Respiratory effects of angiotensin converting enzyme inhibition

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Angiotensin converting enzyme (ACE) inhibitors have been available for the treatment of hypertension and heart failure for several years. This class of drugs is generally well accepted by the patient [1], but an unusual, infrequent, and troublesome side-effect, cough, has become apparent. This article reviews this side-effect and also the possibility of other respiratory effects of ACE inhibition.

Cough

The cough associated with administration of ACE inhibitors [2-4] is non-productive and persistent, with an irritating sensation in the throat. It may become worse on lying down and can cause sleep disturbance. The cough often takes several weeks to become apparent, although it may appear within several hours of the first dose or be delayed for many months [5]. This may reflect individual reaction to the drug as well as differential recognition and reporting of the symptom by patients and doctors. It resolves within several days of discontinuing treatment [2]. On rechallenge with an ACE inhibitor the cough returns, sometimes within several hours. Although the cough is not a serious side-effect, failure to recognize it may result in the patient undergoing unnecessary investigations.

Incidence and predisposing factors

Cough has been reported as a side-effect of at least four ACE inhibitors [2-4], and is likely to be a general class effect of these agents. The size of the problem is not known; reported frequency varies from 0.2% [6] to 33% [7]. One of the main difficulties in assessing the frequency of cough has been the lack of recognition of this symptom as a side-effect. Published studies have not therefore sought cough prospectively, but have merely documented spontaneous reports. However, figures from studies including at least 250 patients suggest the incidence of withdrawal of treatment due to cough to be up to 3% for enalapril and captopril [2, 5, 6, 8, 9].

There does not appear to be any relationship between the occurrence of cough and age, drug dose or heart failure [2]. The cough is more frequent in women [2, Rawson and Leman, personal communication] who account for two thirds of reported cases. Nonsmokers also account for a disproportionately high number of withdrawals for cough. In the captopril post-marketing surveillance study, nonsmokers constituted 88% (113 out of 128 patients) of withdrawals, whereas 77% of the 54, 072 patients entered into the study were nonsmokers (E.R. Squibb and Sons Ltd, personal communication). It is possible that either smokers are less susceptible to this side-effect as a result of prior activation of the cough reflex [10] or they do not report change in a pre-existing cough.

Airflow obstruction

ACE inhibitors are likely to be used in patients with airflow obstruction in whom beta-adrenoceptor antagonists are contra-indicated. It is important, therefore, to determine whether ACE inhibitors cause or exacerbate airflow obstruction.

Sixty four patients with hypertension had no deterioration in forced expiratory volume in one second (FEV1) and forced expiratory flow at 25% vital capacity (V25) after two months treatment with enalapril 20 or 40 mg. Patients with reversible airflow obstruction were excluded from this study in view of possible randomization to atenolol [11]. A smaller study in hypertensives also showed no effect on FEV1 [12], and patients with chronic airflow obstruction had a slight improvement in lung function [13]. Several patients who developed wheezing or an exacerbation of pre-existing asthma when given ACE inhibitors have been reported [14–16]. However, adequate control of the asthma in two patients by inhaled steroids allowed the ACE inhibitor to be re-introduced without adverse effects [17]. Other patients with asthma have not developed worsening wheeze or deterioration in spirometric measurements. One study [2], which included four asthmatic patients, noted an increased wheeze in one patient, and wheeze was noted in 2 out of 52 non-asthmatic patients who reported cough, although one of these patients was also taking atenolol. There are insufficient data to assess whether asthmatic patients are any more prone to develop cough on ACE inhibitors than non-asthmatic patients. Apart from individual case reports there is no evidence to suggest that airflow obstruction is caused by ACE inhibitors in either asthmatic or non-asthmatic subjects.

Pathogenesis of cough

Cough as a side-effect of ACE inhibition may be explained by the known pharmacology of these drugs,
but why only a small percentage of patients treated develop this symptom is not clear. There does not appear to be any “cross-sensitivity” for side-effects, for example between cough and angio-oedema. Cough does not appear to be due to the hypotensive or vasodilating effects of ACE inhibitors [12].

Angiotensin converting enzyme inhibition and bradykinin

Angiotensin converting enzyme has effects other than the conversion of angiotensin I to angiotensin II. It is the same enzyme as kininase II which is responsible, particularly in the lung, for the breakdown of bradykinin [18] and other tachykinins such as substance P [19]. Thus, inhibition of ACE would allow accumulation of these substances, providing this was a rate-limiting step in the metabolic pathways. It has been difficult to demonstrate accumulation of such substances in the plasma since their assay is difficult, changes may be small, and plasma concentrations may not be relevant to tissue effects. In support of accumulation of these substances at tissue level, it has been shown that ACE inhibitors augment skin responses to intradermal bradykinin [20] and potentiate substance P-induced salivation [19].

Bradykinin and other tachykinins are relevant to the pathogenesis of cough. Bradykinin stimulates the unmyelinated afferent sensory c-fibres via type J receptors [21] which through a local axon reflex result in the release of tachykinins [22] and consequent influx of inflammatory cells. Excitation of type J receptors by bradykinin [23], or the specific c-fibre stimulant, capsaicin [24, 25], causes a non-productive cough. Cough can be induced by intradermal bradykinin in normal subjects taking ACE inhibitors [20]. In addition to cough, bradykinin inhalation also causes bronchoconstriction in asthmatic patients [23], but neither captopril (in vitro) [23] or ramipril [26] enhanced bradykinin-induced bronchoconstriction. However, the bronchoconstrictor effects of bradykinin may be dissociated from, and therefore not relevant to, the cough reflex.

