Etiology and Treatment of Angiotensin Converting Enzyme Inhibitor-Induced Cough

Margaret A. Kiesman, Barb Evans and William M. Semchuk

ABSTRACT

Angiotensin-converting enzyme inhibitors (ACEIs) are widely used in the treatment of hypertension and congestive heart failure (CHF). They have also been shown to slow the progression of diabetic nephropathy. In addition, evidence suggests ACEIs may be beneficial in angina and myocardial infarction. Although usually well tolerated, these agents may produce a bothersome cough. The mechanism of ACEI-induced cough remains unclear but has been associated with increased bradykinin and prostaglandin levels, bronchial hyperreactivity, increased sensitivity of the extrathoracic airways and genetic polymorphism. Management principles in ACEI-induced cough are not clear. Treatment often requires discontinuation of the offending agent. This may be relatively simple in the hypertensive patient as many equally efficacious alternative hypertensive agents are available. However, discontinuation of an ACEI may be more difficult in the heart failure patient as these agents decrease morbidity and mortality in this population to a greater extent than the limited number of alternative therapies available. Other options for treating the cough may include dosage reduction or substitution with fosinopril. The addition of a pharmacological agent may also play a role. Bupivacaine, sodium cromoglycate, theophylline, nifedipine, indomethacin, and sulindac have all been utilized with limited success. When adding a pharmacological agent to control the ACEI-induced cough, influence on underlying disease control must be considered. Until large, well designed studies are available, the addition of any agent for the treatment of ACEI-induced cough must be approached with caution.

Key Words: *angiotensin converting enzyme inhibitors, hypertension*

RÉSUMÉ

Les inhibiteurs de l'enzyme de conversion de l'angiotensine (IECA) sont largement utilisés dans le traitement de l'hypertension et de l'insuffisance cardiaque(IC). On a pu également démontrer qu'ils pouvaient ralentir la progression des néphropathies diabétiques. De plus, certaines données laissent croire que les IECA seraient utiles dans l'angine et l'infarctus du myocarde. Bien qu'ils soient généralement bien tolérés, ces agents peuvent provoquer une toux incommodante. On connaît toutefois toujours mal les mécanismes déclencheurs de cette toux, mais on croit qu'ils seraient associés à des taux élevés de bradykinine et de prostaglandines, à une hyperréactivité bronchique, à une hypersensibilité des voies aériennes supérieures ou à un polymorphisme génétique. Malheureusement, il n'existe aucune démarche thérapeutique clairement définie pour le traitement de la toux causée par les IECA. Souvent, la démarche fera appel au retrait du médicament qui cause la toux, ce qui peut être relativement simple chez l'hypertendu, car il existe bon nombre d'autres agents antihypertenseurs tous aussi efficaces. Cependant, chez l'insuffisant cardiaque, le retrait de l'IECA pose une plus grande difficulté parce que ces médicaments diminuent, dans cette population, la morbidité et la mortalité dans une plus large mesure que ne le font les autres médicaments disponibles qui sont en nombre restreint. Parmi les autres mesures thérapeutiques pour traiter une telle toux, on compte la réduction de la dose d'IECA ou la substitution de ces derniers par le fosinopril. L'ajout d'un autre agent pharmacologique pourrait aussi s'avérer utile. En effet, on a eu recours avec un certain succès à la bupivacaïne, au cromoglycate sodique, à la théophylline, à la nifédipine, à l'indométhacine et au sulindac. Lorsqu'on ajoute un autre médicament pour soigner la toux provoquée par les IECA, il faut cependant tenir compte des effets que ces médicaments ont sur le traitement spécifique utilisé contre la maladie sous-jacente. Par conséquent, jusqu'à ce que de grandes études très rigoureuses aient été menées, il faudra user de beaucoup de prudence si l'on décide d'ajouter un autre médicament pour traiter la toux causée par les IECA.

