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ORIGINAL ARTICLE

Vasopressor Use, Critical Care Management, and Outcomes in Dihydropyridine Calcium Channel Blocker Toxicity

Hannah H. Spungen[1,2,4] · John Michael Sherman[3] · Kaitlin Ryan[2] · Jessica J. Krueger[1,2] · Michael Levine[4] · Meghan B. Spyres[1,2]

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Abstract

Introduction Although dihydropyridine calcium channel blockers (DHP CCBs) are considered to have less direct myocardial toxicity than non-dihydropyridines, DHPs remain a common cause of morbidity and mortality. We sought to examine various indices of critical illness and describe the clinical course of a population of DHP CCB-poisoned patients with special attention to vasopressor dosing and ischemic complications.

Methods This is a retrospective chart review of DHP CCB exposures admitted to a single center. The study site was a single tertiary referral center with an in-house medical toxicology consultation/admitting service. Inclusion criteria included age ≥ 14 years and DHP ingestion noted on departmental patient log. Patients were excluded if DHP exposure was not documented in the medical record. The study period ranged from July 1, 2010 through December 31, 2022. Data on clinical presentation, management, and outcomes were reported.

Results Sixty-eight cases of DHP exposure were analyzed; 87% were intentional ingestions. Amlodipine represented 88% of cases. 85% included cases involved co-ingestions. Vasopressors were administered in 42 cases (62%), with a median of three agents (IQR 1–4). Norepinephrine was most common ($N=41$; 98%), followed by epinephrine ($N=23$; 55%); median maximal rates were 45.0 (IQR 13.5–70.0) and 25.0 (IQR 12.0–30.0) mcg/min, respectively. 15% ($N=10$) received high dose insulin-euglycemic therapy (HIE); all had > 2 vasopressors administered before administration of HIE. Twelve (18%) patients had ischemic complications; five (7%) experienced ischemic complications not evident before vasopressor administration. There were five deaths (7%).

Conclusions Multiple vasopressor use was common in this population of patients with DHP CCB toxicity. Despite the high doses of vasopressors used, temporally related ischemic complications were uncommon.

Keywords Calcium channel blockers · Cardiotoxicity · Vasoconstrictor agents · Drug overdose · 1,4-dihydropyridine

Introduction

Calcium channel blocker (CCB) overdose carries substantial morbidity and mortality [1–3]. In 2021, the National Poison Data System report listed calcium antagonists as the sixth most common cause of overdose-related fatalities [4]. CCBs are commonly divided into two structural categories: dihydropyridine (DHP) and non-dihydropyridine (non-DHP) [2, 3]. Though both act by antagonizing L-type voltage-gated myocardial calcium channels, non-DHPs (i.e., verapamil and diltiazem) are thought to cause direct myocardial suppression, while DHPs act peripherally, with specificity for vascular smooth muscle [5, 6]. However, these distinctions can be lost in massive overdose [3, 7], and cardiovascular

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✉ Hannah H. Spungen
hspungen@mednet.ucla.edu

[1] University of Arizona College of Medicine—Phoenix, Phoenix, AZ, USA

[2] Banner—University Medical Center Phoenix, Phoenix, AZ, USA

[3] Atrium Health Carolinas Medical Center, Charlotte, NC, USA

[4] University of California Los Angeles, Los Angeles, CA, USA

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collapse has been well-documented in cases of both DHP and non-DHP toxicity [2, 5, 7, 8].

Existing literature comparing therapies for CCB toxicity, namely vasopressors and high-dose insulin euglycemic therapy (HIE), has focused largely on non-DHPs [6, 9, 10]. This focus likely stems from HIE's proposed ability to increase inotropy and cellular glucose uptake in depressed myocardium and improve contractility in a poisoned heart [10, 11]. It is not established how HIE compares with vasopressors for non-DHP CCB toxicity remains controversial [6, 10, 12].

The optimal therapy for DHP-specific CCB overdose is even less clear. Studies on isolated DHP toxicity are uncommon as most existing literature combines these cases with non-DHP CCBs [12–14]. This represents a significant gap, because DHPs are now more commonly prescribed and DHP-related poison center call volumes have increased over the past decade [5, 15]. In this study we examined the natural history and treatment of patients presenting with DHP CCB overdose.

