

Hyperglycemia and Severe Medical Outcomes in Calcium Channel Blocker Exposures Reported to United States Poison Centers

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ABSTRACT

Introduction: Calcium channel blockers (CCBs) antagonize L-type calcium channels, primarily in the cardiovascular system. In overdose, the pancreas also is affected, which prevents the release of insulin leading to hyperglycemia. We sought to determine the incidence of hyperglycemia in CCB exposures reported to US poison centers and to compare the incidence of hyperglycemia with severe medical outcomes.

Methods: We performed a retrospective chart review of CCB exposures using data from the National Poison Database System from January 1, 2007, through December 31, 2017. Exposures with co-ingestions were excluded. Statistical analysis was performed to determine incidence of hyperglycemia and associated medical effects. Statistical analyses on age and intentionality of exposure also were performed.

Results: There were a total of 49 576 CCB exposures included in the study; 626 exposures (1.2%) had reported hyperglycemia. The relative risk of a severe medical outcome in cases with hyperglycemia compared to cases without hyperglycemia was 21.8 (95% CI, 19.6-24.4). Exposures in cases of people older than age 20 had a relative risk of hyperglycemia of 8.6 (95% CI, 6.8-10.9) and a relative risk of a severe medical outcome of 5.6 (95% CI, 4.9-6.5). In intentional exposures, the relative risk of hyperglycemia was 11.3 (95% CI, 9.6-13.3), and the relative risk of death or a severe medical outcome was 12.1 (95% CI, 10.8-13.7).

Conclusions: In this large retrospective review of CCB exposures, hyperglycemia was an uncommon event. When present, hyperglycemia was associated with a severe medical outcome. Intentional exposures and exposures in people older than age 20 years also were associated with increased incidence of hyperglycemia and a severe medical outcome.

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INTRODUCTION

Calcium channel blockers (CCBs) are medications prescribed for the treatment of several medical conditions, including hypertension, heart failure, angina pectoris, Raynaud's phenomenon, subarachnoid hemorrhage, supraventricular tachycardia, and migraine headache.¹ There are 3 subclasses of calcium channel blockers in the United States: phenylalkylamines (verapamil), benzothiazepines (diltiazem), and the dihydropyridines (amlodipine, nicardipine, nifedipine, nimodipine, felodipine, among others). More commonly, CCBs are grouped into the dihydropyridines and the nondihydropyridines (diltiazem and verapamil). In overdose, these medications can cause significant morbidity and mortality. In 2021, there were 15 945 exposures to CCBs reported to US poison centers. They represent the sixth most common substance associated with overdose-related deaths.²

Calcium channel blocker toxicity is classically described as a triad of bradycardia, hypotension, and hyperglycemia. The cardiovascular effects are mediated primarily by antagonism of voltage-gated L-type calcium channels in the myocardium or vascular smooth muscle. In overdose, these channels are also believed to be affected in the pancreatic β -islet cells, resulting in reduced insulin secretion.³

Hyperglycemia in CCB overdose also may be caused by reduced glucose uptake by peripheral tissues, as CCBs inhibit activation of the ubiquitous glucose transporter 1 (GLUT1).⁴ Hyperglycemia due to L-type calcium channel blockade and GLUT1 inhibition has been correlated to the severity of medical outcomes in CCB

overdose, but only in cases involving nondihydropyridine CCBs. Since that study, there has been limited exploration as to whether this correlation also applies to dihydropyridine CCBs or to the CCB class as a whole.⁵ If such differences exist between CCB subclasses, it may have implications for appropriate treatment of CCB overdose.

CCB overdose presents a wide range of clinical severity. Some patients require only monitoring while others necessitate complex, resource-intensive interventions, such as extracorporeal membrane oxygenation (ECMO) or high-dose insulin euglycemia therapy (HIET). There is already some evidence that dihydropyridine CCBs respond less favorably to HIET compared to nondihydropyridine CCBs.⁶ The ability to predict which patients may require these advanced interventions within a critical timeframe is essential for optimizing care and resource allocation.

Despite the clinical relevance of hyperglycemia in CCB toxicity, there are no studies in the literature evaluating its overall incidence in CCB exposures. Thus, it remains unclear whether hyperglycemia is a common finding in these cases. Additionally, the association between hyperglycemia and severity of a CCB overdose has not been studied in dihydropyridines or comprehensively across entire CCB class. There also has been little research on the demographic and clinical risk factors associated with hyperglycemia in CCB exposures.