Mots clés : *inhibiteurs de l'enzyme de conversion de l'angiotensine; hypertension.*

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INTRODUCTION

Angiotensin-converting enzyme inhibitors (ACEIs) play an important role in the management of hypertension. They are currently indicated as alternative therapy in uncomplicated hypertensive patients who do not respond to or experience adverse drug reactions from thiazide diuretics, beta blockers, or a combination of the two.[1,2] ACEIs are indicated as first line therapy in the treatment of hypertension in patients with concurrent diabetes or congestive heart failure (CHF).[1,2] They have resulted in a reduction in morbidity and mortality in CHF and have been shown to slow the progression of diabetic nephropathy.[3-6] Preliminary data suggest that ACEIs may play a significant role in the treatment of angina and myocardial infarction.[7]

A bothersome, potentially limiting side effect of ACEIs is cough.[8] Case reports and series have reported alleviation of cough with use of various agents including: indomethacin, sulindac, bupivacaine, sodium cromoglycate, theophylline, and nifedipine. Although these agents may decrease the incidence of cough they may also interfere with the beneficial effects of ACEIs. Large, randomized, controlled trials are necessary to confirm the success rate of these interventions. This article will describe ACEI-induced cough and review the proposed etiologic mechanisms. Pharmacological modalities to alleviate cough and potential implications on disease treatment will also be discussed.

The renin-angiotensin-aldosterone system (RAAS) is a closed loop negative feedback system involved in cardiovascular regulation and maintenance of sodium and fluid hemeostasis. Renin is synthesized and stored in the juxtaglomerular apparatus of the kidney. When released, it enzymatically converts angiotensinogen to angiotensin I(AI). Angiotensin-converting enzyme (ACE), also known as kininase II or bradykinin dehydrogenase, catalyzes the conversion of the biologically inactive AI to the biologically active angiotensin II (AII). AII increases blood pressure (BP) secondary to direct contraction of arterial smooth muscle. In the adrenal gland, AII is a potent stimulus for aldosterone release with resultant sodium retention and expansion of intravascular volume.[9] BP is increased secondary to increased blood volume. AII also stimulates pituitary hormone release and may facilitate sympathetic nervous system (SNS) transmission.[10,11]

In summary, overactivity of the RAAS results in an increased systemic vascular resistance (SVR) secondary to increased AII levels and SNS stimulation. AII mediated increases in aldosterone lead to sodium and water retention with a resultant modest increase in preload. The final consequence is an increase in BP in susceptible patients.

ACEIs work by blocking the conversion of AI to AII through competitive inhibition of ACE. Sodium and water retention are decreased by the subsequent prevention of aldosterone stimulation and inhibition of AII and SNS mediated increases in SVR. This class of agents is thereby capable of lowering blood pressure primarily through a decrease in SVR and intravascular fluid volume.

ACEIs have been shown to improve hemodynamic status, enhance diuresis, reduce symptoms and prolong the survival of CHF patients.[12] This is the result of blocking the conversion of AI to AII in the serum as well as at local tissue sites, such as the vascular endothelium. ACEIs will acutely improve cardiac function by causing systemic vasodilation. Consequently, cardiac output increases and cardiac filling pressure decreases. There is a decrease in afterload and preload and a reduction in ventricular diastolic volume and wall stress which favorably alters myocardial oxygen balance and peripheral tissue perfusion. The acute hemodynamic effects of ACEIs coincide with the acute inhibition of the circulating system while the long-term effects appear to be related to the inhibition of tissue ACE, especially in the vasculature and the kidney. In addition, ACEIs may reduce the sympathetic outflow as well as release of other neurohumoral factors reducing the stress on the failing heart.[13]

ACEI have become popular due to their efficacy and low incidence of side effects. Side effects attributed to ACE inhibition include symptomatic hypotension, mild gastrointestinal effects, angioedema, fatigue, headache, and hyperkalemia. Renal dysfunction may occur in patients with bilateral renal artery stenosis, renal artery stenosis of a solitary kidney or severe glomerulonephritis. Side effects, initially believed to be related to the sulfhydryl group in captopril, including skin rash, taste disturbances and rarely neutropenia, have subsequently been reported with all ACEIs.[14]

Cough is the most common and troublesome side effect of ACEIs with reported incidence rates varying from 0.5 - 39% [Table I]. It ranges in severity from mild and infrequent to a continuous, incapacitating cough which interferes with routine daily activities and/or sleep.[15-18] Onset can occur within days to weeks of therapy initiation; a delayed onset (up to 12 months) has rarely been reported. The cough is often preceded by a tickling sensation in the back of the throat which progresses to a dry, non-productive cough that may be more bothersome at night or in the supine position.[19-21] The cough usually disappears within one to four days (no longer than four weeks) following discontinuation of therapy.[22] Studies have shown a higher incidence of cough in women and non-smokers

Table I: Incidence of Cough with Angiotensin-Converting Enzyme Inhibitor Therapy.

