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A case of venlafaxine-induced angioedema in an older adult

Hailee Griffin, Scott Pearson, Sunny Linnebur and Danielle Fixen

Abstract

Angioedema is a serious adverse event that can manifest as lower extremity edema, face swelling, rash, hives, and a swollen tongue, which can sometimes lead to airway constriction and death. It is a well-documented reaction within the angiotensin-converting enzyme inhibitor drug class, where the bradykinin pathway leads to angioedema. We report a case where a patient experienced angioedema after taking venlafaxine. We evaluated other antidepressants as potential treatment options for the patient. We further examined potential cross-reactivity between antidepressants in order to find alternative medications for patients that experience serious adverse effects.

Keywords

Drug-related side effects, adverse reactions, venlafaxine, angioedema, antidepressive agents, cross-reactions

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Introduction

Angioedema is a transient edema caused by increased vascular permeability in deep tissues, most commonly seen in the face, lips, neck, and gastrointestinal (GI) system.[1] Angioedema of the tongue can be life threatening, as it can block the airways. Angioedema can be histamine-mediated, bradykinin-mediated, or idiopathic. The most common medication class known to cause angioedema is angiotensin-converting enzyme (ACE) inhibitors, with very few reports of antidepressants causing angioedema.[1]

Venlafaxine is a serotonin–norepinephrine reuptake inhibitor (SNRI) US Food and Drug Administration (FDA)-approved for use in major depressive disorder (MDD) and generalized anxiety disorder (GAD). The most common adverse effects reported include GI symptoms (e.g. nausea, constipation, anorexia, and diarrhea), nervous system symptoms (e.g. somnolence, dry mouth, dizziness, insomnia, and nervousness), sweating, and sexual dysfunction. Angioedema has only been reported in post-marketing surveillance for venlafaxine. However, as post-market reports are voluntary and are in an uncontrolled environment, it is unclear if venlafaxine was the cause.[2] A literature review on PubMed and Embase, using terms (venlafaxine) AND (angioedema), found two cases of angioedema involving venlafaxine.[3,4] Our report discusses a case of an 81-year-old woman who developed angioedema after initiating treatment with venlafaxine.

Case report

An 81-year-old woman with a past medical history of breast cancer, diabetes mellitus, hypertension, hyperlipidemia, hypothyroidism, osteoarthritis, and neuropathy presented to the emergency department with angioedema 2 days after initiating venlafaxine. Two days prior to developing angioedema, the patient had an appointment with her primary-care provider and expressed depressive symptoms over the prior few months, which coincided with the onset of COVID restrictions. Due to comorbid neuropathy and depression, the patient was started on venlafaxine XR 37.5 mg daily. The patient's other chronic medications at that time were levothyroxine, simvastatin, lisinopril, metformin, omeprazole, and diclofenac gel. Her only documented allergy was amoxicillin-potassium clavulanate, which resulted in shortness of breath. The patient had no history of angioedema.

Two days after starting venlafaxine, the patient contacted her primary-care provider complaining of tongue swelling and was instructed to take diphenhydramine 50 mg orally and proceed to the emergency department. On presentation

Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado, Aurora, CO, USA

Corresponding Author:
Danielle Fixen, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado, Aurora, CO 80045, USA.
Email: Danielle.Fixen@cuanschutz.edu

to the emergency department, in addition to the swollen tongue, the patient reported a gradual symptom onset of nausea, vomiting, and headaches, but no chest pain, rash, or leg swelling. The patient reported that symptoms of nausea, vomiting, and headaches improved after taking diphenhydramine, and her swollen tongue resolved. Venlafaxine was discontinued at that time. Vitals at time of presentation to the emergency department were blood pressure of 181/81 mmHg, pulse of 82 beats per minute, and respiratory rate of 18 breaths per minute. All laboratories were within normal limits. No complement levels or other laboratories specific to angioedema were assessed.

Two days after the emergency department visit, the patient was started on escitalopram 5 mg daily and titrated up to 10 mg daily after 1 week. However, the patient reported symptoms of dizziness, headache, nausea, and loss of appetite and started tapering off the medication after 2 weeks. The patient then trialed sertraline 25 mg but also did not tolerate due to headaches and nausea. The patient was most recently started on mirtazapine 7.5 mg but also discontinued treatment after 1 month due to headaches and nausea and is currently not taking an anti-depressant. Six months after the emergency department visit, the patient reports an improved mood after a reduction in her levothyroxine and family support.

In assessing the role of venlafaxine in the patient's development of angioedema, the patient scored a 5 on the Naranjo Adverse Drug Event Probability Scale, indicating venlafaxine was a probable cause of the reaction.[5] This is due to the following reasons: angioedema started after the venlafaxine was administered (+2), it disappeared when diphenhydramine was administered and did not recur following venlafaxine discontinuation (+1), and there were no known alternative causes for this event (+2).

