the non-DHP group (IQR: 1–3; range 0–5; $p = 0.04$); median difference in maximum concomitant vasopressors between groups was 1 (95% confidence interval: 0–2). Median maximum epinephrine dosing was higher in the amlodipine group (0.31 mcg/kg/min) compared to non-DHPs (0.09 mcg/kg/min; $p = 0.03$). Use of rescue methylene blue was more common in the amlodipine group (7/18 [39%]) than in the non-DHP group (0; $p = 0.009$).

Conclusions: Amlodipine poisoned patients treated with HDI required more vasopressors, higher doses of epinephrine, and more often received rescue methylene blue than similarly treated patients with verapamil or diltiazem poisoning. These differences suggest amlodipine-poisoned patients had more evidence of vasodilation. Further study is warranted to determine if synergistic vasodilation occurs when HDI is used to treat amlodipine poisoning.

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Amlodipine; insulin; methylene blue; shock; poisoning

Introduction

Cardiovascular drugs are a common and increasing cause of poisoning in the U.S. In 2020, they represented the sixth most common reason for a call to U.S. Poison Centers and the third most common cause of fatal poisonings in the National Poison Data System (NPDS) [1]. The majority of these fatal cardiovascular drug poisonings were caused by calcium channel blockers (CCBs) [1].

High-dose insulin (HDI) is a standard therapy for patients with severe CCB poisoning [2–4]. HDI improves shock *via* at least four mechanisms [5]. HDI acts as a potent inotrope, increasing cardiac output by calcium-dependent and calcium-independent pathways in myocardial cells [6]. This subsequent increase in cardiac output results primarily from an increase in stroke volume rather than heart rate [7]. Second, HDI optimizes myocardial energy utilization. Stressed myocardium tends to use glucose for energy rather than its usual preferred source, free fatty acids [8]. Saturation of myocardial insulin receptors optimizes the availability of intracellular glucose for ATP production. Third, HDI improves the endocrine dysfunction and resultant hyperglycemia seen in CCB poisoning [9]. Fourth, HDI acts as a vasodilator *via* enhancement of endothelial nitric oxide synthase (eNOS). This vasodilation results in increased cardiac output and improves the microvascular dysfunction associated with cardiogenic shock [10]. Animal data suggest a dose–response relationship between vasodilation and increasing HDI doses; higher dose HDI is associated with both greater cardiac output and increasing vasodilation [7].

Expert reviews [5,11], consensus recommendations [3], and poison center guidelines [2] make recommendations regarding therapy for CCB poisoning without regard for the individual CCB classes, with the notion that class specificity is

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lost in overdose [12]. In animal models and clinical practice, however, CCB class has important implications in poisoning.

CCBs functionally belong to two categories: dihydropyridines (DHP) and non-dihydropyridines (non-DHP). All CCBs bind L-type calcium channels in the myocardium and smooth muscle. Non-DHPs tend to have more central myocardial effects, resulting in reduced cardiac contractility, depressed sinoatrial node activity, and slowed atrioventricular node activity in addition to decreased systemic vasodilation. DHPs, however, due to subtle binding differences of the α1c subunit of L-type calcium channels, result primarily in vasodilation and reflex tachycardia [12,13]. In both DHP and non-DHP poisoning, animal models suggest that myocardial contractility is reduced early in poisoning regardless of class, while cardiac output is relatively preserved in DHP poisoning compared to non-DHP poisoning [12]. As shock worsens in CCB poisoning, cardiac output falls regardless of CCB class [12], though reflex tachycardia with DHP poisoning is seen even in profound shock [13].

Complicating matters further, not all DHPs are identical. Much of the literature examining DHP poisoning involves animal models of nifedipine, however the most commonly prescribed DHP in the U.S. is currently amlodipine [14]. While toxicologists frequently cite verapamil as the most dangerous CCB because of its high case fatality rate [15], amlodipine is the most common DHP reported to the NPDS. Amlodipine is also responsible for the most fatal CCB overdoses reported to U.S. Poison Centers, accounting for 82 deaths in 2020 [1]. Furthermore, amlodipine is unique among DHPs in that it causes vasodilation *via* an additional mechanism. Amlodipine, like HDI, causes vasodilation *via* stimulation of eNOS [16–18]. The potential exists, therefore, for HDI to cause synergistic iatrogenic vasodilation when used in the setting of amlodipine poisoning.

Because of the potential for synergistic vasodilation between HDI and amlodipine, and because to our knowledge no previous study has addressed this potential interaction, the purpose of this study was to evaluate for evidence of vasodilation in CCB-poisoned patients treated with HDI in amlodipine overdose compared to non-DHP overdose. We chose as our outcomes the maximum number of vasopressors used per poisoning, vasopressor doses, and the use of rescue methylene blue to treat refractory vasoplegia.

