Respiratory effects of angiotensin converting enzyme inhibition

K.E. Berkin*

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 (PGF₂a) 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 produc-
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 true in a 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]. Intal 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 clonidine (through its alpha-agonist effects) counteracts the "pro-inflammatory" effects of ACE inhibition in the skin [12], but its effects on cough have not been reported. Interestingly, inhaled bupivacaine 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