Cough induced by enalapril but not by captopril


ABSTRACT: We report a 68 yr old woman with hypertension who developed a dry cough on enalapril but not on captopril therapy. Pulmonary function tests, methacholine inhalation challenges, total blood eosinophil counts, and changes in plasma concentrations of prostaglandin E₂ and thromboxane B₂ did not explain the difference in the adverse reaction between these two angiotensin converting enzyme inhibitors. Eur Respir J., 1989, 2, 289-291.

Angiotensin converting enzyme (ACE) inhibitors like captopril and enalapril are usually well tolerated. However, in some patients they may cause cough as an adverse reaction [1]. We report a female patient who developed a cough on enalapril but not on captopril therapy. We evaluated her lung function, bronchial reactivity to methacholine, total blood eosinophil count as well as plasma concentrations of prostaglandin E₂ (PGE₂) and thromboxane B₂ (TXB₂) during the two therapies and without any ACE inhibitor.

Table 1. – Pulmonary function tests, methacholine inhalation challenge results, total blood eosinophil counts, plasma concentrations of prostaglandin E₂ and thromboxane B₂ during captopril and enalapril therapies and in absence of angiotensin converting enzyme inhibition.

<table>
<thead>
<tr>
<th>Test</th>
<th>CAP</th>
<th>BRDIL</th>
<th>ENA</th>
<th>BRDIL</th>
<th>CONTR</th>
<th>BRDIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC l</td>
<td>2.7</td>
<td>2.6</td>
<td>2.7</td>
<td>2.7</td>
<td>2.6</td>
<td>2.6</td>
</tr>
<tr>
<td>FEV₁ l</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>FEV₁ %</td>
<td>70</td>
<td>73</td>
<td>70</td>
<td>70</td>
<td>67</td>
<td>69</td>
</tr>
<tr>
<td>MMEF l·s⁻¹</td>
<td>1.14</td>
<td>1.13</td>
<td>1.35</td>
<td>1.25</td>
<td>1.11</td>
<td>1.05</td>
</tr>
<tr>
<td>MVV l·min⁻¹</td>
<td>50</td>
<td>55</td>
<td>50</td>
<td>60</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>TLC l</td>
<td>5.04</td>
<td>5.45</td>
<td>5.05</td>
<td>5.05</td>
<td>5.05</td>
<td>5.05</td>
</tr>
<tr>
<td>FRC l</td>
<td>3.33</td>
<td>3.33</td>
<td>2.82</td>
<td>2.82</td>
<td>2.82</td>
<td>2.82</td>
</tr>
<tr>
<td>RV l</td>
<td>2.16</td>
<td>2.62</td>
<td>2.16</td>
<td>2.16</td>
<td>2.16</td>
<td>2.16</td>
</tr>
<tr>
<td>PEFR l·min⁻¹</td>
<td>355</td>
<td>370</td>
<td>375</td>
<td>390</td>
<td>365</td>
<td>360</td>
</tr>
<tr>
<td>BAPEFR l·min⁻¹</td>
<td>360</td>
<td>345</td>
<td>340</td>
<td>340</td>
<td>340</td>
<td>340</td>
</tr>
<tr>
<td>METHACH</td>
<td>320</td>
<td>360</td>
<td>365</td>
<td>380</td>
<td>285</td>
<td>295</td>
</tr>
<tr>
<td>APEFR%</td>
<td>-11</td>
<td>-16</td>
<td>-16</td>
<td>-16</td>
<td>-16</td>
<td>-16</td>
</tr>
<tr>
<td>ESO x10⁴ l⁻¹</td>
<td>0.23</td>
<td>0.23</td>
<td>0.19</td>
<td>0.19</td>
<td>0.19</td>
<td>0.19</td>
</tr>
<tr>
<td>PGE₂ pg·ml⁻¹</td>
<td>906</td>
<td>369</td>
<td>171</td>
<td>171</td>
<td>171</td>
<td>171</td>
</tr>
<tr>
<td>TXB₂ pg·ml⁻¹</td>
<td>153</td>
<td>147</td>
<td>126</td>
<td>126</td>
<td>126</td>
<td>126</td>
</tr>
</tbody>
</table>

CAP: captopril; ENA: enalapril; BRDIL: values ten minutes after three puffs of a rimiterol aerosol, total dose 600 μg; CONTR: test values without ACE inhibition; FVC: forced vital capacity; FEV₁: forced expiratory volume in one second; FEV₁/FVC%; MMEF: maximal mid-expiratory flow; MVV: maximal voluntary ventilation; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; PEFR: peak expiratory flow rate; BAPEFR: basal PEFR; METHACH: PEFR values after 10 inhalations of 2.5% methacholine solution; APEFR: change from the baseline value of PEFR; EOS: blood eosinophil count; PGE₂: prostaglandin E₂; TXB₂: thromboxane B₂.

Case History

A 68 yr old non-smoking woman with diabetes, hypertension and compensated heart failure, but with no respiratory disease or abnormalities on chest X-ray, developed a dry cough but no dyspnoea or postnasal drip during treatment with enalapril (Renitec®, MSD, 20 mg·day⁻¹) for hypertension. Her blood pressure had been repeatedly recorded as 190/105 mmHg. Her other medication was: atenolol (100 mg·day⁻¹), digoxin (0.25
mg-day^-1^), chlorthalidone (50 mg-day^-1^), metformin (1000 mg-day^-1^) and glibenclamide (7 mg-day^-1^).

