EFFECTS OF ENALAPRIL, AN ACE-INHIBITOR, ON BRONCHIAL RESPONSIVENESS IN ASTHMATICS

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Abstract: To assess the effects of enalapril on bronchial responsiveness, we studied ten stable asthmatics and five healthy normal volunteers. Spirometry and methacholine bronchoprovocation dose (PC_{20}) were measured before and after oral administration of 20 mg enalapril. Significant hypotensive effect was observed in all. More than two fold (2.73) increase in bronchial responsiveness was observed in the asthmatics (P<0.01) without significant change in the expiratory flows. PC_{20} after enalapril fell by 56.8± 23.0% of baseline value (P<0.001). No significant change was observed in spirometric parameters and bronchial responsiveness in normal subjects. We conclude that enalapril significantly enhances BR and cannot be used safely in treatment of hypertension in asthmatics.

Key words: Ace-inhibitors asthma enalapril bronchial-responsiveness bronchoprovocation

INTRODUCTION

Angiotensin converting enzyme (ACE) inhibitors, used to treat hypertension and heart failure, are likely to be used in patients with associated bronchial asthma where beta-blockers are contraindicated. Since ACE in lung is responsible for breakdown of bradykinin and other tachykinins, its inhibition would lead to accumulation of these bronchoconstrictors and exacerbate airways obstruction (1,2). In chronic obstructive lung disease, no deterioration in lung functions was seen with ACE-inhibitor captopril. Also, no change in bronchomotor tone and bronchial reactivity has been reported with captopril in stable asthmatics (4). Hence, this class of drugs were considered safe in treatment of patients with hypertension and airways obstruction.

Recently, dry cough, deterioration in pre-existing asthma and development of asthma de novo following treatment with captopril have been reported (5,6). While dry cough and enhanced bronchial reactivity has been documented in normal subjects, an increased incidence is suggested in asthmatics (7). Normal individuals who do not develop cough on ACE-inhibitor treatment do not show increased bronchial reactivity (8). But, contrary results have been reported by others (2,6).

Effect of newer and potent ACE-inhibitors on airways obstruction is not known. Therefore we chose to study the acute effects of a long-acting and highly potent ACE inhibitor, Enalapril, on bronchial responsiveness in stable asthmatics.

METHODS

Ten stable asthmatics (age 32.1, ± 9.9 yrs) diagnosed on standard clinical and lung function criteria and five healthy, non-smoking volunteers (age 34.6 ± 8.4 yrs) were studied for acute effects of enalapril. Informed consent was obtained before the study. All the subjects were normotensive and maintained 70% FEV₁/FVC ratio on inhaled/oral beta-2 agonists and methylxanthines. None was receiving steroids, antihistamines, anti-cholinergics or disodium chromoglycate. All drugs were withheld 24 hours prior to the study. Those with a history of respiratory tract infection in the preceding 6 weeks, were excluded from the study.

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**Lung function:** Spirometry was done on dry-rolling seal spirometer (Morgan-Spiroflow) and the best of the three curves was taken for calculating forced vital capacity (FVC), forced expiratory volume in one sec (FEV₁), peak expiratory flow (PEF), forced expiratory flow between 200-1200 ml (FEF 200-1200) and forced expiratory flow between 25-75%. The variation in basal FVC and FEV₁ on 2 days of study was 5% or less.

**Bronchial challenge:** Methacholine bronchoprovocation test (BPT) was done using Hudson nebulizer (output = 0.034 ± 0.011 mg/min; MMAD = 1.6 ± 0.5 μm) with airflow at 6 L/min (9). The test was started with 0.03 mg/ml concentration and increased in two fold increments at 5 min intervals upto 10 mg/ml or until FEV₁ fell by 20% of diluent value (PC₂₀).

The cumulative dose of methacholine was plotted logarithmically on the abscissa and response in linear units on the ordinate as percent-fall in FEV₁. The dose corresponding to 20% fall in FEV₁ was taken as PC₂₀.

**Study design:** On the first day after baseline spirometry, the subjects were tested with methacholine BPT to find out basal PC₂₀. On the next day, after spirometry and measurements of heart rate and blood pressure, the subjects were given enalapril (20 mg) orally. One and half hours later (dictated by pharmacokinetic data of drug indicating maximum ACE-inhibition between 1-2 hours), repeat measurements of clinical parameters, spirometry and BPT were done.

**Statistics:** Geometric mean PC₂₀ was calculated before and after enalapril in both groups. PC₂₀ ratio (baseline PC₂₀/PC₂₀ after drug) was computed for all. Any value above unity was taken as a magnitude of increased bronchial-responsiveness. Percent changes in heart rate, blood pressure, lung functions and PC₂₀ were also calculated. Paired student 't' test was used for comparisons. PC₂₀ ratio were tested against unity by 't' test for significance.

