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REVIEW ARTICLE

Drug-induced visceral angioedema

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Angioedema associated with angiotensin converting enzyme inhibitors (ACEIs) is due to the accumulation of bradykinin and its metabolites. Angiotensin receptor blockers (ARBs) produce anti-hypertensive effects by blocking the angiotensin II AT1 receptor action; hence bradykinin-related side effects are not expected. However, we notice the occurrence of ARB-induced angioedema as not a very rare side effect. Visceral drug-induced angioedema has been reported with ACEIs, not with ARBs. This underlying review will help educate readers on the pathophysiology and recent guidelines pertaining to ACEI- and ARB-induced visceral angioedema.

Keywords: *angiotensin converting enzyme inhibitor*; *angiotensin receptor blocker*; *visceral angioedema*; *intestinal angioedema*

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The well-acclaimed advantages of angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in the management of multiple medical conditions have made them widely used drugs globally (1). In 2011, in the United States, there were 164 million prescriptions of ACEIs and 86 million prescriptions of ARBs (2). Here, we discuss the life-story of these two classes of drugs, the underlying pathophysiology behind drug-induced head, neck, and visceral angioedema; and highlight certain theories postulated in current literature. To help us in this venture, we utilized a case of angiotensin receptor blocker-induced visceral angioedema (ARBVA) at the University Medical Center in the setting of prior ACEI-induced visceral angioedema (ACEIVA) and elucidated the morbidity and diagnostic difficulties that were encountered.

History of ACEIs and ARBs

The renin-angiotensin-aldosterone system (RAAS) has a major role in the maintenance of blood pressure. The series of reactions in the RAAS pathway involving angiotensinogen, angiotensin I (Ang I), and angiotensin II (Ang II) is depicted in column 1 of Fig. 1. The discoveries of bradykinin and angiotensin converting enzyme (ACE) in plasma were stepping-stones in the pursuit for drugs affecting the RAAS (3). Bradykinin is a product of the kinin–kallikrein system formed by the proteolytic cleavage of plasma-based HMW-kininogen (4). It was discovered in 1948, when detected in animal plasma after injecting venom from *Bothrops jararaca,* the South American pit viper (5). Later, Brazilian scientist Sergio Ferreira reported a bradykinin-potentiating peptide (BPP) present in the venom of *Bothrops jararaca* (6).

The emergence of bradykinin physiology gave a novel insight into various physiologic and pathological phenomena including hypotension and cardiovascular shock caused by toxins and venoms. Bradykinin is a powerful vasodilator, increases vascular permeability, and enhances contraction of non-vascular smooth muscle. Bradykinin is rapidly neutralized in the circulation and disappears completely in one single passage through the pulmonary vasculature. The inactivation of bradykinin and the conversion of Ang I to Ang II in the lungs were found to be catalyzed by the same enzyme, ACE (7). In 1970, Ng and Vane illustrated that this angiotensin conversion is inhibited by Ferreira's BPP (8). BPPs are members of a family of peptides whose potentiating action is linked to effects of ACE inhibition, and captopril, the first ACEI, was developed from this class of peptide. Further analysis of BPPs showed the greatest ACE inhibition potency and hypotensive effect *in vivo* (9).

As ACEIs were developed, researchers were studying direct Ang II receptor antagonism. Saralasin, an Ang II analogue, was developed as a potent competitive inhibitor, but poor oral bio-availability was a drawback. Thereafter, in the 1980s, a class of imidazole derivatives was found to reduce blood pressure in rats. The structural modification of these compounds looked similar to the Ang II molecule and came out as the first ARB, losartan (10).