Discussion/implications for clinical use

A review of literature found two cases of angioedema with venlafaxine. The first case was in a 34-year-old woman who experienced a swollen tongue 3 days after starting treatment with venlafaxine XR and within 15 min of ingesting the medication.[3] The symptoms resolved that day; however, the patient took venlafaxine the next day and experienced a swollen tongue again.[3] The second case was in a 48-year-old woman who experienced angioedema in her legs, which was characterized by non-pitting edema.[4] Onset occurred 2 days after starting venlafaxine, which was the same time frame as our patient. The patient then initiated mirtazapine and experienced symptoms of angioedema again 3 days later.[4] This would suggest possible cross-reactivity between venlafaxine and mirtazapine; however, our patient has not experienced angioedema with mirtazapine but did discontinue the medication after 1 month due to GI intolerance. GI intolerance is common among anti-depressants due to increased serotonin acting on 5-HT_3 receptors in the GI tract, which can lead to nausea and vomiting.[6] Therefore, mechanism for intolerance is different from the mechanism that may be causing angioedema.

Table 1. Structures of Common Antidepressants.[9]

SSRIs[a]	
Medication	Structure
Sertraline	Tametraline, tetrahydro-naphthalene linked to a phenyl group
Citalopram	Phenylbutylamine
Escitalopram	Phenylbutylamine
Paroxetine	Piperidine, derives from a mono-fluorobenzene
Fluoxetine	Diphenhydramine derivative
Fluvoxamine	2-aminoethyl oxime ether of aralkylketones
SNRIs[b]	
Medication	Structure
Venlafaxine	Phenethylamine bicyclic derivative
Desvenlafaxine	Phenethylamine bicyclic derivative
Duloxetine	Fluoxetine derivative
Other anti-depressants	
Medication	Structure
Bupropion	Amino-ketone
Mirtazapine	Tetracyclic derivative of the piperazino-azepines
Tricyclic antidepressants	Organic tricyclic compounds

[a]Selective serotonin reuptake inhibitors.
[b]Serotonin–norepinephrine reuptake inhibitors.

Other case reports have found possible allergic cross-reactivity between sertraline and escitalopram, as well as paroxetine and sertraline. The first case was a 41-year-old woman who experienced a swollen tongue 2 h after taking sertraline, then months later experienced a full-body rash after her first dose of escitalopram.[7] The second case involved a 21-year-old man who experienced a maculopapular rash after initiating paroxetine, then developed the same type of rash after initiating sertraline.[8] These cases suggest possible cross-reactivity between sertraline, escitalopram, and paroxetine. However, there are little data to inform clinicians regarding possible cross-reactivity between anti-depressants should a patient experience an allergic reaction.

Often times, chemical structures of drugs provide insight into cross-reactivity. A summary of anti-depressant drug structures is included in Table 1. There appear to be no clear similarities between structures between sertraline, escitalopram, and paroxetine, but there are between citalopram and escitalopram, fluoxetine, and duloxetine, and venlafaxine and desvenlafaxine. In regards to our patient, a "structural similarity" report was completed on PubChem of venlafaxine.[9] Results found both desvenlafaxine and tramadol have similar structures.[9] This would suggest that

both desvenlafaxine and tramadol could possibly elicit angioedema in our patient if the cause was related to the chemical structure.

Angioedema can also be caused by increased levels of bradykinin, which increases vascular permeability and causes vasodilation, leading to the characteristic swelling of the subcutaneous tissue.[1] ACE inhibitors can increase bradykinin by blocking the degradation of bradykinin. In bradykinin-induced angioedema, standard treatments for histamine-mediated angioedema, epinephrine, antihistamines, and steroids, are likely ineffective.[1] Our patient was on the same dose of lisinopril, an ACE inhibitor, for at least 3 years prior to starting venlafaxine. However, bradykinin-induced angioedema was unlikely in our patient, as the patient continued taking lisinopril after resolution of angioedema and did not experience further angioedema. This is further supported by a retrospective cohort study that found a significant increase in angioedema in patients who had ACE inhibitor-induced angioedema and continued ACE inhibitor treatment compared to patients that discontinued treatment after the first incidence of ACE inhibitor-induced angioedema.[10] In addition, angioedema in our patient resolved after taking diphenhydramine, suggesting it was a histamine-mediated reaction. As the patient continues to tolerate lisinopril with no other incidences of angioedema, it is appropriate to score the adverse event as a 5 on the Naranjo Adverse Drug Probability Scale, indicating that venlafaxine was the probable cause of the event.[5]

The possibility of a reaction between the lisinopril and venlafaxine cannot be ruled out. Neprilysin inhibitors, such as sacubitril, have increased incidence of angioedema and use is contraindicated with concomitant ACE inhibitors due to increased risk of angioedema.[11] Other medications documented to impact the bradykinin pathway include dipeptidyl peptidase IV inhibitors and renin inhibitor combinations. It is hypothesized that combinations of these medications with ACE inhibitors could increase the risk of angioedema.[11,12] However, there is no current evidence that venlafaxine affects the bradykinin pathway and our patient was not taking a medication in either of these medication classes, which further suggests that angioedema in this patient was induced by a separate mechanism.

Conclusion

Angioedema is a life-threatening adverse drug event that rarely occurs with most drugs. To the best of our knowledge, this is the third reported case of angioedema associated with venlafaxine. The mechanism for venlafaxine-induced angioedema and other anti-depressants is unknown, and there is a lack of research on possible cross-reactivity between anti-depressants. Based on our review, there is no evidence to suggest cross-reactivity between a majority of anti-depressants. Further research is needed in order to safely prescribe an alternative anti-depressant to patients that experience a serious adverse event, such as angioedema.

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ORCID iD

Danielle Fixen https://orcid.org/0000-0002-7193-1756

Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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