Materials and methods

This study is a retrospective chart review of all suspected DHP CCB-related overdoses admitted to a tertiary care center with a medical toxicology admitting service in the Phoenix, Arizona. The study was approved by the center's institutional review board. A patient logbook of bedside toxicology service admissions/consultations maintained by the Department of Medical Toxicology was reviewed to identify patients with suspected DHP CCB ingestion. Each of these cases was evaluated at bedside by a physician toxicologist.

Patient Identification

All entries in the departmental patient logbook from July 1, 2010 through December 31, 2022 were screened by a single reviewer (HS) for inclusion. Inclusion criteria included suspicion of dihydropyridine calcium channel blocker toxicity and age at least 14 years. Cases were excluded if, on review of the chart narrative, DHP CCB toxicity was not documented as a reason for hospitalization. Each excluded case was adjudicated by joint review with a senior reviewer (MS).

Obtaining urine gas chromatography-mass spectrometry (GC-MS) testing on all suspected overdose patients was the usual practice at the study institution. Due to technical limitations, our standard institutional GC-MS separation protocol only inconsistently detected DHP CCBs from patient urine samples. Thus, patients were included even if they did not have confirmatory laboratory testing available.

Data Abstraction

Once eligible patients were identified, data of interest were abstracted directly from patients' medical records. These data included demographic information, specific DHP CCB ingested, co-ingestions reported, comprehensive urine GC-MS drug screen results, vital signs, and selected laboratory results. Hospital and ICU length of stay, need for and duration of invasive organ support, ischemic complications, and 30-day outcomes were also recorded along with the frequency, doses, and/or infusion rates of medications administered. These data were abstracted from pre-hospital ambulance records, medication administration records, nursing flowsheets, and outside hospital records (where applicable).

Data were abstracted and entered directly into a spreadsheet (Excel 2012; Microsoft, Redmond, WA) using a standardized data abstraction form. 10% of the records were randomly abstracted by another reviewer and a kappa was calculated in order to ensure interrater reliability. Each investigator was individually trained in data abstraction methodology using two example charts. All results were reviewed by another investigator, and any discrepancies were resolved by a joint review with all five authors. Because all parameters (vasopressor use and dose, survival, etc.) were objective, there were no issues obtaining consensus agreement.

For the purposes of our study, norepinephrine, epinephrine, vasopressin, phenylephrine, dopamine, dobutamine, isoproterenol, and angiotensin-II were considered vasopressors. Insulin therapy was classified as HIE when the chart narrative explicitly stated it was being used for reversal of CCB toxicity, provided the dose was at least 0.5 U/kg/hr.

The ischemic complications considered for this study were acute tubular necrosis (ATN), digital or extremity ischemia, cerebrovascular accident (CVA), myocardial infarction (MI), mesenteric ischemia, or gastrointestinal bleeding (GIB). ATN was defined by a serum creatinine greater than 1.5 mg/dL for at least two days or a diagnosis of ATN documented by a consulting nephrologist. We defined myocardial ischemia as the presence of an elevated serum troponin along with a diagnosis of "Type II non-ST elevation myocardial infarction" or "demand ischemia" as specified in either progress notes or discharge summaries. Stroke, mesenteric ischemia, and GIB were defined based on a written documentation of the diagnosis in the electronic medical record.

Data Analysis

A Shapiro-Wilk test was used to determine the normality of variables with a continuous distribution. After determining

