Amlodipine-induced angioedema: An unusual complication of a common medication

Merin E. Kuruvilla, M.D.,1 and Neha Sanan, D.O.2

ABSTRACT

Hypersensitivity reactions to dihydropyridine calcium channel blockers (CCB) are exceedingly rare, although sporadic reports of isolated angioedema seem to be gradually increasing in frequency. We present a case of angioedema likely triggered by amlodipine.

Hypersensitivity reactions to dihydropyridine calcium channel blockers (CCB) are exceedingly rare, although sporadic reports of isolated angioedema seem to be gradually increasing in frequency. We presented a case of angioedema likely triggered by amlodipine.

CASE PRESENTATION

A 67-year-old African American woman with chronic hypertension continued to demonstrate suboptimal blood pressure control despite ongoing therapy with hydralazine and metoprolol. Amlodipine 5 mg daily was subsequently added as third-line treatment. Her medical history was also pertinent for hyperlipidemia and congestive heart failure; concomitant medications included atorvastatin and furosemide. Despite a compelling indication for angiotensin-converting enzyme inhibitor (ACE-I) therapy (heart failure), this was precluded by a history of ACE-I-induced angioedema. Approximately 2 weeks into amlodipine therapy, the patient awoke on three consecutive mornings with periorbital and lip angioedema (Fig. 1), partially responsive to oral antihistamine therapy.

The amlodipine was discontinued, and the swelling resolved over the next day. However, after a month, she remained persistently hypertensive and was restarted on amlodipine 5 mg. Within minutes of ingestion of the first dose, the patient developed progressively worsening lip angioedema and swelling that extended into her face, which prompted evaluation at an urgent care. Symptoms began to subside within 1 hour of receiving steroids and antihistamines, gradually improved over the next 2 days, and required no additional therapy. The patient was referred to an allergy specialist, and amlodipine was immediately discontinued. Based on the lack of validated testing protocols and impracticality of skin testing to amlodipine, further investigation was deferred. A diagnosis of amlodipine-induced angioedema was made, and a trial of angiotensin receptor blocker (ARB) therapy was suggested. At 3 months, the patient had not experienced subsequent episodes of angioedema.

DISCUSSION

Here, we described a case of angioedema likely triggered by amlodipine, an uncommon adverse effect of this widely used drug.1–6 There are two broad groups of CCBs: dihydropyridines (DHP) (amlodipine, nifedipine, and others) and non-DHPs (diltiazem and verapamil). Among these, diltiazem has the greatest propensity to induce a wide spectrum of cutaneous hypersensitivity reactions,7 and DHPs to a much lesser extent. Although few and far between, case reports of angioedema attributed to DHPs do exist and more so in recent years.1–5 In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, angioedema occurred in only 0.03% of patients who took amlodipine (3 of 9048 cases).6 All three episodes developed in the first year of use. The characteristics of other reported cases1–5 of DHP-induced angioedema in the literature are examined in Table 1. Although the onset of symptoms is variable, the symptoms usually occurred within the first few weeks after starting the drug. It is important to note that no skin test data or other diagnostic workup was performed in any of these cases, given the absence of validated protocols. The diagnosis of CCB-induced angioedema was based on predictive scores and symptom resolution on drug withdrawal.

From the 1Department of Allergy/Immunology, Emory University, Atlanta, Georgia, and 2Department of Internal Medicine, Saint Vincent Hospital, Worcester, Massachusetts

No external funding sources reported

The authors have no conflicts of interest to declare pertaining to this article

Address correspondence to Merin E. Kuruvilla, M.D., Department of Allergy/Immunology, Emory University, The Emory Clinic, Bldg. A, 3rd Fl., Atlanta, GA 30322

E-mail address: merin.kuruvilla@emoryhealthcare.org

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (http://www.creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).
In our patient, amlodipine was implicated as the trigger due to the strong temporal relationship between drug administration and development of angioedema. Further, the reproducibility of the reaction with rechallenge indicated causality. The pathophysiologic mechanism of DHP-induced angioedema has not been established. In addition to arteriolar vasodilatation and increased vascular permeability, a role for bradykinin and vascular nitrous oxide production has been postulated but remains to be proved. Although limited data on cross-reactivity of CCBs currently exist, patients with DHP allergy seem to tolerate non-DHPs and vice versa. However, in our patient, the underlying diagnosis of congestive heart failure warranted therapy with ACE-I or ARB therapy.

