

The Relationship between Angiotensin Converting Enzyme Inhibitors (ACEIs), Statins and Pneumonia

Anjiotensin Konverting Enzim inhibitörleri (ACEI), Statinler ve Pnömoni Arasındaki İlişki

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Abstract

Özet

Angiotensin converting enzyme inhibitors (ACEIs) and statins have been identified to have possible beneficial effects in the management of pneumonia. ACEIs have been shown to increase cough and reduce dysphagia-two mechanisms that could reduce susceptibility to pneumonia. Studies have found a reduction in pneumonia incidence in those taking ACEIs however overall benefit remains unproven. The reason for this is that studies have only been conducted in those with risk factors requiring ACEI treatment. Statins have multiple cellular effects that could be beneficial in pneumonia. Benefit in animal studies has been shown. While associations between statin use and both reduced pneumonia incidence and better outcomes have been found the results are not consistent between studies and a causal effect has not been proven. Randomised controlled trials in the general population, with pneumonia as an endpoint, are required for both ACEIs and statins to determine whether beneficial effects from such treatments in pneumonia occur.

KEY WORDS: Angiotensin converting enzyme inhibitor, statin, pneumonia

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Anjiotensin konverting enzim inhibitörleri (ACEI) ve statinlerin pnömoni tedavisinde olası yararlı etkilere sahip olduğu belirlenmiştir. ACEI'nin pnömoniyeye yatkınlığı azaltabilen iki mekanizmayı; öksürüğü artırdığı ve disfajiyi azalttığı gösterilmiştir. Çalışmalar, ACEI alanlarda pnömoni insidansında bir azalma olduğunu bulmuşsa da genel yararı kanıtlanmamıştır. Bunun nedeni, çalışmaların sadece ACEI tedavisi gerektiren risk faktörleri olanlarda yapılmış olmasıdır. Statinler pnömonide yararlı olabilecek çoklu hücresel etkilere sahiptir. Hayvan çalışmalarında yararı gösterilmiştir. Statin kullanımı ile hem azalmış pnömoni insidansı hem de daha iyi sonuçlar arasında ilişki bulunduysa da sonuçlar çalışmalar arasında tutarlı değildir ve nedensel bir etki kanıtlanmamıştır. Genel popülasyonda, bir sonlanım noktası pnömoni olan randomize kontrollü çalışmalarda, pnömonide böylesi tedavilerin yararlı etkilerinin olup olmadığını belirlemek için hem ACEI hem de statinler ile yapılacak çalışmalara ihtiyaç vardır.

ANAHTAR SÖZCÜKLER: Anjiotensin konverting enzim inhibitörü, statin, pnömoni

INTRODUCTION

Whether community-acquired, nosocomial or occurring in the immunocompromised, pneumonia is a common condition with a significant morbidity and mortality [1]. Gas exchange correction and fluid balance optimization are important aspects of case management, but by far the most important intervention is antibiotic therapy. This is described in detail in recent international guidelines [2,3]. However despite appropriate therapy patients still die. There is therefore growing interest in non-antibiotic pharmacological interventions for both pneumonia prevention and outcome improvement. Two that have received much recent attention and controversy are ACEIs and statins which are the subject of this short paper.

It is believed that most pneumonia occurs as a result of inhalation or aspiration of upper respiratory tract secretions or droplets contaminated by pathogenic bacteria. The most overt form of this is that which occurs in those with swallowing disorders or gross aspiration events. The healthy lower respiratory tract is defended against such events through an effective cough reflex. Anything that might decrease dysphagia or increase cough may therefore protect against bacterial entry and hence pneumonia. Experimental and clinical evidence suggests that ACEIs can both decrease dysphagia and increase cough, possibly by increase in substance P levels [4], -so is there any evidence to suggest that their use is associated with a lower incidence of pneumonia?

Angiotensin Converting Enzyme Inhibitors (ACEI)

An early, retrospective cohort study in 576 hypertensive adults found a pneumonia incidence of 8.3% in 60 controls on no treatment, 8.9% in those treated with a calcium channel blocker, but only 3.3% in those treated with an ACEI lending credence to the potential beneficial effect of ACEI in pneumonia prevention [4]. The problems with this study are the risk of bias due to intention to treat related to the retrospective design, lack of evidence of objective confirmation of pneumonia

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diagnosis and the limitation of the study to patients with hypertension-problems inherent in most studies on this topic.

