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Dose-response relationship of the H_1-histamine antagonist, ebastine, against histamine and methacholine-induced bronchoconstriction in patients with asthma

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Abstract

In a double blind, randomised, placebo controlled trial in a group of extrinsic asthmatics, we have evaluated the potency and selectivity of ebastine, a new piperidine-type H_1-receptor antagonist, against histamine and methacholine-induced bronchoconstriction. The median histamine $PC_{20}FEV_1$ value following placebo was 3.15 mg/ml (0.24–58.84). When compared with placebo, ebastine produced significant protection at 10 mg (median $PC_{20} = 31.36$ mg/ml, $p = 0.008$) and 30 mg (median $PC_{20} = 42.14$ mg/ml, $p = 0.001$) but there appeared to be no significant dose effect. Ebastine also produced a small shift in the methacholine concentration-response curves to the right. We conclude that ebastine is an effective antagonist of histamine-induced bronchoconstriction in the asthmatic airway with evidence of minor blockade of methacholine-induced bronchoconstriction.

Introduction

Histamine has a number of physiological actions in the human including smooth muscle contraction, mediated via the H_1 receptor, responsible in the airways for bronchoconstriction [1]. Asthmatic patients show a dose-related bronchoconstrictor response to many inhaled mediators including histamine and the pharmacological blockade of this response has been used to identify agents with possible application to the treatment of asthma. We have studied the action of a recently developed H_1-blocking agent, ebastine, in asthmatic airways. Ebastine is a piperidine type antihistamine and undergoes extensive first pass metabolism to carebastine [2], which is 3–4 times more potent than the parent compound in its blockade of the H_1 receptor. The drug has a low incidence of adverse effects when administered at single doses of up to 90 mg.

Methods and materials

Twelve non-smoking atopic (greater than 2 mm diameter wheal response to at least two common allergens on skin-prick testing [Bencard, Brentford, England]) asthmatic patients aged 22 to 57 years (Table 1) were entered into the study. They had a mean forced expiratory volume in one second (FEV_1) of 3.02 litres (SD ± 0.63), representing a mean 90.5% (SD ± 9.7) of predicted. Bronchodilator treatment was witheld for 12 hours prior to each visit. The study was approved by the Southampton Hospitals and University Ethical Committee and written informed consent obtained from each subject.

The study was carried out in two phases and for each phase subjects received three doses of ebastine 10 mg, ebastine 30 mg or placebo (Laboratorios Almirall, Barcelona), at the same time on sucessive days. Each treatment period was separat-

Table 1
Patient demographics.

Vol.	Sex	Age	FEV_1	% PRED FEV_1	Treatment
1	M	27	3.85	97.5	S BM
2	F	57	2.10	79	S BU
3	F	22	3.15	90	S BM
4	M	53	3.15	87.5	S BM
5	F	28	2.90	90.6	S BM
6	F	38	1.85	74	S BM
7	M	31	3.10	76	S BM
8	F	28	3.4	97	S BM
9	F	23	3.30	96	S BM
10	F	53	2.70	100	S BM
11	M	42	4.00	94.5	S BM
12	F	43	2.7	104	S –

S = inhaled salbutamol, BM = inhaled beclomethasone and BU = inhaled budesonide.

Table 2
The effect of ebastine on bronchial provocation.

PC_{20} FEV_1 histamine			PC_{20} FEV_1 methacholine		
Placebo	Ebastine 10 mg	Ebastine 30 mg	Placebo	Ebastine 10 mg	Ebastine 30 mg
2.71	64.0	28.6	1.13	2.95	0.31
0.28	0.14	0.89	0.15	0.58	0.23
58.84	64.0	64.0	–	–	–
0.24	4.29	2.53	0.58	0.36	0.54
4.83	1.62	64.0	0.26	25.54	12.18
0.6	0.32	0.31			
3.59	52.35	64.0	1.11	3.7	1.59
10.31	64.0	64.0	0.93	2.99	1.67
8.95	64.0	64.0	0.59	18.34	10.09
9.49	63.97	55.67	4.38	3.78	6.46
1.48	10.36	1.79			
1.94	2.14	26.56			
Median values:					
3.15	31.36	42.14	0.76	3.35	1.63

