Effects of enalapril and imidapril in the capsaicin cough challenge test and spirometry parameters in healthy volunteers

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Background: Angiotensin-converting enzyme inhibitors are highly effective, well-tolerated drugs, but are associated with respiratory adverse effects such as cough and wheezing. **Objectives:** In this double-blind, randomized, two-way crossover study, the effects of two angiotensin-converting enzyme inhibitors, enalapril and imidapril, in the capsaicin cough challenge test and spirometry parameters were investigated. **Methods:** The study involved two sequential 21-day periods separated by a 7-day washout period. In each period, volunteers received a once-daily oral dose of placebo during the first 7 days, imidapril 5 mg or enalapril 10 mg from days 8 to 14, and imidapril 10 mg or enalapril 20 mg from days 15 to 21. Cough challenge was performed at baseline and at the end of each week of treatment. Spirometry was performed before and immediately after the capsaicin challenge. Fourteen healthy subjects were enrolled, but one was withdrawn while taking enalapril due to dry cough. **Results:** Neither enalapril nor imidapril significantly altered the capsaicin cough threshold. A small but significant reduction in forced expiratory volume in 1 sec and forced vital capacity was demonstrated after treatment with enalapril ($p = 0.017$ and $p = 0.018$, respectively), but not with imidapril. Capsaicin cough challenge was not associated with bronchospasm. **Conclusion:** Studies in asthmatics are needed to assess the clinical relevance of these data.

Keywords: capsaicin, cough, enalapril, healthy volunteers, imidapril, spirometry

Angiotensin-converting enzyme (ACE) inhibitors are used largely alone or in combination with other antihypertensive drugs in the treatment of hypertension, congestive heart failure, left ventricular dysfunction, myocardial infarction and diabetic nephropathy [1]. Inhibition of ACE decreases the concentrations of angiotensin II, a potent vasoconstrictor, and consequently reduces blood pressure (BP). As ACE also degrades the vasodilator bradykinin, ACE inhibitors may increase the levels of bradykinin in plasma or tissues. A dry and usually persistent cough is the most common adverse effect of ACE inhibitors and is a major reason for therapy discontinuation [2]. It has been hypothesized that the underlying mechanism of ACE inhibitor-induced cough could be the accumulation of bradykinin in the respiratory tissues [3]. Bradykinin stimulates unmyelinated afferent sensory C fibers by type J receptors involved in the cough reflex. Substance P, also degraded by ACE, is similarly implicated. Since it is a neurotransmitter for afferent sensory nerves, specifically C fibers, inhibition of ACE enhances its effects [4]. Prostaglandin E synthesis is induced by bradykinin and substance P and may mediate their bronchoconstrictive effects [5]. Limited data suggest that thromboxane A_2, a potent vasoconstrictor, may also be involved in facilitating the effects of bronchoconstrictive substances [6].

The ability of different ACE inhibitors to induce dry cough may vary. The incidence of cough in clinical trials reported in the literature ranges between values as low as 0.9% with imidapril, 7.0% with enalapril, 10.2% with ramipril and can rise as high as 15 or 25% with captopril [7,8]. Differences were also found in animal studies where it has been demonstrated that a cough response was reported less frequently with imidapril than enalapril or captopril when guinea pigs underwent citric acid and capsaicin-induced cough tests [3]. Reasons for such discrepancies in the incidence of cough are not clearly apparent. Possible explanations may include a different ability for inducing accumulation of tussigenic substances in the respiratory tissues or substances that may decrease the cough threshold to other tussigenic stimuli. In our present study, the hypothesis that ACE inhibition could change the cough threshold to inhaled capsaicin in a cough challenge test is explored.