Angiotensin-Converting Enzyme Inhibitor	†Incidence of Cough (%)[18]
Captopril	5-37
Enalapril	1-39
Benazepril	6
Cilazapril	37
Delapril	1
Fosinopril	2
Lisinopril	3-9
Perindopril	3
Quinapril	2
Ramipril	8-30

†Data were extracted from a number of studies and product literature and, therefore, are not comparative.

taking ACEI.[20,23-25] Agents with a longer duration of action may also be associated with a higher incidence of cough.[23]

Proposed Mechanisms of Cough

Although the exact etiology of ACEI-induced cough remains unclear, several potential mechanisms including increased bradykinin and prostaglandins, bronchial hyper-reactivity, increased sensitivity of the extrathoracic airways and genetic polymorphism of the ACE gene have been proposed.

ACEI blocks the conversion of AI to AII and results in accumulation of tachykinins including substance P, a potent bronchoconstrictor. C-fibre nerves which contain substance P, are located in the human lung and upper respiratory tract beneath the respiratory epithelium of the trachea and major bronchi. When ACE is inhibited, local substance P concentrations increase and may be responsible for induction of the cough secondary to afferent sensory C-fibre stimulation.[18,26] All studies do not support this theory; Thysell et al[27] found no statistically significant rise in serum concentration of substance P following administration of enalapril to 22 hypertensive subjects. However, serum concentrations of substance P may not reflect local substance P concentrations.

Bradykinins, normally degraded by ACE, accumulate in lung tissue as a result of ACEI. Inhaled bradykinin has resulted in pulmonary irritation, bronchospasm, edema and cough in susceptible individuals. Bradykinin also stimulates the afferent sensory C-fibres resulting in further release of tachykinins and an influx of inflammatory mediators. In addition, bradykinin stimulates phospholipase A_2 resulting in an increase in prostaglandin (PGE_2) and leukotriene synthesis and histamine release. PGE_2 can also stimulate afferent sensory C-fibres. This theory is supported by earlier studies with prostaglandin synthetase inhibitors and their reported efficacy in alleviating cough. A number of studies have addressed the role of bradykinin with conflicting results.[8,18,26] Many suggest there is no major role for kinins in ACEI-induced cough.

Laryngeal and pharyngeal mucosa are very rich in C-fibre receptors. ACEIs may produce cough by increasing the sensitivity of receptors in the extrathoracic airways. Bucca et al[28] found a strong association with increased extrathoracic hyper-responsiveness to inhaled histamine in individuals on captopril with cough. These abnormalities were not identified in asymptomatic individuals on captopril.

The existence of bronchial hyper-reactivity in patients who cough after receiving an ACEI remains controversial. Hinojosa et al[29] established a clear-cut relationship between initiation of captopril therapy and development of cough and bronchial hyperreactivity in two siblings. However, bronchial hyperreactivity may have been present prior to drug treatment. Bucknall et al[30] noted that patients who cough after ACE treatment show persistent bronchial hyperreactivity at one year follow-up. Conversely, long-term administration of captopril to 15 hypertensive patients with asthma did not alter their sensitivity to methacholine as defined by the dose that resulted in a 20% fall in the forced expiratory volume.[31] Boulet et al[31] reported that the development of cough was not associated with bronchial hyper-responsiveness. Similarly, Overlack et al[8] indicated that the role of bronchial hyper-reactivity remains doubtful as cough or broncho-constriction could not be observed in asthmatic patients. Larger studies are necessary before commenting on the role of bronchial hyper-reactivity in ACEI-induced cough.

Genetic polymorphism of the ACE gene could also be implicated in ACEI-induced cough.[32] Rigat et al[33] described a polymorphism for the ACE gene. Allele frequencies were 0.4 for the longer allele and 0.6 for the shorter allele of the gene for ACE. Approximately 16% of the population are homozygous for the longer allele; these individuals have decreased serum concentrations of ACE. This percentage is similar to the reported prevalence of a persistent dry cough among ACEI users thus, a correlation may exist between the two (i.e., the population homozygous for the longer allele ACE gene may be at increased risk of cough). Genotyping patients

with the ACEI-induced cough would confirm or refute this theory.