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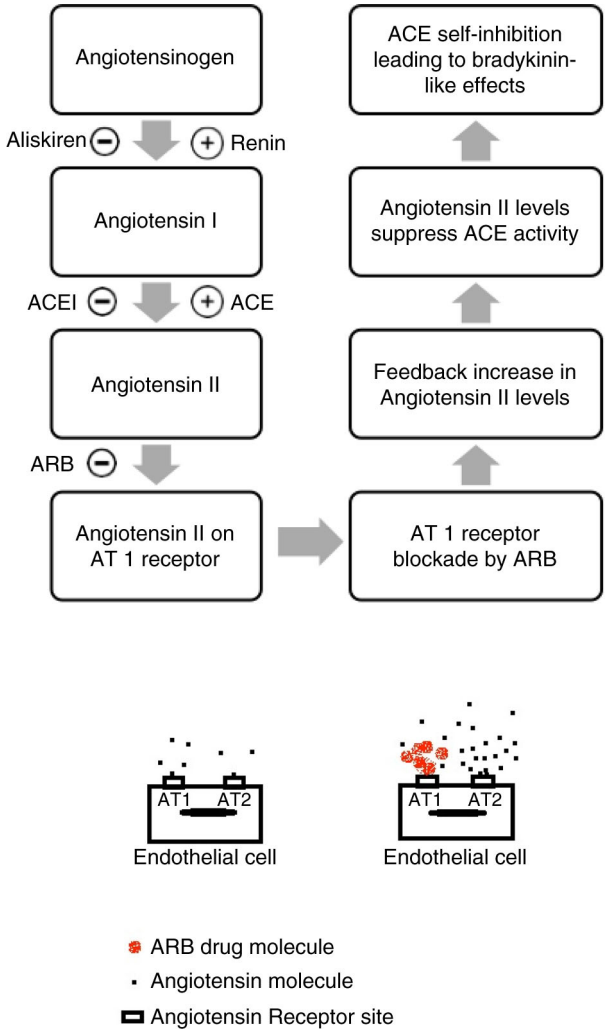

Fig. 1. Renin-angiotensin system. Mechanisms behind ARB-induced angioedema. Flow diagram showing feedback-induced increase in Angiotesin II levels and subsequent ACE self-inhibition. Also shown is an illustration of feedback-induced AT2 receptor-mediated bradykinin stimulation associated with ARB administration. ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; AT = angiotensin.

Case illustration

We describe the case of a 31-year-old African-American woman with a history of hypertension, hemodialysis-dependent end-stage renal disease, and a 6-year long history of recurrent abdominal pain. She presented to the hospital with another bout of severe abdominal pain, nausea, vomiting, and diarrhea. She had episodic pain and tenderness over the epigastrium and right lower quadrant without guarding or rigidity. She was afebrile and denied sick contacts. Bowel sounds were hypoactive. Complete blood count, basic metabolic panel, liver function tests, lactate, and lipase were unremarkable. For hypertension, her current regimen included nifedipine, losartan, and clonidine. Review of records indicated that the onset of symptoms coincided with the initiation of lisinopril 6 years ago. Previous non-contrast abdominal CTs showed isolated peri-hepatic fluid collection. Contrast was repeatedly avoided given her dialysis dependent kidney disease because immediate dialysis could not be planned during the majority of her ER visits. The diagnosis had remained elusive and her complaints persisted. After 5 years on lisinopril, she experienced some dry cough and was transitioned to losartan. The transition to losartan resulted in resolution of the cough. However, 12 months into losartan therapy, her abdominal symptoms still persisted. Having reviewed the entire course of her illness, drug-induced visceral angioedema was suspected.

Eventually, an abdominal CT scan (Fig. 2) with contrast was requested with planned hemodialysis. It revealed small bowel wall edema, a classic 'target sign' and peri-hepatic fluid. C1-inhibitor and C4 levels were

