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Case Report

A case report on angioedema induced by ramipril in a patient treated in a tertiary care hospital in north India

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ABSTRACT

Angioedema is non-pitting edema, or swelling, of the area beneath the deep dermis, subcutaneous, and/or mucosal layers of tissue resulting from fluid buildup, and it can be fatal if the larynx and pharynx are implicated. Drug-induced angioedema, like other cutaneous drug reactions, is most frequently elicited by non-steroidal anti-inflammatory drugs and beta-lactam antibiotics, while reliable information obtained from epidemiologic research is lacking. The latest studies have revealed that angiotensin-converting enzyme inhibitors have an increasing role in the development of life-threatening angioedema. Because of its safety and efficacy, ramipril is a commonly prescribed ACEI. This case report describes the clinical manifestations, management, and outcome of ramipril-induced facial angioedema in a 70-year-old Indian man.

Keywords: Ramipril, Angioedema, Adverse drug reaction, Angiotensin-converting enzyme inhibitor, Urticaria

INTRODUCTION

An adverse drug reaction (ADR) is defined by the World Health Organization, or WHO, as an unpleasant and unexpected response to a medication that occurs at normal human dosages.[1] Cutaneous adverse drug reactions (CADRs) are the most prevalent form of ADR documented.[2] There is minimal information available on ADRs among men from poor countries, notably North India. Angioedema, first reported in 1586, is often characterized as substantial swelling of the area beneath the deep dermis, subcutaneous, and/or mucosal layers of tissue caused by vascular leakage that lasts 1 to 3 days.[3,4] Other terminology for this illness, including angioneurotic edema, Quincke edema, and giant urticarial, had been utilized in the past. Clinically, it is typically non-pruritic and non-pitting.[5-7] The affected skin frequently does not change color or is somewhat erythematous. It's most often seen affecting the eyes (periorbital) and lips. The other typically implicated parts include the genitalia, feet, hands, and face.

According to the Japanese guidelines, AE is classified into 3 types: idiopathic AE, extrinsic factor-induced AE, and AE with C1-INH deficiency.[8,9] The first kind is idiopathic AE, which has no recognized etiology. The second type of AE was caused by allergic and non-allergic responses to diverse antigens like venom, medications, foods, infections, animals, latex, and so on. The third type is caused by C1-INH deficiency and can be further categorized into two distinct subtypes: acquired angioedema (AAE) and hereditary angioedema (HAE). Angioedema is caused by a variety of variables, including foods, medicines, illness, and hereditary factors, and it can be mediated by a variety of pathways.[10-13] The number of drugs that can cause AE has risen in recent years, which

includes calcium channel blockers, beta-blockers, psychotropic drugs (serotonin reuptake inhibitors), diuretics, estrogens, fibrinolytic agents, statins, proton pump inhibitors, radiocontrast media, antibiotics, angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs), and non-steroidal anti-inflammatory drugs (NSAIDs).[14] Drug-induced AE, like other cutaneous drug responses, has been reported most commonly to be evoked by NSAIDs and β-lactam antibiotics; however, reliable data from epidemiological research is sparse.[15] In roughly 50% of cases, drug-induced AE is coupled with urticaria and can be worsened by life-threatening anaphylaxis.[15] While urticaria and/or AE are frequently associated with systemic symptoms that include hypotension in IgE-mediated allergic responses and aspirin intolerance, other medications, like ACEIs, produce isolated angioedema via a kinin-dependent mechanism distinct from urticaria but not AE. Recent data, specifically, imply that ACEIs are playing a growing role in the development of AE, which can lead to life-threatening episodes due to upper airway obstruction. AE occurs in 0.1 to 0.7% of ACEI patients and affects around 1 in 2500 people during the first week after being exposed.[16,17] Despite the low documented prevalence of ACEI-associated AE, it is one of the most prevalent causes of recurring drug-induced AE.[18] We present a case of angioedema caused by Ramipril treatment.

