

Development of persistent late onset asthma following treatment with captopril

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ABSTRACT: We describe the first case of *de novo* asthma following treatment with the angiotensin converting enzyme (ACE) inhibitor captopril. Despite drug withdrawal there was evidence of persistent airways obstruction and bronchial hyperreactivity. This suggests the possibility that ACE inhibitors may uncover an asthmatic tendency in patients with pre-existing bronchial hyperreactivity.

Eur Respir J., 1989, 2, 586-588.

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Keywords: Asthma; bronchial hyperreactivity; captopril.

Received: April 30, 1988.

Angiotensin converting enzyme (ACE) inhibitors are a novel treatment in the management of hypertension and heart failure. This class of drug is generally well tolerated [1], although recently dry cough [2-4] and deterioration in pre-existing asthma [4-6] have been reported. The course of asthma after drug withdrawal is unknown because follow-up studies are not available, although dry cough usually resolves rapidly after stopping ACE inhibitors. We report the first case of *de novo* asthma following treatment with the ACE inhibitor captopril.

Case Report

A 79 year old caucasian male accountant was first referred in June 1987 for control of hypertension and heart failure, with an exercise tolerance limited to half a mile on flat ground. He had never smoked and had no cough, wheeze or diurnal variation in breathlessness. He was non-atopic and neither was there a family history of asthma. He was taking frusemide 80 mg and triamterene 100 mg once daily, digoxin 0.25 mg daily and slow-release nifedipine 20 mg twice daily. On examination, he had atrial fibrillation with a well controlled ventricular rate. He had signs of mitral regurgitation and biventricular heart failure, with a blood pressure of 210/110 mmHg. A chest examination revealed bilateral basal crackles, without wheezes. Chest radiograph showed cardiomegaly and changes of pulmonary venous congestion. Echocardiogram revealed an enlarged left ventricle and atrium, mitral regurgitation and moderate impairment of left ventricular function. He was started on oral captopril for his heart failure

and was discharged on frusemide 80 mg daily, captopril 25 mg three times daily and digoxin 0.25 mg daily.

At review 2 months later (August 1987) there was little change in his exercise tolerance and the patient spontaneously reported the development of dry cough and wheeze which had started one week after discharge from hospital. His wheeze was worse on waking and on exertion. He still had signs of biventricular failure, but now also had audible wheezes in both lung fields. Chest radiograph was unchanged. Pulmonary function tests (table 1) showed a reduction in both dynamic and static lung volumes with evidence of air trapping and a reduced transfer factor. His flow-volume loop showed typical changes of airways obstruction and there was 16% reversibility in forced expiratory volume in one second (FEV_1) with 500 μ g of terbutaline. These changes were in keeping with a mixed obstructive and restrictive ventilatory defect. A histamine challenge test was performed with a modification of Cockcroft's method [8, 9] using a Nebichek dosimeter (PK Morgan, UK) and Unicorn Nebuliser (Medic-Aid, UK). This showed marked bronchial hyperreactivity with a PC_{20} of 0.9 $mg \cdot ml^{-1}$ (concentration of histamine causing a 20% fall in FEV_1 from saline control value). The eosinophil count was $0.5 \times 10^9 l^{-1}$ serum IgE level was normal (25 $U \cdot ml^{-1}$) and skin prick tests to common allergens were negative. Circulating immune complexes were slightly elevated and levels of complement C_3C_4 were reduced. Antinuclear factor was negative and serum ACE was $12U \cdot l^{-1}$ (17-52 $U \cdot l^{-1}$).

The captopril was therefore stopped and the patient was restarted on his original dose of frusemide 80 mg and triamterene 100 mg per day. There was no

clinical improvement and there were persistent wheezes on auscultation. This was mirrored in pulmonary function and histamine challenge which showed little change at one and two months after withdrawal of the captopril (table 1). He was therefore commenced on inhaled budesonide in a dose of 400 µg twice daily in addition to terbutaline 500 µg as required. Within one month of treatment with inhaled corticosteroids his asthma had improved and by February 1988 he had no morning symptoms and his chest was now free of wheezes. This was accompanied by a marked improvement in lung volumes, air trapping flow volume loop and bronchial reactivity (table 1).

The association between ACE inhibitors and dry cough is well documented, and the cough usually disappears soon after drug withdrawal [3, 4]. Post-marketing surveillance studies in New Zealand and the United Kingdom have shown an incidence of cough between 1% to 3% [4, 11]. MORICE and coworkers [12] recently showed a small but significant left shift in the dose-response curve to capsaicin-induced cough in normal subjects given captopril. Prostaglandin E₂ may produce cough *via* C fibre stimulation [13], and inhibitors of prostaglandin synthetase have been shown to attenuate cough due to ACE inhibitors [14]. TOWN *et al.* [3] reported mild bronchial hyperreactivity in 2 out of 7