Methods

Study design and setting

This was a retrospective cohort study of patients with CCB poisoning treated with HDI from 2019 through 2021 at a single U.S. Poison Center. The dates of this study were chosen for two reasons. First, 2019 was the first year in which NPDS allowed HDI to be coded as a therapy [19]. Second, in 2019, our poison center, as part of a quality improvement project, began to systematically record doses and infusion rates of vasopressors as part of usual care. The local human subjects research committee approved this study.

The study setting is an American Association of Poison Control Centers (AAPCC) accredited regional Poison Center covering three U.S. states. In 2021, our Poison Center handled 59,999 calls, of which 56,893 were exposure calls. This Poison Center is pharmacist-based; 100% of our eligible pharmacists are AAPCC Certified Specialists in Poison Information (CSPIs). Our Poison Center utilizes a previously published [2] clinical guideline that recommends HDI be started prior to (or concomitantly with) vasopressors for hypotension from CCB poisoning. Board-certified medical toxicologists are available at all times *via* phone consultation; however, CSPIs routinely recommend starting HDI prior to medical toxicologist consultation.

Selection of participants

Patients were identified by querying our electronic database (Toxicall®, version 4.7.37, 1999–2013, Computer Automation Systems, Inc., Aurora, CO) for the generic substance code "Calcium Antagonists" (262000) in which the therapy "High Dose Insulin/Glucose" was "performed, whether or not recommended" from 2019 to 2021. Each case in Toxicall® consists of categorical (such as gender) and continuous (such as age) data fields as well as free text case notes that describe the case in a manner similar to traditional hospital medical records. Patients were identified by searching for patients coded to AAPCC generic substance code for "Calcium Antagonists" (262000) in the "substance description" data field, "exposure" in the "call type" data field, and the therapy "High Dose Insulin/Glucose" (recommended or performed) coded in the "therapies" data field for the complete years 2019–2021. All cases were handled and documented by trained CSPIs prospectively.

Measurements

All cases were reviewed and abstracted by a single medical toxicologist. Data collection was managed by generating a Microsoft Excel spreadsheet from a data query of Toxicall®. Outcome variables, including demographic data, clinical outcomes, clinical effects, and therapies used, were defined according to the NPDS coding manual [20]. In addition to standard data recorded as part of usual Poison Center case records, the following variables were recorded: specific vasopressors and their maximum infusion rates as recorded on routine poison center callbacks, whether or not HDI was started before, after, or concomitantly with vasopressors, HDI maximum infusion rate, and the duration (in days) of HDI infusion. We chose use of methylene blue as a marker of vasodilation because in our experience, and in the medical literature [21], it is typically used as a salvage therapy for vasodilatory shock.

Data analysis

Descriptive statistics are reported. Means, medians, interquartile ranges, ranges, and confidence intervals were calculated and reported when appropriate. We calculated the median difference between the maximum number of concomitant vasopressors in each group. Comparisons were made using

Fisher's Exact and Mann–Whitney-U tests based on sample sizes as appropriate. We were unable to adjust for confounding covariates because of the sample size. All data were analyzed using Stata® (Version 15; StataCorp®, College Station, TX).

Results

Characteristics of study subjects

We identified a total of 33 CCB-poisoned patients treated with HDI during the study period; 18 were poisoned with amlodipine, 15 with non-DHPs (10 by verapamil, 5 by diltiazem). A total of six patients had single-substance ingestions; three patients ingested only amlodipine, two ingested only verapamil, and one ingested only diltiazem. No patients were poisoned with any other DHPs and treated with HDI during the study period. Baseline characteristics, including age, gender, nadir vital signs, and co-ingestions, were similar between groups (Table 1). Clinical outcomes, including clinical effects, were similar between groups (Table 2). Most patients experienced a major outcome in terms of poisoning severity; three patients in each group died during the index hospitalization.

HDI dosing

Median maximum HDI infusion rate was 10 units/kg/h in the amlodipine group (IQR 3.4 – 11; range 1 – 20) and 5 units/kg/h in the non-DHP group (IQR: 1–10 units/kg/h; range, 1 – 20). Median duration of HDI infusion was three days in both the amlodipine group (IQR: 2 – 3 days, range 1 – 5) and the non-DHP group (IQR: 2 – 3 days, range 1 – 6). Regarding the sequence in which HDI was started in comparison to vasopressors, in the amlodipine group, HDI was started before vasopressors in 8 patients (44%), after vasopressors in 7 patients (39%) and concomitantly in 3 patients (17%); whereas in the non-DHP group, HDI was started before vasopressors in 2 patients (13%), after vasopressors in 12 patients (80%), and simultaneously in one patient (7%).