Several mechanisms for the cough have been proposed. Although understanding of the mechanism is unclear, a combination of the above factors may be responsible.

Management

A number of anecdotal reports and small studies of the efficacy of various agents in the treatment of the ACEI-induced cough have appeared in the literature. A patient may first seek treatment with non prescription cough suppressants, including dextromethorphan. However, these agents do not suppress or alleviate the cough.[18,21]

Initial treatment for ACEI-induced cough may include a reduction in the ACEI dose.[34-36] Case reports suggest this may reduce or alleviate the cough in a small subgroup of patients, however, close monitoring of blood pressure and CHF symptomatology is mandatory. When dosage reduction is unsuccessful, discontinuation of the ACEI may be necessary.[34-39] Although no firm recommendations for methods to reduce the dose exist, decreases in dose should be gradual and individualized.

Switching to an alternate ACEI (captopril to enalapril) resulted in alleviation of cough in one case report.[40] However, most other literature contradicts this report, stating that selecting an alternative ACEI does not help when comparable therapeutic endpoints are achieved.[19,36,40]

Two recent reports in the literature suggested that a change to fosinopril would result in significant improvement in the cough symptom profile. Germino et al[41] studied the effect of switching hypertensive patients with an ACEI-induced cough to fosinopril therapy for six weeks. After six weeks of fosinopril therapy, there was a significant decrease in both cough severity and frequency; seven of the twenty-four patients reported complete resolution of the cough. During this time, there was no statistically significant difference in blood pressure, heart rate, or respiratory rate when compared to baseline. Sharfit et al[42] reported a case of a 68 year-old woman who developed a dry irritating cough within one month of starting quinapril therapy. One month after changing to fosinopril therapy, the patient reported resolution of the cough. Possible difference in tissue binding or elimination of fosinopril, compared to the other ACEIs, may explain this phenomenon. Further studies are necessary to address this issue.

An alternative to the discontinuation of the ACEI is to use nebulized bupivacaine 0.5% (3mL), a local anesthetic that is proposed to work by blocking sensory receptors that initiate the cough. A single case report by Brown et al[43] reported complete cessation of cough after a single inhalation of nebulized bupivacaine in a 73 year-old male, post-myocardial infarct, with a severe captopril-induced cough. The cough was controlled for five to six weeks after each nebulized treatment. Limitations with nebulized bupivacaine include bronchospasm and the loss of the swallowing reflex for four hours post inhalation. Therefore, bupivacaine should only be considered for use in an ACEI dependent hospitalized patient.

The efficacy of sodium cromoglycate in treating ACEI-induced cough has been described. A 35 year-old man with cardiac failure was treated with 10 mg sodium cromoglycate twice daily by inhalation to treat his severe ACEI-induced cough. The cough improved after one week with complete resolution at 12 weeks.[44] Aldis et al [45] used a trial of cromolyn inhaler in usual dosage in six CHF patients with severe ACEI-induced cough. After two weeks of therapy, three patients had complete remission of cough and two reported greater than 90% improvement which allowed them to continue with ACEI therapy. The single patient who did not improve experienced immediate relief when the enalapril was discontinued. Keogh[46] also reported resolution of cough after prescribing a sodium cromoglycate inhaler, two puffs three times a day, in a 63 year-old male with CHF who required an ACEI but found the cough intolerable.

Theophylline may have a potential role in the treatment of ACEI-induced cough. Pomari et al[47] reported, after one week's treatment with theophylline (Theodur™) in four female hypertensive patients, complete remission of clinical symptoms of cough and return to basal ventilatory patterns. These results support the hypothesis that ACEIs cause epithelial inflammatory reactions even in patients with no previous history of respiratory disorders. Mean plasma theophylline concentrations were 8.8 ± 1.3 ug/mL.