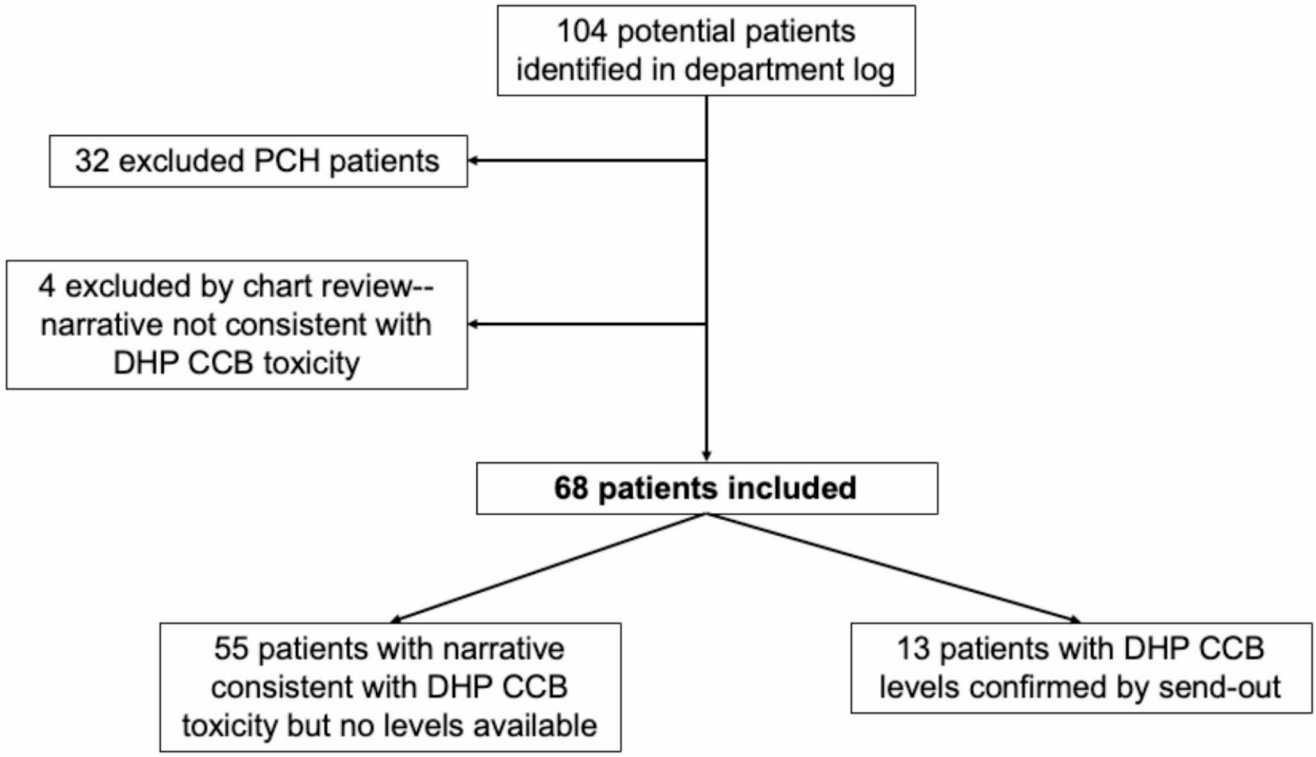

Fig. 1 Study inclusion flow diagram

Table 1 Measured selected parameters in the study group ($N=68$ unless otherwise specified)

Parameter	Median (range; IQR) initial measurement	Median (range; IQR) nadir value during hospitalization	Median (range; IQR) peak value during hospitalization
SBP, mmHg	104 (49–154; 88–121)	78 (0-123; 65–91)	
DBP, mmHg	61 (29–116; 50–71)	41 (0–82; 33–49)	
HR	78 (28–156; 65–91)	60 (0-102; 49–69)	
Serum creatinine, mg/dL	1.1 (0.4–6.1; 0.8–1.6)		1.7 (0.5–6.9; 0.9–1.8)
Serum lactate, mmol/L ($n=44$)	3.3 (0.5–18.5; 2.1–5.7)		5.8 (0.7–19.1; 2.4–8.3)
Serum potassium, mmol/L	3.8 (2.3–7.7; 3.3–4.2)	3.2 (1.9–4.2; 2.9–3.6)	

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

the data were non-normally distributed, medians and interquartile ranges (IQR) were reported. Specific subgroups were compared using a Mann-Whitney U test or an independent t-test for nonparametric and parametric data, respectively. Categorical data were compared using Fisher's Exact Test. Data analysis was performed using R (R Foundation for Statistical Computing, Vienna, Austria). A kappa statistic was performed. Data were analyzed for both isolated DHP ingestions compared with those with co-ingestants, and as all DHP ingestions without dividing between isolated and non-isolated DHP ingestions.

Results

A total of 104 patients were screened. 68 met inclusion and exclusion criteria and were included for analysis (Fig. 1). Most cases (87%) were intentional self-harm ingestions. 63% were female with a median age of 51 years (IQR 33–62). Amlodipine was the most common DHP CCB ingested ($N=60$). All eight remaining cases were nifedipine ingestions; five were extended release and three were unspecified formulations. Coingestions were reported in 85% of cases ($N=58$). The three most common coingestions reported were lisinopril ($N=13$), metoprolol ($N=11$), and atenolol ($N=10$). 40% ($N=27$) of cases involved a reported beta blocker (BB) coingestion, 89% of which were confirmed by GC-MS. Ten patients reported single-agent DHP CCB ingestions.