Capsaicin (8-methyl-*N*-vanillyl-6-nonenamide) is the pungent extract of red (capsicum) pepper. At low concentrations, this vanilloid acts by opening a nonselective cation channel on the afferent

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neurons of the unmyelinated nerve C fibers, resulting in a flow of calcium and sodium down their concentration gradient. When inhaled, it produces concentration-dependent and reproducible cough and is safe and easy to use [9]. Cough challenge with capsaicin has been used in patients with interstitial lung disease, asthma and chronic obstructive pulmonary disease (COPD) without major safety concerns [10,11]. It has been proposed that cough receptor sensitivity may not be directly influenced by bronchoconstriction and that capsaicin can be safely used in patients with a diminished forced expiratory volume in one second (FEV_1) [12], however, the specific problem of capsaicin-induced bronchoconstriction is seldom addressed.

Studies attempting to elucidate for the effect of ACE inhibitors in patients with bronchial asthma or COPD demonstrate either no change or a slight improvement in lung function [2]. However, there are a few published cases reporting exacerbation of asthma symptoms during treatment with ACE inhibitors [13,14].

Enalapril and captopril are the most frequently used ACE inhibitors in comparative studies of efficacy and tolerability with new drugs. Enalapril is widely used worldwide; for example, in the USA, enalapril and lisinopril are ranked highest in the sales list of all prescription ACE inhibitors [101]. For these reasons, enalapril was chosen as a comparator in the present study, where we have investigated the

- Effects of two ACE inhibitors – enalapril and imidapril – in the capsaicin cough challenge test
- Effect of ACE inhibition by enalapril and imidapril in the spirometry parameters
- Effects of inhaled capsaicin in the spirometry parameters in healthy volunteers

Materials & methods

Study design

This study was conducted at a single center – Human Pharmacology Unit, Department of Research and Development, Bial, S Mamede do Coronado, Portugal. The study was performed according to the Declaration of Helsinki. An Independent Ethics Committee revised and approved the study protocol and the information provided to the volunteers. Subjects' written informed consent was obtained prior to enrolment in the study.

This was a double-blind, randomized, two-way crossover study in 14 healthy adult volunteers. It involved two sequential 21-day treatment periods separated by a 7-day washout period. In each period, volunteers received:

- Day 1 to 7: placebo, once daily
- Day 8 to 14: imidapril 5 mg or enalapril 10 mg, once daily
- Day 15 to 21: imidapril 10 mg or enalapril 20 mg, once daily

Product administration was supervised by a member of the clinical staff. For such purpose, subjects attended the research facilities daily in the morning. Heart rate, BP and adverse events were monitored before drug administration. Capsaicin cough challenge test and spirometry were performed at day 1 (before the first placebo dose), day 8 (before the first ACE inhibitor dose) and day 22 (after the last ACE inhibitor dose) of each period (**Figure 1**).

Subjects were assigned to a treatment sequence according to a randomization table generated by a computer.

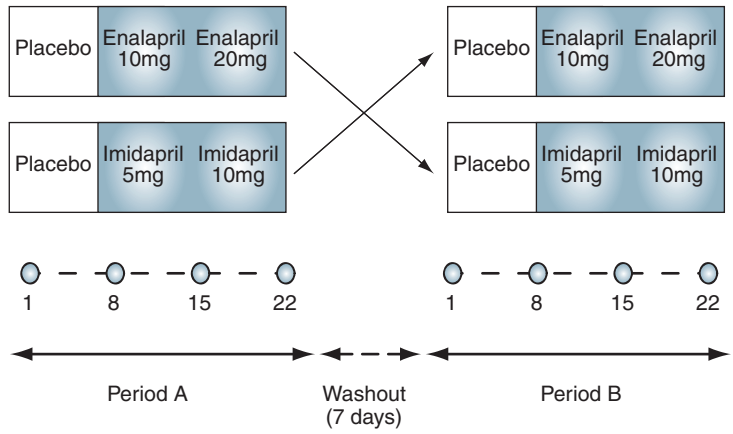
Study population

Healthy male or female volunteers aged between 18 and 35 years were enrolled. At the screening visit, subjects should comply with the following criteria: FEV_1 and forced vital capacity (FVC) greater than or equal to 80% of the predicted value for gender, age, height and weight; evidence of a cough response after capsaicin challenge, absence of response after inhalation of physiologic saline and evidence of good tolerability to capsaicin cough challenge. Subjects with evidence of drug addiction, smokers or ex-smokers, history of abnormal drug reactions or drug allergies, history of bronchial asthma or other chronic respiratory or allergic diseases, history of respiratory symptoms in the previous 4 weeks, history of hypersensitivity or any other contraindication to ACE inhibitors and who received any medication within 1 week prior to the study were excluded from participation.

