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DPP-IV Inhibitor–Associated Angioedema in Patient With Known History of ACE Inhibitor Angioedema

Chidinma Ejikeme, MD[1], Chinedu Nwachukwu, MD[1], John Luis Viechweg, MD[1], Ifunanya Ejikeme[2], and Micheal Brescia, MD[1]

Abstract

The patient is a 69-year-old male with a past medical history of intellectual disability, hypertension, type 2 diabetes mellitus, and angiotensin-converting enzyme (ACE) inhibitor–associated angioedema who presented to the emergency department with difficulty breathing. On physical examination, the patient had significant facial edema. Nasal fiber-optic visualization revealed extensive airway edema involving the supraglottic region and the arytenoids. The patient was successfully intubated through the collective teamwork of ENT, anesthesia, and critical care teams. He was managed in the intensive care unit until recovery. Workup for markers for allergic causes of angioedema were within normal limits. Further investigation revealed that symptoms developed following the initiation of a dipeptidyl peptidase 4 (DPP-IV) inhibitor. The angiotensin-converting enzyme and DPP-IV play a significant role in the metabolism of bradykinin and substance P to their inactive metabolites. The complex interplay between the enzymes in the high-molecular-weight kininogen (HWMK) system may increase the risk of angioedema in patients with a known history of ACE inhibitor–associated angioedema when placed on a DPP-IV inhibitor. This case report highlights the pathophysiology involved.

Keywords

angioedema, DPP-IV inhibitor, ACE inhibitor, bradykinin, substance P

Introduction

Postmarketing surveillance reports show that the dipeptidyl peptidase 4 (DPP-IV) inhibitor is associated with angioedema development. Angioedema occurs as a result of an allergic or nonallergic reaction to the medication. Although a rare adverse effect, the DPP-IV inhibitor–associated angioedema could be severe and life-threatening. Nonallergic angioedema results due to a disruption in the high-molecular-weight kininogen (HMWK) system.

Enzymes including angiotensin-converting enzyme (ACE), neutral endopeptidase (NEP), and DPP-IV works to metabolize bradykinin and substance P.

The complex interplay of the enzymes on the HMWK system may result in an increased risk of angioedema when medications inhibit the pathway like ACE inhibitors and DPP-IV inhibitors.

Case Presentation

The patient was a 69-year-old male with a past medical history of intellectual disability, hypertension, type 2 diabetes mellitus who presented to the emergency department (ED) with difficulty breathing and tongue swelling. The patient lived in a group home that provided the skilled support he needed for day-to-day activities.

The patient was transferred due to acute difficulty breathing, accompanied by facial swelling. His symptoms started an hour before the presentation.

Initial vital signs in the ED revealed a temperature of 99 °F, heart rate of 72 bpm, blood pressure of 164/88 mm Hg, and his oxygen saturation (SpO_2) 98% on room air.

On physical examination, the patient had significant facial and tongue edema resulting in tongue protrusion. The airway

[1]Trinitas Regional Medical Center, Elizabeth, NJ, USA
[2]Kansas City University, Kansas City, MO, USA

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Corresponding Author:
Chidinma Ejikeme, MD, Department of Internal Medicine, Trinitas Regional Medical Center, 225 Williamson Street, Elizabeth, NJ 07202, USA.
Email: cejikeme@sgu.edu

was difficult to visualize as a result of the edema. Cardiac examination was unremarkable, with S1/S2 present and absent murmurs, gallops, or rubs. The abdomen was soft, nontender with normoactive bowel sounds. His extremities also showed equal pulses bilaterally.

The nasal fiber-optic visualization revealed severe edema of the supraglottis, arytenoids, and aryepiglottic folds resulting in airway obstruction. The patient was transferred to the operating room for emergent intubation.

In the operating room, an endotracheal tube was inserted through the right naris to the level of the oropharynx with the aid of a fiber-optic scope. The fiber-optic scope was placed in the endotracheal tube as it was inserted through the true vocal cords, visualized between the severely edematous aryepiglottic folds and arytenoids. The endotracheal tube was then passed over the laryngoscope into the trachea and secured.

Following successful nasotracheal intubation, the patient was placed on a ventilator and transferred to the intensive care unit (ICU) for further management.

The patient was started on intravenous fluid hydration, methylprednisolone, and epinephrine to decrease angioedema. Bloodwork for serum levels of C1 inhibitor, tryptase, and histamine was performed to evaluate the origin of the patient's angioedema. Results revealed C1 inhibitor, tryptase, and histamine levels within normal ranges.