Baseline and extreme values for blood pressure, heart rate, creatinine, lactate, and potassium concentrations are summarized in Table 1. Vasopressors were administered in 62% ($N=42$) of cases. Details of vasopressor administration,

Table 2 Maximum doses of vasopressors in the study group ($N=68$)

Drug	Number of patients (%)	Median (IQR) Maximal infusion rate	Maximal infusion rate
Norepinephrine	41 (60)	45.0 (13.5–70.0) mcg/min	200 mcg/min
Epinephrine	23 (34)	25.0 (12.0–30.0) mcg/min	200 mcg/min
Phenylephrine	21 (31)	200 (163–230) mcg/min	800 mcg/min
Vasopressin	17 (25)	0.04 (0.03–0.04) units/min	0.04 units/min
Dopamine	7 (10)	15.0 (6.3–23.8) mcg/kg/min	100 mcg/kg/min
Angiotensin II	1 (2)		20.0 ng/kg/hr
Dobutamine	1 (2)		2.5 mcg/kg/min
Isoproterenol	1 (2)		4.0 mcg/min

Table 3 Baseline characteristics in patients who went on to receive HIE versus those who did not

Parameter	Received HIE ($N=10$)	Did not receive HIE ($N=58$)	Difference (95% CI)*	p-value
Initial SBP (mmHg; mean [IQR])	61.5 (53.5–68.8)	105.5 (92.3-122.8)	44.0 (19.1–57.7)	$p=0.0011$
Initial DBP (mmHg; mean [IQR])	38.0 (35.0-50.3)	63.0 (51.0-73.5)	25.0 (5.7–31.7)	$p=0.0086$
Initial HR (beats per minute; mean [IQR])	72.0 (62.3–76.8)	80.5 (65.5–96.5)		$p=0.069$
Initial serum creatinine (mg/dL; mean [IQR])	1.39 (1.2–2.2)	1.1 (0.8–1.5)	0.3 (0.04–0.8)	$p=0.022$
Initial serum lactate (mmol/L; mean [IQR])	4.7 (2.8–8.1)	2.8 (1.7–5.5)**		$p=0.064$

*For statistically significant inter-group differences only

**Available for $N=34$ of 58 non-HIE patients

including maximum dosing rate of individual agents, are described in Table 2. Among the 42 patients who received vasopressors, the median number of vasopressor agents used was 3 (IQR 1–4).

Ten patients received HIE therapy, with a median rate of 1.0 units/kg/hour (IQR 0.8–1.3). The maximum insulin infusion rate recorded was 4.0 units/kg/hour. A comparison of specific laboratory and vital sign parameters between those who did and did not receive HIE therapy is shown in Table 3. The median peak NE dose was higher in the HIE versus no HIE group (72.5 vs. 37.1 mcg/min, difference = 35.4 mcg/min, ($p=0.003$), 95% confidence interval [CI] 16.0-70.3 mcg/min). There was no statistically significant difference between these subgroups for median peak epinephrine, phenylephrine, or dopamine doses. Nine out of ten (90%) of patients who received HIE had a formal echocardiogram done within 24 h of admission; two of these cases were read by a cardiologist as having decreased systolic function (both mild). HIE was added after initiation of at least two vasopressors in all ten of these cases. Four of the five deaths in the study population received HIE, and five patients who received HIE also experienced ischemic complications (described below).

For non-vasopressor/HIE therapy, 56% ($N=38$) of patients received intravenous calcium salts. Glucagon was administered in 40% ($N=27$) of cases, the majority of which involved a reported BB coingestion (74%, $N=20$). 44% ($N=30$) underwent mechanical ventilation, and 22% ($N=15$) were initiated on hemodialysis or continuous renal replacement therapy during their hospitalization. One patient had an intraaortic balloon pump placed. No patients were cannulated for extracorporeal membrane oxygenation. The median overall duration of hospitalization was 5 days (IQR 3–11 days). 84% ($N=57$) of patients were admitted to ICU, with a median ICU length of stay of 4 days (IQR 2–10 days).