ed by at least 7 days and administered as identical tablets (three per dose) in a double blind and randomised manner. During the first phase subjects attended on the third day of each treatment period. A 15 minute rest period was followed by two baseline measurements of FEV_1 after which the final treatment was administered. Measurements of FEV_1 were performed using a dry wedge spirometer (Vitatograph, Buckingham, UK) and on each occasion the highest recording of three attempts was used for analysis. FEV_1 was measured at hourly intervals for three hours and was followed by a histamine inhalation challenge, modified from the method described by Chai et al. [3]. Briefly, subjects initially inhaled five breaths of nebulised physiological saline diluent from end-tidal volume to maximal inspiratory capacity. Providing the FEV_1 did not fall from starting baseline by greater than 10% at three minutes, doubling concentrations of histamine acid phosphate (BDH Limited, Poole, England) from 0.03 to 32 mg/ml (0.1 to 104 mmol/litre) were administered. Solutions were nebulised using an Inspiron MiniNeb nebuliser (C.R. Bard International, Sunderland, UK) driven by compressed air at 8 l/min. Under these conditions the nebuliser output was 1 ml/min and the mass median particle diameter was 4.7 μm. The challenge was terminated when >20% fall from the post-saline FEV_1 value had been achieved or the maximum concentration of agonist (32 mg/ml) had been reached.

During the second phase of the trial the subjects underwent inhalation challenge with methacholine 0.03 to 32 mg/ml (0.16 to 164 mmol/litre), using the same challenge procedure as for histamine. The inhalation challenge was performed three hours after the last dose of ebastine or placebo.

Results

In Phase 1, there was no significant difference between baseline FEV_1 measurements, nor was there any significant change in FEV_1 measurements after any of the treatments. Following placebo and active treatments, histamine caused a fall in FEV_1 in all subjects which was expressed as a percentage of the post-saline value and plotted against the cumulative agonist concentration on a logarithmic scale. The provocation concentration of agonist causing a 20% fall in FEV_1 ($PC_{20}FEV_1$) was derived by interpolation of the linear portion of the curves. On nine occasions following ebastine, subjects failed to reach a 20% fall from the post saline value and a value of 64 mg/ml was assigned for analysis. When analysed using the method of Fieller none of the concentration-response curves departed significantly from parallel. Compared to placebo, ebastine produced significant (3–27 fold) protection against histamine induced bronchoconstriction at both the 10 mg ($p = 0.008$) and 30 mg ($p = 0.001$) doses, which represents minimum estimates on account of the censored values (Table 2). Four subjects failed to complete Phase 2, the methacholine arm of the study, due to non-atten-

dance (1), the development of excluding medical conditions (1), or deterioration in their asthma requiring additional medical treatment (2). In the remaining 8 subjects methacholine caused a concentration related fall in FEV_1 following all treatments. While the concentration-response curves with methacholine did not significantly depart from parallel for any of the treatments, ebastine produced a small displacement of the curves to the right when compared to placebo, which was significant for the 10 mg dose ($p=0.025$).

Discussion

We have shown that ebastine at 10 and 30 mg administered orally on three sucessive days is effective in antagonising bronchoconstriction provoked by inhaled histamine in asthmatic subjects, although no dose effect could be found. However, we failed to show any bronchodilatation following the last dose of ebastine 10 mg or 30 mg, reported following other new short-acting H_1-blocking agents administered as single doses [4], even in those subjects with reduced basal measurements of FEV_1. One explanation for this may be found in the pharmacokinetic profile of ebastine. Inhibition of histamine induced skin wheals reaches a maximum 2–6 hours post dosing, suggesting that maximal histamine blockade may have been attained by the time of final dosing. Moreover, the subjects recruited to the study had a baseline FEV_1 approaching their predicted normal and thus the potential for any further increase was limited.

The ability of ebastine to produce a small protective effect against bronchoconstriction provoked by methacholine may reflect physiological antagonism. Alternatively, the drug or its metabolites may have a limited anti-muscarinic effect in the airways but when compared to the histamine blocking activity the effect is small.

In conclusion, we have shown that ebastine is a potent H_1-histamine antagonist in asthmatic airways. Since histamine is known to contribute as a mediator of bronchoconstriction provoked by allergen [5] and exercise [6], ebastine may produce some beneficial effect in certain forms of asthma, particularly associated with repeated allergen exposure e.g. seasonal allergic asthma. Histamine, however, is just one of many mediators contributing to airways obstruction in asthma, making it unlikely that ebastine, along with other new H_1-antagonists will provide a major benefit to patients with chronic persistent asthma. Nevertheless, its use in treating seasonal rhinitis may have the additional benefit of producing some protection of the lower airways in patients with coexistent asthma, as recently reported for terfenadine [7].

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