Capsaicin cough challenge test

A 0.01 M capsaicin stock solution was prepared by dissolving 30.5 mg of capsaicin in 1 ml of ethanol, 1 ml of polyoxyethylene sorbitan (Tween 80) and 8 ml of physiologic saline solution. This solution was stored at -20°C and further diluted with physiologic saline to make serial doubling capsaicin concentration solutions ranging from 0.49 to 1000 µM (0.49, 0.98, 1.95, 3.9, 7.8, 15.6, 31.2, 62.5, 125, 250, 500 and 1000 µM). Fresh dilutions were prepared on each testing day. Before use, capsaicin solutions were warmed at 35°C. Inhalation occurred through the mouth and with the nose

Figure 1. Study scheme.



Capsaicin cough challenge test and spirometry were performed at day 1 (before the first placebo dose), day 8 (before the first ACE inhibitor dose) and day 22 (after the last ACE inhibitor dose) of each period.

clipped, from a compressed-air-driven nebulizer controlled by a dosimeter Spira™ Elektro 2 (SensorMedics).

Each cough challenge test commenced with the inhalation of a control physiologic saline solution. Subjects then inhaled capsaicin solutions in ascending concentrations, with breaths of saline randomly interspersed to increase blindness, until a concentration inducing five or more coughs (C_5) was reached. The duration of aerosol delivery was set at 1.4 s, thereby providing 21 µL of each capsaicin concentration solution. The number of coughs in response to each concentration during the 1-min period immediately after each inhalation was recorded by both direct observation of a clinical staff member and with a microphone connected to a computer. Volunteers were unaware that the end point of the study was the number of induced coughs. If five or more coughs were not achieved, then C_5 was denoted as the maximum concentration of capsaicin inhaled.

Spirometry

Spirometry was performed before the cough challenge test and immediately after (less than 1 min) reaching C_5 in the capsaicin challenge test. A standard portable spirometer MicroLab™ 3500 (Micro Medical) was used. The best of three measurements of FEV_1 and FVC was considered [15].

Statistical considerations

The primary analysis consisted of comparing the capsaicin challenge test results obtained with enalapril and imidapril in relation to placebo. Assuming a standard deviation (SD) in C_5 of 0.2, a sample size of 12 is enough to detect differences of at least 0.03 µM in geometric means of C_5 for enalapril and imidapril, with a power of 80% at a significance level of 5%.

Secondary analysis consisted of comparing mean FEV_1 and FVC (determined before capsaicin challenge) before and after ACE inhibitor treatment and looking for differences between treatments. Spirometry results were also compared before and after capsaicin challenge test.

Only volunteers who completed the study were considered in the analysis. The statistical significance was defined at the 5% level. Parametric tests (paired two-tailed Student's t test) were applied in normal and constantly distributed variables. Where appropriate, 95% confidence intervals (CI) for the differences between the group means were calculated.

Descriptive analysis included, in the case of continuous variables, number, minimum, maximum, mean, and SD. Tolerability data were evaluated descriptively.