Main results

The median number of maximum concomitant vasopressors in the amlodipine group was 3 (IQR: 2–5; range 0–6) and 2 in the non-DHP group (IQR: 1–3; range 0–5; Mann–Whitney-U $p = .04$); median difference in maximum concomitant vasopressors between groups was 1 (95% confidence interval: 0–2). Use of rescue methylene blue was more common in the amlodipine group (7/18 [39%]) than in the non-DHP group (0; $p = 009$, Fisher's exact). All 7 amlodipine poisoning cases that received methylene blue contained clear documentation methylene blue was used to treat hypotension. In six of these seven cases, patients had HDI and three or more concomitant vasopressors already initiated and infusing prior to methylene blue administration; in the remaining case, methylene blue was administered during cardiac arrest. Median maximum epinephrine dosing was higher in the amlodipine group (0.31 mcg/kg/min) compared to non-DHPs (0.09 mcg/kg/min; $p = .03$ Mann–Whitney-U). Use of epinephrine ($n = 11$), vasopressin ($n = 11$), phenylephrine ($n = 7$), and angiotensin II ($n = 4$) were more common in the amlodipine group than in non-DHPs ($n = 6$, 6, 2, 0, respectively) (Table 3). Other coded therapies and vasopressor infusion rates are also reported in Table 3.

Table 1. Demographics and background.

	Amlodipine ($n = 18$)	Non-DHP CCBs ($n = 15$)[a]
Age in years, median (range)	56 (16–74)	61 (16–87)
Male sex (%)	11 (61%)	7 (47%)
Nadir pulse, median (range)	53 beats/min (0–110)	50 beats/min (0–74)
Nadir SBP, median (range)	76 mmHg (0–100)	70 mmHg (0–94)
Maximum HDI infusion rate		
Median (units/kg/h)	10	5
Mean (units/kg/h)	8.4	6.4
Interquartile range	3.4–11	1–10
Range	1–20	1–20
Co-ingestions, n (%)[b,c]		
Beta-blockers	6 (33%)	3 (20%)
Ethanol	6 (33%)	1 (7%)
Antidepressants	5 (28%)	2 (13%)
ACEIs/ARBs	4 (22%)	2 (13%)
Acetaminophen	3 (17%)	1 (7%)
Benzodiazepines	3 (17%)	2 (13%)
Hydrochlorothiazide	3 (17%)	–
Antihistamines	3 (17%)	2 (13%)
Antiepileptics	–	3 (20%)
NSAIDs	2 (11%)	2 (13%)
Opioids	2 (11%)	–
Prazosin/hydralazine	2 (11%)	–
Alpha-2 agonists	1 (6%)	2 (13%)

[a]Non-DHP (dihydropyridine) CCBs (calcium channel blockers) include verapamil ($n = 10$) and diltiazem ($n = 5$).
[b]For amlodipine, 1 each of insulin, methamfetamine, carbon monoxide, immunosuppressants, metformin, rosuvastatin, allopurinol.
[c]For verapamil/diltiazem, 1 each of baclofen, digoxin, lithium, amlodipine, warfarin, nitroglycerin.

Table 2. Outcomes and effects.

	Amlodipine ($n = 18$)	Non-DHP CCBs ($n = 15$)[a]
Medical outcome, n (%)		
Death	3 (17%)	3 (20%)
Major effect	13 (72%)	9 (60%)
Moderate effect	2 (11%)	3 (20%)
Clinical effects, n (%)		
Acidosis	10 (55%)	9 (60%)
Bradycardia	9 (50%)	8 (53%)
Cardiac arrest	3 (17%)	2 (13%)
Creatinine increased	11 (61%)	5 (33%)
EKG-QRS prolonged	2 (11%)	2 (13%)
EKG-QT prolonged	5 (28%)	5 (33%)
Electrolyte abnormality	5 (28%)	3 (13%)
Hypoglycemia	3 (17%)	1 (7%)
Hypotension	18 (100%)	15 (100%)
Oliguria/anuria	4 (22%)	4 (27%)
Renal failure	4 (22%)	3 (20%)
Vomiting	5 (28%)	4 (27%)

[a]Non-DHP (dihydropyridine) CCBs (calcium channel blockers) include verapamil ($n = 10$) and diltiazem ($n = 5$).

Discussion

Based on the maximum number of concomitant vasopressor infusions and increased use of rescue methylene blue as a vasopressor, our data suggest patients with amlodipine

Table 3. Selected other therapies.