Further discussion with the group home staff revealed that the patient had a similar episode 2 years ago. He was brought to the hospital and received supportive treatment. During that hospitalization, allergic reaction markers were not elevated. His angioedema was suspected to be a result of ACE inhibitor medication, which was recently prescribed at the time. His symptoms resolved following discontinuation, and the patient was discharged with outpatient follow-up.

The group home staff also described that patient recently started on sitagliptin—a DPP-IV inhibitor for better glycemic control.

Given this new information, sitagliptin was discontinued, and management continued in the ICU.

The patient remained intubated until he had a positive leak test, suggestive of a marked reduction in airway edema. Sedatives were titrated off, and he was extubated once alert, responsive, and low rapid shallow breathing index of 40.

The patient's hospitalization was complicated by ventilator-associated pneumonia, which resolved with antibiotic treatment. He was then transferred to the medical floor, from where he was discharged with instructions to avoid the use of DPP-IV inhibitor and ACE inhibitor and a medical appointment for outpatient follow-up.

Discussion

Angioedema is tissue edema that occurs as a result of increased vascular permeability.[1] It is a severe and fatal adverse reaction associated with several medications, including antibiotics, nonsteroidal anti-inflammatory drugs, and ACE inhibitors.

The angioedema effect from ACE inhibitors has been well documented for years. It occurs due to substance P and bradykinin accumulation as a consequence of the direct inhibition of the ACE.

In the HMWK system, the ACE and NEP are essential enzymes in the metabolism of bradykinin and substance P.[2] However, the system is redundant as several other enzymes metabolize both bradykinin and substance P, though to a lesser extent.[1,2]

The level of activities of these various enzymes on bradykinin and substance P vary. Some have a higher affinity for bradykinin with less affinity for substance P and vice versa. For instance, enzymes like DPP-IV metabolize both substance P and bradykinin. Its main activity is on substance P, sequentially cleaving it to SP3-11, and SP5-11, less potent metabolites.[1,3] However, the DPP-IV metabolism of bradykinin is minor.

The DPP-IV inhibitors are a class of medications used for glycemic control in diabetic patients.[4,5] They work by inhibiting the degradation of incretin (like GLP-1 and GIP), which usually stimulate insulin release from the pancreas.[5]

Postmarketing reports show that gliptins, particularly sitagliptin, are associated with an increased risk of angioedema.[6,7] The mechanism is a result of an allergic reaction, nonallergic reaction, or both. In allergic angioedema, allergic reaction markers like histamine and tryptase are elevated. Our patient's normal levels of serum histamine and tryptase levels ruled out angioedema of allergic origin.

Conversely, nonallergic angioedema results from the disruption of the metabolism of vasoactive substances like bradykinin and substance P, resulting in angioedema.[8-10]

Patients on DPP-IV inhibitors have an increased risk of angioedema due to the accumulation of substance P and bradykinin. This risk is further increased when patients are concurrently on DPP-IV inhibitors and ACE inhibitors.[8,11]

Our patient's case is unique in that he initially developed angioedema following exposure to an ACE inhibitor. However, his angioedema reoccurred after a DPP-IV inhibitor was initiated.

Several mechanisms have been hypothesized as to why this could occur. Reports show that the sera of patients with a history of ACE inhibitor–associated angioedema compared with that of patients on ACE inhibitor without angioedema have an innate decrease in DPP-IV enzyme activity in these patients.[8,12,13]

Additionally, Beaudouin et al show that serum levels of ACE, aminopeptidase P, and carboxypeptidase N decreased to 17%, 42%, and 64%, respectively, of reference range values and remained chronically inhibited for at least a year after the inhibition by DPPIV and ACE inhibitors.[8,14] The chronic inhibition from a history of ACE inhibitor exposure combined with possible innate enzyme deficiency further

increases bradykinin and substance P levels, thus increasing the risk of angioedema.[14,15]

Consequently, given these different pathophysiologies, patients with a history of angioedema from either an ACE inhibitor or DPP-IV inhibitor could be at risk of recurring angioedema when subsequently initiated on either medication.[16-18]

Therefore, a history of angioedema from either ACE or DPP-IV inhibitors could potentially be predictive of an increased risk of recurrence.[19-21]

Treatment of angioedema is mainly supportive; corticosteroids and epinephrine help decrease inflammation and edema. Intubation should also be considered for airway protection in cases of severe angioedema.

Given the high mortality rate associated with angioedema, early recognition and management are crucial to improving outcomes.

