

Angioedema due to the renin inhibitor aliskiren

(MAY 2011)

TO THE EDITOR: The interesting report by Korniyenko and colleagues of the delayed diagnosis of visceral angioedema due to angiotensin-converting enzyme (ACE) inhibitor therapy¹ should alert readers that a long duration of use of ACE inhibitors should not rule out the diagnosis of ACE inhibitor-induced angioedema, as symptoms can be delayed for up to a decade.

Risk factors for angioedema for patients on ACE inhibitor therapy that have been identified so far include black race, the XPNPEP2 C-2399A polymorphism in men (which leads to decreased aminopeptidase P activity),² and concomitant use of the mTOR inhibitors sirolimus (Rapamune) or everolimus (Afinitor) in renal transplant recipients.³ All of these factors further decrease metabolism of the vasoactive peptide bradykinin. However, the effect of cofactors such as use of nonsteroidal anti-inflammatory drugs, aspirin, simvastatin, estrogen, or a tendency for angioedema (such as in patients with recurrent or episodic idiopathic angioedema) on lowering the threshold for angioedema or increasing the severity of the angioedema episode or episodes after starting ACE inhibitor therapy remains unknown.

Physicians should also be aware of angioedema as a significant side effect of the new renin inhibitor aliskiren (marketed by Novartis Pharmaceuticals as Rasilez in the United Kingdom and as Tekturna in the United States) for treatment of essential hypertension.⁴ A pooled analysis of 31 studies in 12,188 patients showed the incidence of angioedema associated with aliskiren monotherapy to be 0.4%, similar to that with ACE inhibitors: relative risk 0.31, 95% confidence interval 0.07–1.47 for 150 mg; relative risk 0.57, 95% confidence interval 0.17–1.89 for 300 mg).⁵ However, no patients were hospitalized with a serious angioedema event.

Although the mechanism of action of

aliskiren via renin inhibition would suggest that bradykinin may not be the causative agent of angioedema, physicians should ensure that patients who report significant angioedema episodes or those who present with angioedema have their medication history thoroughly reviewed to prevent a serious untoward event.

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IN REPLY: We agree with Dr. Khan that the duration of ACE inhibitor therapy should never be used to rule out ACE inhibitor-associated angioedema. In an Italian study of 85 cases of angioedema with ACE inhibitor therapy, the mean ACE inhibitor exposure was a full 12 months before angioedema was diagnosed.¹ More disturbing was the fact that another 12 months elapsed before the ACE inhibitor actually was discontinued. This would indicate that neither the patient nor the physician related the angioedema to ACE inhibitor therapy. In patients with visceral angioedema, since the diagnosis is unusually challenging, even a further delay can be expected.

Angioedema has been reported with aliskiren, but the 0.04% incidence reported by White et al² may reflect very simply that physicians are more alert and on the lookout now more than they ever were when ACE inhibitors were first available. Obviously, greater awareness will lead to more frequent diagnosis. As Dr. Khan points out, there is no known mechanism by which aliskiren should cause angioedema, whereas there is fairly solid evidence that ACE inhibitor-associated angioedema is mediated by bradykinin.^{3,4}

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