Therapy, n (%)	Amlodipine ($n = 18$)	Non-DHP CCBs ($n = 15$)[a]
Antiarrhythmic	2 (11%)	–
Atropine	2 (11%)	5 (33%)
Calcium	18 (100%)	15 (100%)
Cardiopulmonary resuscitation	1 (6%)	1 (7%)
Extracorporeal membrane oxygenation	2 (11%)	1 (7%)
Glucagon	6 (33%)	4 (27%)
Hemodialysis	2 (11%)	2 (13%)
High-dose insulin	18 (100%)	15 (100%)
Hydroxocobalamin[b]	1 (6%)	–
Lipid emulsion therapy	2 (11%)	2 (13%)
Methylene blue	7 (39%)	–
Pacemaker	2 (11%)	3 (20%)
Vasopressors	16 (89%)	13 (87%)
Norepinephrine	13 (72%)	13 (87%)
Epinephrine	11 (61%)	6 (40%)
Vasopressin	11 (61%)	6 (40%)
Phenylephrine	7 (39%)	2 (13%)
Dopamine	6 (33%)	4 (27%)
Angiotensin II	4 (22%)	–
Vasopressor maximum dose		
Median (IQR; range)		
Norepinephrine (mcg/kg/min)	0.34 (0.23–0.50; 0.08–1.50)	0.28 (0.24–0.39; 0.05–0.50)
Epinephrine (mcg/kg/min)	0.31 (0.15–0.50; 0.10–1.0)	0.09 (0.04–0.13; 0.03–0.14)
Vasopressin (units/min)	0.04 (0.04–0.05; 0.02–0.10)	0.04 (0.04–0.04; 0.04–0.08)
Phenylephrine (mcg/kg/min)	2.5 (2.5–2.5; 1.5–2.5)	2.1 (2.1–2.1; 2.1–2.1)
Dopamine (mcg/kg/min)	10 (10–20; 8–20)	5 (1–12; 1–12)
Angiotensin II (ng/kg/min)	60 (40–80; 40–80)	–

[a]Non-DHP (dihydropyridine) CCBs (calcium channel blockers) include verapamil (n = 10) and diltiazem (n = 5).
[b]Hydroxocobalamin documented to be used as a nitric oxide scavenger/vasopressor.

poisoning treated with HDI experience more vasoplegia than similarly treated patients with verapamil or diltiazem poisoning. Angiotensin II, a rarely used rescue therapy for vasodilatory shock from poisoning [22], was also more commonly used in amlodipine cases, further supporting the notion these patients had more severe vasoplegia. While causality cannot be inferred by these data given our study design, both HDI and amlodipine stimulate eNOS which could result in synergistic vasoplegia in amlodipine-poisoned patients.

For nearly a century it has been known that insulin has an inotropic effect on mammalian cardiac tissue [23]. However it was not until the 1990s when a series of experiments examining verapamil poisoning in mongrel canines demonstrated HDI to have superior hemodynamic and metabolic effects compared to more traditional therapies that its use for poisoning was proposed. These experiments showed HDI resulted in improved end-systolic elastance and end-diastolic elastance, increased cardiac contractility, and increased myocardial lactate utilization all leading to and increased survival benefit [9,24–27]. These studies paved the way for the first human case series in 1999 where HDI was used to treat CCB poisoning; a small series of four patients poisoned with verapamil and one poisoned with amlodipine [28]. Subsequently, as numerous case reports [29–33] and case series [2,4,34–36] demonstrated, the use of HDI expanded to all CCBs under the notion that class specificity among CCBs is lost in overdose. Despite expansion of HDI use in CCB poisoning to the point where amlodipine is now the most common CCB treated with HDI [2], we know of only a single comparative effectiveness study that has evaluated HDI in dihydropyridine poisoning [13], and none have yet evaluated HDI for amlodipine (Table 4). The possibility of iatrogenic synergistic vasodilation between amlodipine and HDI remains largely unexplored.

HDI causes vasodilation, likely by enhancing eNOS activity *via* activation of the phosphatidylinositol 3-kinase (PI3K) pathway [38,39] (Figure 1). Amlodipine, in contrast to other CCBs such as nifedipine, verapamil, and diltiazem, directly stimulates synthesis of nitric oxide in a dose-dependent fashion [16,17,40]. The largest contribution is *via* its R-enantiomer, which actually has less activity at the L-type calcium channel [18]. Amlodipine's activation of eNOS is driven by at least two mechanisms: dominantly through regulation of the bradykinin B2 pathway as well as by changing the phosphorylation of protein kinase C (PKC) which in turn affects the phosphorylation, and therefore activity, of eNOS. Other pathways including the localization of eNOS to caveolin islands are less well studied but likely contribute as well [41,42]. Synergistic production of nitric oxide, and therefore worsening vasodilation, thus theoretically exists when HDI is used in the setting of amlodipine poisoning. We emphasize this synergism is speculative, and that further study is needed to determine whether such an interaction truly exists. Though less commonly used than HDI, some investigators have evaluated the use of the nitric oxide scavenger, methylene blue [21], as a potential therapy for amlodipine poisoning (see Figure 1) given its unique nature, with mixed results [43–46]; yet animal studies of HDI for amlodipine poisoning are lacking despite its increasing use. Evidence exists, in fact, that amlodipine poisoning may have unique toxicologic effects compared to verapamil. In addition to the differences in hemodynamic effects noted above between amlodipine and verapamil, these two drugs also appear to be uniquely different in terms of metabolic effects. While verapamil has clearly

Table 4. Summary of comparative effectiveness animal studies evaluating HDI in CCB poisoning.