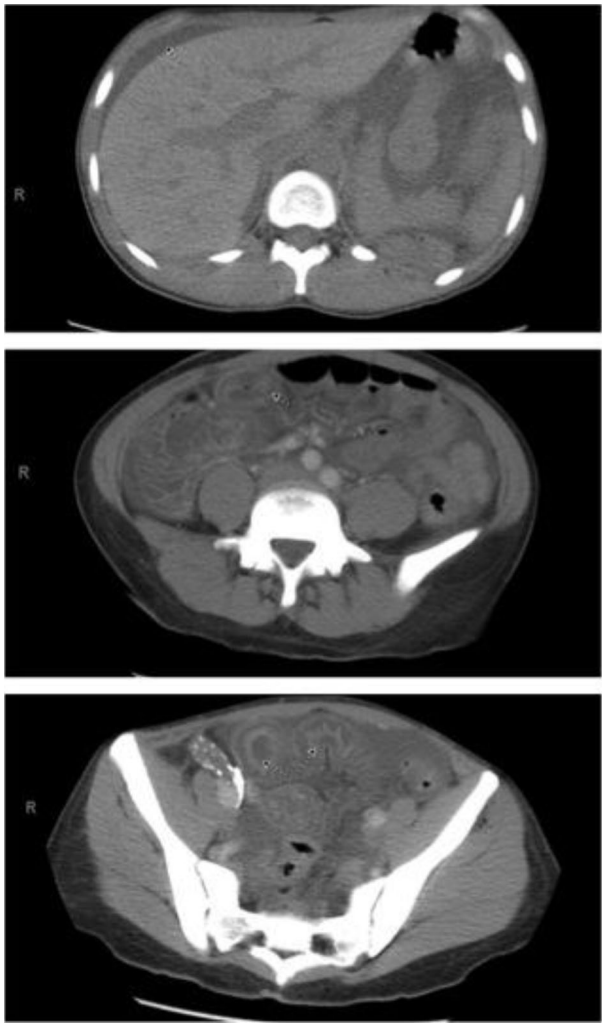

Fig. 2. Contrast CT findings of visceral angioedema. (a) Peri-hepatic fluid accumulation. (b, c) Small bowel wall edema, Target sign.

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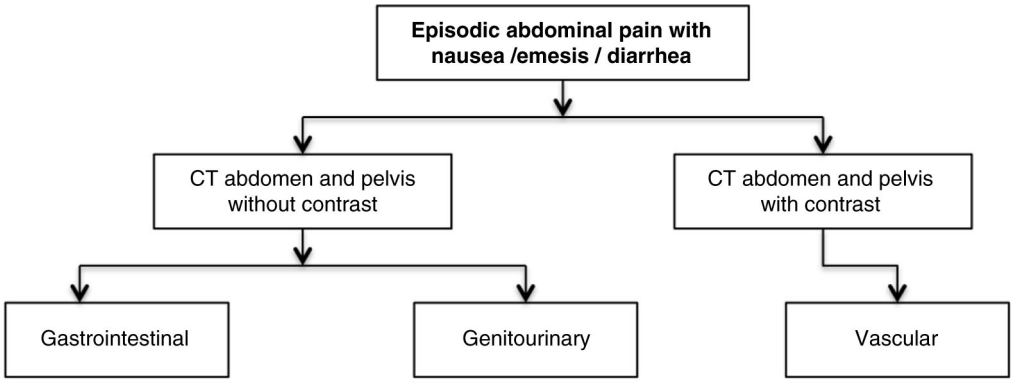

Acute / acute on chronic pancreatitis	Patient had normal Lipase & Amylase. Absence of peripancreatic stranding or calcifications on CT. Stool negative for fat.
Small bowel obstruction/perforation	Normal CBC. No air fluid levels. No air under diaphragm
Acute gastroenteritis	Symptoms were episodic. Normal colon on CT, Stool test negative for pathogens, toxins or wbc.
Inflammatory bowel disease	Absence of pseudopolyps, strictures, fissures in bowel wall on CT. Normal Colonoscopy.
Acute cholecystitis/ biliary colic/hepatitis/ gastritis	No jaundice, intact LFT. Murphy sign negative. Endoscopy unremarkable. Normal liver and gall bladder on CT.
Acute intermittent porphyria	Unable to test due to lack of urine sample-ESRD status.
Lactose intolerance/ celiac disease	Endoscopic biopsy negative for celiac disease. No response to dietary change.

Nephrolithiasis	No evidence of renal or ureteric or bladder calculi.
Mass lesions	No polycystic appearance or renal masses. Chronic allograft rejection less likely to cause such pain after 6 years.
Pelvic Inflammatory Disease/Obstetric emergency	Normal uterus and appendages. Normal pelvic exam.

