

## Hypersensitivity reaction induced with renin-angiotensin-aldosterone system blocker antihypertensive agents

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### ABSTRACT

Renin-angiotensin-aldosterone system (RAAS) blockers are commonly prescribed to patients with hypertension. This class of drugs includes angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). Like many other drugs, mild to severe allergic reactions may occur with the use of these drugs. In this case report, we present a 67-year-old male patient who was treated for hypertension at the Istanbul Medical Faculty Department of Clinical Pharmacology. The patient had experienced severe allergic symptoms thought to be related to treatment with ACE inhibitors and ARBs. After switching the hypertensive medication to calcium channel blockers, the patient developed no allergic symptoms and his blood pressure levels returned to normal.

**Keywords:** Angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, hypersensitivity reaction.

Renin-angiotensin-aldosterone system (RAAS) blockers are drugs that are widely used in the treatment of hypertension. This class of drugs includes angiotensin-converting enzyme (ACE) inhibitors and ARBs (angiotensin receptor blockers). Although ACE inhibitors and ARBs have many benefits in treating hypertension, they may cause hyperkalemia and also have teratogenic effects. In addition to these effects, they can cause hypersensitivity and anaphylactoid reactions, especially ACE inhibitors but also ARBs. This case demonstrates a patient who developed hypersensitivity reaction as a result of using ACE inhibitor and ARB group drugs.

### CASE REPORT

A 67-year-old male patient was undergoing treatment in our hypertension clinic. He had been taking daily combination tablets of losartan 100 mg and hydrochlorothiazide (HCTZ) 12.5 mg as anti-hypertensive treatment for about 10 years

without complaints. The patient had 40 pack/day smoking history. Coronary angiography was performed six years prior but he had no coronary stents. At the time of presentation, our patient had erythema on his tongue and hands and he also had shortness of breath. He immediately consulted to an emergency department and his symptoms were thought to be related to an allergic reaction to his anti-hypertensive medication. The emergency physician stopped the losartan and HCTZ treatment and started perindopril 5 mg and HCTZ 12.5 mg combination tablet once daily. On month into this new treatment, the patient presented to our hypertension clinic for a routine visit. There were no abnormal signs in physical examination and he had a blood pressure of 137/91 mmHg, and 94 bpm pulse, and normal electrocardiogram. His uric acid level was 10.4 mg/dL (2.5-7.5 reference interval). Due to elevated uric acid levels, HCTZ treatment was discontinued and perindopril 5 mg/amlodipine

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5 mg combination treatment of one tablet daily was initiated. After two months of this treatment, the patient presented to an emergency department again with a rash on his face and erythema on his chest, hand, and legs. His IgE level was 287 IU/mL (0-165 normal interval) and WBC was 11.42/ $\mu$ L (3.98-10.2 normal interval) with neutrophilia. He was consulted to an allergy doctor and tests were carried out for food and dust allergies but they were all negative. The next day the patient arrived at our clinic for control and we believed his allergic reactions may be related to RAAS-blocking agents. We stopped the perindopril 5 mg and amlodipine 5 mg combination treatment and instead started lercanidipine 10 mg 2 oral tablets daily. After three months of this treatment, the patient arrived at our hypertension clinical for a routine control. His physical examination was normal and he had no complaints and no allergic symptoms.

## DISCUSSION

Drug hypersensitivity reactions are one of the most common side effects of drugs.<sup>[1]</sup> The drug allergy can occur as an immediate or delayed reaction, depending on the type of drug taken and the exposure time to the drug.<sup>[1]</sup> Angiotensin-converting enzyme inhibitors can cause angioedema and hypersensitivity reactions.<sup>[2]</sup> Angioedema occurs in approximately 0.1-2.2% of patients treated with ACE inhibitors.<sup>[2]</sup> Increased bradykinin levels induced by ACE inhibitors is thought to be the factor that causes allergic reactions.<sup>[2]</sup> Most cases occur in the first week of the therapy but ACE inhibitor-induced angioedema (ACEiIA) may occur at any time during treatment.<sup>[3]</sup> Risk factors for ACEiIA include: age older than 65, female gender, smoking, aspirin/NSAID use, seasonal allergies, and cough associated with ACE inhibitors.<sup>[4]</sup> Angiotensin-converting enzyme inhibitor use together with cholesterol-lowering drugs such as statins is also considered a risk factor for ACEiIA.<sup>[5]</sup> Lapostolle et al.<sup>[6]</sup> reported a case of lingual angioedema with perindopril use. There are many other case reports on different types of ACE inhibitors. Allergic reactions associated with ACE inhibitors are thought to be class effects not bound to a single type of ACE inhibitor.

The risk of allergic reaction occurrence with ARBs seems less compared to ACE inhibitors in certain studies. Since ARBs do not have any

effect on bradykinin metabolism, it is thought that prescribing ARBs to patients who experienced adverse reactions with ACE inhibitors would be appropriate. However, some studies showed that ARBs may actually increase bradykinin levels. As ARBs bind to and block type 1 angiotensin II receptors, angiotensin II binds to type 2 receptors, and this binding increases the level of bradykinin and nitric oxide.<sup>[7]</sup> Neutral endopeptidase (NEP) and ACE are enzymes that break down bradykinin, and ARBs may increase bradykinin levels by inhibiting ACE and NEP.<sup>[7,8]</sup> This is thought to be a class effect of ARBs and therefore, ARBs should not be prescribed to patients with a recent history of allergic reactions with ACE inhibitors. There are also case reports of allergic reactions related to different types of ARBs. Nielsen documented an angioedema case associated with Irbesartan.<sup>[9]</sup> In a study that evaluated bradykinin levels in hypertensive patients using losartan, it was concluded that losartan increased bradykinin levels by twofold.<sup>[7]</sup> Additionally, eprosartan produced changes in kinin levels similar to losartan, however, eprosartan did not significantly affect bradykinin levels.<sup>[7]</sup> It has also been reported that the risk of allergic reactions is higher in patients using ARBs who have previously experienced allergic reactions with ACE inhibitors.<sup>[10]</sup>

In conclusion the evidence is indicative that ACE inhibitors and ARBs may cause allergic reactions. Angiotensin-converting enzyme inhibitors are known to increase bradykinin levels which leads to allergic reactions. In this case, the use of losartan also caused allergic reactions. This finding supports other studies that showed increased allergic reaction risk with the use of losartan. This is believed to be a class effect, therefore, other type of ARBs should also be avoided in these patients. Furthermore, non-RAAS blocking antihypertensive agents should be prescribed in patients who have previously developed allergic reactions related to ACE inhibitors and ARBs.

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