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Losartan Induced Angioedema, a Rare Case Report and the Dilemma of Using Angiotensin II Receptor Blockers in Patients with Previous Angioedema with Angiotensin Converting Enzyme Inhibitors

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Abstract

Angiotensin Receptor Blockers (ARB) are used as an alternative of Angiotensin Converting Enzyme Inhibitors (ACEI) in patients where ACEIs cannot be used because of their known adverse effects, cough and angioedema. Thus ARB induced angioedema is considered to be a rare phenomenon and it is continued to be used as an alternatives of ACEIs. In this case report, we reported a case of 78-year-old gentleman who presented to emergency department with losartan, an ARB induced angioedema, who did not have history of any previous use of ACEIs. He was given steroids and antihistamine as a treatment. His angioedema resolved rapidly and he was discharged after six hours of emergency department (ED) observation with stable hemodynamically. We, the authors by reporting this case, wants to make clinicians aware ARB, however rarely, can cause angioedema, which can be life threatening if clinicians are not aware of it and diagnose and stop the offending drug promptly and treat it early.

Keywords

Angioedema, Airway Emergency, Acute Presentation

1. Introduction

Angiotensin Converting Enzyme Inhibitor (ACEI) and Angiotensin II Receptor

Blockers (ARBs) are groups of drugs that affect the renin-angiotensin-aldosterone system (RAAS) [1]. Both have been shown to be beneficial in the treatment of disease states, such as hypertension, chronic heart failure, chronic kidney disease, and myocardial infarction, in which the RAAS system plays a significant role. Angiotensin Receptor Blockers (ARB) are used as an alternative of ACEI in patients where ACEIs cannot be used because to their known adverse effect, cough and angioedema [2]. However in this case report we will discuss a case of ARB induced angioedema. In literature, only very few cases of ARB induced angioedema had been reported so far [3]. Thus ARB induced angioedema are considered to be a rare phenomenon and it is continued to be used as an alternatives of ACEIs. Authors obliged to report this case to make the clinicians aware of the certitude that, ARBs are potential to cause angioedema and may not be a safe alternative to ACE Inhibitors [ACEIs].

2. Case Presentation

2.1. Case Discussion

A 78-year-old gentleman was brought by ambulance to emergency department with swelling of his lips and tongue, unable to talk and shortness of breath, which started since he has taken his blood pressure medication, which has newly added to his medication by his General Practitioner (**Figure 1**).

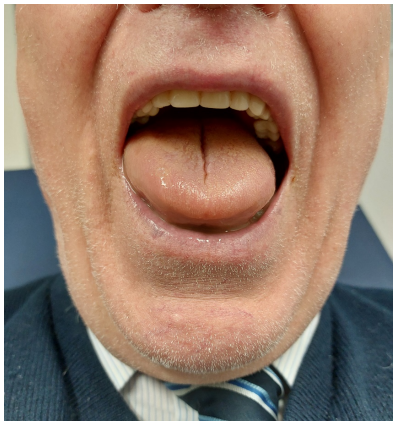

Figure 1. Settling/reduced angioedema in our patient at emergency department.

His initial vital signs in ambulance were HR-120/min, BP = 178/112mmhg, SpO2 = 95% on Room Air, RR = 25/min. Ambulance crew diagnosed him to have angioedema and administered hydrocortisone and chlorphenamine to treat it, following which is swelling of lips and tongue improved, he started talking again, his breathing difficulty subsided.

On presentation in emergency department, he was talking in full sentences, his HR-108/min, BP = 158/98mmhg, SpO2 = 98% on Room Air, RR = 18/min, Chest = bilateral (B/L) normal vesicular breath sound, CVS = S1, S2 audible and no murmur, Abdomen = soft, bowel sound present and non-tender, no skin

changes with capillary refill time < 2 seconds, temperature—36.7 degree Celsius, Glucose = 20 mmol/L.

Among significant past medical history, our patient was known case of essential hypertension, chronic kidney disease stage 3, angina pectoris, and type 2 diabetes mellitus. He had no known drug or food allergy in past, neither any similar incidence before.