A placebo controlled study of ACEI in those with a history of stroke or transient ischaemic attack did not find a significantly reduced pneumonia rate in those treated with ACEI, but interestingly subgroup analysis found a significant pneumonia rate reduction with ACEI compared to placebo in Asian patients which was absent in non-Asian patients [5].

Turning the question around a group of investigators from the Netherlands compared rates of ACEI use in 1108 first hospital admissions for CAP matched with 3817 population-based controls. No protective effect on the occurrence of pneumonia was found in this presumably predominantly non-Asian population [6]. Similar results were found in a US population based case-control study [7]. In a much larger case-control study, again in a predominantly Caucasian population, ACEI use was associated with a significantly reduced pneumonia 30-day mortality compared to those not using these agents. Use of angiotensin receptor blockers (ARBs) was also associated with reduced pneumonia 30-day mortality.

Now a systematic review and meta-analysis has been performed of available studies to try to reconcile the confusing findings from individual studies [8]. The authors of this review were careful to separate pneumonia incidence and pneumonia mortality as separate study endpoints and to investigate the effects of ARBs in addition to ACEIs. 37 studies (18 randomised controlled trials, 11 cohort studies, 2 nested case-control studies and 6 case-control studies) were included in their analysis. Use of ACEIs was associated with a 34% reduction in pneumonia incidence compared with controls with a similar magnitude of effect across studies although study heterogeneity was considerable. An effect was present in non-Asian patients but was greater in Asian patients. ARBs were not associated with any reduction in pneumonia risk. While there also appeared to be a reduction in pneumonia-related mortality in those treated with ACEIs this data was less robust.

Ultimately the potential benefit from ACEIs (and ARBs) remains unproven. All studies have been performed in populations with an indication for ACEI use which introduces bias and means that there is no data on potential benefits for those without an indication for ACEIs. Although a number of RCTs (usually the strongest level of evidence) have been performed all have been directed at an endpoint related to the ACEI indication (eg hypertension, stroke) and none have had pneumonia incidence or mortality as the primary endpoint. Finally pneumonia has been confirmed and defined variably across studies. The answer will only be known when RCTs using pneumonia incidence or mortality as the primary endpoint are performed.

Statins

These drugs are widely used to reduce cardiovascular risk. They act as potent inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) and through this mechanism reduce blood cholesterol levels. This was believed to be the mechanism of cardiovascular benefit. However it has become increasingly apparent that these molecules also pos-

sess anti-inflammatory, immune-modulating and anti-oxidant properties that may play a part in cardiovascular risk reduction, but which may suggest other roles for these agents where infection and inflammation are important.

A reduced incidence of sepsis and intensive care unit admission in those taking statins was found in a study of those admitted to hospital with bacterial infections [9] which has led to interest in whether statin use in pneumonia may improve both incidence and outcomes. In a study of statin-fed mice with experimental *S. pneumoniae* infection simvastatin therapy showed a dose-dependent improvement in bacterial burden, neutrophil infiltration, vascular integrity, and chemokine production in the lung, but no reduction in mortality compared to controls [10].

In man at least two cohort studies [11,12] have shown a reduced 30-day mortality in adults admitted to hospital for community-acquired pneumonia who were prior users of statins. However these and other studies may be biased by the 'healthy user effect' (patients who regularly take statins are likely to be healthier and comply better with other-usually unmeasured - health protective interventions eg influenza vaccination), and bias in case acquisition because of the necessity for cardiovascular risk to be present before a statin has been prescribed.

To try to address this a number of systematic reviews and meta-analyses have been published. The first [13] found benefit from statins but concluded that this could still be due to the 'healthy user effect'. Confusingly two more recent systematic review and meta-analyses found either a beneficial effect from statins in the treatment of pneumonia [14] or no benefit in pneumonia prevention [15]! A more recent systematic review and meta-analysis found benefit from statins both in prevention and treatment of pneumonia. Potential confounding factors, study heterogeneity and risk of publication bias could account for the differing conclusions of these studies which are predominantly based on retrospective research. A more recent systematic review and meta-analysis [16] did find a beneficial effect of statin use in the reduction of pneumonia mortality, but the data quality in the 18 studies included was poor and the same limitations described above still applied.

Just as for ACEIs, randomised controlled trials are required if we are to gain a definitive answer to the question of whether statins prevent pneumonia or reduce its mortality. Until these appear we cannot yet give a recommendation to our patients about whether use of ACEIs or statins will be associated with improved pneumonia outcomes.

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