This study aimed to clarify the prognostic value of hyperglycemia in CCB overdose, specifically to determine if its presence reliably indicates poor outcomes or whether its absence may offer false reassurance. By assessing the individual variables that influence clinical judgment, the study sought to enhance decision-making in CCB toxicity cases and evaluate whether hyperglycemia and similar markers should inform clinical expectations or be reconsidered in overdose management.

The primary objective was to determine the overall incidence of hyperglycemia in CCB exposures reported to US poison centers. Secondary objectives included assessing the relative risk of severe medical outcomes in the presence of hyperglycemia and to evaluating whether exposure intentionality or patient age increases the likelihood of developing hyperglycemia following a CCB exposure.

METHODS

Study Design and Data Source

We conducted a retrospective cohort study using data from the National Poison Database System (NPDS) from January 1, 2007 to (through) December 31, 2017. This study was deemed exempt from Institutional Review Board review, as the dataset did not meet the criteria for human subjects research.

Data in NPDS are collected by specialists in poison information at regional poison centers, who are specifically trained and certified in the management of poisoned patients and in standardized data collection. The NPDS includes information on the class of

toxin exposure, the route of exposure, patient age and sex, adverse effects, treatments used, location of care, and medical outcome. The American Association of Poison Control Centers (AAPCC) defines an exposure as any contact with a substance, including swallowing, breathing, or absorbing it through the skin or eyes.⁷

Inclusion criteria for this study were cases of CCB exposures. Cases with co-exposure to sulfonylureas or insulin were excluded, as these are the most common diabetic medications known to cause hypoglycemia in toxicity. Patients with a diagnosis of diabetes were not excluded. A total of 49 576 cases met inclusion criteria and were analyzed.

Data Processing and Analysis

Data were grouped by presence or absence of hyperglycemia. Hyperglycemia was defined by the AAPCC coding manual as a blood glucose concentration greater than 150 mg/dL present at any time during the exposure case.⁷ Exposures in which a blood glucose level was not recorded were placed in the “absence of hyperglycemia” group. Data also were stratified by intentional and unintentional exposures and by age ranges. Age ranges were defined as 0 to 5 years, 6 to 12 years, 13 to 19 years, 20 to 64 years, and 65 years and older.

Data also were grouped by the medical outcomes “no effect,” “minor effect,” “moderate effect,” “major effect,” and “death,” as defined by the AAPCC coding manual.⁷ “No effect” was defined as the absence of symptoms following exposure. “Minor effect” was defined as a minimally bothersome symptoms from which the patient fully recovered without residual disability or disfigurement as a result of the exposure. “Moderate effect” was defined as pronounced, prolonged symptoms that may have required treatment but were not life-threatening, will full recovery and no residual disability or disfigurement. “Major effect” was defined as life-threatening symptoms resulting in significant residual disability or disfigurement. “Death” referred to a fatality directly attributable to the exposure or its complications. For statistical analysis in this study, any exposures that resulted in “major effect” or “death” were categorized similarly as a “severe medical outcome.”

Statistics

Descriptive statistics were calculated using percentages and relative risk estimates. Confidence intervals between 2 independent variables were calculated using the Wilson procedure. All statistical analyses were calculated using VassarStats: Website for Statistical Computation.⁸

RESULTS

Characteristics of Study Subjects

Of the 49 576 CCB exposures reported during the 10-year study period, 23 643 (47.7%) involved males patients (Table 1). The highest proportions of exposures occurred in the youngest and second-oldest age groups: 18 233 (36.8%) were in individuals aged

Table 1. Baseline Demographic Characteristics of Calcium Channel Blocker Exposures Reported to the National Poison Database System, January 1, 2007–December 31, 2017, n=49 576

Characteristics	n	%
Sex		
Male	23 643	47.7
Female	25 893	52.2
Unknown	40	0.1
Age		
0–5 years old	18 233	36.8
6–12 years old	6532	13.2
13–19 years old	3321	6.7
20–64 years old	13 239	26.7
≥ 65 years old	8167	16.5
Unknown	84	0.2

0 to 5 years, and 13 239 (26.7%) were in individuals aged 20 to 64 years old. A total of 6910 (13.4%) exposures were reported as intentional.

