Angiotensin-Converting Enzyme Inhibitors, Asthma, and Cough: Relighting the Torch

Woo-Jung Song, MD, PhD, and Akio Niimi, MD, PhD
Seoul, Korea; and Nagoya, Japan

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Angiotensin-converting enzyme inhibitor (ACEI) is a class of medication well known not only for its cardiovascular benefits but also for respiratory adverse effects. In the late 1970s, captopril, one of the first orally active ACEIs, demonstrated clinical effectiveness in patients with hypertension or congestive heart failure. However, respiratory side effects, particularly cough, became widely recognized in less than a decade. Captopril induced significant left-shifts in dose-response curves during capsaicin inhalation cough challenges, prompting the hypothesis that cough-reflex hypersensitivity is a mechanism of drug-induced coughing.

Since the clinical observations, coughing has been widely accepted as a major complication of ACEI treatment. The coughing rates related to ACEI use are variable (0%-28%) across studies depending on patient characteristics or outcome definitions, but a cough risk is evident in a pooled analysis of randomized controlled trials. Because the risk is not elevated by angiotensin receptor blocker (ARB) treatment compared with placebo, ARB is preferred in patients with ACEI-induced cough.

However, unlike ACEI-induced cough, an increased risk of bronchoconstriction or clinical worsening in patients with asthma with ACEI treatment has not been clearly established. Bradykinin is a proinflammatory mediator that is released from activated mast cells and can trigger airway sensory nerves to release neuropeptides including substance P. Angiotensin-converting enzyme can degrade bradykinin and substance P, which are not only capable of stimulating afferent C-fibers but also inducing cough (and bronchoconstriction in patients with asthma). Thus, it is hypothesized that ACEI therapy may lead to accumulation of those proinflammatory mediators and then possibly aggravate asthma including bronchoconstriction. Earlier studies suggested that underlying airway hyperresponsiveness (AHR) or asthma was a predisposing factor for developing ACEI-induced cough. Furthermore, ACEI use was significantly associated with the risk of airway obstructive symptoms in an analysis of a large population-based adverse drug event reported in Sweden. However, the risk of bronchoconstriction or asthma worsening was not consistently observed in other studies. These inconsistencies are possibly due to the different but small sample sizes involved in individual studies, because the incidence of airway obstructive symptoms was much less than that of coughing. The findings collectively suggest that worsening of ACEI-induced bronchoconstriction or asthma is not universal to every patient with asthma, and if a risk is present, individual susceptibility should be further explored.

In the context of previous uncertainties, the study by Morales et al is a meaningful addition to the literature. In this issue of the Journal of Allergy and Clinical Immunology: In Practice, they report that when compared with the general UK population, patients with active asthma were at increased risk for switching from ACEI to ARB treatment. Using the UK Clinical Practice Research Datalink, they analyzed a large longitudinal data set of 642,336 people initiating ACEI therapy, including 40,953 patients with active asthma and 601,383 controls without asthma. Overall, 17.4% of patients with active asthma switched to ARB, compared with 14.6% of the general population, with an adjusted hazard ratio (HR) of 1.16 (95% CI, 1.14-1.18). The risk of switching was also associated with sex (female vs male: HR, 1.46; 95% CI, 1.45-1.47), older age (≥60 years vs <40 years: HR, 1.66; 95% CI, 1.62-1.70), and higher body mass index (≥25 kg/m² vs <20 kg/m²: HR, 1.55; 95% CI, 1.51-1.59). Among patients with active asthma, the risk of switching to ARB was greater in older patients (age ≥60 years) with more severe asthma (British Thoracic Society treatment step ≥3). Notably, the risk was decreased in patients with chronic obstructive pulmonary disease (HR, 0.89; 95% CI, 0.87-0.91), supporting the validity of the conclusions. Clearly, this is the largest study to date suggesting that asthma is a risk factor for ACEI intolerance.

The findings of the study by Morales et al. however, warrant careful interpretation for several reasons. First, the study was observational and could not confirm a causal relationship. Second, the study population of patients with active asthma was defined using a diagnostic code for asthma and the receipt of at...
least 2 asthma medications in the database but was not verified by objective testing or diagnosis by a specialist. Third, the reason for switching from ACEI to ARB was not documented. However, as the authors discussed, the switch may have represented development of ACEI intolerance because a high positive predictive value (up to 90.5%) for switching was found in the adverse drug events reported in previous electronic database analyses.7

Incidence-wise, coughing is likely to have been a major reason for the switch to ARBs, because the incidence was about 10 times higher than that of airway obstructive symptoms in the Swedish population–based study of adverse drug events.5 In large-scale randomized controlled trials included in the meta-analysis for the risk of ACEI-induced cough (vs placebo),2 asthma was not present in the participant selection criteria but asthma worsening was not reported as an outstanding adverse drug reaction. Notably, the demographic risk factors for switching (increased age, female sex, and obesity in the present study7) are consistent with those for chronic cough.8 Also, within patients with asthma, patients showing cough-reflex sensitivity to capsaicin are more frequently females and have poorer asthma control and more severe disease.9,10 Because cough is one of the main symptoms of asthma, the incidence of coughing might be misinterpreted as loss of asthma control in patients with asthma. Meanwhile, expectation (or nocebo effects) might also have played a part in the drug switch, even without the occurrence of actual drug side effects. ACEI-induced cough is a relatively well-known adverse reaction, and thus, the expectation might increase the chance of developing symptoms in patients with asthma.

Despite the limitations and uncertainties, the study findings allow us to consider potential implications for research and clinical practice. Next steps might include (1) cohort analyses of patients with severe or poorly controlled asthma to examine the rate of ACEI exposure and causal relationships between the drug exposure and asthma control, and if a risk is confirmed, then proceed to (2) identification of biomarkers to precisely predict individuals at risk for developing ACEI-induced asthma worsening. Given that its incidence is likely much lower than that of coughing, further cohort studies should have a large sample size. Also, because asthma is a multifactorial disease involving airway inflammation, airflow obstruction, AHR, or neuronal hypersensitivity including cough, the disease end points mainly affected by ACEI exposure should also be investigated. AHR and cough-reflex hypersensitivity may interact and be overlapped but indeed have independent mechanisms from each other.10 In patients with asthma, airway obstructive symptoms (including cough) are induced by bronchoconstriction on the basis of AHR, whereas cough can be specifically mediated by cough-reflex hypersensitivity. Either of these pathophysiologic characteristics might predominate in individual patients with asthma, and respiratory adverse effects of ACEI might differ between patients (as airway obstructive symptoms or isolated cough). Further studies will help to guide clinical practice on the use of ACEI in patients with asthma, and the study by Morales et al1 relights the torch on this topic.

REFERENCES