The cough disappeared when enalapril was replaced by captopril (Capoten®, Squibb, 75mg-day^-1^). The other medication remained unaltered. During this regimen she was asymptomatic. After two months on captopril medication she underwent physical examination, blood tests, dynamic (Bernstein) and volumetric spirometry (Godart expirograph) (table 1).

Methacholine inhalation challenge was performed with increasing concentrations (0.025–2.5%) and numbers of inhalations of a methacholine solution from a DeVilbiss nebulizer No. 40, with an air flow of 5 l·min^-1^, until a decrease of 15% or more in peak expiratory flow rate (PEFR) (Wright) values was reached. Pulmonary function was in the normal range, but plasma concentrations of PGE_2 (906 pg·ml^-1^) and TXB_2 (153 pg·ml^-1^) were rather high (table 1).

Thereafter, the patient discontinued captopril and restarted enalapril at the same dosage without changing her other medication. The study had the approval of the local Hospital Ethical Committee. During the first week of enalapril medication she again developed a dry cough but no dyspnoea or postnasal drip. The cough was worse at night and did not disappear while continuing the enalapril treatment. After two months the laboratory tests were repeated, and the enalapril medication was stopped. The cough disappeared within a few days. Pulmonary function tests showed similar values as on captopril, but a remarkable decrease in plasma PGE_2 was detected (table 1).

After one month without any ACE inhibitor therapy and with the other medication unchanged, the tests were repeated again (table 1). At this time methacholine inhalation challenge showed mild bronchial hyperreactivity, and plasma PGE_2 was at its lowest level. The patient was asymptomatic, and her blood pressure was 160/80 mmHg.

During the whole study, the patient was in good clinical condition besides the cough during the enalapril phase, and the findings on physical examination, including pulmonary auscultation, were normal.

**Discussion**

The diagnosis of enalapril-induced cough in this patient was verified by rechallenge, which is usually required to prove a drug-induced side effect. Another ACE inhibitor, captopril, caused no adverse reactions. Additional medication, including the adrenergic beta-receptor blocker atenolol, was similar during both of these therapies and the patient had used this regimen earlier without any cough. She did not suffer from asthma, atopy or any other disease known to increase bronchial reactivity.

Pulmonary function tests were the same during treatment with both of the ACE inhibitors and without any ACE inhibition. No bronchodilatation response was induced by inhalation of rimiterol. This indicates that no major reversible bronchoconstriction was responsible for the cough during the enalapril phase. The methacho-line inhalation challenges were in the normal range during captopril and enalapril treatment but, interestingly, a mild bronchial hyperreactivity was found in the period without any ACE inhibition (APEFR -16%) (table 1). The patient was asymptomatic, and had no sign of any viral respiratory infection during the preceding six weeks which could have explained the results. The total blood eosinophil count was normal at each test, indicating that no allergic disease was present.

The prevalence of cough related to ACE inhibition has been reported to be in the range 1–6% among patients on captopril [2, 3] and 3–10% among those on enalapril [2, 4]. Patients with heart failure show this side effect more rarely [2], probably due to lower doses or the usual absence of concomitant beta-blocker therapy in these patients [5]. Town et al. [6] noticed bronchial hyperreactivity in three of their ten patients with cough from enalapril. However, BUCKNALL et al. [7] found that patients coughing during ACE inhibitor treatment had increased sensitivity to inhaled histamine even before therapy, which was further enhanced during ACE inhibition. We found an abnormal response to methacholine inhalation challenge in only one of our twelve patients with enalapril-induced cough [5]. Furthermore, some authors have reported induced or worsened asthma during ACE inhibitor therapy [8, 9]. The mechanism of this adverse reaction is unclear.

Substance P and bradykinin have been suggested to play a role since their levels probably increase in the respiratory tract during ACE inhibition [10]. These mediators have been proved to cause cough: substance P by initiating an axon reflex, and bradykinin by inducing inflammation of the mucosa [11]. Several actions of bradykinin are in fact mediated through cyclo-oxygenase products [12]. Interestingly, in an open study, sulindac, a non-steroidal anti-inflammatory agent, inhibited cough produced by ACE inhibition in six hypertensive subjects [13]. Captopril enhances the release of a prostaglandin-like substance from guineapig lungs [14] and increases plasma PGE_2 in patients having hypertension [15]. Accordingly, in our patient PGE_2 concentration was at its highest during captopril therapy and lowest during the control period. TXB_2 was at the same level during all treatments. These findings do not support the role of any prostanoids in the aetiology of cough although they have previously been suspected. This is supported by our unpublished data of plasma PGE_2 concentrations in four patients with enalapril-induced cough: only one had a higher concentration during the therapy and in three patients the PGE_2 concentration was higher without any ACE inhibition.

**References**


5. Puolijoki HJ, Nieminen MM, Siitonen LO, Lahdensuo AHS, Reinikainen PMO. – Is a simultaneous beta-blocker therapy a risk factor for enalapril-induced cough. Submitted for publication


RÉSUMÉ: Observation d’une femme de 68 ans atteinte d’hypertension et souffrant d’une toux sèche après prise d’enalapril, mais non après captopril. La différence dans les réactions secondaires à l’égard de ces deux inhibiteurs de l’enzyme de conversion de l’angiotensine ne s’explique ni par l’exploration fonctionnelle pulmonaire, ni par les provocations par inhalation de méthacholine, ni par les décomptes d’œsino­philes totaux dans le sang, ni par des modifications des concentrations plasmatiques de prostaglandine E ou de throm­boxane B₂.