Drug-induced Angioedema: A Rare Side Effect of Mirabegron

Harley Davis, Medical Student
Joan. C. Edwards School of Medicine, Department of Internal Medicine

Troy Wallace, MD
Joan. C. Edwards School of Medicine, Department of Internal Medicine

Christine Gilkerson, MD
Joan. C. Edwards School of Medicine, Department of Internal Medicine

Elizabeth Saunders, MD
Joan. C. Edwards School of Medicine, Department of Internal Medicine

Corresponding Author: Elizabeth Saunders, MD, JCESOM. Dept. of Internal Medicine, 1249 15th Street Huntington, WV 25701. Email: saunde27@marshall.edu.

Abstract
Drug-induced angioedema can be allergic or non-allergic depending on the specific mediators leading to the reaction. Drug-induced allergic angioedema is due to histamine release and has a rapid onset of action associated with an urticarial rash that responds to antihistamines and glucocorticoids. Drug-induced non-allergic angioedema is likely due to increases in bradykinin and has a much slower onset of action without an urticarial rash; it only resolves with discontinuation of the offending medication. Mirabegron, a beta-3-adrenergic receptor agonist, is a widely prescribed medication for urinary urge incontinence and overactive bladder. This case report presents a patient with angioedema following the use of mirabegron for urinary incontinence whose angioedema symptoms had been previously misattributed. The history, clinical examination, and diagnostic parameters led to the diagnosis of mirabegron induced non-allergic angioedema and she was successfully treated with discontinuation of the medication. Though rare, angioedema is a side effect of mirabegron and can be life-threatening. Therefore, thorough history taking and a high index of suspicion are crucial to correlate relevant exposure with onset of symptoms and should be considered in all patients prescribed mirabegron who have a consistent presentation.

Case Presentation
A 53 year-old female presented with complaints of non-productive cough, dyspnea, dysphagia, throat tightness, and hoarseness for three to four weeks duration. Symptoms first began after the patient had been outside for a prolonged period of time following a rainstorm. Significant past medical history included depression, urinary incontinence, gastroesophageal reflux disorder, hyperlipidemia, hypothyroidism, and hypertension. The patient is a lifetime non-smoker and denied any associated fever, sputum production, chills, or rashes. Her medications included mirabegron 50 mg oral once daily, bensomra 20 mg oral at bedtime, buspirone 30 mg oral twice daily, akrinexine XR 150 mg oral twice daily, apremilast 30 mg oral daily, pravastatin 20 mg oral daily, premarin 0.3 mg oral daily, protonix 40 mg oral twice daily, levothyroxine 50 mcg oral once daily and cetirizine 10 mg oral once daily. Prior to presenting to our clinic, she had been unsuccessfully treated on four separate occasions over a three to four-week time span. Her initial treatment, through her primary care physician, was one week after symptom onset with cefdinir 300 mg oral twice daily for seven days and lisinopril was discontinued. The primary care physician also obtained a pulmonary function test which was normal. After completing the cefdinir, patient was treated a second and a third time in an urgent care setting first with levofloxacin 750 mg oral once daily and prednisone 40 mg once daily for five days initially and subsequently with an additional ten-day steroid taper starting with prednisone 60 mg. Her fourth treatment consisted of benzontate 100 mg oral three times a day after a negative CT scan of chest with contrast was obtained upon evaluation in an emergency room.