Reference	Model	Treatment arms (survival)	Important results
Kline et al. J Pharmacol Exp Ther 1993 [24]	Canine (verapamil)[a]	Control (initial 0/6, final NA) Epinephrine (initial 4/6, final 2/6) Glucagon (initial 3/6, final 0/6) HDI (initial 6/6, final 6/6)	HDI significantly improved maximum elastance at end of systole, left ventricular end-diastolic pressure, & coronary blood flow
Kline et al. Crit Care Med 1995 [25]	Canine (verapamil)[a]	Control (initial 0/6, final NA) Epinephrine (initial 4/6, final 2/6) Glucagon (initial 3/6, final 0/6) Calcium (initial 3/6, final 0/6) HDI (initial 6/6, final 6/6)	Verapamil renders myocardium dependent on carbohydrates. HDI increased myocardial glucose & lactate uptake five-fold, increased the ratio of myocardial O2 delivery/work, & improved myocardial contractility compared to other arms.
Kline et al. J Cardiovasc Pharmacol 1996 [26]	Canine (verapamil)[b]	Control (no toxicity, HDI only, $n = 6$) Saline ($n = 6$) HDI ($n = 6$)	Verapamil inhibits myocardial fatty acid & glucose uptake; in these conditions HDI increases myocardial contractility independent of glucose transport.
Kline et al. Cardiovasc Res 1997 [9]	Canine (verapamil)	Control (no toxicity, HDI only, $n = 8$) Saline ($n = 5$, $LD_{100} = 149$ min) Epinephrine ($n = 5$, $LD_{100} = 125$ min) Glucagon ($n = 5$, $LD_{100} = 208$ min) HDI ($n = 5$, $LD_{100} = 360$ min)	HDI only treatment that increased LV efficiency, elastance, and contractility. HDI also significantly improved LV work and blood pressure. HDI had no effect on non-poisoned hearts. HDI increased lactate uptake and improved arterio-coronary sinus pH but did not increase myocardial glucose uptake. HDI was the only treatment to increase the lethal dose of verapamil.
Kline et al. Toxicol Appl Pharmacol 1997 [27]	Canine (verapamil)	Control (no toxicity, HDI only, $n = 6$) Saline (0/6) Glucagon ($n = 5$)[c] HDI (6/6)	Verapamil causes hyperglycemia by inducing insulin resistance and blocking insulin release. Dogs treated with HDI had much lower glucose requirements when poisoned with verapamil compared to no poisoning.
Engebretsen et al. Clin Toxicol 2010 [13]	Swine (nifedipine)	Control (1/5) HDI (4/5) HDI + phenylephrine (5/5)	HDI effective compared to saline control; addition of phenylephrine to HDI did not improve hemodynamic parameters.
Kline JA. Ann Emerg Med 2014 [37]	Canine (verapamil)	Epinephrine Glucagon HDI	Glucagon & epinephrine generate a fast but modest response in contractility but result in tachyphylaxis. HDI generated a slow but eventually large and nearly indefatigable response in contractility; HDI also reversed epinephrine tachyphylaxis

[a]Includes a bolus verapamil dose at end of 240-min resuscitation to test sustainability of treatment.
[b]Survival not evaluated.
[c]Survival for glucagon group not reported.

been shown to have diabetogenic effects [27], amlodipine has not been associated with altered insulin sensitivity or reduced insulin resistance [47–51]. Additionally, while non-diabetic patients poisoned with verapamil or diltiazem exhibiting hyperglycemia demonstrated more severe poisoning [52], a similar trend was not observed in patients severely poisoned with amlodipine, providing evidence for different clinically relevant mechanisms of action in the setting of overdose [36]. Considering many of the therapeutic effects of HDI in CCB poisoning are metabolic in nature [9,25–27], this has important implications for the effectiveness of HDI in amlodipine poisoning. These metabolic effects are also closely tied to the cardiovascular effects of insulin. Previous work has demonstrated that insulin-mediated vasodilation does not occur in insulin-resistant states [53]. Given there appears to be a difference in the degree of insulin resistance induced by amlodipine poisoning compared to verapamil or diltiazem, it is possible verapamil and diltiazem poisoned patients may be less susceptible to insulin-associated vasodilation. As such, studies of HDI compared to more traditional therapies in amlodipine poisoning that lack the same vasodilatory effects, such as norepinephrine, are warranted.

