patients with genital ulcers in this study gave a short history, so they must have been infected with HIV 2 before developing their ulcer. Several of them had attended the clinic for sexually transmitted diseases previously, and thus a common behavioural factor probably predisposes to both genital ulceration and infection with HIV 2—for example, recourse to a certain type of prostitute.

The recent discovery of one if not two new pathogenic human retroviruses in west Africa suggests that there may be other as yet undiscovered retroviruses in this region. One of our patients (case 5) may have been infected with a retrovirus that was neither HIV 1 nor HIV 2 because she had clinical AIDS but was negative for antibody to HIV 1 and only borderline positive for antibody to HIV 2.

The prevalence of human retroviral infections in The Gambia is at present low but seems to be increasing. There is an urgent need not only for a public education programme to try to limit the spread of these viruses but also for further research into the epidemiology and course of infection with HIV 2. Before an effective retroviral vaccine can be developed many isolates of the retrovirus from west African subjects must be characterised to establish its antigenic diversity.

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Bronchial hyperreactivity in patients who cough after receiving angiotensin converting enzyme inhibitors

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Abstract

Angiotensin converting enzyme inhibitors cause cough in some patients, but the mechanism of this effect is not known. Six patients in whom these inhibitors had caused cough and a further two patients in whom they were suspected to have caused worsening of bronchial asthma were studied. Nine patients in whom angiotensin converting enzyme inhibitors had not been associated with cough served as controls. In the controls lung function and bronchial reactivity were measured once; for the study patients these and the cough index were measured twice before rechallenge for two weeks with an angiotensin enzyme inhibitor and once afterwards. Rechallenge with drug for two weeks caused a significant decrease in the mean concentration of histamine causing a 35% fall in airways conductance and a significant increase in the cough index. Patients with cough showed bronchial hyperactivity compared with the controls, which increased after rechallenge with the inhibitors.

Cough associated with converting enzyme inhibitors may be a variant of the cough in asthma.

Introduction

Angiotensin converting enzyme inhibitors are being used increasingly in the treatment of hypertension and heart failure. One of us (PFS) reported the occurrence of cough in several patients treated with drugs of this class,[1] and a series of case reports have described this effect.[2-5] Postmarketing surveillance of captopril and enalapril has confirmed this association[6] but initially suggested that the incidence was low at around 1%.[7] This is probably an underestimate because cough is common in the general population and not widely recognised as an effect related to drugs: indeed, a retrospective analysis estimated the incidence to be 14%.[8] To try to identify the mechanism of this side effect we rechallenged with converting enzyme inhibitor a series of patients who had previously reported cough or wheeze in association with this type of drug.

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Patients and methods

We studied six patients with hypertension who had developed cough during treatment with enalapril or captopril, which had resolved when the treatment was stopped; one patient had coughed after both drugs. We also studied two patients with hypertension and bronchial asthma who had reported increased wheeze after treatment with enalapril, but another patient with severe cough after treatment with enalapril declined to take the drug again. The side effects caused by these drugs in two of the patients have

been described.[1] Other treatment for hypertension was continued, although no patient was taking a β adrenoceptor blocker. Nine hypertensive patients whose age and smoking habits were similar to those of the eight patients studied and who were taking angiotensin converting enzyme inhibitors without any complaint of cough served as controls. Tables I and II show clinical details of the patients in the study and control groups, respectively.

LUNG FUNCTION TESTS

Lung volumes were measured by helium dilution and body plethysmography. Other measurements included single breath diffusing capacity, forced expiratory volume in one second, forced vital capacity before and after taking 5 mg nebulised salbutamol, and airways conductance.

Bronchial reactivity to inhaled histamine was measured by using a modification[9] of Cockcroft's method.[10] Histamine was delivered by a dosimeter that had a thermistor fitted to one limb of a T piece from a Unicorn nebuliser (Medic Aid Ltd) and a mouthpiece on the other. The thermistor, sensing the change of temperature at the end of expiration, triggered a valve that drove the nebuliser with oxygen at 1.41 kgf/cm² for 1.2 seconds at the start of inspiration. Patients were instructed to breathe slowly and deeply, and each dose of histamine consisted of 10 deliveries by the dosimeter (volume in each dose=0.095 (SD 0.002) ml). Airways conductance was recorded 30 and 90 seconds after each dose of histamine. The initial concentration of histamine used was 0.03 g/l after saline, which served as the control, and this concentration was doubled every three minutes to a maximum of 16 g/l or until there was a fall in airways conductance of more than 35%. The concentration of histamine that caused a 35% fall from baseline values was derived by linear interpolation from the dose-response curve.

