The effect of an angiotensin converting enzyme inhibitor, ramipril, on bronchial responses to inhaled histamine and bradykinin in asthmatic subjects

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The effect of a potent inhibitor of angiotensin-converting enzyme, ramipril, was studied on both inhaled histamine and bradykinin-induced bronchoconstriction in six male, normotensive, mild asthmatic subjects. Oral administration of 10 mg ramipril caused no change in lung function or airway reactivity to inhaled histamine or bradykinin despite achieving adequate reduction in angiotensin-converting enzyme activity.

Keywords asthma histamine bradykinin ramipril HOE 498

Introduction

Ramipril (HOE 498) is a new and potent angiotensin converting enzyme (ACE) inhibitor which reduces the plasma concentration of ACE (Witte *et al.*, 1984) for up to 8 h following a 5 mg dose. Recently, it has been reported that hypertensive patients treated with other ACE inhibitors, captopril or enalapril, have developed cough (Sesko & Kaneko, 1986) and one patient treated with enalapril had a relapse of her bronchial asthma (Semple & Herd, 1986). However, chronic bronchitis on treatment with enalapril, demonstrated an increase, rather than a decrease, in FEV₁ (Howard *et al.*, 1987). Inhaled bradykinin causes cough and bronchoconstriction in asthmatics (Fuller *et al.*, 1986; Simonssen *et al.*, 1973). Bradykinin is metabolised by ACE (Regoli & Barab, 1980) present on lung endothelial cells. If ACE also contributes significantly to bradykinin metabolism in the airways, inhibition of this enzyme would lead to an increase in bradykinin, which would explain the cough and altered airway function following treatment with this class of drugs. We have, therefore, explored the effect of ramipril (10 mg orally) and matched placebo on the bronchoconstriction caused by inhalation of histamine and bradykinin in a double-blind randomised study in six asthmatic subjects.

Methods

Subjects

Six male, normotensive, mild asthmatics, whose characteristics are shown in Table 1, gave their informed consent to take part in this study which had the approval of the hospital Ethics Committee. All the subjects were asked to refrain from bronchodilator therapy and drinks containing caffeine for 12 h prior to study.

Airway function

Specific airways conductance (sGaw) was measured using a computer-assisted whole-body plethysmograph (Chowienzyk *et al.*, 1982) each measurement being the mean of six sequential readings.

Bronchial provocation tests

On arrival all subjects had baseline measurements of sGaw before inhaling five breaths of control solution, (0.9% normal saline) from a breath actuated dosimeter (Mefar, Brescia, Italy) which delivers 0.024 ml per breath, mass median droplet diameter 5–7 μ . Inhalation of saline was then followed by measurement of sGaw. Cumulative dose-response curves were constructed by

Table 1 Subject details

	Age (years)	Smoking	Duration of asthma (years)	Therapy	sGaw (kPa ⁻¹ s ⁻¹)	PD ₃₅ Histamine (μmol)	PD ₃₅ Bradykinin (μmol)
1	24	+	20	Salbutamol p.r.n.	1.07	4.42	0.036
2	32	+	10	Terbutaline p.r.n.	1.11	0.07	0.05
3	32	—	28	Salbutamol reg	0.45	0.11	0.0047
4	42	+	30	Salbutamol reg	0.83	2.16	0.043
5	40	—	5	Salbutamol reg	0.67	4.17	1.21
6	26	—	15	Salbutamol p.r.n.	2.46	2.75	0.72

p.r.n. = as required, reg = regular

inhalation of doubling concentrations of either histamine (range 0.06–8 mg ml⁻¹ in normal saline), or bradykinin (range 0.03–8 mg ml⁻¹ in 10% ethanol), sGaw was measured 1 min after each inhalation, and the concentration of spasmogen increased until a greater than 35% fall in sGaw was achieved. The cumulative provocative dose of spasmogen causing a 35% fall in sGaw (PD₃₅) was then calculated by interpolation.