Taking the present data under advisement, our approach to amlodipine poisoning, and CCB poisoning more generally, has changed as we attempt to maximize the benefits of HDI while mitigating any potential harms. Previously, we recommended HDI in lieu of vasopressors for CCB poisoning, as animal data suggested vasopressors were either ineffective, transiently effective, or potentially even harmful when compared to HDI [9,13,24,54]. As such we previously recommended titration of HDI up to its maximally studied dose of 10 units/kg/h before initiating vasopressors [2,34,55]. The changing epidemiology of CCB poisoning and our clinical experience prompted a re-examination of our practice. For instance, in 2011, the year we first began using our HDI guideline recommending HDI titrated to 10 units/kg/h in lieu of vasopressors, there were 32 fatal verapamil cases and 26 fatal amlodipine cases reported to NPDS. In 2020, verapamil accounted for 25 fatalities reported to NPDS while amlodipine resulted in 82 deaths. During this period of increasing amlodipine fatalities, our clinical experience has been that while HDI has improved the cardiogenic component of amlodipine-induced shock, large doses of vasopressors were needed to maintain MAP. The changing epidemiology of CCB poisoning combined with our lived experience precipitated changes in our practice and clinical guidelines.

Evidence supporting the use of HDI in CCB poisoning remains strong; however, iatrogenic harms from HDI that appear to be dose-related have become apparent in recent years, including not only the possibility of dose-related (and synergistic) vasoplegia, but also volume overload [56].

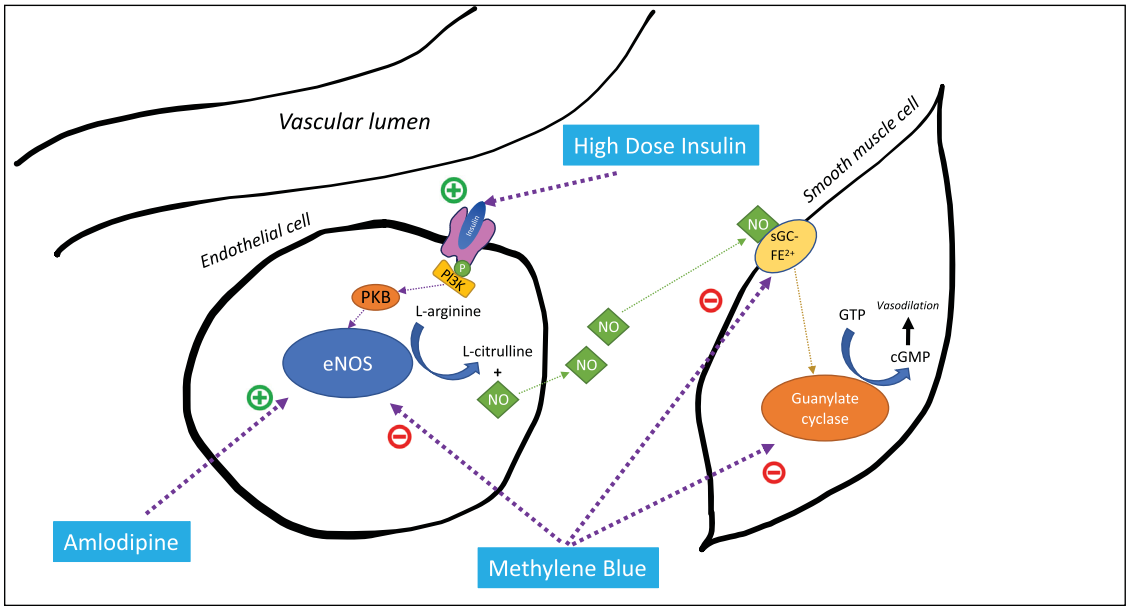

Figure 1. Mechanisms of potential synergistic vasodilation between amlodipine and high-dose insulin. Vasoconstrictive pathways of methylene blue are also displayed. Insulin binds its receptor which stimulates glucose entry into the cell *via* a series of phosphorylation reactions. Phosphatidylinositol 3-kinase (PI3K) phosphorylates protein kinase B (PKB), which, in addition to recruiting glucose transporters to the surface of the cell, activates endothelial nitric oxide synthase (eNOS). eNOS then converts L-arginine into L-citrulline and nitric oxide (NO). NO is then released from the endothelial cell and then diffuses into nearby vascular smooth muscle cells, binding the iron site on the enzyme soluble guanylate cyclase (sGC-Fe2+). Guanylate cyclase then transforms guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP) which signals smooth relaxation and ultimately vasodilation. Amlodipine also acts to directly stimulate eNOS, which theoretically could lead to synergistic release of NO and worsening vasodilation in the setting of high-dose insulin therapy. Methylene blue could theoretically counteract such vasodilation *via* direct inhibition of eNOS, scavenging NO, and inhibiting guanylate cyclase.