Results

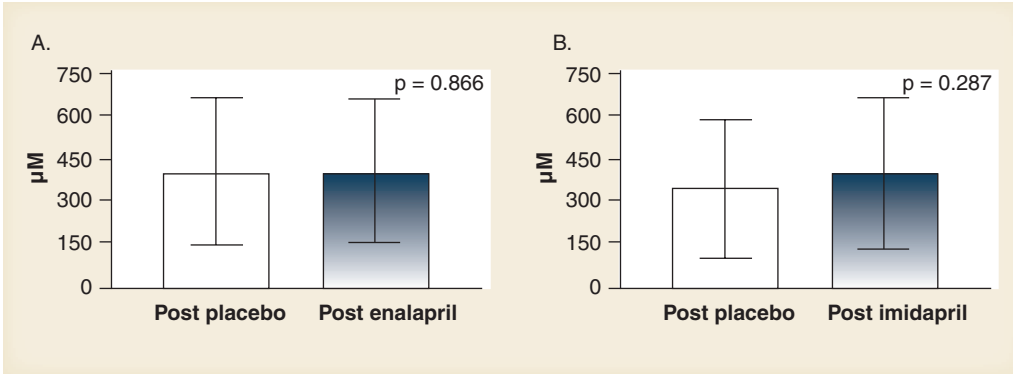
A total of 14 Caucasian volunteers were enrolled, however, one female was prematurely withdrawn due to severe dry cough. A total of five males and eight females, with a mean age of 22.7 ± 3.2 (range 18–29) years, a mean weight of 64.5 ± 8.3 (50–77) kgs, and a mean height of 169.6 ± 8.1 (160–184) cms, completed the study. A total of 78 capsaicin challenge tests and 156 spirometric evaluations were performed in these 13 volunteers.

Capsaicin cough challenge test following treatment with ACE inhibitors versus placebo

As shown in **Figure 2**, no statistically significant differences were found between enalapril or imidapril in relation to placebo (enalapril: C_5 = 403.2 ± 435.3 µM and C_5 = 398.4 ± 425.4 µM) following placebo and ACE inhibitor treatment, respectively (95% CI from -55.86–65.47, p = 0.866); imidapril: C_5 = 348.5 ± 395.1 µM and C5 = 399.6 ± 435.6 µM, respectively (95% CI from -151.0–48.83, p = 0.287)] nor between enalapril and imidapril (95% CI from -180.0–182.0, p = 0.989).

When the results with both enalapril and imidapril were plotted, the mean C_5 were 375.9 ± 408.2 µM and 399.0 ± 421.9 µM after placebo and ACE inhibitor, respectively. Treatment with ACE inhibitors did not significantly affect the cough challenge test in relation to placebo (95% CI from -78.48–32.21, p = 0.397).

Figure 2. Differences between enalapril or imidapril in relation to placebo following placebo and ACE-inhibitor treatment.



Mean and 95% confidence intervals of capsaicin concentration necessary to elicit five or more coughs (C_5) after placebo and treatment with enalapril **(A)** and imidapril **(B)**.

Spirometry following treatment with ACE inhibitors versus placebo

A small but significant reduction in FEV_1 and FVC was demonstrated after treatment with enalapril compared with the postplacebo results (95% CI from 0.013–0.111, p = 0.017; 95% CI from 0.015–0.134, p = 0.018 respectively). This effect was not observed with imidapril (95% CI from -0.039–0.089, p = 0.401; 95% CI from -0.090–0.078, p = 0.876 respectively) (**Tabl 1**). These changes in spirometric results were not followed by respiratory symptoms.

Effect of capsaicin inhalation on spirometry results

The mean FEV_1 prior to capsaicin challenge was 3.86 ± 0.67 L, ranging from 2.70 to 5.06 L. Immediately after capsaicin challenge, mean FEV_1 was 3.84 ± 0.65 L, ranging from 2.56 to 5.05 L (95% CI from -0.001–0.043, p = 0.060). The mean FVC before capsaicin challenge was 4.21 ± 0.72 L, ranging from 3.17 to 5.58 L. After capsaicin challenge, the mean FVC was 4.23 ± 0.75, ranging from 3.06 to 5.89 (95% CI from -0.052–0.010, p = 0.181) (**Figure 3**).

Tolerability

From a total of 40 adverse events reported (20 in enalapril group and 20 in imidapril group), 19 were considered as not related or unlikely to be related with treatement (12 in the enalapril group and 7 in the imidapril group). All but one were primarily transient in duration, of mild-to-moderate intensity and resolved without any sequelae or need for drug treatment. The most reported adverse events were cough (two in enalapril and one in imidapril), headache (two in enalapril), dizziness (two in imidapril), asthenia, somnolence and insomnia (one in each group). One subject discontinued the trial due to intolerable dry cough. This symptom started under imidapril medication (in period A), was initially well tolerated, disappeared during the washout period and restarted again with enalapril (period B), with progressive worsening to the point of subject discontinuation. The cough resolved spontaneously after discontinuation. As expected, both products reduced BP but within levels considered to be safe to subjects.

