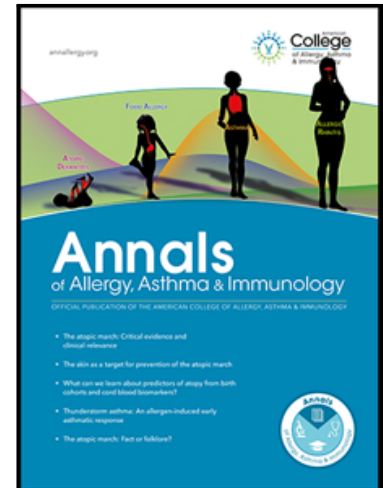


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PII: S1081-1206(21)01215-1
DOI: <https://doi.org/10.1016/j.anai.2021.10.030>
Reference: ANAI 3759



To appear in: *Annals of Allergy, Asthma Immunology*

Received date: 16 September 2021
Revised date: 22 October 2021
Accepted date: 26 October 2021

Please cite this article as: Jose Manuel Martinez Manzano MD , Kevin Bryan Lo MD , Simone A. Jarrett MD , Brenda Chiang DO , Zurab Azmaiparashvili MD, MSc , Angioedema associated with the use of dihydropyridine calcium channel blockers—A case series, *Annals of Allergy, Asthma Immunology* (2021), doi: <https://doi.org/10.1016/j.anai.2021.10.030>

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Angioedema associated with the use of dihydropyridine calcium channel blockers – A case series

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Funding source: none.

Conflict of interests: none.

Angioedema is the soft tissue swelling of skin and mucous membranes localized in non-dependent areas of the body such as face, lips, tongue, upper respiratory airway, and intestines, as a result of intravascular fluid extravasation.¹

Several drugs have been described as the causative agents or triggers of angioedema. Dihydropyridine CCBs have been rarely associated with angioedema, and the mechanism has not been clarified.^{2,3}

A large randomized trial of antihypertensive treatment showed that the incidence of angioedema due to amlodipine was 6%.² Meanwhile, another large randomized trial of antihypertensive combined therapy showed that angioedema was more common among patients randomized to the benazepril-amlodipine group, as compared to benazepril-hydrochlorothiazide group.⁴

Therefore, we aim to describe the demographic characteristics, clinical features, and outcomes of eighteen (18) subjects diagnosed with angioedema due to dihydropyridine CCB therapy.

This study was a retrospective and observational case series of patients older than 18-year-old admitted to our institution with diagnosis of angioedema secondary to dihydropyridine CCBs from 2015 to 2020.

The diagnosis of angioedema was established by emergency department physicians (ED). All the subjects were on treatment with dihydropyridine CCBs at the time of presentation. Patients on concomitant therapy with ACEI, angiotensin receptor blockers (ARBs) or NSAIDs were excluded. We recorded data related to demographics, comorbidities, angioedema location (face/lips, tongue, pharynx/larynx) and treatments received, including steroids, histamine receptor 1 blockers, histamine receptor 2 blockers and epinephrine. Also, we recorded clinical outcomes, including length of stay, rates of intubation and mortality.

Continuous variables were presented as means and standard deviations (SD) when the data was normally distributed or as medians and ranges if the data was skewed. Categorical variables were presented in frequencies and percentages. The study was approved by the institutional review board.

We identified 210 subjects that were on CCB therapy while at the same time admitted for angioedema but only 18 (9%) cases were attributed to CCB use. We excluded 192 subjects, 136 (65%) were concomitantly using ACEI, whereas other causes of angioedema were identified in 56 (27%) subjects, including ARBs, NSAIDs, food-related and other drugs.

The mean age was 67.5 ± 7.8 and 11 subjects (62.2%) were females. All the patients were African Americans and were hypertensive. Fourteen subjects were on amlodipine and 4 on nifedipine. Ten subjects (55.5%) had prior episodes of angioedema; 6 were related to ACEI, 3 were unknown, 1 was related to amlodipine. None of them had family history of angioedema.

Only one patient presented with histaminergic symptoms (hives and pruritus). None had hypotension or evidence of peripheral eosinophilia (defined as absolute eosinophil peripheral count >500 eosinophils/microL). Nobody had any history of urticaria.

Most subjects had tongue involvement (77.7%), whereas face/lips were involved in 66.6% and pharynx/larynx in 33.3% of cases. Most subjects were treated with steroids, H1 and H2 blockers (100%, 94.4% and 88.8% respectively) and only 3 received epinephrine (16.6%). A total of five

patients (27.7%) were intubated, and all of them had tongue involvement. The median length of stay was 2 days (range=0.13-9).