2.2. Investigation & Management

The venous blood gas showed no acidosis, lactate 1.8mmol/L. His serum ketone was 0.1.

His full blood count was within normal limits without any eosinophilia.

Whole Blood Count (WBC)—8.05 × 109/L, neutrophil: 5.82 × 109/L, lymphocyte: 1.10 × 109/L, monocyte: 0.90 × 109/L, eosinophil: 0.21 × 109/L, basophil: 0.02 × 109/L;

Hemoglobin (HB)—125 gm/L [gram per liter];

Hematocrit—0.38 L/L [liter/liter];

Platelet—162 × 109/L;

His liver function test was within normal limits.

Sodium—135 mmol/L [millimoles per liter];

Potassium—4.4 mmol/L;

Urea—9.5 mmol/L;

Creatinine—150 umol/L [micromole per liter];

eGFR/1.73m^2—36 ml/min [eGFR = estimated glomerular filtration rate];

eGFR Comment—Chronic Kidney Disease stage 3;

His anaphylaxis screening came back normal as well, which exclude presence of hereditary angioedema or C1 esterase acquired deficiency.

C1 Esterase Inhibitor Function—>100%

C1 Esterase Inhibitor Antigen—0.312 g/L [gram per liter]

Complement C3—1.08 g/L

Complement C4—0.15 g/L

Patient improved completely in few hours of time and discharged home after 6hours observation in emergency department, with advice to stop his new blood pressure medication, losartan. His GP was requested to start another anti-hypertensive medication for him.

3. Discussion

3.1. What is Angioedema

What is Angioedema? Angioedema is a non-pitting localized swelling of deep dermis, subcutaneous, or submucosal tissue caused by the vascular extravasation of fluid into the interstitium, affects face, neck and mucous membrane, may or may not be associated with urticarial/skin changes [4].

Angioedema without urticarial is poorly understood in literature. Zingale et al in their very large clinical survey found that out of 776 patients (with angioede-

ma without urticaria) attending an angioedema clinic, 25% of cases are hereditary; 11% are caused by ACE inhibitors; 23% are caused by autoimmune disease, other drugs, insect bites, or food; and 41% are idiopathic [5].

3.2. Different Types of Angioedema (Figure 2)

[A] Mast cell medicated angioedema: Release of preformed vasoactive mediators such as histamine, leukotriene C4, and prostaglandin D2 from mast cells and basophils, after activation of either the innate or the adaptive immune system results in vasodilation, increased vascular permeability, and sensory nerve activation, leading to urticaria, pruritus, cutaneous flushing, and hypotension. Mast cells are distributed throughout the body, including within the dermis, subdermis, and mucosal surfaces [6].

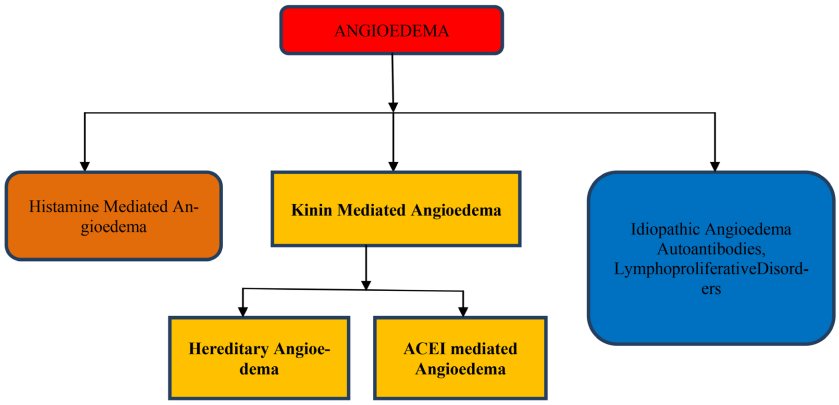

Figure 2. Angioedema classification.