Finding the optimal dose of HDI has become more paramount. Similarly, evidence for HDI's titrated effectiveness beyond 1 unit/kg/h is also quite sparse and largely limited to case reports [34,57] and a single animal study [7]. In addition, the harms of vasopressors demonstrated in animal studies have not generally been seen in human poisonings [58]; a systematic review of vasopressors for toxin-induced shock demonstrated paradoxically that while animal studies of vasopressors frequently show harm, human case experience does not [59]. Furthermore, new evidence suggests that in poison-induced shock, vasopressors and HDI are synergistic in improving both cardiovascular parameters and brain perfusion [60]. As such, we now recommend that for CCB poisoning refractory to basic supportive measures, such as IV calcium salts, isotonic fluids, and atropine, clinicians start HDI at 1 unit/kg/h (after a 1 unit/kg IV bolus) and a norepinephrine infusion simultaneously (Figure 2). We then recommend clinicians at the bedside reassess chronotropy (pulse rate), inotropy (contractility, typically *via* bedside echocardiography, or *via* clinical exam for cardiogenic shock if bedside echocardiography is not feasible), and vasotropy (*via* mean arterial pressure in the context of skin exam and other clinical measures of vasodilation) and choose additional therapies based on each of these three parameters [61]. Using this new guidance, HDI titrated higher than 1 unit/kg/h would be recommended only if augmented cardiac contractility is not adequate to treat shock, or if cardiogenic shock persists [3]. We believe future work should examine the effectiveness, in a dose-dependent manner, each of these interventions to maximize benefits while minimizing iatrogenic harms.

Limitations

Our study has several limitations. First, our measure of vasodilation involved the use of the surrogate markers of rescue methylene blue and vasopressor usage, rather than direct measurements of systemic vascular resistance as such measurements are rarely recorded in poison center data. Furthermore, as this was an analysis of usual care, there was no standardized protocol as to when to add specific vasopressors or use methylene blue for rescue vasoplegia, introducing additional possible variation into the groups. Like all retrospective studies, unmeasured bias and convenience sampling could influence our results. As noted previously, though we observed an association with worsening vasodilation in patients with CCB poisoning from amlodipine treated with HDI compared to similarly treated patients with non-DHP poisoning, causality from HDI cannot be proven due to the retrospective nature of the study and its multiple confounders. As an example, patients with amlodipine poisoning tended to receive higher peak infusion rates of HDI than non-DHP poisoned patients and more often received HDI before vasopressors. Given HDI causes vasodilation [38,39], and that such vasodilation may occur in a dose-dependent fashion [7], amlodipine-poisoned patients may have experienced more vasodilation simply from higher doses of HDI rather than from a synergistic interaction between HDI and amlodipine. Similarly, amlodipine-poisoned patients may also have had more severe poisoning in and of themselves, necessitating more aggressive interventions. Conversely, it is also possible amlodipine-poisoned patients had persistent hypotension that was subsequently treated with increasing doses of HDI that inadvertently worsened hypotension (regardless of whether synergism