On physical examination, pulse rate 53, blood pressure 120/88, temperature 98.5, respiratory rate 18 and oxygen saturation of 94% on room air. HEENT exam: No face, lip, or tongue swelling. Patient had noted subcutaneous swelling of the neck but no findings of crepitus on examination. Respiratory: normal chest expansion, good air entry bilaterally with mild wheezing throughout lung fields. CVS: normal s1, s2, no murmurs or gallop. The remainder of the physical exam was unremarkable. Peak flows within normal limits. She was treated with ipratropium bromide/albuterol sulfate nebulizer along with an intramuscular dose of methylprednisolone 125 mg. Further evaluation with a neck soft tissue x-ray confirmed supraglottic airway narrowing (Figure 1, 2) and a c1 esterase inhibitor function was normal. Careful history taking revealed the patient was being prescribed mirabegron for urinary incontinence and her dose was recently increased from 25 mg to 50 mg oral once daily one day prior to the onset of her symptoms of cough, shortness of breath and throat tightness. She had previously been prescribed and taking mirabegron...
25 mg once daily for approximately two months without development of any symptoms. The patient did not attribute her symptoms in relation to the mirabegron medication dosage change. Considering the history, clinical, and diagnostic findings, diagnosis of non-allergic mirabegron-induced head and neck angioedema was made and the patient was advised to discontinue the offending agent. Three days after discontinuation of mirabegron patient reported complete resolution of her shortness of breath and neck swelling. At follow-up with her urologist two months later, she reported no reoccurrence of her symptoms and her urinary incontinence was being managed with oxybutynin 5 mg oral once daily.

**Discussion**

Angioedema is the swelling of mucosal and submucosal tissue.\(^1,2\) It typically manifests as swelling of the face, lips, and tongue and maybe life threatening when it involves the respiratory tract.\(^2\) There are two types of drug-induced angioedema; allergic and non-allergic.\(^3\) Drug-induced allergic angioedema is a type I hypersensitivity reaction, mediated by histamine being released from mast cells after the medication crosslinks with IgE molecules on the surface of the mast cells.\(^3\) This type of reaction usually leads to rapid swelling of the mucosal and submucosal tissues and patients will likely develop an urticarial rash. The symptoms of the allergic reaction respond rapidly to antihistamine, epinephrine and corticosteroid treatment. In the case of drug-induced non-allergic angioedema, the reaction is mediated by bradykinin and no urticarial rash is present.\(^3\) The onset of this reaction is usually more gradual when compared to the allergic angioedema reaction.

The symptoms are not relieved with antihistamines or corticosteroids and the mainstay in treatment of non-allergic drug-induced angioedema is cessation of the offending agent.\(^3\) Mirabegron is a beta-3 adrenergic agonist commonly used in the treatment of urinary urge incontinence and overactive bladder to cause smooth muscle relaxation in the detrusor muscle and improve bladder capacity.\(^4,5\) Mirabegron is the preferred agent in individuals who are at risk for central nervous system anticholinergic side effects of other urinary incontinence medications or in those with contraindication to antimuscarinic medications.\(^6,7\)

Generally, mirabegron is a well-tolerated medication with common side effects including hypertension, nasopharyngitis, urinary tract infections, headache and tachycardia.\(^8\) Serious reactions of mirabegron include hypersensitivity reactions and head and neck angioedema which occurs in <1% of patients. While post-marketing drug information lists angioedema as a side effect, we believe we have the first documented case report of angioedema of neck caused by mirabegron.

Our patient presented with symptoms of three to four weeks duration after her mirabegron dose...
had been increased from 25 mg to 50mg. Initially, the etiology of her symptoms was unclear and multiple medical interventions as discussed above in combination of discontinuation of lisinopril failed to improve her symptoms. Failure to recognize non-allergic angioedema as the cause of her symptoms and delay in recognizing mirabegron as the particular offending agent prolonged her symptom duration and risk for complications.

The exact mechanism for mirabegron causing head and neck angioedema has not been well studied. Because our patient had no urticarial rash and no improvement with corticosteroids treatment, we believe she had a non-allergic drug reaction mediated through the bradykinin pathway.

**Conclusion**

Drug-induced angioedema is well documented throughout the medical literature. Thorough history taking and correlation of symptoms with medication use are critical for diagnosis. Our patient experienced delays in diagnosis contributing to overall morbidity. Although angioedema secondary to mirabegron is rare, it is important for physicians to maintain a high index of suspicion and recognize this potentially life-threatening medical condition and treat urgently. Clinical symptoms of non-allergic angioedema range in severity and resolve with avoidance of offending agent and are resistant to supportive care including addition of antihistamines and corticosteroids, which was the case for our patient.

Attention to potential side effects of drugs and close follow up with patients upon initiation of a medication or adjustment of dosages is medically necessary to monitor for such adverse reactions.

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