Protocol

Subjects attended the laboratory on 2 days at the same time of day at least 1 week apart. Following baseline measurement of sGaw, a histamine bronchial provocation test was performed and the PD₃₅ then calculated. A 5 ml blood sample was then taken, the plasma separated by centrifugation and stored at -80° C for analysis of ACE activity. ACE activity was measured by a spectrophotometric method (Macguire & Price, 1985).

Subjects then took 10 mg ramipril or matched placebo in a randomised, double-blind manner. Ninety minutes later a further blood sample was taken for measurement of ACE concentration. Baseline measurements of sGaw were again recorded and a second histamine provocation test performed. The subjects were allowed to rest until their sGaw had returned to baseline values and a bradykinin provocation test then performed.

Data analysis

The data were analysed by two way analysis of variance, *P* values of less than 0.05 were accepted as significant. Airway function and PD₃₅ values for histamine and bradykinin are expressed as geometric mean (range). ACE concentrations are expressed as mean (± s.d.).

Results

Airway function

No significant difference was found between baseline values of sGaw on the two study days. Geometric mean values were 0.95 (0.451–2.461) kPa⁻¹ s⁻¹ and 0.75 (0.303–2.135) kPa⁻¹ s⁻¹ on days 1 and 2 respectively.

No significant difference was found in the percentage change from baseline sGaw 90 min after the drug administration. The changes were 22.7 ± 31% after placebo and 11.8 ± 27% after ramipril.

Histamine and bradykinin sensitivity

No significant difference was found between mean baseline histamine sensitivity on the 2 days. Neither active nor placebo treatment altered histamine sensitivity. The geometric mean PD₃₅ was 0.97 (0.07–4.42) μmol before and 1.13 (0.092–4.4) μmol after placebo and 0.84 (0.11–3.89) μmol before and 1.08 (0.09–3.54) μmol after ramipril (Table 2). Similarly, neither treatment altered bradykinin sensitivity. The geometric mean was 0.083 (0.036–1.21) μmol after placebo and 0.18 (0.0058–1.54) μmol after ramipril.

ACE concentrations

The mean plasma concentration of ACE was 48 ± 6.8 u l⁻¹ before and < 10 u l⁻¹ after ramipril administration (*P* < 0.05). There was no significant change after placebo (41.5 ± 12.0 before and 48.6 ± 17 u l⁻¹ after).

Discussion

An acute reduction in plasma angiotensin converting enzyme concentration did not change

Table 2 Provocative doses of histamine and bradykinin which caused a 35% fall in specific airway conductance (PD_{35} μ mol) before and after placebo and 10 mg ramipril orally

Subject	Histamine				Bradykinin	
	placebo		ramipril		placebo	ramipril
	Pre	Post	Pre	Post		
1	4.42	1.94	0.5	0.5	0.036	0.38
2	0.07	0.46	0.11	1.9	0.05	0.08
3	0.11	0.092	0.19	0.09	0.0047	0.0058
4	2.16	2.02	2.26	1.84	0.043	0.12
5	4.17	2.89	3.88	3.54	1.21	1.12
6	2.75	4.4	3.89	2.8	0.72	1.54

non-specific sensitivity of six mild asthmatics to histamine or bradykinin, nor was cough frequency increased with ramipril treatment. This implies that the previously reported respiratory symptoms in association with ACE inhibition (Sesko & Kaneko, 1986; Semple & Herd, 1986) may not be due to inhibition of bradykinin degradation.

There may be several reasons why acute administration of an ACE inhibitor failed to alter airway responses to bradykinin. First insufficient drug may have reached the airway to inhibit ACE in that tissue. However, animal studies show that large amounts of radiolabelled ramipril can be found in the lung following oral administration (Eckert *et al.*, 1984). Secondly,

the symptoms occurred in patients after prolonged treatment and, therefore, extrapolation from an acute study in a small number of mild asthmatics to what may occur following prolonged treatment in more severe patients has to be made with caution. Thirdly, in the airway bradykinin may be metabolised by kininase I rather than ACE, challenging the hypothesis that ACE-inhibitors cause respiratory symptoms by increasing tissue levels of bradykinin.

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