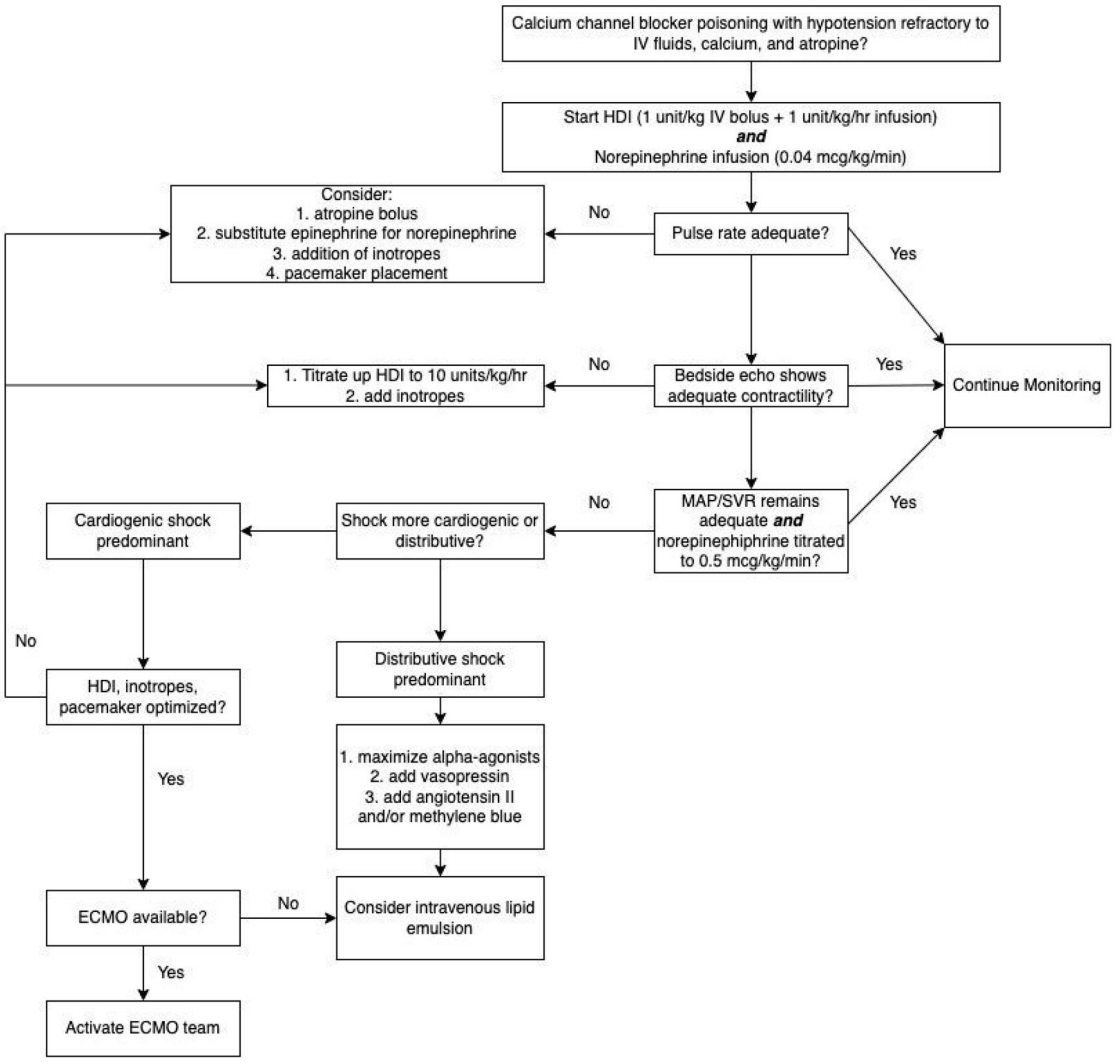

Figure 2. Proposed updated treatment algorithm for calcium channel blocker poisoning.

occurred) leading to higher subsequent vasopressor doses. We emphasize that synergism between amlodipine poisoning and HDI is speculative based on available evidence, and that further study is needed to determine whether such an interaction truly exists.

Poison center studies have additional limitations, including inaccurate clinical data compared to the medical record [62] and reporting of non-exposures as poisonings; i.e., including patients in studies that were purportedly poisoned but in actuality were not [63]. While non-exposures included in Poison Center data are a problem in many studies, in this study we believe this is highly unlikely. Hypotension, a hallmark of CCB poisoning, occurred in 100% of our cases. In addition, patients were ill enough that providers (and presumably patients or their surrogates) were willing to accept the known risks of HDI [4]. While it is true we did not confirm poisoning in each of our cases with blood or urine chromatography, therapy in CCB poisoning is typically guided by clinical data and not by drug screening; as such drug screening is rarely performed clinically. Furthermore, in clinical literature on CCB poisoning confirmatory drug screening is the exception [36] rather than the rule [2,4,5,35]. Co-ingestions resulting in vasodilation also represent a possible source of confounding. For example, drugs that affect the renin-angiotensin axis result in synergistic vasodilation in dihydropyridine poisoning [64]. A small number of patients in both the amlodipine and non-DHP groups in our study did report ingesting angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-II receptor blockers (ARBs) (Table 1). Nevertheless, the possibility for additional synergistic vasodilation from drugs like ARBs and ACEIs underscores the point that careful observation of worsening vasoplegia when utilizing HDI in CCB poisoning (and particularly amlodipine poisoning) is warranted, regardless of the cause.

Last, the relatively small sample size of our study could lead to erroneous conclusions. Small sample size is a common limitation in literature addressing both CCB poisoning and HDI. As of 2019 the National Poison Data System allows cases to be specifically coded for HDI; a larger study involving a query of the entire NPDS database could now be conducted to confirm our findings and address this limitation.

Conclusion

Amlodipine-poisoned patients treated with HDI required more vasopressors, higher doses of epinephrine, and more often received rescue methylene blue than similarly treated

patients with verapamil or diltiazem poisoning. These differences suggest that amlodipine-poisoned patients had more evidence of vasodilation. Further study is warranted to determine whether synergistic vasodilation occurs when HDI is used to treat amlodipine poisoning.

Prior presentation

This study was presented as a platform presentation at the 2022 North American Congress of Clinical Toxicology in San Francisco, CA, USA. The abstract was published in a supplement of *Clinical Toxicology*:

Cole J, Lee S, Prekker M, Kunzler N, Considine K, Driver B, Olives T. Vasodilation in Patient with Calcium Channel Blocker Poisoning Treated with High Dose Insulin: A Comparison of Amlodipine versus Non-dihydropyridines. Clin Toxicol 2022; 60(sup2):3-4 (abstract #6)

Author contributions

JBC conceived and designed the manuscript. JBC collected all the data. MEP, BED, MAP, and TDO provided guidance on data analysis. BED and JBC performed the data analysis. All authors critically appraised the article and contributed substantially to its revision. JBC drafted the manuscript, and all authors contributed substantially to its revision. JBC takes responsibility for the paper as a whole.

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