[B] Histamine-mediated angioedema is caused by the same mast cell and basophil processes responsible for urticaria. Most patients with idiopathic acquired angioedema have histamine-mediated angioedema and respond well to antihistamine treatment [4].

[C] Kinin medicated angioedema is caused by aberrant activation of the contact-kinin system. Coagulation factor XII after contact with negatively charged surface like activated platelets, gets activated and converts plasma prekallikrein to kallikrein, kallikrein converts high molecular weight kininogen to bradykinin. Bradykinin binds to B2 receptor on endothelial cell and increases vascular permeability, resulting in tissue oedema by extravasation of fluids [7] (**Figure 3**).

Angiotensin Converting Enzyme (ACE) break down bradykinin. ACEIs, by inhibiting ACE activity, increases circulating bradykinin [8].

Risk factors of ACEIs induced angioedema are: previous angioedema, age > 65 years, use of non-steroidal anti-inflammatory drug, (NSAID), smoking, seasonal allergy, surgery, history of ACEIs induced angioedema, underlying C1esterase deficiency [9].

Hereditary angioedema: autosomal dominant disorder, mutations in the SERPING1 gene, which codes for C1 inhibitor, resulting in deficiency of C1 es-

terase (type 1 HAE) in 85% cases and C1 esterase dysfunction (type 2) in 15% of cases [4]. C1 esterase inhibitor, a component of the complement system, inhibits the conversion of prekallikrein to kallikrein and also inhibits the cleavage of high molecular weight kininogen to bradykinin [10].

Thus, hereditary or acquired C1 esterase deficiency and ACEIs causes angioedema as a result of increase circulating bradykinin.

Other drugs which account for small percentage of angioedema are, angiotensin receptor blockers (ARBs), non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, and certain antibiotics.

Idiopathic angioedema are less frequent, may be associated with chronic conditions, like autoimmune conditions.

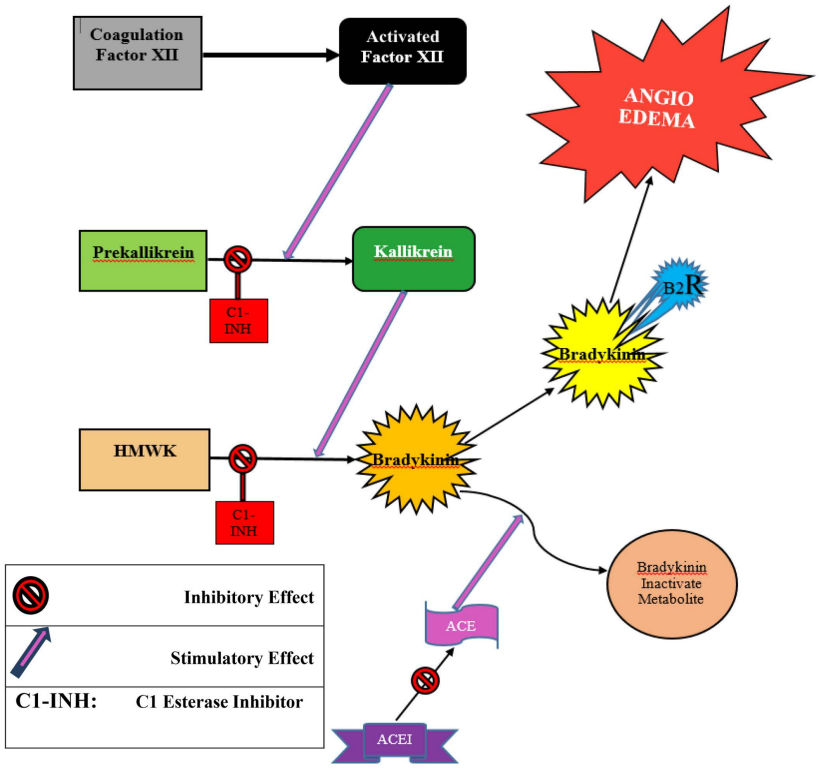

Figure 3. Pathophysiology of Bradykinin Mediated Angioedema. ACE Inhibitor group of drugs inhibits ACE mediated degradation of bradykinin to inactive metabolites. C1 esterase inhibitors (C1INH) inhibits bradykinin (B) production by inhibiting conversion of prekallikrein to kallikrein and high molecular weight kininogen (HMWK) to kinin. In hereditary angioedema there is deficiency/dysfunction of C1INH resulting into increase level of bradykinin.