Bowel ischemia	Normal serum lactate. No filling defect in mesenteric arteries. No pneumatosis in Small bowel / colon.
Hereditary/Acquired C1 esterase deficiency angioedema	Bowel wall thickening noted, no pneumatosis. But, our patient had normal C1 esterase and C4 levels.
Drug-induced angioedema: ACEIs or ARBs	Bowel wall edema noted. Clinical and radiological improvement on discontinuation of drug confirms diagnosis.

Fig. 3. Flowchart depicting the algorithmic approach to episodic abdominal pain that was used in the described case.

normal. This provided stronger evidence that it could be ARB-induced visceral angioedema. Losartan was discontinued and patient's symptoms resolved. Follow up until 12 months later confirmed sustained relief of her symptoms and established the diagnosis of ARB-induced visceral angioedema (ARBVA). Awareness is key to early suspicion and diagnosis. Besides prior clinical experience, an important step in the diagnosis of visceral angioedema is the prompt use of a contrast-based multi-detector CT scan (MDCT) (11). Patients with suspected or recurrent visceral angioedema may also benefit from the effective use of ultrasound (11). Figure 3 shows an algorithm followed in the case described above.

Drug-induced head, neck, and visceral angioedema

The protection offered by ARBs against adverse effects like angioedema thought to be mediated by kinins may not be absolute. There is considerable evidence for ARB-induced angioedema in literature (12, 13).

The ONTARGET trial showed the incidence of head and neck angioedema to be lower with telmisartan versus ramipril at 0.1% versus 0.3%, RR 0.4 (14). Amongst ARBs, losartan had the highest hazard ratio for angioedema events, considering the fact that losartan is the most widely used ARB (13).

We conducted MEDLINE search for 'ACE inhibitor and ARB angioedema' and 'visceral angioedema' and reviewed the literature. Korniyenko et al. have reported a case series in which, citations and references indicate not less than 27 case reports on ACEIVA (15). Having searched the MEDLINE database, the case described here may well be the first case of ARB-induced isolated intestinal angioedema and it has occurred in the setting of previous ACEIVA. ARBVA is a constellation of symptoms and signs in the setting of ARB use as described in Table 1. Visceral angioedema is rare but also underreported and poorly recognized by the physicians. Hence, the variables determining the susceptibility to visceral angioedema versus facial angioedema are difficult to appreciate. There is a well-known female predominance for ACEIVA and ACEI-induced facial angioedema; however, the same has been found to be negative with ARB-induced angioedema (15, 16). The time period from initial presentation to diagnosis of ACEIVA was 2–9 years (15).

Pathophysiology of ACEI- and ARB-induced angioedema

ACEIs were created from a class of molecules representing BPPs; hence, it is not surprising that bradykinin accumulation/potentiation is an adverse effect of ACEI administration. According to one study, during an acute episode of angioedema with ACEIs, bradykinin levels can rise as high as 12 times normal (17). The mechanism is described below: the effects of bradykinin on B1 and B2 receptors are similar including increase in nitric oxide and prostacyclin leading to vasodilation and hypotension. The kinin-system substrate, called Kininogen (high molecular weight and low molecular weight Kininogen), is primarily metabolized by ACE (kininase II), aminopeptidase P (APP), and neutral endopeptidase (NEP) and secondarily by enzymes dipeptidyl peptidase IV (DPPIV) and kininase I. The primary enzymes usually metabolize bradykinin into inactive metabolites. When the primary metabolizing enzyme is inhibited by ACEI drug, bradykinin substrates are available for metabolism by secondary enzymes alone. However, these secondary enzymes produce active, rather than inactive, metabolites including Lys-bradykinin and Des-Arg-bradykinin that function at both B1 and B2 receptors and this leads to overwhelming vasodilation (1) (Fig. 4). Defects or deficiencies in some of these enzymes including APP and DPP IV have been found in cases that were predisposed to ACEI-induced facial angioedema (18, 19). To further strengthen this observation, the use of DPPIV inhibitors for diabetes mellitus has been associated with risk of ACE-inhibitor-induced angioedema (18). Information on rise in bradykinin level has not documented in case reports on ACEIVA (15).