CASE REPORT

A male in his seventies with k/c/o hypertension and valvular heart disease with permanent atrial fibrillation and controlled ventricular rate presented to the CTVS OPD with complaints of dyspnea (NYHA Class II-III) and exertional palpitations. His echocardiography showed moderate mitral regurgitation and moderate tricuspid regurgitation with rheumatic degeneration of the valves.

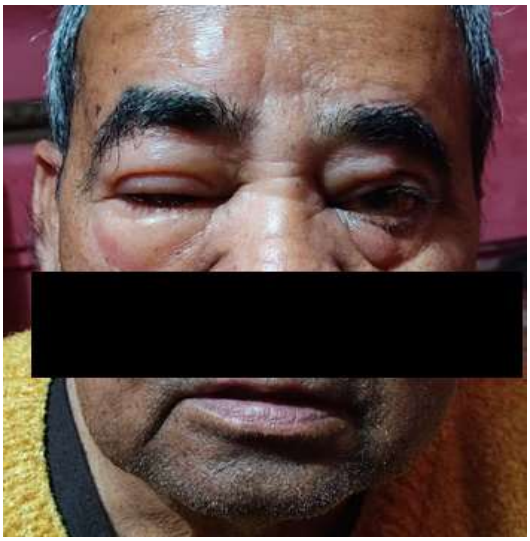

Figure 1: Patient at the time of angioedema.

Left ventricle function was preserved with dimensions within the normal range. He was started on anticoagulation (rivaroxaban), diuretics (torsemide, aldactone), rate-control agents (metoprolol succinate and digoxin), and an afterload-reducing agent (ramipril). The consultant received a call the next evening that the patient had developed facial swelling.

Figure 2: Patient after resolution of angioedema.

There was no respiratory embarrassment, stomach ache, urinary difficulty, giddiness, or falls. There was no history of insect bites or similar episodes in the past. Ramipril was stopped over the phone. He was managed symptomatically at a local hospice with antihistamines and steroids. His swelling improved, with facial swelling subsiding fully over two days. Subsequently, metoprolol was changed to carvedilol for afterload reduction. He has been followed up on for two years now. His functional class is NYHA Class I-II for dyspnea on exertion. His blood pressure and heart rate are under control. Serial echocardiography reveals no progression of mitral regurgitation or left ventricular dilatation.

DISCUSSION

Ramipril is an ACEI that is used for multiple indications, including hypertension, in addition to being used to provide renal and cardiovascular protection in patients with chronic kidney disease and heart failure and others who are at an elevated risk of cardiovascular events.[12,13] Common side effects include hyperkalemia, elevated serum creatinine, postural hypotension, dry cough, anxiety-like symptoms, and AE, whereas unusual side effects include oral disorders, onycholysis, movement disorders, and hypoperfusion. When greater dosages are used, adverse effects tend to occur more frequently.[13] In these instances, the global mortality rate is 0.1%. Since over forty million people globally are now being treated with ACE inhibitors, this medicine class might be responsible for hundreds of fatalities each year owing to laryngeal edema, based on a paper that was published in 2000 by Messerli et al.[19] In this case report, a male in his

seventies had developed facial swelling. Ramipril was discontinued, and the patient was treated symptomatically at a nearby hospice with antihistamines and steroids. His edema decreased, with the facial swelling completely disappearing after two days. In reality, the incidence of AE as an adverse response to ACEIs is low. Despite this, ACEI-induced AE requires specific care since it can develop into a potentially fatal syndrome with upper airway blockage.[10] The suppression of bradykinin degradation has been linked to ACEI-induced AE, and this mechanism is unique to AE but not to urticaria. To distinguish a kinin-dependent mechanism for AE, such as ACEI-related AE, from an IgE-mediated mechanism and NSAID intolerance, it is helpful to determine if AE is preceded by urticaria or not. As various new drugs have been licensed in recent years, the number of drugs that may cause AE has also increased. According to reports, more than one percent of newly approved drugs might induce AE, including tacrolimus, laronidase (a drug for Hurlers syndrome or mucopolysaccharidosis I), lepirudin (recombinant hirudin, an anticoagulant that functions as a direct thrombin inhibitor), fluoxetine (a selective serotonin reuptake inhibitor), alteplase (a recombinant tissue plasminogen activator), and rituximab (chimeric anti-CD20 antibody), although their mechanisms have never been elucidated.[11]

