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Simvastatin: A Risk Factor for Angioedema?

SARAH A NISLY, AREEBA KARA, TAMARA B KNIGHT

Objective: To report a case of simvastatin-induced angioedema in a patient with near nightly episodes of orofacial angioedema.

Case Summary: A 75-year-old African American female presented to the emergency department with recurrent face, lip, and tongue swelling. The patient described frequent episodes of orofacial edema, with 4 emergency department visits over the previous 6 months. Her home medications were reviewed and simvastatin was identified as a possible contributing medication. Simvastatin was discontinued with resolution of the symptoms during hospitalization and a significant reduction in episodes.

Discussion: Drug-induced angioedema has been documented with several agents, most commonly angiotensin-converting enzyme inhibitors. The association with different drug classes has led to several postulated pathways for the development of angioedema. Notable mechanisms include mediation by bradykinin, inhibition of arachidonic acid metabolism, and complement activation. Each pathway culminates in increasing vascular permeability causing fluid accumulation in subcutaneous tissues. While statin use has been associated with drug-induced angioedema in postmarketing reports, there are no published cases involving simvastatin. Use of the Naranjo probability scale demonstrated a probable relationship between simvastatin use and the patient's recurrent angioedema.

Conclusions: While statin use is not commonly associated with angioedema, clinicians must be aware of this possible adverse reaction. Consideration must also be given to potential drug interactions, increasing the risk of this adverse event.

Angioedema is the abrupt onset of swelling involving the mucosa and submucosa of the skin. It can affect the face, lips, tongue, pharynx, and larynx, causing life threatening airflow obstruction.^{1,2} Angioedema is mediated by inflammatory cytokines, such as prostaglandin D₂, leukotrienes, cytokines, bradykinin, and complement components, which cause vasodilation and increase the permeability of capillaries. This allows plasma to leave the intravascular space and cause submucosal swelling.² It may be accompanied by urticaria, identifying it as an acute allergic response mediated by histamine. Urticaria differs from angioedema in that it only affects the skin and not the subcutaneous or submucosal tissue and is almost always pruritic.² Angioedema without urticaria can be a result of an adverse drug reaction as is the case with angioedema due to angiotensin-converting enzyme (ACE) inhibitors.¹

Approximately 17.5% of patients with cutaneous drug eruptions have angioedema.³ In addition, it is estimated that angioedema is caused by a drug in 32% of cases.⁴ Lastly, ACE-inhibitor use is associated with 25-38% of all angioedema-related emergency department (ED) visits.⁵ Simvastatin, as well as atorvastatin, fluvastatin, lovastatin, rosuvastatin, and pravastatin have been associated with postmarketing reports of hypersensitivity reactions, including angioedema.⁶⁻¹¹ A review of the literature reveals 4 case reports of statin-induced angioedema. These reports described a case of atorvastatin induced angioedema with dermographism and urticaria, atorvastatin-induced angioedema with rash and eosinophilia, pravastatin-induced angioedema, and lovastatin-induced angioedema with urticaria. Time to onset of these reactions varied from 2 days to 9 months.¹²⁻¹⁴

Despite postmarketing reports, there have been no published case reports of simvastatin-induced angioedema. We present a case of angioedema without urticarial associated with simvastatin use.

Case Report

A 75-year-old African American female with a medical history of diabetes mellitus type 2, diabetic retinopathy, obstructive lung disease, hypertension, obstructive sleep apnea, dyslipidemia, diastolic heart failure, pulmonary hypertension, and a single transient ischemic attack was admitted to the hospital with recurrent face, lip, and tongue swelling.

Her known allergies to medications included penicillin, which caused rash and itching. ACE inhibitors and angiotensin receptor blockers (ARBs) were listed as drug intolerances secondary to the development of angioedema. Her routine home medications included insulin NPH, simvastatin, clopidogrel, isosorbide dinitrate-hydralazine, furosemide, potassium chloride, hydrochlorothiazide, amlodipine, and carvedilol. Diphenhydramine and famotidine were used as needed. With the exception of diphenhydramine, she denied use of any other over-the-counter agents. Of note, her simvastatin dose had been increased from 10 mg to 20 mg each night 9 months prior to presentation.