The cough response to inhaled citric acid ws also measured. The acid was delivered by a Unicorn nebuliser driven with oxygen at 10 l/min. The nebuliser was connected by a T piece to a mouthpiece and a Gould flow transducer, which measured airways flow. The flow and cough were recorded on a Servoscribe potentiometric recorder. After breathing to residual volume patients inhaled from the mouthpiece to total lung capacity in about 5 seconds. After breathing out to functional residual capacity they continued to breathe normally for a further 20 seconds unless coughing occurred. The citric acid was prepared at concentrations of 0.06%, 0.125%, 0.25%, 0.5%, 1%, and 2%. On each day of the study these concentrations were given as a single inhalation, starting with the lowest and increasing every two minutes to the highest. The cough response was analysed by the method of Pounsford and Saunders.[11] After each inhalation the number of coughs was counted and the time between the start of inhalation and the first cough, or latency, measured. A cough index was obtained by dividing the number of coughs by the latency.

STUDY DESIGN

We measured lung function and bronchial reactivity only once in the nine control patients. For the eight study patients we measured baseline lung function on two occasions a fortnight apart and at the same time of day. During this two week run in period patients also monitored morning and evening peak expiratory flow rates with a mini Wright peak flow meter and recorded the occurrence of nocturnal cough, nocturnal wheeze, daytime wheeze, daytime dyspnoea, and nasal symptoms on a scale of 0-3. Treatment with enalapril 20 mg/day (cases 1-7) or captopril 75 mg/day (case 8) was then started, and patients continued to record peak flow rates and symptoms for a further two weeks. In two patients (cases 1 and 2) the dose of enalapril was increased to 40 mg a day for the second week. At the end of the two weeks of rechallenge with enalapril or captopril the lung function tests were repeated. In five of the patients histamine reactivity was also measured one year after complete withdrawal of treatment with angiotensin converting enzyme inhibitor.

Statistical analysis was by paired Wilcoxon and Mann-Whitney U tests. The tests were two tailed, and p values of <0.05 were considered significant. The study was approved by the ethical committee of Glasgow Royal Infirmary.

Results

Two patients (cases 1 and 5) regularly showed poor control of their asthma before the start of the rechallenge protocol, and both were treated with inhaled corticosteroids for the first time after the initial treatment with enalapril. Thereafter further exposure to enalapril did not increase symptoms or change variables of pulmonary function. Before rechallenge with angiotensin converting enzyme inhibitor none of the six other patients had symptoms of wheeze, diurnal variation in peak flow rate, or evidence of reversible air flow obstruction, but the group as a whole had bronchial hyperreactivity, the geometric mean histamine concentration causing a 35% fall in the baseline value of airways conductance being 0.68 g/l (table III). Treatment with angiotensin converting enzyme inhibitor did not cause significant changes in lung volumes, dynamic lung function, or peak flow rates (data not shown), but there was a significant fall in the mean histamine

TABLE I—*Clinical details of patients rechallenged with angiotensin converting enzyme inhibitors*

Case No	Age (years)	Sex	Duration of initial treatment with angiotensin converting enzyme inhibitor (months)	Drug and daily dose	Time between stopping treatment and rechallenge (weeks)	Other treatment	Smoking history
1*	38	M	5	Enalapril 20 mg	6	Bendrofluazide 5 mg, salbutamol inhaler	Ex-smoker
2	63	F	5	Enalapril 40 mg	12	Frusemide 80 mg, glibenclamide 5 mg	Never smoked
3	73	F	6	Enalapril 10 mg	12	Hydralazine 100 mg	Never smoked
4	64	M	8	Enalapril 10 mg	28	Metformin 1700 mg, glipizide 30 mg	Never smoked
5*	43	F	5	Enalapril 20 mg	12	Frusemide 40 mg	Never smoked
6	59	F	7	Enalapril 40 mg	12		Never smoked
7	61	F	4 (Captopril) 2 (Enalapril)	Captopril 100 mg Enalapril 20 mg	4		Never smoked
8	67	M	48	Captopril 75 mg	6	Frusemide 80 mg, allopurinol 200 mg	Ex-smoker

*Patient had bronchial asthma.

TABLE II—*Clinical details of patients being treated with angiotensin converting enzyme inhibitor without cough or wheeze*

Case No	Age (years)	Sex	Duration of treatment with angiotensin converting enzyme inhibitor (months)	Drug and daily dose	Other treatment	Smoking history	Airways conductance (/kPa/s)	$PC_{35}SG_{aw}$* (g/l)
9	69	M	22	Enalapril 40 mg	Frusemide 40 mg	Cigarette smoker	1·43	10·3
10	48	M	19	Enalapril 10 mg		Never smoked	1·44	2·5
11	48	M	15	Enalapril 40 mg	Hydrochlorothiazide 25 mg	Never smoked	1·42	5·1
12	70	F	17	Enalapril 40 mg		Ex-smoker	0·84	4·9
13	46	M	6	Enalapril 20 mg		Ex-smoker	1·25	3·4
14	64	M	12	Enalapril 40 mg	Hydrochlorothiazide 25 mg	Never smoked	1·38	7·3
15	60	M	1	Enalapril 10 mg		Ex-smoker	1·26	0·9
16	65	F	10	Enalapril 40 mg	Hydrochlorothiazide 25 mg	Never smoked	0·82	1·0
17	45	F	7	Enalapril 40 mg	Hydrochlorothiazide 25 mg	Never smoked	1·13	5·7

*$PC_{35}SG_{aw}$=Concentration of histamine causing a 35% fall in baseline values of airways conductance.

concentration causing a 35% reduction in baseline airways conductance (p<0·02) (table III). Table III also shows that there was a significant increase in the cough index for inhaled citric acid after treatment with angiotensin converting enzyme inhibitor (p<0·02).

