

## **Could lisinopril cause angioedema after 1 year?**

### **Are angiotensin receptor blockers (ARBs) safe in patients with angiotensin-converting enzyme (ACE) inhibitor-induced angioedema?**

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Angioedema, characterized by swelling of the mouth, face, and extremities, is a well-documented adverse reaction of ACE inhibitors, occurring at an incidence of 0.1 to 1%.<sup>1</sup> Per the manufacturer, black patients receiving ACE inhibitors have been reported to have a higher incidence of angioedema compared to non-black patients (incidence not stated); this is corroborated by the results of a retrospective review by Brown et al in which blacks were found to have a 5-fold higher incidence of angioedema than whites.<sup>2</sup> Patients with ACE inhibitor-induced angioedema have also been described as older (age not specified) and without a history of other allergies.<sup>3</sup> Per a consult found on Micromedex, the earliest reported onset of angioedema after initiation of an ACE inhibitor is 4 hours, and the latest onset is 7 years, with duration of symptoms ranging from 5 to 24 hours (with therapy), up to 72 hours (without therapy).<sup>1</sup> The cases appear to occur more commonly during the first week of therapy. However, a search of the literature revealed multiple case reports/reviews describing late-onset angioedema. Ricketti et al described a 52 year old male who they diagnosed with type I hereditary angioedema (HAE), an autosomal disorder characterized by low levels of active C1 esterase inhibitor (C1-INH), “unmasked” after 7 years of treatment with lisinopril.<sup>4</sup> The patient had been taking other medications, including simvastatin, ezetimibe, amlodipine, lansoprazole, and valdecoxib; none were thought to significantly interact with ACE inhibitors or C1-INH pathways. Lisinopril was discontinued and the patient was observed to be symptom-free at the time of publication (24 months). Pillans et al conducted a retrospective review of 116 reports of angioedema and urticaria associated with ACE inhibitors including captopril, enalapril, and lisinopril.<sup>5</sup> Of these, 68 reports involved angioedema alone, 37 involved urticaria alone, and 11 involved both. There were 47 reactions with documented occurrence between 3 weeks and 4 years after ACE inhibitor initiation.

Regarding management of ACE inhibitor-associated angioedema, immediate discontinuation of the offending agent is recommended.<sup>1</sup> Antihistamines may be useful to relieve symptoms but are not always essential. Administration of epinephrine is recommended in patients with respiratory distress.

As this reaction is considered to be a class effect, therapy with an agent from an alternative class of antihypertensives is recommended. There is controversy surrounding the issue of initiation of an ARB in patients with a history of ACE inhibitor-associated angioedema. Based on the speculation that this reaction is caused by bradykinin accumulation, substitution with an ARB may seem reasonable.<sup>6</sup> However, several articles have been published suggesting possible cross-reactivity of ACE inhibitors and ARBs. In a review on the tolerability of ARBs,<sup>7</sup> a study was identified in which 19 patients experienced angioedema (18 receiving losartan, 1 receiving valsartan); of these, 6 (32%) had a history of ACE inhibitor-induced angioedema. In the same review, findings from an overview of the Food and Drug Administration’s (FDA) Adverse Event

Reportings System (AERS) revealed a total of 851 and 6642 cases of angioedema reported, attributed to ARBs and ACE inhibitors, respectively, indicating that angioedema is more commonly seen with use of ACE inhibitors. The number of patients experiencing cross-reactivity was not reported. Of note, a case series and clinical study of safe substitution of an ARB in patients with confirmed ACE inhibitor-induced angioedema were also described in this review.

More recently, Haymore et al conducted a meta-analysis assessing the risk of angioedema associated with ARB use in patients with ACE inhibitor-induced angioedema.<sup>8</sup> The study included 1 randomized controlled trial and 2 retrospective cohorts describing confirmed and suspected cases of angioedema. The risk of developing confirmed angioedema associated with an ARB in these patients was determined to be 3.5% (95% CI: 0 to 9.2%). For suspected cases, the risk was determined to be 9.4% (95% CI: 1.6 to 17%). The results of this study were updated in a letter by the investigators,<sup>9</sup> in which they combined data from the Telmisartan Randomised Assessment Study in ACE intolerant subjects with cardiovascular disease (TRANSCEND) trial.<sup>10</sup> Including this data, the risk for developing angioedema with ARB use was determined to be 1.5% for confirmed cases (95% CI: 0 to 5.1%) and 2.5% for suspected cases (95% CI: 0 to 6.6%). The authors concluded that there is a risk for development of angioedema with ARB use in patients with history ACE inhibitor-associated angioedema, but the incidence is low.<sup>9</sup>

In summary, while usage of an alternative class of antihypertensives is advised in patients with suspected ACE inhibitor-associated angioedema, ARBs should be used with caution.

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