**RESULTS**

Mean spirometric lung functions in both normal-volunteers and asthmatics did not change after enalapril (Table I). Baseline systolic and diastolic blood pressures in both normal subjects and asthmatics showed significant decline (P<0.001) after enalapril, but no change in heart rate was observed in either group.

| Table I: Lung functions before and after Enalapril* |
|---------------------------------|---------------------------------------------|
| **Normal subjects** | **Asthmatic patients** |
| **Baseline Mean±SD** | **After Enalapril Mean±SD** | **Baseline Mean±SD** | **After Enalapril Mean±SD** |
| FVC (L) | 3.378±0.938 | 3.189±1.042 | 2.575±0.298 | 2.561±0.972 |
| FEV₁ (L) | 2.946±0.786 | 2.865±0.794 | 2.009±0.829 | 1.987±0.861 |
| FEV₁/FVC(%) | 88.50±3.35 | 89.35±4.8 | 77.23±8.1 | 76.67±8.1 |
| PEF (L/min) | 484.0±111 | 468±132 | 367±150 | 344±139 |
| FEF 25-75% (L/min) | 245±45.6 | 269.1±84.9 | 123.1±78.9 | 121.8±84.3 |
| FEF (200-1200) (L/min) | 451.0±151.0 | 456.1±151 | 249.0±160 | 247.0±114 |

*No significant change in any parameter (P>0.05)
Bronchial-responsiveness in normal subjects did not change after enalapril (Table II). In asthmatics, $PC_{20}$ fell significantly (>50%, $P<0.001$) after the drug. $PC_{10}$ ratio was nearly unity in normals but 2.73±1.16 in asthmatics (Table II). None of the patients showed increase in $PC_{20}$ after the drug. 'Geometric-mean' (±SD) of 0.102±0.82 mg/ml after enalapril was significantly ($P<0.05$) less than the initial $PC_{20}$ of 0.373 ± 0.176 ml/ml indicating enhanced bronchial hyperresponsiveness.

**Table II**: Bronchial Responsiveness as measured by $PC_{20}$ before and after Enalapril.

<table>
<thead>
<tr>
<th>Normal Subject</th>
<th>Asthmatics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD</td>
<td>Mean±SD</td>
</tr>
<tr>
<td>Geometric Mean (mg)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.539±1.600</td>
</tr>
<tr>
<td>After</td>
<td>4.671±1.601</td>
</tr>
<tr>
<td>Net change (mg)</td>
<td>0.095±0.103</td>
</tr>
<tr>
<td>$PC_{20}$ Ratio*</td>
<td>0.901±0.181</td>
</tr>
<tr>
<td>% Change</td>
<td>2.32±2.50</td>
</tr>
</tbody>
</table>

*Baseline $PC_{20}$ after enalapril; **$P<0.05$; ***$P<0.001$

**DISCUSSION**

Angiotensin converting enzyme has effects other than conversion of angiotensin I to angiotensin II. It is identical to enzyme Kininase II required for inactivation of bradykinin and substance P, particularly in the lungs (1). Hence, ACE inhibitors would allow accumulation of these substances in the body (1,2). Data on blood bradykinin levels after ACE inhibition are conflicting & inconclusive and may not be related to tissue effects (2,4). In support of accumulation of these substance at tissue level, is the observation that ACE inhibitors augment skin - responses to intradermal bradykinin and potentiate substance - P induced salivation (10). ACE-inhibition may also cause increase in prostaglandin - production directly or via bradykinin e.g. captopril showed increased lung concentrations of $PGF_2$α. This drug also prevented accumulation of CAMP in smooth muscle & decreased bronchodilating effect of VIP and beta-agonists. All these bronchoconstrictor mediators have been shown to increase bronchial responsiveness in animal experiments. Bradykinin inhalation causes bronchoconstriction in human asthmatics partly via cholinergic mechanism and partly via $PGF_2$α stimulating rapidly adapting 'irritant' receptors which mediate cough and broncho-constriction.

The findings of this study support the view that ACE inhibitors may be asthmogenic. The absence of change was observed in basal bronchomotor tone in either normal subjects or asthmatics. In a large study, no deterioration in expiratory flows was reported after 2 months of enalapril (12). But asthmatics were not included in that study (12). A few patients developing wheeze or exacerbation of pre-existing asthma by ACE inhibitors have been reported, while most did not show deterioration of spirometric measurements (13). Also, adequate control of asthma allowed inhibitors to be reintroduced without worsening (6).

Dry cough has been reported in 0.2-3.3% of patients taking ACE inhibitors, which was associated with increased sensitivity of the cough reflex (2). A high proportion of patients who reported cough during treatment with ACE inhibitors were non-smoker asthmatics (5,8). Since modestly enhanced BR and bronchoconstriction per se can stimulate cough receptors, an association between cough, BR and bronchoconstriction was proposed (12,14). Therefore, enalapril may not be safe to use in asthmatics.

**REFERENCES**


