Why Do Antihypertensives Cause Cough?
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Question
What are the mechanisms of cough caused by angiotensin-converting enzyme inhibitors, beta-blockers, and calcium channel blockers, and how can this adverse effect be managed?

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Although all 3 classes of antihypertensive drugs have been associated with cough as a side effect, the causal explanation differs between classes, and the level of evidence is strongest with angiotensin-converting enzyme (ACE) inhibitors -- a first-line antihypertensive drug class for many patients.

ACE inhibitors affect the renin-angiotensin-aldosterone system and block the conversion of angiotensin I to angiotensin II, which is involved in vasoconstriction. ACE inhibitors are associated with a dry, persistent cough in 5%-35% of patients who take them. The mechanism of cough is likely multifactorial. ACE inhibitors prevent the breakdown of bradykinin and substance P, resulting in an accumulation of these protussive mediators in the respiratory tract. In addition, bradykinin can stimulate the production of prostaglandin. This side effect is not dose-dependent and often precludes the use of all agents within the drug class.

Beta-blockers are used for their antagonistic effect on cardiac beta-1 adrenoceptors. Two types of beta-blockers are available: beta-1 selective adrenoceptor antagonists (eg, metoprolol, atenolol) and nonselective beta-1/ beta-2 adrenoceptor antagonists (eg, carvedilol, propranolol, sotalol, timolol). Beta-2 receptor antagonism is associated with bronchoconstriction. Baker demonstrated that many commercially available beta-1 selective blockers have high affinity for beta-2 receptors. Therefore, both selective and nonselective beta-blockers may cause bronchoconstriction, which can lead some patients to experience a cough reflex.

Calcium channel blockers (CCBs) block calcium influx into cardiac muscle and vascular smooth muscle. Although there are reported incidences of cough associated with CCBs, the rates are low, ranging from < 1% to 6%. A literature search for drug-induced cough associated with CCBs yielded no relevant studies or case reports. However, the search yielded studies on the
potential *antitussive* benefits of CCBs. It may be reasonable to suggest that the incidence of cough reported for CCBs may be more aptly associated with other concomitant antihypertensive medications for which cough is a well-documented adverse effect, such as the afore mentioned ACE inhibitors.

Patients experiencing ACE inhibitor-induced cough often can be prescribed an angiotensin receptor blocker for hypertension without the cough risk.\(^1\) For patients experiencing cough on beta-blocker therapy, ensure the cardioselective agent is at the lowest effective dose and underlying respiratory problems are being managed. Patients should not be withheld appropriate antihypertensive therapy due to cough.

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