Hyperglycemia and Medical Outcome

Hyperglycemia was reported in 626 (1.2%) of the total 49576 CCB exposures. The proportion of exposures with hyperglycemia increased with severity of medical outcome, including exposures resulting death, which had the highest incidence of hyperglycemia (35.5%)(Figure 1).

Of the 626 cases of hyperglycemia, 274 (43.7%) resulted in a severe medical outcome (major effect or death). Comparatively, of the 48 950 cases without hyperglycemia, 979 (2.0%) resulted in a severe medical outcome (difference 41.7%; 95% CI, 37.9%–45.7%). Overall, the relative risk of experiencing a severe medical outcome in the presence of hyperglycemia was 21.8 (95% CI, 19.6–24.4).

Age, Hyperglycemia, and Medical Outcome

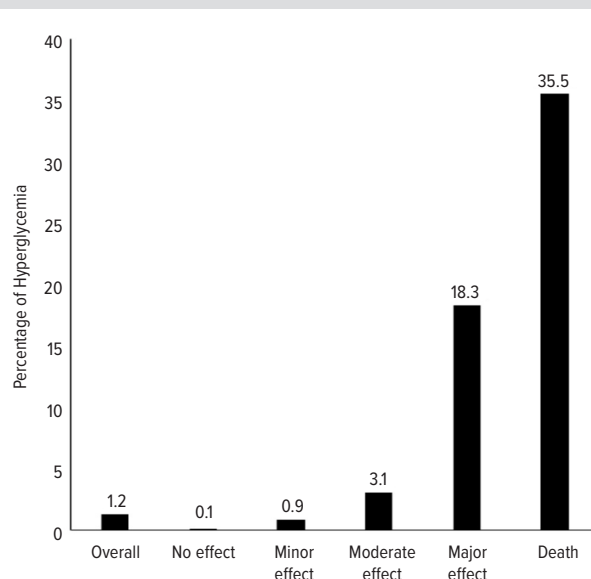
In general, the proportion of exposures with reported hyperglycemia increased with age, starting at 0.14% in individuals 0 to 5 years, peaking at 3.0% in individuals 20 to 64 years, and decreasing 1.8% 65 years and older (Figure 2). Similarly, the proportion of exposures that resulted in a severe medical outcome also increased generally with age, from 0.45% in individuals 0 to 5 years old to 5.4% in those aged 20 to 64 years (Figure 2).

When comparing exposures in people aged 20 years and older to those younger than 20 years, the relative risk of developing hyperglycemia was 8.6 (95% CI, 6.8–10.9), and the relative risk of the exposure resulting in a severe medical outcome was 5.6 (95% CI, 4.9–6.5).

Intentionality, Hyperglycemia, and Severity of Illness

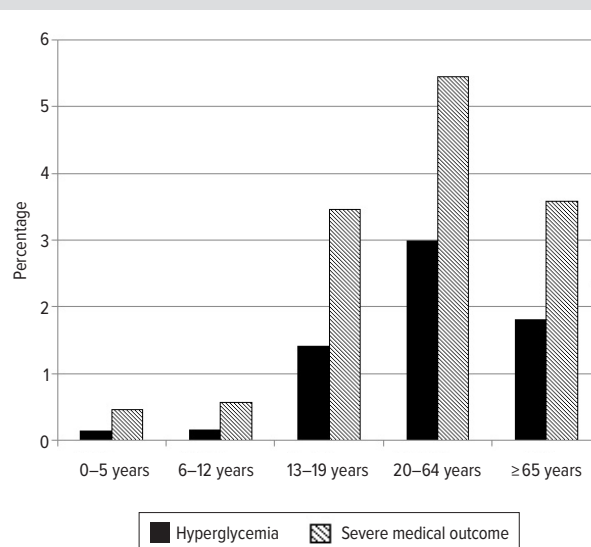
Hyperglycemia was reported in 5.7% (391/6910) of intentional exposures compared with 0.5% (212/42341) of unintentional exposures (difference 5.2%; 95% CI, 4.6%–5.7%). The relative risk of hyperglycemia in intentional versus unintentional expo-

Figure 1. Proportion of Hyperglycemia in Each Medical Outcome of Calcium Channel Blocker Exposures Reported to National Poison Database System, January 1, 2007–December 31, 2017