Table 1. – Serial changes in pulmonary function and histamine challenge test

	FEV ₁	FEF _{50%}	FVC	RV	TLC	Tlco	TGV	sGAW	PC ₂₀	Treatment
	(l)	(l·s ⁻¹)	(l)	(l)	(l)	(mmol·min ⁻¹ kPa ⁻¹)	(l)	(s ⁻¹ ·kPa ⁻¹)	(mg·ml ⁻¹)	(daily dose)
Predicted	3.39	6.32	4.41	2.94	7.23	8.58	4.60	1.24	>8	
Aug 1987	1.43	0.92	2.05	2.89	5.72	5.27	4.54	0.32	0.90	CPT 75 mg FRU 80 mg
Sep 1987	1.52	0.97	2.30	2.42	5.22	7.81	4.67	0.46	1.35	FRU 80 mg TRM 100 mg
Oct 1987	1.30	0.68	2.30	2.50	4.87	6.13	4.33	0.21	0.95	FRU 80 mg TRM 100 mg
Feb 1988	2.01	1.54	2.82	2.48	5.44	8.36	2.98	0.67	5.80	FRU 80 mg TRM 100 mg BUD 800 mg

Predicted values are those of CORES [7]. CPT: Captopril, FRU: Frusemide, TRM: Triamterene, BUD: Budesonide

Discussion

Our patient developed late onset asthma for the first time at the age of 79, following treatment with captopril. He had spontaneously reported the onset of cough and wheeze with diurnal variability one week after starting treatment. The evidence for drug induced asthma is somewhat speculative in the absence of pulmonary function tests prior to captopril therapy, although 3 separate experienced physicians had not heard wheezes before starting captopril. Following withdrawal of captopril there was little clinical or physiological improvement. Three months of treatment with inhaled corticosteroids resulted in marked improvement in symptoms, pulmonary function tests and bronchial hyperreactivity. The presence of circulating immune complexes may indicate a type III hypersensitivity reaction as the underlying immunological trigger and could possibly account for the persistent disease activity in our patient. So called 'cardiac asthma' is sometimes seen in left ventricular failure, although bronchial responsiveness is unchanged in this condition [10]. The marked steroid response with unchanged diuretic therapy is more in keeping with a bronchial rather than cardiac aetiology for the airways obstruction in our patient. We have not been able to perform a repeat challenge when off inhaled corticosteroids because of our patients wishes.

atopic patients who developed cough with ACE inhibitors given for hypertension. There was no change in bronchial reactivity following rechallenge with ACE inhibitors. This is in contrast to the findings of BUCKNALL and co-workers [6], namely increased bronchial reactivity in 6 non-asthmatics who developed cough with ACE inhibitors following treatment for hypertension. After rechallenge with ACE inhibitors there was a significant increase in bronchial reactivity to histamine and in the cough reflex to inhaled citric acid. These findings were not mirrored by changes in baseline airways resistance. Five of the patients who were rechallenged one year after withdrawal of ACE inhibitors, showed persistent bronchial hyperreactivity to histamine. Details of atopic status were not included, and histamine provocation was not performed prior to commencing initial therapy with an ACE inhibitor. These findings suggest that pre-existing bronchial hyperreactivity may predispose to the development of cough with ACE inhibitors. BUCKNALL *et al.* also reported 2 cases with worsening asthma after ACE inhibitors, with persistent bronchial hyperreactivity 12 months after drug withdrawal. Our patient also had persistent airways obstruction and bronchial hyperreactivity 5 months after drug withdrawal and would therefore support the hypothesis that ACE inhibitors may uncover an asthmatic tendency where there is pre-existing bronchial hyperreactivity.

The underlying mechanism behind wheeze due to ACE inhibitors remains unclear, but may be due to inhibition of pathways for bradykinin breakdown. Bradykinin is inactivated by kininase II which is an enzyme identical to ACE [15]. Inhaled bradykinin is a potent bronchoconstrictor in asthmatic but not in normal subjects [16]. Studies in asthmatic subjects have shown no effect of ACE inhibitors on bronchial responsiveness to inhaled bradykinin [17], histamine [17] and methacholine [18]. Furthermore, inhaled bradykinin does not potentiate bronchial responsiveness to inhaled histamine or methacholine in asthmatic airways [19]. Despite this, there is evidence that ACE inhibitors augment the cutaneous wheal response to intradermal bradykinin in non-atopic subjects [20]. This may explain the role of ACE inhibitors in causing the rare association with angio-oedema [21].

In conclusion, we describe the first case of *de novo* asthma following captopril therapy, with persistent disease activity following drug withdrawal. This suggests that asthma may have been uncovered in a patient with pre-existing bronchial hyperreactivity. Prospective longitudinal studies are required to show whether pre-existing bronchial hyperreactivity predisposes to the development of asthma following treatment with ACE inhibitors.

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Observation clinique. Développement d'un asthme persistant à d'ébut tardif, après un traitement au captopril.. B. Lipworth, J. McMurray, R. Clark, A. Struthers.

Nous décrivons le premier cas d'asthme survenant de novo après un traitement au moyen de l'inhibiteur de l'enzyme de conversion de l'angiotensine, le captopril. Après arrêt du traitement médicamenteux, une obstruction persistante des voies aériennes et une hyperréactivité bronchique ont été constatées. Ceci suggère la possibilité que les inhibiteurs de l'enzyme de conversion de l'angiotensine pourraient démasquer une tendance asthmatique chez les patients ayant une hyperréactivité bronchique préalable.

Eur Respir J., 1989, 2, 596-598.