CASE REPORT

ACE inhibitors: upper respiratory symptoms

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SUMMARY

Cough and angioedema are well-known adverse reactions of ACE inhibitors. However, other adverse effects of upper airways such as postnasal drainage, rhinitis and nasal blockage, are less frequently recognised. These might share the same pathophysiological mechanism: bradykinin accumulation. We present two patients with ACE inhibitor-induced upper respiratory symptoms that improved after the discontinuation of ACE-inhibitors and substitution with angiotensin II receptor blockers. The incidence of these adverse events is not accurately known, since these are not required to be reported, but it is estimated to be low. This presents challenges to the physician and demonstrates the importance of keeping it as a differential diagnosis. Most physicians are aware of ACE inhibitor-induced cough but not of ACE inhibitor-induced nasal blockage, rhinitis or postnasal drainage. Identifying these can avoid unnecessary diagnostic tests and inappropriate treatment.

BACKGROUND

ACE inhibitors have been considered one of the most common and useful drugs for controlling hypertension, congestive heart failure, proteinuria, etc. Different adverse reactions have been reported such as cough, bronchospasm, asthma, angioedema, among others.¹ ACE inhibition causes substance P and bradykinin, a bronchoconstrictor, to accumulate in the airways,^{2,3} which makes histamine to be released from mast cells.⁴ Histamine contributes to local inflammation and can be a cough mediator. On the other hand, bradykinin can also interfere with substance P on type I receptors at peripheral nerve endings, perhaps mediated by unmyelinated or vagal afferent C-fibers, having irritating effects on the bronchial mucosa.⁵ This may partially explain ACE inhibitor-induced cough.

Some patients are more susceptible to ACE inhibitor-induced cough than others. This might be due to a bradykinin receptor gene polymorphism.⁶ Patients genetically predisposed to ACE inhibitor cough have shown a lower activity of aminopeptidase P, which plays an important role in degradation of bradykinin.⁷ Therefore, this might possibly explain why cough does not occur in every patient taking ACE inhibitors.

CASE PRESENTATION**Case 1**

A 67-year-old man with no known allergies presented to our clinic with a chief concern of postnasal drainage and a tickle sensation in the throat that triggered cough spells, sometimes associated with gagging and even vomiting. He described

symptoms starting about 5 or 6 years prior but became progressively more troublesome. The episodes were paroxysmal with no recognisable trigger, characterised by episodes of rhinorrhoea, profuse drainage and changes in the voice. The patient's medical history is significant for diabetes, obstructive sleep apnoea, osteoarthritis, Barrett's oesophagus, hyperlipidaemia, and hypertension for which amlodipine and benazepril were prescribed. On physical examination, there were no remarkable findings; nasal endoscopy revealed moderate septal deformity to the left and a small nodular cystic lesion in the rhinopharynx of no clinical significance. CT scan of the sinuses confirmed the septal deviation with no additional findings. Allergy and pulmonary function tests were all negative. ACE inhibitor-induced nasal sinus symptoms were suspected; therefore, the patient was instructed to discontinue the use of benazepril, and losartan was prescribed instead, with clonidine patches added later. In the follow-up evaluation, the patient described resolution of symptoms 24–48 h after benazepril withdrawal.

Case 2

A 78-year-old man with no known allergies presented to our clinic with a chief concern of postnasal drainage, rhinorrhoea, nasal obstruction and sneezing. He described some symptoms, when benazepril was prescribed for the management of his hypertension, the nasal sinus symptoms have become more intense with marked impact in his quality of life. Allergy tests were all negative. Nasal endoscopy was normal, CT scan revealed minimal mucosal thickening of the sinuses. Chest X-ray was normal. ACE inhibitor-induced nasal sinus symptoms were suspected so the patient was instructed to discontinue the use of benazepril, and losartan was prescribed instead. In the follow-up evaluation, the patient described complete resolution of symptoms.

DIFFERENTIAL DIAGNOSIS

Allergic rhinitis, flu-like symptoms, sinusitis and upper respiratory infections.

TREATMENT

ACE inhibitor discontinuation and substitution with angiotensin II receptor blockers.

OUTCOME AND FOLLOW-UP

There was remission of symptoms.

DISCUSSION

ACE inhibitors have been known to produce different adverse reactions such as cough, severe

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bronchospasm,⁸ maculopapular rash, severe angioedema and others. Irritation of bronchial and nasal mucosa is a relatively common upper respiratory symptom, due to known mechanisms of proinflammatory cytokine accumulation consequence of ACE inhibition.

The clinical presentation of ACE inhibitor-induced upper respiratory symptoms is variable, presenting most frequently with rhinorrhoea, tickling sensation in the throat, and nasal obstruction. Some other ACE inhibitor-induced upper respiratory symptoms have also been reported in the literature, such as: postnasal drainage,¹ rhinitis and dysgeusia.⁹ Adverse reactions of ACE inhibitors were studied in 36 Swedish patients who had been taking captopril, enalapril or lisinopril for hypertension or heart failure where cough, dyspnoea and bronchospasm were the most commonly reported. A case of enalapril-induced nasal blockage was reported: a 45-year-old woman with severe nasal obstruction who had been taking enalapril as treatment for hypertension presented complete resolution after enalapril discontinuation.¹⁰ Captopril-induced lymphocytic interstitial pneumonia and rhinorrhoea have been reported as well, in an 8-month-old patient with heterotaxy syndrome.¹¹

ACE inhibitor bronchial mucosa irritation has been partly explained by bradykinin and substance P accumulation, which also explains the nasal mucosa congestion seen in these patients. Histamine release from mast cells due to bradykinin can also potentiate this reaction. Leukotrienes and prostaglandin E2 and I2 can potentiate this inflammatory reaction as well.³

ACE inhibitor-induced cough incidence might range in 5–10% of treated patients.¹² In fact, some studies report an incidence of 7–15% within the general population.¹³ However, ACE inhibitor-induced rhinitis has not been determined, probably because it is quite underestimated due to poor recognition of presentation, and therefore, few cases have been reported. Furthermore, genetically predisposed patients, probably those with bradykinin receptor polymorphism^{7 14} might influence its incidence too.

On the other hand, approximately 5.1 million people in the USA have clinically manifested hypertension, and the prevalence continues to rise.¹⁵ The overall prevalence of hypertension appears to be around 30–45% of the general population, with a steep increase with ageing.¹⁶ It is therefore of major importance

to recognise these adverse reactions, since a considerable percentage of patients are and will be under ACE inhibitor treatment. Most physicians are aware of ACE inhibitor-induced cough but may not be as aware of less frequently reported ACE inhibitor-induced upper respiratory symptoms such as nasal blockage, rhinitis or postnasal drainage. Correctly identifying these can avoid unnecessary diagnostic tests and inappropriate treatment.

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Learning points

- Cough is not the only adverse effect that should be considered when prescribing ACE inhibitors.
- Nasal blockage, rhinitis and postnasal drainage should also be considered so that unnecessary diagnostic tests can be avoided.
- Prevalence of hypertension and heart failure is increasing; therefore, the use of ACE inhibitors is increasing as well.

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