Fogari et al[48] demonstrated that indomethacin and to a lesser extent nifedipine reduced both the intensity and incidence of captopril-induced cough. The proposed mechanism for both agents is inhibition of PG synthesis. Despite the favourable effect of indomethacin on cough, consideration must be given to the potential deleterious effect of an NSAID on blood pressure control. This issue is unclear as a recent meta-analysis of the effects of NSAIDs on blood pressure revealed that NSAID use induced virtually no change in blood pressure among normotensive individuals.[49] In hypertensive subjects, indomethacin and naproxen caused average increases in blood pressure of 3.6 to 6 mmHg depending on concurrent intake of dietary sodium. Other NSAIDs were noted to have no measurable effect on blood pressure. There is also the possibility of significant nephrotoxicity when using ACEIs and NSAIDs in those patients with concomitant conditions that predispose them to renal compromise.[50] Since NSAIDs are capable of reducing the hypotensive effects of

ACEIs and causing nephrotoxicity, NSAID therapy is not advocated until further well designed studies supporting their use are completed. An additional benefit in using nifedipine would be potential ACEI dose reduction due to additive pharmacodynamic effects, however polypharmacy is not optimal.[51] Nifedipine may be a more likely alternative in the hypertensive population as it is an effective vasodilator. Nifedipine use cannot be endorsed in patient's with congestive heart failure due to its negative inotropic effects.

Sulindac has also been studied for the treatment of ACEI-induced cough. It has demonstrated a reduction in the cough symptomatology and associated increase in cough reflex sensitivity. Nicholls et al[52] utilized 100mg of sulindac twice daily in six patients with chronic debilitating cough due to ACEI. Five patients experienced cough remission while the sixth patient only coughed one to two hours before each dose of sulindac. McEwan et al[53] in a double-blind, randomized, small cross-over study found that 200mg/day of sulindac significantly decreased the cough score. As well, no changes in blood pressure control in the hypertensive patients were noted which would make sulindac a better choice than indomethacin and other NSAIDs. Gilchrist[54] studied the effect of sulindac (100 mg twice daily) on ACEI-induced cough in eight hypertensive subjects in a randomized, placebo-controlled, double-blind, cross-over trial. Sulindac was found to be effective in some patients in decreasing ACEI-induced cough but overall no significant improvement in cough or well-being was noted. Before sulindac can be uniformally recommended, more information is required pertaining to the effects of sulindac on blood pressure, cardiac and renal function, and electrolyte balance in those patients concurrently receiving ACEIs.

In conclusion, ACEI's Achilles' heel continues to be an elusive, dry, nonproductive cough. These effective agents often have to be discontinued due to this bothersome side effect. In a hypertensive patient, a number of alternative pharmacologic classes of antihypertensives exist. Unfortunately, the situation is more serious in the ACEI dependent patient with CHF. Other therapies may not be as effective, and thus, it is essential to address possible ways to alleviate the cough. Treatment with antitussives and cough suppressants is ineffective. Initial treatment considerations should include dosage reduction, where possible, or substitution with an alternative ACEI. Preliminary reports with fosinopril indicate it may show promise as a substitute agent although it is not formally approved for use in CHF.

When the above measures fail and it is essential to continue the ACE inhibitor, consideration should be given to prescribing adjunctive therapy. It is important to note that no treatments have achieved overwhelming success in alleviating the ACEI-induced cough. Larger trials in patients with confirmed ACEI-induced cough are necessary to determine the success rate of many of these proposed therapies before any firm recommendations can be made. Small studies and anecdotal reports have suggested that cautious use of indomethacin, sulindac, bupivacaine, sodium cromoglycate, theophylline, and nifedipine may have efficacy in alleviating or decreasing cough severity. However, most of these agents were not studied in patients with CHF and may, in fact, be detrimental to CHF control. When it is essential to continue treatment with an ACEI, a cautious, common-sense approach to adjunctive drug selection is warranted. Sodium cromoglycate, a relatively innocuous agent, has shown efficacy in suppressing and alleviating the cough in CHF patients and should be tried first. Although anecdotal evidence suggests that NSAIDS may be beneficial in alleviating ACEI-induced cough, the potential for a serious pharmacodynamic drug interaction between ACEI and NSAIDs exists. Thus each case must be approached on an individual basis. Nifedipine should be avoided in the CHF population. With the addition of any drug, close monitoring of the patient during the first several weeks of therapy is essential. Prior to prescribing any agent, risk versus benefit in the individual patient must be carefully considered.

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