Medical Outcome	N	Proportion of Hyperglycemia	
		n	%
No effect	32 481	626	0.1
Minor effect	7580	65	0.9
Moderate effect	8262	255	3.1
Major effect	994	182	18.3
Death	259	92	35.5
Total	49 481	626	1.3

Figure 2. Proportion of Exposures With Hyperglycemia and Portion of Exposures With a Severe Medical Outcome Based on Age in Calcium Channel Blocker Exposures Reported to National Poison Database System, January 1, 2007–December 31, 2017



sure was 11.3 (95% CI, 9.6-13.3). Intentional exposures were also more likely to result in a severe medical outcome: 11.4% (791/6910) of intentional exposures resulted in a severe medical outcome compared with 0.9% (399/42314) in unintentional exposures (difference 10.5%; 95% CI, 9.8%-11.3%), with a relative risk of 12.1 (95% CI, 10.8-13.7). See Figure 3.

Among intentional exposures, 3.2% (193/6119) of patients developed hyperglycemia despite experiencing no effect, minor effect, or moderate effect. Comparatively, hyperglycemia was present in 25.0% (198/791) of those who experienced a severe medical outcome (difference 21.8%, 95% CI, 19.0%-25.0%). The relative risk of a severe medical outcome in intentional exposures with hyperglycemia compared to those without hyperglycemia was of 5.6 (95% CI, 4.9-6.3).

DISCUSSION

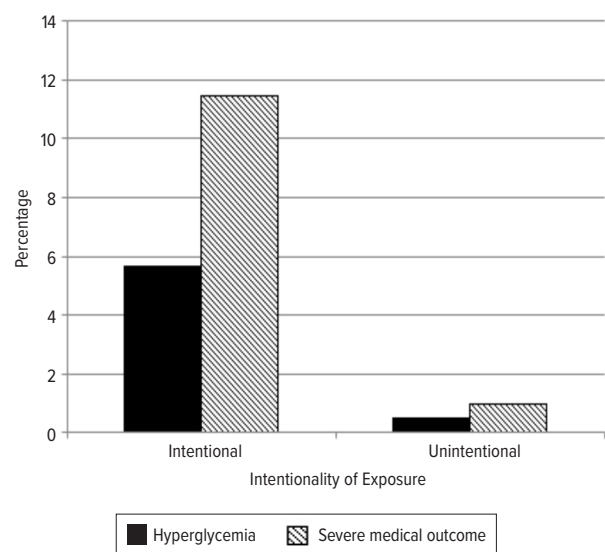
Hyperglycemia was not commonly documented in calcium channel blocker exposures reported to US poison centers over the 10-year period; only 1.2% of cases reported hyperglycemia at any point during the exposure. Additionally, hyperglycemia was not documented in the majority of exposures that resulted in a severe medical outcome. This finding is unexpected, as hyperglycemia has traditionally been considered a hallmark of CCB toxicity.⁹

Although the overall incidence of hyperglycemia was low, its presence was associated with increased risk of severe medical outcomes, consistent with previous findings in nondihydropyridine CCB exposures.⁵ Exposures in adults aged 20 years and older were more likely to be associated with hyperglycemia and severe medical outcomes. Similar to our findings, previous studies also have reported that most pediatric CCB exposures result in minimal to no clinical effects. This may be explained in part by tendency for medication exposures in children tend to be small amounts—typically 1 to 2 tablets.¹⁰ There also may be a relative difference in the incidence of diabetes and other comorbidities in children versus adults that may lead to more severe medical outcomes in adults.

Intentional exposures were more likely to be associated with hyperglycemia and severe medical outcomes, perhaps because intentional exposures tend to result in a higher blood concentration.¹¹ This is consistent with previous evidence that hyperglycemia is a marker of toxicity severity in overdoses involving nondihydropyridine CCBs.⁵

A key question remains: why did hyperglycemia not occur in all, or even most, fatal cases? It may be that a certain CCB subclass is more likely to induce hyperglycemia than others, despite both causing significant deleterious effects from the resulting hemodynamic changes. While a previous clinical study in diltiazem and verapamil demonstrated a correlation between hyperglycemia and severe medical outcomes,⁵ similar studies have not been conducted for dihydropyridine CCBs. It might be assumed that dihydropyridine CCB overdose leads to hyperglycemia, as previous *in vivo*