Table 1  Case reports of angioedema caused by CCBs

| Culprit Drug | Age, y/Race/Sex | Clinical Presentation | Time to Onset | Duration of Reaction |
|--------------|-----------------|-----------------------|---------------|---------------------|
| Nifedipine, 2 patients [Ref. 1] | 55/unknown/woman; 58/unknown/woman | Periorbital angioedema | N/A | N/A |
| Amlodipine [Ref. 2] | 50/African-American/woman | Facial edema and macroglossia | 24 hr | 5 days |
| Amlodipine/nisoldipine [Ref. 3] | 56/African-American/woman | Small bowel angioedema | N/A | N/A |
| Nicardipine/amlodipine [Ref. 4] | 8/white/boy | Macroglossia | 3 days | 1 wk |
| Amlodipine [Ref. 5] | 2/Hispanic/boy | Laryngeal edema | 15 mo | 2 days |

CCB = Calcium channel blocker; N/A = not available.
Therefore, a trial of an ARB was recommended for blood pressure control instead of an alternative CCB. ARBs may be initiated with close monitoring despite a history of ACE-I angioedema.\textsuperscript{9}

**CONCLUSION**

The investigation of angioedema should take into consideration unlikely drug-induced causes, and CCBs should be added to that list.

**ETHICAL APPROVAL**

This study was approved by our institutional review board.

**STATEMENT OF HUMAN AND ANIMAL RIGHTS**

This article does not contain any studies with human or animal subjects.

**STATEMENT OF INFORMED CONSENT**

There are no human subjects in this article and informed consent is not applicable.

**REFERENCES**

1. Tordjman K, Rosenthal T, Bursztyn M. Nifedipine induced periorbital angioedema. Am J Cardiol. 1985; 55:1445.
2. Southward J, Irvine E, Rabinovich M. Probable amlodipine-induced angioedema. Ann Pharmacother. 2009; 43:772–776.
3. Turcu AF, White JA, Kulaga ME, et al. Calcium channel blocker-associated small bowel angioedema. J Clin Gastroenterol. 2009; 43:338–341.
4. Pierce WA, Hederman AD, Gordon CJ, et al. Angioedema associated with dihydropyridine calcium-channel blockers in a child with Burkitt lymphoma. Am J Health Syst Pharm. 2011; 68:402–406.
5. Hom KA, Hirsch R, Elluru RG. Antihypertensive drug-induced angioedema causing upper airway obstruction in children. Int J Pediatr Otorhinolaryngol. 2012; 76:14–19.
6. Piller LB, Ford CE, Davis BR, et al. Incidence and predictors of angioedema in elderly hypertensive patients at high risk for cardiovascular disease: A report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). J Clin Hypertens (Greenwich). 2006; 8:649–656; quiz 657–658.
7. Knowles S, Gupta AK, Shear NH. The spectrum of cutaneous reactions associated with diltiazem: Three cases and a review of the literature. J Am Acad Dermatol. 1998; 38:201–206.
8. Mason RP, Marche P, Hintze TH. Novel vascular biology of third-generation L type calcium channel antagonists: Ancillary actions of amlodipine. Arterioscler Thromb Vasc Biol. 2003; 23:2155–2163.
9. Bezalel S, Mahlab-Guri K, Asher I, et al. Angiotensin-converting enzyme inhibitor-induced angioedema. Am J Med. 2015; 128:120–125.