

# BRONCHIAL HYPERREACTIVITY INDUCED BY ANGIOTENSIN CONVERTING ENZYME INHIBITOR

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## ABSTRACT

Cough is a recognised side effect of angiotensin converting enzyme (ACE) inhibitors although its exact mechanism is still unknown. Reports on the side effect of ACE inhibitors on asthma have been conflicting. These drugs either had no effect on bronchial reactivity or resulted in an increase in pre-existing hyperreactivity. We report a case of a non-asthmatic patient who had lisinopril-induced cough and bronchial hyperreactivity.

**Keywords:** cough, ACE inhibitor, bronchial hyperreactivity

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## CASE REPORT

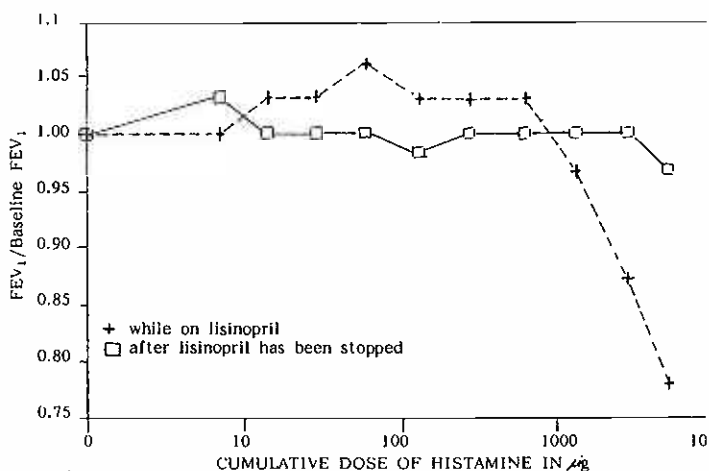
AHS, a 43-year old man, was first detected to be hypertensive at the age of 25 years. He has been treated and followed up by our colleagues in the Department of Cardiovascular Medicine. Investigations for evidence of secondary causes of his hypertension were all normal. He was initially treated with diuretic. The treatment was changed to propranolol 9 years ago. Three years later, this was converted to atenolol 50 mg om for the convenience of once a day dose. He remained completely asymptomatic. In December 1988, the cardiologist decided to start him on lisinopril 5 mg om instead of atenolol although he did not have any adverse effect from the latter. He started coughing 3 weeks after the commencement of lisinopril and he presented himself at our clinic another 4 weeks later.

His cough was dry and was worse in the middle of the night and early morning. It was sometimes associated with wheeze. He had no nasal or other symptoms to suggest upper respiratory tract infections. He had no past or family history of asthma, and had no history of rhinitis or eczema. Clinical examination revealed polyphonic wheeze on deep expiration. His chest X-ray was normal. There was no blood eosinophilia. Spirometry, lung volumes and single breath carbon monoxide transfer factor and coefficient were normal.

He was asked to use salbutamol inhaler 200µg qds while he continued lisinopril. The cough disappeared completely for 4 to 5 weeks but then recurred. He still had expiratory wheeze as before. Beclomethasone inhaler 100µg qds was added. Eight weeks later, his cough had improved and his lungs were clear. Histamine provocation test using Mefar dosimeter was performed after he had stopped the beclomethasone and salbutamol inhalers for 2 days but lisinopril was continued. His FEV<sub>1</sub> dropped from 3.20 L (predicted normal = 3.04 L) to 2.50 L and the provocation dose that caused a 20% drop in FEV<sub>1</sub> (PD<sub>20</sub>FEV<sub>1</sub>) was 4.9mg (Fig 1).

He became completely free from cough within a week of stopping lisinopril. Histamine provocation test was repeated 8 weeks after the first test. He was only on nifedipine for his hypertension then. The baseline FEV<sub>1</sub> was again 3.20 L but there was no significant fall at the maximum cumulative dose of 5 mg of histamine (Fig 1).

Fig 1. Dose response curves to histamine with and without lisinopril



He could not tolerate nifedipine because of headache. His blood pressure was not controlled when indapamide was substituted and the cardiologist then prescribed atenolol again. He has remained asymptomatic.

## DISCUSSION

The mechanism of cough induced by ACE inhibitors is still uncertain although involvement of bradykinin or prostaglandins has been postulated. There are several reports of increased sensitivity of the cough reflex as measured after capsaicin inhalation. However, the reports on the effects of ACE inhibitors on asthma and bronchial hyperreactivity have been conflicting<sup>(1-3)</sup>. Dixon et al<sup>(1)</sup> reported no change in airway reactivity to inhaled histamine after one dose of ramipril in asthmatics. On the other hand, Bucknall et al<sup>(2)</sup> found a significant increase in bronchial hyperreactivity to histamine on rechallenge with captopril or enalapril in those who developed cough with the drugs. However, in their patients, there was pre-challenge bronchial hyperreactivity which also persisted one year after the drug was stopped. They suggested that the cough associated with ACE inhibitors may be a variant of the cough in asthma.

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ACE inhibitor-induced cough usually takes a few weeks to develop<sup>(4)</sup>. It is therefore not surprising that Dixon et al found no demonstrable change in bronchial response to histamine after one dose of ACE inhibitor, even though there was significant fall in the plasma ACE concentration<sup>(5)</sup>. Coulter and Edwards<sup>(4,5)</sup> objected to Bucknall et al's suggestion that ACE inhibitor-induced cough may be a variant of asthma on the ground that there was a significant preponderance of females in ACE inhibitor-induced cough and this was not seen in asthma. It is possible that smokers who have cough associated with ACE inhibitors may attribute it to smoking instead. As females are less likely to be smokers, they are more likely to report to their doctors their cough associated with ACE inhibitors.

In our patient, the temporal association between cough and treatment with lisinopril suggests a cause and effect relationship. The slope of the dose response curve was higher when he was taking lisinopril than when the drug was stopped (Fig 1). Although we do not know his bronchial reactivity before commencement of his treatment, it is not likely that he had pre-existing asthma or bronchial hyperreactivity as he had no past or family history of asthma and he had no cough or bronchospasm while he was taking  $\beta$ -blockers. Propranolol and, to a lesser extent, atenolol would have induced bronchospasm if he had asthma. He had no recent upper respiratory tract infection which might induce bronchial hyperreactivity. No doubt his  $PD_{20}FEV_1$  was much higher than those in patients with classical asthma. But the  $PD_{20}FEV_1$  of those who presented with chronic

cough as a manifestation of mild asthma was usually greater than the cumulative dose of 1.2 mg commonly used as the cut off point for asthma<sup>(6)</sup>. His cough was associated with audible wheeze and was worse at night and early morning, quite similar to the cough in asthma. It also responded, albeit temporarily or partially, to inhaled  $\beta$ -agonist and corticosteroid. These would further support the suggestion that his cough was related to an increase in bronchial reactivity.

This case showed that lisinopril was capable of inducing an increase in bronchial reactivity and an asthma-like cough in a non-asthmatic individual who had no baseline bronchial hyperreactivity. The possibility that ACE inhibitors may induce cough through bronchial hyperreactivity cannot be totally discounted.

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