Discussion

ACE inhibitors have been used in the treatment of hypertension and congestive heart failure since 1977 when captopril, the first orally active ACE inhibitor, was introduced [16]. Apart from arterial hypertension where ACE inhibitors are recommended as first-line therapy by current guidelines [17], they are also recommended in several conditions. However, ACE inhibitors are associated with a dry, dose-independent, nonproductive cough with an incidence that has been reported to be as low as 0.9 to 2.9% with imidapril and as high as 15 to 25% with captopril [2,7].

Other adverse reactions that have been reported include increased bronchial obstruction in asthmatics and increased airway hyper-reactivity, however, there are also reports suggesting that ACE inhibitors are not associated with lung function impairment [18–22]. In a retrospective cohort study, the relative risk of bronchospasm as an adverse reaction was higher for a patient on an ACE inhibitor compared with a patient on a lipid-lowering drug [21]. It had been demonstrated previously that

Table 1. Mean FEV_1 and FVC results after placebo and after enalapril or imidapril treatment.

	Enalapril group			Imidapril group		
	Placebo	*Enalapril*	*95% CI*	*Placebo*	*Imidapril*	*95% CI*
FEV_1	3.86	3.80	0.013–0.111	3.88	3.85	-0.039–0.089
Mean (SD)	(0.67)	(0.67)	(p = 0.017)	(0.68)	(0.69)	(p = 0.40)
FVC	4.26	4.19	0.015–0.134	4.20	4.20	-0.090–0.078
Mean (SD)	(0.69)	(0.71)	(p = 0.018)	(0.81)	(0.77)	(p = 0.88)

CI: Confidence interval; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; SD: Standard deviation.

in patients who developed cough as an adverse effect, enalapril could be also associated with an increase in the bronchial reactivity to histamine, in contrast with ramipril and cilazapril [18,22].

Some possible mechanisms have been postulated to explain ACE inhibitor-induced cough and bronchospasm [2]

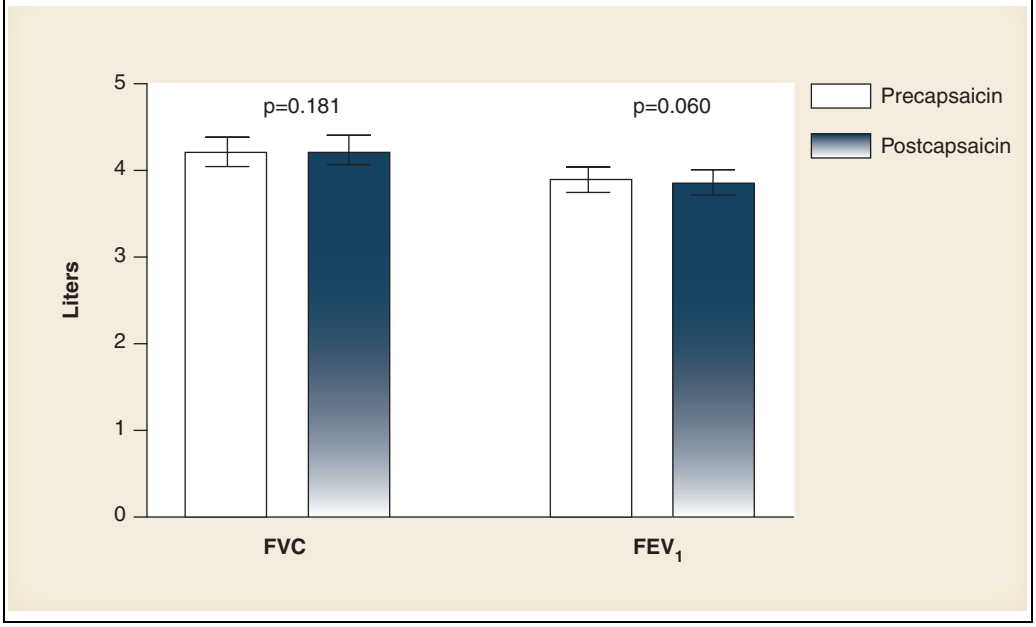
- Release of substance P by C fiber receptors in the respiratory tract. Substance P is a potent bronchoconstrictor, it is degraded by ACE and its action is potentiated by ACE inhibitors
- Accumulation of kinins during treatment with an ACE inhibitor. ACE (kininase II) breaks down bradykinin and other peptides participating in inflammation. Inhalation of bradykinin is associated with cough, throat irritation and bronchospasm in healthy subjects and asthmatics
- The association of the two previous mechanisms: both bradykinin and substance P enhance the formation of prostaglandins and stimulation of C fibers by prostaglandin E_2 resulting in cough
- The genetic mechanism – there is evidence of a polymorphism in the gene for ACE and the population who are homozygous for the longer allele have lower serum ACE levels – this may lead to increased levels of bradykinin, prostaglandins and substance P

