REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Angiotensin-converting Enzyme Inhibitor-induced Angioedema

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ABSTRACT

Angiotensin-converting enzyme inhibitors (ACE-I) are widely used, effective, and well-tolerated antihypertensive agents. The mechanisms by which those agents act can cause side effects such as decreased blood pressure, hyperkalemia, and impaired renal function. ACE-I can induce cough in 5%−35% and angioedema in up to 0.7% of treated patients. Because cough and angioedema are considered class adverse effects, switching treatment to other ACE-I agents is not recommended. Angioedema due to ACE-I has a low fatality rate, although deaths have been reported when the angioedema involves the airways. Here, we review the role of bradykinin in the development of angioedema in patients treated with ACE-I, as well as the incidence, risk factors, clinical presentation, and available treatments for ACE-I-induced angioedema. We also discuss the risk for recurrence of angioedema after switching from ACE-I to angiotensin receptor blockers treatment.

 • *The American Journal of Medicine (2015) 128, 120-125*

KEYWORDS: ACE-I (angiotensin converting enzyme inhibitor); Angioedema; ARBs (angiotensin receptor blockers); Bradykinin; Cough; Ecallantide; Icatibant

The first angiotensin-converting enzyme inhibitor (ACE-I), captopril, was approved by the Food and Drug Administration (FDA) in the early 1980s.[1] The treatment was proven to be effective in lowering blood pressure with an excellent tolerability profile. Since then, ACE-I agents have been widely used for the treatment of hypertension, congestive heart failure, diabetic nephropathy, post myocardial infarction, and chronic kidney disease with proteinuria.[2]

ACE-I medications are divided into 3 groups based on their molecular structure at the active site of the drug: sulfhydryl containing agents (eg, captopril) have the strongest chelating function and may cause skin rash and loss of taste. Dicarboxylate-containing agents are weaker chelators (eg, enalapril, ramipril) and are designed as prodrugs. The phosphonate-containing agents (eg, fosinopril) are also a prodrug eliminated from the body via both renal and hepatic pathways.[3]

Funding: None.

Conflicts of Interest: None.

Authorship: All authors had access to the data and a role in writing the manuscript.

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0002-9343/$ -see front matter
http://dx.doi.org/10.1016/j.amjmed.2014.07.011

MECHANISM OF ACTION

The mechanism of ACE-I was considered a breakthrough in the treatment of hypertension. It is based on blocking the renin-angiotensin-aldosterone cascade. Normally, renin is produced and secreted by the juxtaglomerular apparatus in the kidneys in response to a decrease in blood pressure or to a decrease in filtered sodium chloride concentration. The secreted renin cleaves the hepatic angiotensinogen to the inactive peptide angiotensin I. Angiotensin I is then converted into the active angiotensin II by angiotensin-converting enzyme (ACE), which is produced mainly in the lung capillaries. Angiotensin II has a number of physiological effects. It increases blood vessel resistance, acts on the adrenal cortex to release aldosterone, stimulates the release of the antidiuretic hormone vasopressin from the posterior pituitary, stimulates thirst centers, facilitates norepinephrine release from sympathetic nerve endings, and inhibits norepinephrine re-uptake (**Figure 1**).[1,2] ACE-I is a competitive inhibitor of the ACE enzyme, preventing the conversion of angiotensin I to the active angiotensin II. ACE is also responsible for the degradation of bradykinin. Active bradykinin is produced once its precursor, kininogen, is cleaved by kallikrein. Bradykinin has a short half-life due to rapid degradation primarily by ACE. Thus, the inhibition of

ACE by ACE-I medications can prolong the half-life of bradykinin, increasing its concentration and activity (Figure 1).[4]

Angiotensin receptor blockers (ARBs), also known as AT1 receptor antagonists, block the binding of angiotensin II to its receptors, causing vasodilation, reduced secretion of vasopressin, and reduced production and secretion of aldosterone (Figure 1).[5] As ACE-I, the ARBs are indicated for the treatment of hypertension, heart failure, and diabetic nephropathy. ARBs do not have any effect on the activity of ACE. Therefore, ARB medications do not inhibit the breakdown of bradykinin (Figure 1).[6] Consequently, ACE-I and ARBs differ in some of their adverse effects.

