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EDITORIALS

Pneumonia and ACE inhibitors—and cough

Too early to use ACE inhibitors to prevent pneumonia

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Angiotensin converting enzyme (ACE) inhibitors are widely used to treat heart failure and hypertension. They act through blocking the conversion of angiotensin I to angiotensin II; this inhibits the breakdown of bradykinin, which in turn lowers arteriole resistance and increases venous return. Many patients taking ACE inhibitors experience a persistent dry cough, which is thought to be caused by increased concentrations of bradykinin; the cough is triggered by the endothelial effects of bradykinin and other peptides. Refractory cough is the most common reason for switching from ACE inhibitors to angiotensin II receptor blockers (ARBs), which do not inhibit the breakdown of kinins and are less likely to cause troublesome coughing. In the linked study (doi:10.1136/bmj.e4260), Caldeira and colleagues examined the risk of pneumonia with both classes of drug, hypothesising that the cough associated with ACE inhibitors might protective against pneumonia.[1]

Coughing is one of the most common reasons that patients consult a primary care doctor, and it has a substantial effect on quality of life. It also has a large economic impact—annual expenditure on cough treatments is unknown because many are over the counter preparations, but it is estimated to run into millions of pounds in the United Kingdom. In patients taking ACE inhibitors the chronic cough is associated with throat irritation, and the only wholly effective way to prevent it is to stop taking the drug.[2] However coughing helps protect the respiratory tree from aspiration of pharyngeal contents and increases clearance of inhaled organisms. It therefore follows that ACE inhibitors, but not ARBs, could protect against lower respiratory tract infection, and this has been suggested by some earlier trials.

Caldeira and colleagues studied this question by performing a systematic review and meta-analysis of trials and studies of ACE inhibitors and ARBs.[1] Their review seems to support the pharmacological and pathological hypothesis and suggests a protective role for ACE inhibitors in reducing the incidence of (and possibly mortality from) pneumonia.

The authors undoubtedly made stringent attempts to pool all available data and undertook a thorough search of clinical studies of ACE inhibitors and ARBs with few eligibility restrictions. The review was not restricted to prospective randomised controlled trials and included both retrospective and prospective observational cohort and case-control studies. Most data came from unpublished studies identified from a search of regulatory documents placed on the Food and Drug Administration website.

Respiratory infection was not a primary outcome in most of these studies, and data were collected predominantly from reporting of adverse events (in randomised controlled trials) or from database coding for pneumonia or lower respiratory tract infection (in observational studies). Pneumonia and lower respiratory tract infections represent a heterogeneous group of overlapping disorders with multiple causes and several different ICD9/10 (international classification of diseases, 9th/10th revision) and other codes.

Meta-analysis is a useful tool if the quality and evidence base of the contributing studies is satisfactory. In this study, the quality of reporting was assessed using several different tools, and the results suggest a high risk of reporting bias, together with substantial heterogeneity. This is explained by the variety of study designs included, and it probably excludes further quantitative and subgroup analysis.[3] The efficacy findings should therefore be interpreted with caution.

It is unclear why, in the overall comparison of ACE inhibitors and ARBs in preventing pneumonia, the effect was noted only in the cohort and nested case-control studies and not in the randomised trials. The analysis of randomised controlled trials is probably more robust owing to the inherent bias in the design of observational studies.

This does not mean an effect was not present, but it is difficult to agree with the authors that “best evidence” points to ACE inhibitors protecting against pneumonia. Is it right on the basis of this study to recommend that patients should put up with their resistant cough because it could reduce their risk of pneumonia? This is an important clinical question, but to agree would run counter to current evidence based guidelines that recommend discontinuation.[2] Extrapolation of results could lead to serious misconceptions: could a smoker’s cough ever be considered to confer a health benefit? Further studies are needed and should include full health economic analyses and investigation of alternative hypotheses. Immunomodulatory

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effects and a reduction in systemic cytokine responses have been noted with ACE inhibitors,[4] and improvements in respiratory function with increases in exercise tolerance, perfusion, and gas transfer have been reported.[5] The ACE inhibitor cough has been associated with a genetic variant of the bradykinin B2 receptor promoter,[6] and linkage to other genes that influence susceptibility to infection is a possibility. A better understanding of the pharmacological properties and effects of these widely prescribed drugs is needed before we advise patients to put up with their cough because it may prevent them from getting pneumonia.

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