According to FDA data, AE, including laryngeal edema, can occur infrequently with ACEI treatment, particularly after receiving the first dosage. Recommend patients notify their physician of any AE symptoms right away, such as swelling of the tongue, lips, face, eyes, or nose, as well as problems with breathing, and to postpone taking any additional medications until they have spoken with the physician who prescribed them. Adverse responses to ACEIs, unlike other drug-induced AEs, are commonly ignored due to their erratic clinical course.

Clinicians anticipate that AE, whether allergic or non-allergic in origin, will emerge within a short period after the causative medicine is administered. Despite this, ACE-related side effects might appear years after the medicine was initiated, as well as sporadically while the patient is receiving therapy. Furthermore, certain cases of late-onset AE have been recorded weeks after the withdrawal of ACEIs.[18,19] The time between the first ACEI intake and the development of AE in ACEI-related AE ranges from a few hours to 8 years. An instance of severe AE following the first dose of ACEIs has been reported in Japan.[20] In 60% and 59% of patients, AE involving the face and viscera occurred within the 1st week.[21]

Furthermore, life-threatening upper airway edema occurs in up to 40% of patients and can be resistant to therapy or even fatal.[21,22] The initial phase in evaluating AE is to understand the numerous probable causes. Allergic and drug-induced AE responds to the elimination of the cause. Creatinine and Blood Urea Nitrogen, Haemoglobin and Haematocrit, blood glucose uric acid, serum bilirubin, and liver enzymes are all tests that can be performed in the event of AE. Additionally, because no accurate testing can discriminate between AE brought on by ACEIs and AE brought on by other variables, patients on ACEIs may still have adverse events (AE) even after several years of trouble-free ACEI medication.

Following basic emergency care, drugs suspected of causing AE must be discontinued. The initial care of systemic response centers on anaphylaxis, for which antihistamines and steroids are the treatment of choice. Following epinephrine administration, an antihistamine such as hydroxyzine (Atarax, Vistaryl) or diphenhydramine (Benadryl) may be given to treat pruritus and inflammation.[23,24] When traditional H1 and H2 antihistamines fail, additional medications such as nifedipine are used as an adjuvant to antihistamines. According to clinical presentation, some studies advise corticosteroids, while others suggest the administration of corticosteroid medication using intravenous hydrocortisone or dexamethasone sodium phosphate, which is still the most common therapy for AE.)

Weber et al have proposed icatibant, a bradykinin inhibitor, as a potential therapy for ACEI-associated AE and suggested that because bradykinin is a primary mediator of AE from ACEIs, icatibant, which is currently being utilized in patients with HAE, might be beneficial in these individuals.[25] It is of note that the angioedema induced by ACEis bradykinin-mediated rather than histamine-mediated. Hence, antihistaminics, corticosteroids and epinephrine, the staple drugs of choice in such emergencies, are of little use.

While airway compromise needs to be managed with standard methods (intubation/cricothyroidotomy/ tracheostomy), observation in less severe cases may be all that is needed. C1 INH concentrate, available commercially in India, will help in severe cases. In absence of C1 INH concentrate, FFP transfusion may serve as a cheaper and readily available alternative.[26] Shortly, new techniques targeting the kalliklein-kinin system (KKS), like bradykinin type-2 receptor antagonists and kalliklein inhibitors, may enhance therapy for ACEI-induced AE.

CONCLUSION

This case report highlights the occurrence of angioedema induced by Ramipril in a patient treated at a tertiary care hospital in northern India. It emphasizes the importance of vigilance in identifying adverse drug reactions, particularly those associated with ACEIs. Healthcare professionals should be aware of the potential risks and promptly manage such complications to ensure patient safety and optimal outcomes. Further research is warranted to explore the underlying mechanisms and risk factors associated with Ramipril-induced angioedema.

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