We described 18 subjects with angioedema due to dihydropyridine CCB therapy. It only represents 9% of patients that were on CCB therapy at the time of diagnosis of angioedema; most cases (65%) were better explained by the concomitant use of ACEI. Angioedema due to CCBs is an uncommon event, as shown by a randomized controlled trial of antihypertensive medications which reported that the odds of developing angioedema were 11-folds higher with lisinopril compared to amlodipine, the later was involved only in 6% cases of angioedema.²

The mechanism of angioedema due to CCBs has not been well described. The vasodilator properties of CCBs, especially amlodipine, have been associated to the endothelial release of bradykinin and nitric oxide.⁵ At the present study, all the subjects with CCB-angioedema were African Americans, a group that is at risk of developing bradykinin-mediated angioedema.⁸ Furthermore, we observed that six subjects had somewhat evidence of bradykinin-kallikrein dysregulation, as they had prior reported episodes of ACEI-induced angioedema. None of the subjects were treated with bradykinin inhibitors, which have shown conflicting results in patients with ACEI-induced angioedema and, to our knowledge, have not been tested in CCB-induced angioedema.⁸

On the flip side, allergic reactions are uncommon among patients using dihydropyridine CCBs. Allergies are more commonly described with diltiazem, a non-dihydropyridine CCB, and cross reactivity among different classes of CCBs has not been well established.⁹ In our study, only one

patient had histaminergic symptoms, reported as hives and pruritus, and none had peripheral eosinophilia, hypotension, abdominal pain, or diarrhea.

The location and severity of angioedema observed at the present study was similar to the characteristics described in subjects with bradykinin-mediated angioedema.¹⁰ Angioedema was predominantly located in the tongue (77.7%), followed by face/lips (66.6%) and larynx/pharynx (33.3%). Furthermore, 5 subjects (27.7%) developed severe angioedema that prompted endotracheal intubation for airway protection, and all of them had tongue involvement. This finding differs from a randomized controlled trial in which none of the patients who developed angioedema secondary to amlodipine use were intubated.² Nonetheless, we did not observe any fatalities. We also noted that CCBs were discontinued in 16 subjects, whereas 2 patients were switched from amlodipine to nifedipine – in whom we did not observe recurrent hospitalizations due to angioedema within a year after discharge date.

Our study had multiple limitations, including the retrospective nature and small sample size. The diagnosis of angioedema, causes and clinical features described in the study were based on ED physician's assessments, which could lead to observer bias. However, we included a strict inclusion criterion to filter out all potential medications that may provoke angioedema to come up with a more homogenous patient sample to analyze. An appropriate assessment of response to antiallergic therapies such as H1 blockers, H2 blockers and steroids could not be assessed due to the lack of control group and the use concomitant medications, and serum tryptase levels – surrogate of histaminergic reactions – were not obtained.

In conclusion, CCB therapy may precipitate angioedema with a potentially clinically significant rate of intubation. This observation deserves further investigation.

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Table 1. Demographics, past medical history, comorbidities, clinical features on admission, angioedema location, treatments, and outcomes in patients with CCB-related angioedema.

Demographics	Results
Age (mean)	67.5 ± 7.8
Body Mass Index (mean)	30.5 ± 2.6
Sex-Male (%)	7 (38.8)
Race-African American (%)	18 (100)
Prior history and comorbidities	
Prior episodes of angioedema (%)	10 (55.5)
Family history of angioedema (%)	0 (0)
Hypertension (%)	18 (100)
Chronic lung disease (%)	4 (22.2)
Smoking (%)	2 (11.1)
Clinical features on admission	
Skin rash – hives, erythema, pruritus (%)	1 (5.5)
Abdominal pain/diarrhea (%)	0 (0)
Systolic blood pressure (mean)	165 ± 12.6
Absolute peripheral eosinophil count (median)	66 (0-481.6)
Angioedema location	
Face/lips (%)	12 (66.6)
Tongue (%)	14 (77.7)
Pharynx/Larynx (%)	6 (33.3)
Treatments	
Steroids (%)	18 (100)
H1 blockers (%)	17 (94.4)
H2 blockers (%)	16 (88.8)
Epinephrine (%)	3 (16.6)
Clinical outcomes	
Intubation (%)	5 (27.7)
Mortality (%)	0 (0)
Hospital length of stay – days (median)	2 (0.13-9)

Abbreviations: H1 blockers, histamine receptor type 1 blocker; H2 blocker, histamine receptor type 2 blocker. Continuous variables are presented as means ± SD or as medians and ranges. Categorical variables are presented in frequencies and percentages.