At presentation, the patient described waking up in the middle of almost each night, with facial, tongue, and lip swelling. She denied associated shortness of breath, rash, difficulty swallowing, abdominal pain, wheezing, or pruritus. She reported frequent self-medication with oral diphenhydramine in an attempt to abort the episodes. If her symptoms did not resolve with diphenhydramine, she would present to the ED. In the 6 months prior to admission, she had presented to the ED 4 times, each time reporting that self-medication did not resolve her symptoms. During each visit to the ED, she received corticosteroids, diphenhydramine, and famotidine prior to being released home after a period of observation. On the day of presentation, she was referred for inpatient admission after intravenous administration of diphenhydramine 50 mg, famotidine 20 mg, and dexamethasone 10 mg. In reviewing her previous history, clinicians determined that the first episode occurred 19 months prior to admission, which prompted the discontinuation of trandolapril. Despite this, the episodes continued and increased in frequency in the 9 months prior to hospitalization, correlating with the increase in simvastatin dose.

Her review of systems was negative except for occasional lower-extremity edema. On physical examination, the patient was found to be hemodynamically stable, with a blood pressure of 140/73 mmHg, heart rate 75 beats/min, respiratory rate 16 breaths/min, and oxygen saturation 100% on room air. Her weight was recorded at 120.7 kg. She had significant facial, tongue, and lip edema. There was no wheezing appreciated or rash noted on exam. Her abdominal and cardiovascular examinations were also benign.

Basic chemistry screen and blood counts were within normal limits, with a creatinine level of 0.9 mg/dL, serum calcium of 9.6 mg/dL, serum glucose of 275 mg/dL, hemoglobin of 13.5 g/dL, and white blood cell count of $8.8 \cdot 10^9/L$. A diagnosis of hereditary angioedema was excluded by normal measurements of the C1q binding assay, complement C4 levels, and C1 esterase inhibitor levels.

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ACE inhibitors are traditionally
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angioedema.

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The patient was observed in the hospital for 48 hours, with continuous monitoring of her oxygen saturations. No further corticosteroids were administered and simvastatin was discontinued. Cetirizine was initiated and famotidine was continued orally. Over the next 36 hours her facial, tongue, and lip swelling resolved. Given the fact that her symptoms occurred reliably in the middle of the night and worsened after a dosage increase, simvastatin was considered as a possible inciting agent. She was instructed to discontinue simvastatin and her primary care physician was notified. She was discharged home on her admission medication list, with the exception of simvastatin. Additionally, she was instructed to use cetirizine as needed for facial swelling. Six months after discontinuation of simvastatin, the patient reported continued resolution of her nightly episodes. She did have 1 presentation to the ED for nonnocturnal angioedema, a drastic improvement in frequency.

Discussion

There are several potential mechanisms for drug-induced angioedema. Our patient had experienced recurrent angioedema that persisted after the cessation of trandolapril. ACE inhibitors are traditionally associated with drug-induced angioedema. Theoretically, the effect is mediated by bradykinin. ACE inhibitors inhibit the degradation of bradykinin, leading to an increase in vasodilation, histamine release,

and vascular permeability. Although the ARB drug class does not inhibit the degradation of bradykinin, it has been associated with angioedema. This raises the question of alternate pathways.

Several other medications have been associated with drug-induced angioedema, including calcium channel antagonists, thienopyridines, and hydrochlorothiazide.¹⁵⁻¹⁹ Identification of additional medications associated with angioedema has led to other proposed mechanisms for drug-induced angioedema. Many mechanisms lead to increased vascular permeability, causing fluid accumulation in the subcutaneous tissues.

At the time of symptom onset, our patient was receiving 4 medications that have been linked to angioedema. Amlodipine, clopidogrel, hydrochlorothiazide, and simvastatin each have postmarketing reports of angioedema. Amlodipine has been linked to angioedema development in adults and children receiving therapy for days to months before symptom onset.¹⁵⁻¹⁷ In all 3 cases, cessation of amlodipine led to complete resolution of angioedema. Due to the long half-life of amlodipine, symptoms persisted for 2-7 days after stopping therapy. While the mechanism remains unknown, it is postulated that amlodipine stimulates the kinin system via activation of kallikrein. Additional consideration of the simvastatin and amlodipine drug interaction is necessary. Currently, the simvastatin manufacturer recommends limiting the dose of simvastatin to 20 mg in patients receiving amlodipine.⁶ While our patient did not exceed the maximum daily dose, amlodipine leads to decreased metabolism of simvastatin. This drug interaction may result in higher serum drug concentrations of simvastatin and potentially more adverse effects, including angioedema. Currently, there is not enough information to know whether statin-induced angioedema is dose dependent or related to serum drug concentrations. However, it seems plausible, based on case reports of drug induced angioedema that resolved with dose reduction or medication rechallenge at lower doses.^{18,19} Our patient received amlodipine throughout her hospitalization and was discharged on her home regimen.