3.3. Further Discussion in Perspective

In our patient anaphylaxis screening blood test showed, normal C1 esterase inhibitor function, normal C1 esterase inhibitor antigen, normal level of complement C3 & C4. He experienced angioedema after being started on Losartan, without any prior history of similar episode. Hence in this case, the angioedema was diagnosed to be as a result of losartan.

The mechanism by which losartan or other ARBs cause angioedema are not well understood in literature. Some studies suggest that ARBs activates prostaglandin-bradykinin and nitrous oxide cascades, including bradykinin mediated angioedema [11]. Others proposed elevated bradykinin theory, which hypothesize that Angiotensin II Receptor Blockers (ARBs) blocks the activity of angiotensin II type 1 receptors (AT type1), hence increase activity of angiotensin II on angiotensin II type 2 receptors (AT type1), which therefore increase bradykinin activity [9]. There is a report which shows that ARB use (losartan) directly increased bradykinin level [12]. Cross reactivity is seen to be another proposed mechanism, as studies found that increased risk of angioedema in patients with previous use of ACEIs [13].

Chiu *et al.* [14] proposed a very useful classification in respect to emergency presentation of angioedema based on it risk to airway:

- Class 1 when the oedema involves the face and oral cavity,
- Class 2 when the oedema extends to floor of the mouth and oropharynx, and
- Class 3 when glottis and supra-glottis involvement occurs.

Class 3 and often class 2 require a definitive airway protection. In our case, patient presented with class 1 angioedema, did not require airway protection as it subsided in response to oral steroids, intravenous antihistaminic.

Acquired ACEI or ARB induced angioedema is a clinical diagnosis which depends on history, clinical presentations and diagnosis by exclusion of other causes, like hereditary angioedema. No specific investigation is required.

Primary objective in treating Acquired ACEI or ARB induced angioedema in an emergency department is to stop the offending drug and protect and maintain the airway, may require early endotracheal intubation before the swelling from angioedema extends beyond epiglottis, larynx and blocks the airway completely. An emergency physician should remember this condition may pose a difficult airway situation which may warrant a front of neck access (FONA). Following airway protection next goal is to maintain breathing, ventilation, circulation and organ perfusion. Steroids, anti-histaminic and adrenaline are often used to treat Acquired ACEI or ARB induced angioedema, with limited proven benefit. Angioedema is self-limiting, typically resolves within 24 - 72 hours of onset [15]. Fresh frozen plasma has been used off label to manage ACEI/ARB induced angioedema, but so far no proven benefit. Ecallantide is an inhibitor of the protein kallikrein and a 60-amino acid polypeptide which mimics antibodies inhibiting kallikrein, Lanadelumab is a humanized monoclonal antibody which inhibits plasma kallikrein activity, thereby limiting the production of bradykinin, Berotralstat is an inhibitor of plasma kallikrein, which are now being used for the treatment of hereditary angioedema (HAE), also could be potential treatment for other bradykinin mediated angioedema [16].

4. Conclusion

ACEIs induced angioedema is well known phenomenon and ARBs are often used as an alternative medication. We, the authors by reporting this case, wants

to make clinicians aware ARB, however rarely, can cause angioedema, which can be life threatening if clinicians are not aware about it and diagnose and stop the offending drug promptly and treat it early. There are few reported cases are available so far and mechanism of ARB induced angioedema is obscure. Further indagation is required to conclude the safety of ARBs as a substitute of ACEIs. We also need further novel research on possible treatment of potent fatal airway emergency like ARB or ACEI induced angioedema.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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