TABLE III—*Mean values for bronchial reactivity and cough index before and after rechallenge with angiotensin converting enzyme inhibitors and after one year*

Case No	Airways conductance (/kPa/s)		$PC_{35}SG_{aw}$* (g/l)			Cough index (No of coughs/latency)	
	Before	After	Before	After	After one year	Before	After
1†	0·7	0·6	0·2	0·1	0·3	1·8	2·7
2	0·8	0·6	1·7	0·5	1·3	2·7	7·0
3	1·2	1·0	1·4	0·7	1·2	2·5	6·7
4	1·0	1·0	1·0	0·9		1·5	9·3
5†	0·3	0·2				2·0	5·0
6	1·4	1·6	0·9	0·3	0·8	4·6	4·5
7	1·2	0·9	0·8	0·7	2·2	0·5	1·8
8	1·1	0·9	0·2	0·1		2·4	4·3

*$PC_{35}SG_{aw}$=Concentration of histamine causing a 35% fall in baseline values of airways conductance.
†Patient had bronchial asthma.

Histamine provocation tests were repeated one year later for four of the patients without asthma. During this year none of the patients experienced recurrence of cough or developed symptoms of wheeze. Table III shows that bronchial reactivity was similar to or less than that during the run in period.

Table II shows the concentrations of histamine causing a 35% reduction in baseline airways conductance in the nine control patients. These were significantly greater than those in the study patients before the rechallenge with converting enzyme inhibitor (p<0·02), and the difference increased during drug treatment (p<0·002). Differences in airways conductance between the two groups were not significant.

Discussion

To prove that a drug has caused a side effect often requires rechallenge with the suspected agent,[12][13] but there may be problems in interpreting the results.[14] In our study treatment was given for only a fairly short period compared with the long duration of treatment when the side effect was first recognised: in one study cough did not occur until treatment with captopril had been given for a year.[5] In the two patients with bronchial asthma inhaled steroids had been introduced to control the increased wheeze that occurred during treatment with converting enzyme inhibitor; thus the results for these patients should be interpreted cautiously. In the six other patients with cough alone rechallenge with angiotensin converting enzyme inhibitor resulted in an increase in the cough index, which therefore established a causal role for the drug.

Cough is a prominent symptom of bronchial asthma and, indeed, may be the presenting symptom.[15] A characteristic of the patients with cough associated with angiotensin converting enzyme inhibitor compared with the controls was their initial bronchial hyper-reactivity; the mean concentration of histamine causing a 35% reduction in airways conductance in normal subjects in our laboratory is 6·2 g/l with a 95% confidence interval of 2·0 to 10·4. This hyperreactivity was probably not a carry over effect from previous treatment with angiotensin converting enzyme inhibitor as the same abnormality was still seen in most of the patients who were re-examined a year after the drug had been withdrawn. It would be interesting to know whether cough in patients taking converting enzyme inhibitors responds to bronchodilator drugs.

Although the mechanism of the cough is unknown, a link with bradykinin metabolism has been suspected[1] as angiotensin

converting enzyme is identical with kininase II, an enzyme that degrades bradykinin; the wheal response to subcutaneous injection of bradykinin is increased by converting enzyme inhibitors[16][17]; and enalapril has precipitated angioneurotic oedema, which may be mediated by kinins.[17] That cough may be due to kinins is strengthened by the observations that bradykinin causes broncho-constriction in patients with asthma,[18-20] fluid from bronchoalveolar lavage in asthmatic subjects generates kinins,[21] and cough occurs in normal subjects taking converting enzyme inhibitors after intradermal injection of bradykinin.[17] Barnes proposed a hypothesis for the pathogenesis of bronchial asthma that envisaged a role for bradykinin in exciting C fibre afferent nerve endings, leading to bronchoconstriction by means of an axon reflex.[22] Bradykinin constricts guinea pig bronchial muscle by causing a release of bronchoconstrictor prostaglandins.[23] This effect is potentiated by captopril and blocked, as expected, by cyclo-oxygenase inhibitors.[24] Responses of airways to inhaled bradykinin were not, however, potentiated by a single dose of enalapril (5 mg) in a small series of patients with bronchial asthma,[25] but the effect of a longer period of treatment was not examined.

Patients who cough after converting enzyme inhibitor treatment show persistent bronchial hyperreactivity, and some hyper-reactivity may have been present before drug treatment. Doctors should be aware of this side effect as patients may otherwise be subjected to unnecessary investigation and treatment for presumed respiratory disease.

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