Less evidence exists for clopidogrel-induced angioedema; however, it has been reported in a 71-year-old male receiving clopidogrel for coronary artery disease.²⁰ At the time of symptom onset, he was receiving clopidogrel, verapamil, aspirin, and an unknown statin. After developing angioedema, all therapy was stopped and he was admitted to the hospital for a placebo-controlled testing of his therapy to identify the culprit. Three hours after receiving clopidogrel, he developed angioedema, solidifying the diagnosis. Again, our patient received clopidogrel throughout her hospitalization and was discharged on her home regimen.

Lastly, hydrochlorothiazide-induced angioedema has been reported in a patient with a known angioedema reaction to sulfonamides.²¹ Hydrochlorothiazide was suspected after continuation of symptoms despite cessation of valsartan in an 82-year-old female. The authors speculated that the sulfur dioxide moiety in hydrochlorothiazide was responsible for the subsequent angioedema reaction in this patient. Our patient had no known previous reactions to sulfonamides, continued on her home hydrochlorothiazide regimen throughout hospitalization, and was discharged on her home regimen.

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receptors.
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To date, few case reports of statin-induced angioedema have been published. Detailed review of this patient case, using the Naranjo probability scale, shows a probable association between simvastatin and angioedema. Positive associated factors included previous postmarketing reports, occurrence after simvastatin administration, improvement after stopping therapy, and symptom increase with dose escalation.²²

While the mechanism of statin-induced angioedema is unknown, the effect may also be mediated by bradykinin via the upregulation of bradykinin type 2 receptors. Lovastatin has been shown to upregulate the expression of bradykinin type 2 receptors in human coronary arteries. Upregulation of these receptors could potentiate the actions of circulating bradykinin, resulting in release of nitric oxide, prostacyclin, and endothelium-derived hyperpolarizing factor, which then cause vasodilation and, potentially, angioedema.²³

Our patient did not present with urticaria or rash, indicating a non-histamine-mediated mechanism of angioedema. While the patient did report self-medicating with antihistamines when she developed angioedema, this was frequently unsuccessful. A bradykinin-mediated mechanism is plausible, based on the patient's history of angioedema with ACE inhibitors. Concomitant use of statin medications has been a proposed predisposing risk factor for ACE-inhibitor-induced angioedema, lending consideration to other drug interactions.²⁴ An increase in bradykinin type 2 receptors from statin use, coupled with an activation of the kinin system from amlodipine may precipitate the development of angioedema. Based on this proposed mechanism, it is plausible that statin use may predispose patients to experiencing angioedema when another inciting factor that increases circulating bradykinin is present. Of the 4 case reports of statin-induced angioedema described previously, 1 did not state the patient's concomitant medications. Of the remaining 3 cases, 2 of the patients were on another medication associated with the development of angioedema, including estrogen in 1 case and diltiazem in the other. These were not the suspected causative agents in these cases because the angioedema did not occur until after the addition of the statin medication and resolved after statin discontinuation.^{1,12-15}

Our patient reported near nightly symptoms and frequent ED visits prior to stopping simvastatin. The long duration between simvastatin discontinuation and her next ED visit demonstrates significant improvement in her frequent symptoms.

Case reports of drug-induced angioedema are scattered throughout the literature. Most statin manufacturers note postmarketing reports of angioedema; however, specific case reports in the literature are lacking. We report a probable association between simvastatin and angioedema that improved significantly after cessation of simvastatin. While simvastatin may not have been the sole cause of angioedema in our patient, this adverse effect should be considered in patients with persistent angioedema who are receiving a statin medication, especially in combination with other medications associated with the development of angioedema.

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