Table 1. Teaching pearls for diagnosis of ARBVA. Angiotensin receptor blocker-induced visceral angioedema

Angiotensin receptor blocker-induced visceral angioedema (ARBVA):
• Abdominal pain with or without nausea, vomiting, and diarrhea.
• Occurs as acute exacerbations on chronic low-grade pain.
• Symptom onset within days to many years since starting on an ARB.
• CT abdomen with contrast showing visceral edema.
• Normal C1 esterase inhibitor and C4 level.
• Symptoms resolving with discontinuation of ARB within days to weeks.
• Absence of alternative diagnoses.

ARBs are thought to produce anti-hypertensive effects via manipulation of the RAAS cycle by directly blocking the Ang II AT1 receptor action. Hence, while using ARBs one would not expect side effects attributed to ACE inhibition and bradykinin accumulation (20). However, sufficient data is lacking that ARBs do not cause bradykinin accumulation. On the contrary, there is evidence from Campbell et al. that bradykinin levels were elevated in patients on losartan. The decrease in the ratios of BK-(1–7)/BK-(1–9), Ang II/Ang I, and Ang-(1–7)/Ang I point out that the high bradykinin levels were the result of lower metabolism by ACE and NEP. Elevated bradykinin levels may represent a class effect of AT1 receptor blockers that contributes to their therapeutic actions and may also contribute to the angioedema that may accompany this therapy (21). Based on data from MEDLINE search, we have consolidated the theories behind ARB angioedema with background evidence in literature.

Feedback inhibition of ACE

The use of ARBs is thought to cause feedback-induced increase in angiotensin II levels in plasma (22). This may result in feedback-related self-inhibition of the rate-limiting step involving ACE (23). Thus, it is hypothesized that intrinsic ACE inhibition and bradykinin accumulation may well be the final pathway leading to ARB-induced angioedema (Fig. 1). The intrinsic, rather than extrinsic, suppression of ACE activity and the variable threshold in different populations may account for the lower intensity and incidence of this adverse effect of ARBs.

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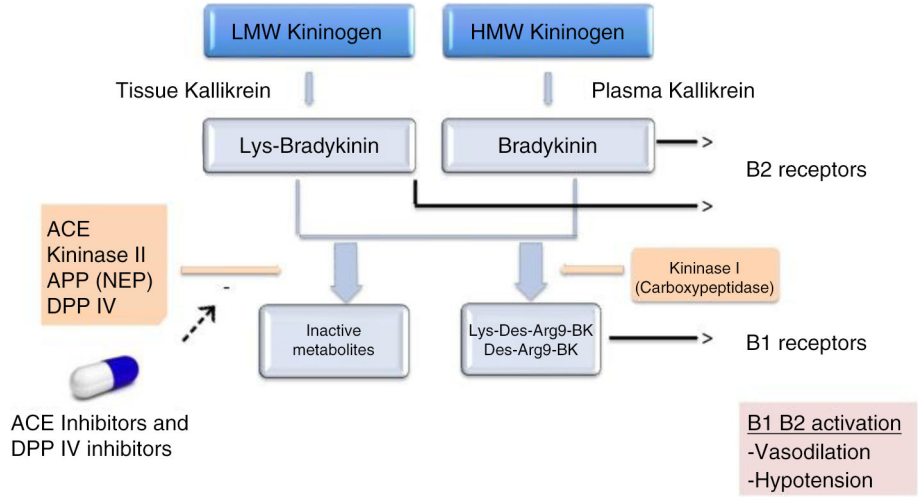

Fig. 4. Mechanism of bradykinin accumulation associated with ACEI use. ACE inhibition leads to diversion of substrates toward secondary enzymes rather than primary metabolizing enzymes thereby producing physiologically active metabolites. LMW = low molecular weight; HMW = high molecular weight; B1 = bradykinin 1; B2 = bradykinin 2.