Twelve patients (18%) experienced ischemic complications. Ischemic complications included ATN ($N=9$), limb ischemia ($N=2$), mesenteric ischemia ($N=2$), GIB, MI, and CVA ($N=1$ each). Cases involving ischemic complications are detailed in Table 4. The median dose of NE used in ischemic cases was significantly higher than that used in those without ischemic complications (72.5 mcg/min versus 45 mcg/min, difference 27.5 mcg/min, ($p<0.001$), 95% CI 20.0–65.0 mcg/min), while no significant difference was found between these groups with respect to the median peak dose of phenylephrine or epinephrine. Ischemic complications were not present prior to vasopressor administration in five patients as seven events. Of these, two cases of limb ischemia were attributed to complications from femoral arterial lines. One CVA was attributed to carotid atherosclerosis by the consulting stroke neurologist after the patient had been weaned off vasopressors. One GIB occurred in a patient more than a week after initially having been weaned off vasopressors in the setting of ongoing multiorgan system failure and was not thought to be related to complications from her initial vasopressor therapy. One case of ATN and two cases of mesenteric ischemia developed after vasopressor initiation and prolonged hypotension.

At 30 days post-ingestion, 5 (7%) patients were known to be dead, 47 (69%) were known to be alive and the remaining 24% had an unknown outcome. All patients who were deceased at 30-day follow up died during the index hospitalization. The majority of patients ($N=52$, 77%) were

Table 4 Characteristics of patients in the main study group with ischemic complications

Pt	Age	Sex	Number of vasopressors	Ischemic complications	Ischemia present prior to vasopressor	30 d follow up	Co-ingestion of other anti-hypertensives*
1	69	M	4	ATN	Yes	Dead	No
3	36	M	4	ATN	Yes	Unknown	No
9	30	F	4	MI	Yes	Alive	No
10	66	M	6	ATN CVA	Yes No	Unknown	No
11	51	F	4	ATN, GIB	No	Dead	No
2	50	F	3	ATN	Yes	Alive	Yes
4	77	M	4	ATN	Yes	Dead	Yes
5	48	M	4	ATN	Yes	Alive	Yes
6	49	F	1	Limb ischemia	No	Alive	Yes
7	55	F	5	Mesenteric ischemia, limb ischemia	No	Dead	Yes
8	55	F	3	ATN, mesenteric ischemia, limb ischemia	Yes	Alive	Yes
12	97	M	2	ATN	Yes	Unknown	Yes

* Reported/confirmed other antihypertensives including beta blockers, diuretics, angiotensin converting enzyme inhibitors/angiotensin receptor blockers

Pt = patient number; M = Male; F = Female; ATN = Acute Tubular Necrosis; CVA = Cerebrovascular accident; MI = Myocardial infarction

discharged to an inpatient psychiatric facility. Of the four in-hospital deaths, two occurred more than a week after initial arrival. Both were attributed to complications of multi-organ system dysfunction that accompanied critical illness, and both occurred after initial vasopressor doses had been decreased or weaned off entirely. The other two in-hospital deaths occurred within 24 h of arrival to our center, and both occurred in patients who were receiving HIE and multiple vasopressor agents as well as methylene blue as salvage therapy. One of these patients had an echocardiogram that showed mild global hypokinesis while another had an echocardiogram showing hyperdynamic cardiac function.

In order to account for differences between isolated DHP ingestions and those with co-ingestions, the data for these two groups were also analyzed to detect differences. There was no significant difference identified in any of the variables, including clinical parameters and pharmacologic treatments (Table 5), between patients with single-agent DHP ingestions and those with poly-drug ingestions. One patient with a reported single-agent DHP CCB ingestion experienced two ischemic complications (ATN and GIB), both occurring after initiation of vasopressors.

For the subgroup of patients who had a confirmed BB coingestion ($N = 24$; 35%), there was no significant difference between median peak vasopressor dose or nadir blood pressure compared to those without confirmed BB coingestion, although nadir HR was lower (median 48 versus 65 bpm, difference 17 bpm, [$p = 0.002$]; 95% CI 5–23 bpm). Similarly, for the subgroup of patients with ACE inhibitor coingestions was analyzed, there were also no major differences between peak vasopressor dosing, mechanical ventilation rates, or 30-day mortality when compared to those with non-ACE inhibitor coingestions or no non-DHP coingestions.