Figure 3. Proportion of Exposures With Hyperglycemia and Proportion of Exposures With a Severe Medical Outcome Based on Intentionality of Exposure in Calcium Channel Blocker Exposures Reported to National Poison Database System, January 1, 2007–December 31, 2017



studies suggest that dihydropyridines are more likely to cause hyperglycemia at therapeutic doses.¹² However, other data indicate that dihydropyridine CCB overdose responds poorly to high-dose insulin therapy.⁶ A dedicated analysis comparing the incidence of hyperglycemia in dihydropyridine versus nondihydropyridine CCB exposure may help clarify these findings.

Limitations

This study has several limitations. First, the timing of hyperglycemia during the course of each exposure is unknown, making it more difficult to determine if the hyperglycemia was due directly to the CCB or treatment for the overdose, or simply a result of critical illness.¹³ For example, vasopressors such as epinephrine—often used in critical patients with CCB overdose—are known to cause hyperglycemia.^{14,15} Additionally, it was unknown if a patient received any dextrose-containing fluid or insulin therapy during their care, although cases involving initial sulfonylurea or insulin exposures were excluded. Patients with diabetes were not excluded, which may be considered a limitation because of their high propensity to become hyperglycemic. However, given the overall low rates of hyperglycemia observed, these patients were kept in the study to improve the generalizability of the findings.

Additionally, the dataset does not include the total dose of CCB ingested or drug serum levels to confirm that there was a CCB exposure at all—especially in exposures in young children. The formulation of the CCB ingested (immediate vs sustained release) also was unknown, which may affect medical outcomes. These limitations reflect the nature of using a national reporting

system that collects data from various regions, which may have varying training and expectations for information gathering. Additionally, many of these details are unavailable, as the patient may be nonverbal, have altered mental status, or unwilling to provide a detailed account of the ingestion.

Another limitation is that these data originate from passive, voluntary reporting to poison centers. While this leads to a great volume of information, there is a possibility of underreporting of cases or clinical effects, which may significantly alter study results. As mentioned previously, regional differences in reporting practices also may lead to missing data, including specific CCB type, accurate ingestion quantities, and comorbidities.

Additionally, exposures that were reported at home and did not result in medical care were coded as having no hyperglycemia, despite not knowing the actual blood glucose concentration. Typically, these cases are also coded as having no clinical effect. Although this likely had minimal impact of the data related to the more severe medical outcomes, it should still be noted as a significant limitation. Lastly, because the data analyzed are database-dependent, the study was limited to a retrospective review, which in turn limits its power.

Finally, home exposures that did not present for medical care and were coded as “no effect” were included in the study and classified as “no hyperglycemia,” despite the likelihood that blood glucose concentrations were not measured in most homes. The assumption was that those exposures were unlikely to result in hyperglycemia, as they did not necessitate medical evaluation or intervention. While this may risk underestimating the true incidence of hyperglycemia in this group, the impact on overall findings is likely minimal, as even among exposures resulting in death, only 35% of presentations developed hyperglycemia.

Future Directions

This study raises several important questions for future research. Given the data available, there is potential to determine whether a specific subclass of CCBs is more likely to result in hyperglycemia and severe outcomes. While this has been studied previously in nondihydropyridines CCBs,⁵ data on dihydropyridines only and a comparison to the nondihydropyridines is noticeably absent, despite documented differences in response to high-dose insulin therapy.⁶

Additionally, it would be beneficial to determine if the level of hyperglycemia correlates with the severity of medical outcome in all CCB classes, as previous studies in nondihydropyridine CCBs found that the best predictor of a poor medical outcome was actually the percent increase in blood glucose concentration rather than absolute concentration for those classes.⁵ Also, it would be ideal to analyze a smaller subset of these cases to determine if the dose of each CCB correlates with hyperglycemia levels and toxicity severity, as this information was not available in our dataset.

CONCLUSIONS

The overall incidence of hyperglycemia in calcium channel blocker exposures reported to US poison centers was surprisingly low, but the presence of hyperglycemia in these exposures was associated with increased risk of severe medical outcomes. Intentional exposures and exposures in people older than 20 years were also associated with increased hyperglycemia and severe medical outcomes.

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