Enalapril was the second ACE inhibitor to be developed. It was introduced in the 1980's and was the first to be administered orally once daily. It is effective in lowering BP in all grades of essential and renovascular hypertension. Enalapril is at least as effective as other established and newer ACE inhibitors and members of other antihypertensive drug classes [23].

Imidapril hydrochloride, one of the most recently developed ACE inhibitors, is a long-acting drug developed by Tanabe-Seiyaku Co. Ltd, Japan. It is a prodrug and acts after being hydrolyzed *in vivo* and converted to a diacid metabolite, imidaprilat. The ACE inhibitory activity of imidaprilat in human serum is about twice that of enalaprilat (the active metabolite of enalapril) and about ten times that of captopril [7]. In human comparative clinical trials, a lower drug-related cough incidence with imidapril when compared with enalapril has been reported [7]. One possible explanation for the difference in cough induction by imidapril and enalapril relies on the different potencies of ACE inhibitors in inhibiting the hydrolysis of bradykinin and angiotensin I [8]. ACE is a zinc metallopeptidase that converts the inactive angiotensin (angiotensin I) to the vasopressor and aldosterone-stimulating angiotensin II and also degrades bradykinin, a vasodilatory nonpeptide that has been implicated in inflammatory responses [24]. Sasaguri and colleagues have demonstrated that ACE inhibitors have different potencies in targeting angiotensin I and bradykinin and drugs like imidapril may preferentially inhibit angiotensin I conversion, drugs such as ramipril may preferentially inhibit bradykinin breakdown and drugs such as enalapril and captopril are included in a combined or intermediate group [8]. The reduced inhibition of bradykinin breakdown exhibited by imidapril may explain the disappearance or improvement of cough demonstrated in 70% of patients who reported cough with enalapril and were switched to imidapril [25].

In our study, neither imidapril nor enalapril significantly changed the cough threshold to capsaicin. After treatment with imidapril, the mean C_5 increased 14.6% versus a decrease of 1.1% after enalapril, but the differences from baseline did not attain statistical significance. Two of the reference studies to evaluate the influence of ACE inhibitors in the cough challenge reported a significant decrease in the capsaicin cough challenge threshold with captopril and enalapril [26,27]. The influence of several drugs in the cough reflex sensitivity along time

Figure 3. Mean and 95% confidence intervals of forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) pre- and postcapsaicin inhalation test.



was evaluated before by other authors through capsaicin cough threshold [28–30]. Changes in C_5 vary between a 3.6% increase with zafirlukast and 51.6% with baclofen. These results are not unexpected as baclofen has an antitussive effect via a central mechanism [28] and leukotriene antagonists are not intended to treat cough [30]. In all these trials, as expected, placebo did not affect cough threshold. An ACE inhibitor, cilazapril, administered to healthy subjects with genotype II of the ACE gene caused a decrease of 24% in the cough threshold, while the same treatment increased the cough threshold by 3.3% in subjects with the genotype DD [31]. In contrast, McGarvey and colleagues concluded that the susceptibility to develop chronic cough is not associated with ACE genotype [32]. The influence of the polymorphism in the ACE gene in the susceptibility to develop cough is controversial and further studies are needed to clarify this subject.