Discussion

Though amlodipine is now the most commonly prescribed CCB, few studies focus specifically on DHP toxicity. Our DHP overdose population had a high rate of critical illness and often required multiple vasopressors. The doses of vasopressors used were relatively high, in line with the previous study by Levine et al. focusing on non-DHP toxicity [6]. When comparing our data to the aforementioned non-DHP paper from the same institution, the median peak doses for norepinephrine (200 vs. 100 mcg/min), epinephrine (200 mcg/min vs. 150 mcg/min), phenylephrine (800 mcg/min vs. 250 mcg/min) and high-dose insulin (4 u/kg/min vs. 2 u/kg min) were higher in this DHP-only population. Because there were no non-DHP coingestions reported in our population, these study populations did not overlap. Our results are concordant with more recent publications describing higher vasopressor dosing for DHP CCB toxicity compared to non-DHP CCB toxicity [16]. This may in part be due to multiple mechanisms of vasoplegia specific to DHP-mediated endothelial nitric oxide synthase inhibition in addition to L-type calcium channel blockade in vascular smooth muscle.

One of the major concerns in patients receiving high doses of vasopressors is ischemic complications due to decreased blood flow secondary to systemic vasoconstriction. Of the

Table 5 Selected baseline parameters and maximum Pharmacologic agent dosing in patients with isolated DHP CCB ingestions versus poly-drug ingestions

Parameter	Single-agent DHP ingestion ($N=10$)	Coingestions reported ($N=58$)	p-value
Initial SBP (mmHg; mean [IQR])	99 (77.8-124.5)	104 (88.5–121)	0.64
Initial DBP (mmHg; mean[IQR])	51.5 (41.5–68.3)	60.5 (50.3–71.8)	0.16
Nadir SBP (mmHg; mean [IQR])	74.4 (66-92.8)	77 (67.5–89.8)	0.80
Nadir DBP (mmHg; mean [IQR])	40 (32.3–46.5)	43 (34.3–49.8)	0.77
Initial HR (beats per minute; mean [IQR])	78.5 (73.8-100.3)	78 (64–90)	0.53
Nadir HR (beats per minute; mean [IQR])	72.5 (62.3–77.8)	58.5 (49.5–67.0)	0.06
Initial serum creatinine (mg/dL; mean [IQR])	1.30 (0.64–2.11)	1.11 (0.85–1.55)	0.86
Peak serum creatinine (mg/dL; mean [IQR])	1.85 (0.64–3.49)	1.21 (0.89–1.71)	0.80
Initial serum lactate (mmol/L; mean [IQR])	5.8 (2.1–6.2)	4.1 (2.1–5.4)	0.58
Peak serum lactate (mmol/L; mean [IQR])	5.6 (6.2–6.8)	4.6 (2.2–8.9)	0.79
Maximum norepinephrine dose (mcg/min, median [IQR])	($N=5$) 60 (34–60)	($N=36$) 42.5 (10.5–70)	0.34
Maximum epinephrine dose (mcg/min, median [IQR])	($N=4$) 11.5 (7.5–18.8)	($N=19$) 25 (17–50)	0.12
Maximum phenylephrine dose (mcg/min, median [IQR])	($N=3$) 200 (125–200)	($N=18$) 200 (175–245)	n/a
Maximum dopamine dose (mcg/kg/minute, median [IQR])	($N=0$)	($N=7$) 15.0 (6.3–23.8)	n/a
Maximum HIE infusion rate (units/kg/hour, median [IQR])	($N=2$) 1.23 (1.21–1.24)	($N=8$) 1.0 (0.67–1.2)	n/a

*For statistically significant inter-group differences only

**Available for $N=34$ of 58 non-HIE patients

seven cases of ischemic complications occurring after vasopressor initiation reported here, all but three had a clear unrelated explanation (i.e., arterial line complication or atherosclerosis—see Results section). Two of these were cases of mesenteric ischemia in critically ill patients with concomitant multisystem organ failure, one of whom died shortly thereafter and another of which sustained a cardiac arrest and was resuscitated on the day prior to the ischemic event. A third patient experienced both ATN and a GIB that were not present prior to vasopressor initiation—however, the ATN also occurred in the setting of multisystem organ failure and high doses of both vasopressors and insulin, while the GIB occurred about a month after her initial admission. Thus, even for those patients with ischemic complications occurring after vasopressor initiation, we believe the explanation is more likely to be refractory shock than to be due to the high vasopressor dose itself.

Though this study involved a high percentage (35%) of BB coingestions, maximum median doses of vasopressors were not significantly different when those cases were separated for subgroup analysis; thus, it is less likely that BB coingestants alone were responsible for the severity of illness in these cases.