Conclusion and Learning Points

Patients with a history of ACE inhibitor angioedema may be at risk of recurring angioedema when placed on a DPP-IV inhibitor. Careful monitoring of these patients is essential to decrease the fatality rate from angioedema. Permanent cessation of these medications may be necessary to mitigate the future risk of angioedema.

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Ethics Approval

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

Informed Consent

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ORCID iD

Chidinma Ejikeme https://orcid.org/0000-0002-1989-9779

References

1. Byrd JB, Touzin K, Sile S, et al. Dipeptidyl peptidase IV in angiotensin-converting enzyme inhibitor–associated angioedema. *Hypertension*. 2008;51:141-147.
2. Skidgel RA, Erdös EG. Angiotensin converting enzyme (ACE) and neprilysin hydrolyze neuropeptides: a brief history, the beginning and follow-ups to early studies. *Peptides*. 2004; 25:521-525.
3. Grouzmann E, Monod M, Landis B, et al. Loss of dipeptidyl-peptidase IV activity in chronic rhinosinusitis contributes to the neurogenic inflammation induced by substance P in the nasal mucosa. *FASEB J*. 2002;16:1132-1134.
4. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369:1317-1326.
5. Schmidt WE, Siegel EG, Creutzfeldt W. Glucagon-like peptide-1 but not glucagon-like peptide-2 stimulates insulin release from isolated rat pancreatic islets. *Diabetologia*. 1985;28: 704-707.
6. Januvia (sitagliptin tablets) prescribing information. Published 2011. Accessed July 7, 2021. http://www.merck.com/product/usa/pi_circulars/j/januvia/januvia_pi.pdf
7. Li XK, Ji WJ, Zhao J, et al. Ammonia decomposition over Ru and Ni catalysts supported on fumed SiO_2, MCM-41, and SBA-15. *J Catalysis*. 2005;236:181-189.
8. Beaudouin E, Defendi F, Picaud J, et al. Iatrogenic angioedema associated with ACEi, sitagliptin, and deficiency of 3 enzymes catabolizing bradykinin. *Eur Ann Allergy Clin Immunol*. 2014;46:119-122.
9. Scott SI, Andersen MF, Aagaard L, et al. Dipeptidyl peptidase-4 inhibitor induced angioedema—an overlooked adverse drug reaction? *Curr Diabetes Rev*. 2018;14:327-333.
10. Hudey SN, Westermann-Clark E, Lockey RF. Cardiovascular and diabetic medications that cause bradykinin-mediated angioedema. *J Allergy Clin Immunol Pract*. 2017;5:610-615.
11. Brown NJ, Byiers S, Carr D, et al. Dipeptidyl peptidase-IV inhibitor use associated with increased risk of ACE inhibitor-associated angioedema. *Hypertension*. 2009;54:516-523.
12. Nussberger J, Cugno M, Cicardi M. Bradykinin-mediated angioedema. *N Engl J Med*. 2002;347:621-622.
13. Byrd JB, Adam A, Brown NJ. Angiotensin-converting enzyme inhibitor-associated angioedema. *Immunol Allergy Clin North Am*. 2006;26:725-737.
14. Kaplan AP. Angioedema. *World Allergy Organ J*. 2008;1: 103-113.
15. Gosmanov AR, Fontenot EC. Sitagliptin-associated angioedema. *Diabetes Care*. 2012;35:e60.
16. Obtułowicz K. Bradykinin-mediated angioedema. *Pol Arch Med Wewn*. 2016;126:76-85.
17. Russell JS, Chi H, Lantry LE, Stephens RE, Ward PE. Substance P and neurokinin A metabolism by cultured human skeletal muscle myocytes and fibroblasts. *Peptides*. 1996;17: 1397-1403.
18. Straka BT, Ramirez CE, Byrd JB, et al. Effect of bradykinin receptor antagonism on ACE inhibitor-associated angioedema. *J Allergy Clin Immunol*. 2017;140:242-248.e2.
19. Bas M, Greve J, Strassen U, Khosravani F, Hoffmann TK, Kojda G. Angioedema induced by cardiovascular drugs: new players join old friends. *Allergy*. 2015;70:1196-1200.
20. Arcani R, Martinez S, Gayet S. Sitagliptin and angioedema. *Ann Intern Med*. 2017;167:142-143.
21. Williams-Herman D, Engel SS, Round E, et al. Safety and tolerability of sitagliptin in clinical studies: a pooled analysis of data from 10,246 patients with type 2 diabetes. *BMC Endocr Disord*. 2010;10:7.