CLINICAL SIGNIFICANCE

- Angioedema, like cough, is a class effect of angiotensin-converting enzyme inhibitors (ACE-I).
- The estimated incidence of ACE-I-induced angioedema is 0.68%. Due to worldwide usage of these medications, ACE-I-induced angioedema is not uncommon.
- ACE-I-induced angioedema typically involves the lips and tongue, but involvement of the gastrointestinal mucosa is an important presentation, which might cause unnecessary invasive procedures.
- Acute life-threatening events should be addressed by measures that inhibit bradykinin.
- Patients who experienced angioedema with one ACE-I will typically have angioedema with all other ACE-I agents; hence, switching to another ACE-I medication is contraindicated.

ACE-I ADVERSE EFFECTS

Some of the adverse events of ACE-I result from the drug's action. Hypotension, causing weakness, dizziness, or syncope, caused about 1.7% of the patients to discontinue the drug.[6] Hypotension is marked in hypovolemic patients. Severe reduction in the glomerular filtration rate (GFR) may be seen in patients with bilateral renal artery stenosis, hypertensive nephrosclerosis, heart failure, polycystic kidney disease, or chronic kidney disease.[7] In the above disorders, the intrarenal perfusion pressure is reduced and the GFR is maintained mainly by angiotensin II, which increases the resistance at the postglomerular arterioles. Hence, treating these patients with ACE-I may cause renal dysfunction.[6] Hyperkalemia is another common side effect. ACE-I inhibits aldosterone release, which is the major stimulus for urinary potassium excretion. The overall incidence of hyperkalemia in patients treated with ACE-I is about 3.3%. Usually the potassium increment does not exceed 0.5 mg/L.[6] More prominent ACE-I-induced hyperkalemia may be seen in patients with concomitant renal insufficiency, diabetes, or concurrent use of potassium-sparing agents or nonsteroidal anti-inflammatory agents.[8]

ARBs treatment also may cause the above adverse events because they block angiotensin II activity (Figure 1). Indeed, Fried et al[9] recently recommended the avoidance of ACE-I and ARBs combination in patients with diabetic nephropathy due to hyperkalemia and renal failure.[9]

Captopril may cause sulfhydryl-related adverse events, such as rash, neutropenia, taste abnormalities, and nephritic syndrome. Some of those side effects are idiosyncratic, while others are dose related.[10] In the current dosage used (up to 150 mg/day), those side effects are quite rare and do not reoccur with the other groups of ACE-I.[10]

ACE-I-INDUCED COUGH

Cough is a well-described class adverse effect of ACE-I. The incidence of ACE-I-induced cough is reported to be 5%–35%[11] (9.9% in controlled randomized trials and 1.7% in cohort studies).[12] In the ONgoing Telmisartan Alone and in combination with the Ramipril Global Endpoint Trial (ONTARGET), cough caused the discontinuation of ramipril in 4.2% of the treated patients.[6] The precise mechanism by which ACE-I causes cough is not yet defined, but increased concentrations of bradykinin, substance P, prostaglandins, and thromboxane (as discussed below) are most likely involved.[13] Cough may occur within hours following the first dose of the medication, but it may be delayed for weeks to months after the initiation of ACE-I agents. Switching treatment from one ACE-I to another is not effective because cough is a class adverse effect.[11] When ACE-I is discontinued, improvement of the cough occurs within 1 to 4 weeks. In some patients, resolution of the cough may take a few months.[11] The incidence of ARB-induced cough is much lower (3.2% in controlled trials and 0.6% in cohort studies).[12] Although cough may occur with ARBs, they are considered an alternative treatment for patients who discontinued ACE-I due to cough and who need the blockade of the renin-angiotensin cascade.

ACE-I-INDUCED ANGIOEDEMA

Angioedema is a self-limiting swelling (edema) of the skin (dermis and subdermis), mucosal tissues, and organs such as the tongue, lips, eyelids, intestine wall, or genitalia, all of which are rich in capillary blood supply.[14] The edema is caused by hyperpermeability of postcapillary venules due to vasoactive agents. There are 2 main types of angioedema. The allergic-histamine-mediated angioedema develops rapidly and is associated with pruritus and rash (urticaria). In some patients, systemic anaphylaxis may also occur,[14] caused either by allergen-specific immunoglobulin E (eg, food, drug, insect bite, aeroallergens) or by direct mast cell degranulation.[15] On the other hand, the nonallergic angioedema (nonimmunoglobulin E mediated) is mediated mainly by bradykinin. The latter is a nonpruritic