Conclusions regarding the cases in which HIE was used are challenging in this study. Specific group practice at our institution is to reserve HIE as a rescue therapy. Thus, the subgroup of patients who received HIE consisted of those with shock refractory to first- and often second-line vasopressor treatment, and therefore more likely to have high vasopressor requirements and worse outcomes independent of HIE use. A recent review of Poison Center data by Cole et al. [16] compared insulin dosing and vasopressor requirements between amlodipine and non-DHP CCB cases. Higher vasopressor dosing was found in the amlodipine cases. However, in this latter series and congruent with the practice pattern at that institution, HIE was the first line agent administered, followed by vasopressors for refractory cases. They concluded that the intrinsic vasodilatory properties of HIE contributed to a higher vasopressor requirement in the amlodipine overdose cohort due to multifactorial vasoplegia. While our data similarly suggest maximum vasopressor dosing in DHP CCB overdose is higher than previously reported for non-DHP CCB overdose, the cohort in Cole et al. received HIE under different clinical circumstances than in the present study (i.e., as first-line therapy as opposed to rescue therapy). This dichotomy highlights the difficulty in external generalizability comparing HIE and vasopressor dosing between institutions and geographic locations. It is unlikely that the vasodilatory properties of insulin itself was the sole driver of increased vasopressor requirements in our HIE group, since they had significantly lower initial blood pressures compared to the non-HIE group.

There were two deaths that occurred within 24 h of ingestion. Since both HIE and methylene blue were used in these two cases of moribund patients in refractory shock, few conclusions can be drawn about the relative efficacy of either of agent beyond the widely accepted observation that there does not seem to be a single antidotal rescue therapy capable of reversing the effects of profound DHP CCB toxicity.

Limitations

This is a retrospective chart review, with all of the typical limitations inherent to retrospective data analysis. Specifically, the ability to abstract data is limited to the

completeness and accuracy of the information in the medical record. To account for this, we have largely tried to include dichotomous variables (e.g. lived or died; meeting pre-defined ischemic complications or not) rather than variables such as electrocardiogram interpretation. Other standardized practices for retrospective chart review were performed to reduce some of the limitations inherent to retrospective studies. [17–18].

The lack of universal confirmatory lab testing for DHP CCBs is another limitation of our data, as it is possible that some patients without DHP CCB ingestions may have been included based on erroneous history. Unfortunately, DHPs are inconsistently detected on the urine GC-MS. Thus, if a patient clearly reported overdose of a DHP calcium channel blocker and had a clinical state consistent with DHP overdose, the patient was included in this study. Nonetheless, inclusion of patients without definitive confirmation of the ingestion via comprehensive drug testing may have incorrectly resulted in inclusion of patients who should not have been included.

The study is a single center study in which patients were evaluated by a toxicologist at the bedside. These features may limit external validity of the study. In addition, most patients received vasopressors prior to HIE. It is not clear if the results would be different if HIE were administered as a first line therapy with vasopressors for refractory cases. In addition, while dobutamine is more of an inotropic support agent rather than a vasopressor per se, we have included dobutamine and dopamine, along with classical agents such as norepinephrine in order to be consistent with prior published literature [6]. Furthermore, most patients who received HIE had an echocardiogram performed which did not reveal significant decrease in the ejection fraction. Due to the few number of patients who received HIE and who had echocardiograms performed, we were unable to perform analysis as to the timing of HIE with regards to the echocardiogram. Thus, it is possible there was some improvement in the ejection fraction following insulin administration had the echocardiogram clearly been performed prior to HIE administration.

We were only able to account for 76% of patients after discharge. Thus, there is a 24% loss to follow up regarding 30-day mortality. While we would expect most deaths to have occurred during the index hospitalization, we nonetheless acknowledge this is a potential limitation. Lastly, formal echocardiograms were not obtained on every patient. However, many additional patients had a bedside echocardiogram performed by the treating providers, which would not necessarily be recorded as a formal echocardiogram. Thus, an echocardiogram may have been used to guide management, but not be included in the overall number of subjects receiving echocardiograms.

Conclusion

This study shows a high frequency of critical illness in DHP CCB toxicity managed primarily with high dose vasopressors. Ischemic complications attributable to vasopressor use were uncommon. Rather, in many cases, the ischemic complications were the result of prolonged shock, rather than the vasopressors themselves. Further research is needed to determine the relative importance and risks of higher-dose vasopressors and HIE/other adjunctive therapies in cases of DHP CCB-related toxicity.

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Declarations

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Conflict of Interest The authors have no conflicts of interest or financial disclosures to report.

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