There is evidence to suggest that ACE inhibitor-induced cough is not quite the same as bradykinin-induced cough, as the former is inhibited by prostaglandin synthetase inhibitors [27], in contrast to the latter which is inhibited by sodium cromoglycate and anticholinergics [23]. Prostaglandins are probably involved.

Angiotensin converting enzyme inhibition and prostaglandins

ACE inhibitors may cause increased prostaglandin production via bradykinin [18]. Prostaglandin E2 (PGE₂) can stimulate the unmyelinated afferent c-fibres and may therefore cause cough [28]. That prostaglandins are important in the mechanism of cough production by ACE inhibitors is suggested by the observation that sulindac, a prostaglandin synthetase inhibitor, inhibited the cough in six patients in whom it was tried [27]. Captopril, unlike other ACE inhibitors, has effects on prostaglandin production independent of its effects through bradykinin [29], and may increase lung concentrations of PGE₁ and prostaglandin F₂α (PGF₂α). However, this direct effect of captopril on prostaglandin production is probably not important in the pathogenesis of cough, as the incidence of cough does not appear to be any greater with captopril than with enalapril and sulindac was as effective in inhibiting cough in patients on captopril as it was in those on enalapril [27].

Neural pathways - the type J receptor

Whereas the exact roles of kinins and prostaglandins in the production of cough are not established, the neural pathway predominantly involved is probably the type J receptor (one of three types of receptor involved in the cough reflex) and the unmyelinated c-fibres forming a local axon reflex. It has been demonstrated that ACE inhibition causes increased sensitivity to inhaled capsaicin, the specific c-fibre stimulant, in patients who cough [24, 25], but whether this also occurs in subjects not affected by cough is not clear [25, 30]. Further evidence for c-fibre afferent involvement with ACE inhibition comes from the observation that the wheal and flare reactions in the skin are potentiated by enalapril [20].

Rapidly adapting “irritant” receptors and bronchial reactivity

Whilst the above mechanisms explain the possible pharmacological basis for cough, they do not explain why a minority of patients are affected. There is evidently some individual susceptibility. The increased incidence of this side-effect in nonsmokers and women does not offer any obvious unifying explanation.

Another group of receptors involved in the cough reflex are the rapidly adapting receptors. Although PGE₁ does not stimulate these receptors, PGE₂, can do so [28] and may be involved in addition to PGE₂. Captopril did not alter the cough response to inhaled citric acid, a potent “irritant” receptor stimulant, in normal subjects [25], but ACE inhibitors increased the cough index in patients affected by ACE inhibitor-induced cough [17].

In addition to cough the rapidly adapting receptors mediate bronchoconstriction, and therefore the role of bronchial reactivity has been investigated. Bucknall et al. [17] found that six patients who coughed had increased bronchial reactivity compared to normal subjects. Bronchial reactivity remained high a year after stopping ACE inhibition suggesting that bronchial hyperreactivity was a predisposing factor. Lindgren [12] found that bronchial reactivity was within the normal range in patients with this side-effect, but that ACE inhibition caused a modest increase in bronchial reactivity. No change in bronchial reactivity on ACE inhibitors was seen in the patient reported in this issue of the Journal [31] and an earlier study found no ACE inhibitor-induced changes in bronchial reactivity in patients who coughed, even in the presence of pre-existing airway obstruction [7]. Carefully controlled assessments of bronchial reactivity...
have not been done in sufficiently large numbers of patients to exclude a small effect or an effect present in only a small percentage of the population. Bronchoconstriction itself can lead to cough, but several studies have shown no adverse effect of ACE inhibition on airflow, even in patients who cough [7, 11, 31].

**Management of cough**

It is important to recognize cough as a possible side-effect of ACE inhibition. If other causes of cough have been excluded, the relationship of cough to the ACE inhibitor should be documented if possible. In some circumstances, it may be desirable to continue treatment. The cough may become less troublesome particularly if the dose of ACE inhibitor is reduced, which may not necessarily lead to loss of therapeutic effect [32]. Some patients may cough less on an alternative ACE inhibitor [31], but whether this is due to a true difference in sensitivity or merely dosage differences is hard to say.

The cough is not responsive to usual cough remedies. The inhaled anticholinergic drug, ipratropium bromide, has been shown to inhibit bradykinin-induced bronchoconstriction [23], but it may not be effective for ACE inhibitor-induced cough [33], and as might be expected [28], beta-agonists have not been helpful [32]. Iralol does not block capsaicin-induced cough [34] and is unlikely to be helpful. Although sulindac prevented ACE inhibitor-induced cough [27], prostaglandin synthetase inhibitors can exacerbate hypertension and heart failure [29]. There is some evidence to suggest that chloroquine (through its alpha,-agonist effects) counteracts the "proinflammatory effects" of ACE inhibition in the skin [12], but its effects on cough have not been reported. Interestingly, inhaled bupivicaine was effective in preventing cough in one patient [33], presumably by blocking the J receptors. The effect of one dose lasted several weeks. Inhaled local anaesthetics can occasionally cause bronchoconstriction, but they may prove useful in selected patients.

**References**