Contrary to imidapril, enalapril caused a small but statistically significant decrease in mean FEV_1 and FVC in the population of this study, free of respiratory symptoms or asthma history. As in the induction of cough, differences between imidapril and enalapril could be explained by the different potencies of ACE inhibitors in inhibiting the hydrolysis of bradykinin and angiotensin I. The significance of such a small effect might be questioned and is probably not clinically relevant. However, it has been demonstrated that enalapril was associated with an increase in bronchial reactivity, as assessed by histamine provocation [18]. A fall of 30% in the concentration of provocateur producing a decrease in FEV_1 of 20% from baseline (PC_{20}) has been observed in subjects treated with enalapril, however, spirometry was not performed in that study [18]. Conversely, a 14-day course of oral lisinopril was not related with a decrease in PC_{20} with methacholine provocation [33]. The consensus is that ACE inhibitors do not increase the risk of developing bronchoconstriction in patients with primary airway disease [34]. However, as stated before, there are reports contradicting this statement and to date, there has been a shortage of studies aiming to evaluate this phenomenon. Data are missing regarding the effect of ACE inhibitors upon spirometry parameters in asthmatic subjects or coughing patients.

The capsaicin cough challenge test is a simple and reproducible laboratory method for the assessment of cough susceptibility in a wide range of diseases. It is widely used, both in volunteers and patients [35], but its potential influence in the airways' diameter is seldom addressed. In initial investigations, it was stated that capsaicin inhalation was associated with a bronchoconstrictor effect mediated by a cholinergic reflex [36]. It has been used safely in patients with airway obstruction [11,37], however, episodes of bronchoconstriction (fall in FEV_1 up to

Highlights

- Angiotensin-converting enzyme (ACE) inhibitors are largely used in the treatment of hypertension, congestive heart failure, left ventricular dysfunction, myocardial infarction and diabetic nephropathy.
- ACE inhibitors are associated with a dry, dose-independent, nonproductive cough.
- Cough challenge with capsaicin has been used in patients with interstitial lung disease, asthma and chronic obstructive pulmonary disease (COPD) without major safety concerns.
- Neither imidapril nor enalapril altered threshold to inhaled capsaicin.
- Contrary to enalapril, imidapril was not associated with impairment of the spirometry parameters forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC).
- Capsaicin inhalation challenge test was not associated with bronchoconstriction.

40.4%) have been reported [37]. It is argued that the overall airway response to inhaled capsaicin is determined by the relative amount of constrictor and dilator neurotransmitters released from capsaicin-sensitive primary afferent fibers.

In healthy subjects, a mean decrease in FEV_1 of 0.1% after capsaicin inhalation has been reported [38]. Our results, obtained in one of the largest samples, confirm the absence of bronchoconstriction after inhalation of tussigenic doses of capsaicin in healthy volunteers (decrease of 0.02 L in FEV_1 and increase of 0.02 L in FVC). These results support the fact that the mechanisms of coughing and bronchoconstriction are regulated by distinct pathways.

The results we have obtained may suggest the influence of different mechanisms mediating the ACE inhibitors induced cough and bronchospasm. The potential for inducing each of the symptoms varies between different ACE inhibitors according to the pharmacodynamic properties of each drug and its capacity to act in a specific receptor. The pathophysiology of ACE inhibitors induced cough and bronchospasm might be somehow different and these phenomena can be seen as different and independent side effects of antihypertensive therapy.

Conclusions

Neither imidapril nor enalapril altered the cough threshold to inhaled capsaicin in a population of healthy volunteers. Contrary to enalapril, imidapril was not associated with impairment of the spirometry parameters. Studies in asthmatics are needed to assess the clinical relevance of these data. Capsaicin inhalation challenge test was not associated with bronchoconstriction.

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Accessed July 2004