Ang II AT2 receptor mechanism

Another concept that may describe the phenomenon behind ARB angioedema is that the ARB molecule exerts a competitive inhibition on the AT1 receptor. Hence, the feedback-induced increase in plasma levels of angiotensin II levels may, per se, activate vascular AT2 receptors that are available and generate bradykinin (22). This, in turn, may stimulate bradykinin BK_2 receptors in the endothelium and causes vasodilation and angioedema (23, 24).

Current practice and guidelines

Authors in the recent past have recommended that physicians not prescribe ARBs to patients who have had an episode of angioedema with ACEIs because it can be life-threatening (15, 24). Recurrent angioedema has been reported to occur in 1.5–10% of patients after changing from ACEI to ARB. But, it is believed that this could represent residual effects of ACEI angioedema, with the majority of cases occurring within a month of ACEI discontinuation. From more recent meta-analysis studies, it is recommended that ARBs should be considered for use in patients with a history of ACE induced angioedema who have a high therapeutic need for angiotensin inhibition as long as the patient is warned about the risks (25–27). The reason is that when compared to ACEIs, the incidence of ARB-induced angioedema, besides being relatively low in number, was similar to that of beta-blockers and placebo (incidence rates of 4.38, ACEI, ARB and beta-blockers, respectively) (13). After discontinuing ACEI, waiting for at least 4 weeks before cautiously starting ARB is recommended, so that residual ACEI-induced recurrent angioedema is not mistaken as a new ARB-induced angioedema (28).

In our patient's case, ideally, an ARB is an important medication given the history of HTN so as to prevent or delay cardiovascular morbidity. She is scheduled for a kidney transplant and it becomes even more beneficial to have an ARB in her regimen. However, she clearly had a 12-month long period of symptoms and signs of ARBVA, and it is unlikely to be a phenomenon that is comparable to placebo effect. ACE inhibitors are dialyzable, and she underwent hemodialysis regularly, indicating that this is unlikely to be a case of recurrent ACEIVA after months of ACEI discontinuation. Re-challenging her with an ARB may produce symptoms most likely at some point of time, which may be lethal if it affects the head and neck. This has been the fear for many years and continues to be so amongst many clinicians. The patient was informed about these recommendations and was not willing to take the risk of recurrent ARBVA or head and neck angioedema.

Unlike research in ACEIs, there is scarce knowledge on biochemical changes in bradykinin and other metabolites with the use of ARBs. Research modalities with biochemical or radio-nuclear evidence in animals or humans could be utilized. There is a serious need to study the nature of the feedback regulation of RAA system while using ARBs and its effect on pulmonary ACE activity, plasma ACE levels, plasma levels or *in vivo* activity of bradykinins, des-Arg-BK, DPP IV, APP and NEP, kininase 1 and substance P.

Conclusion

Attempts to further understand this phenomenon of angioedema associated with ARBs may help introduce novel therapeutic medical therapies and throw light on

future guidelines for transitioning patients with a history of ACEI angioedema from ACEIs to ARBs. The results of NICE guidelines from the United Kingdom recommending ACEIs and ARBs as first-line anti-hypertensive for people under 55 years of age may lead to further increase in the use of ACEIs and ARBs (29). Clinicians should be aware that cross-reactivity of angioedema between ACE inhibitors and ARBs, albeit low, could affect visceral organs and cause significant morbidity that can be missed for years. Creating this awareness amongst physicians will help in avoiding delays in diagnosis, unnecessary testing, and considerable morbidity. Visceral angioedema should receive the same level of attention by physicians, as head and neck angioedema. Care should be taken to avoid prematurely considering such cases with abdominal pain and hospital readmissions as secondary gain. After all, the eyes can only see what the mind knows.

Key points

Cross-reactivity of angioedema between angiotensin converting enzyme inhibitors (ACEIs) and ARBs could affect visceral organs.

Meta-analyses recommend cautious use of ARB after an episode of ACEI-induced head, neck, and visceral angioedema after appropriate counseling.

As against current evidence, it could be hypothesized that bradykinin metabolism may potentially be a driving factor behind ARB-associated angioedema.

Conflict of interest and funding

We have no conflicts of interest with respect to this manuscript.

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