Effect of azelastine on bronchoconstriction induced by histamine and leukotriene C4 in patients with extrinsic asthma

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ABSTRACT  Azelastine, a new oral agent with antiallergic and antihistamine properties, has been shown to inhibit the effect of histamine and leukotriene (LT) in vitro, though not a specific leukotriene receptor antagonist. The effect of both a single dose (8-8 mg) and 14 days' treatment (8-8 mg twice daily) with azelastine on bronchoconstriction induced by LTC4 and histamine has been examined in 10 patients with mild asthma in a placebo controlled, double blind, crossover study. LTC4 and histamine were inhaled in doubling concentrations from a dosimeter and the results expressed as the cumulative dose (PD) producing a 20% fall in FEV1 (PD20FEV1) and 35% fall in specific airways conductance (PD35gGaw). The single dose of azelastine produced a significantly greater FEV1 and gGaw values than placebo at 3 hours, but this bronchodilator effect was not present after 14 days of treatment. Azelastine was an effective H1 antagonist; after a single dose and 14 days' treatment with placebo the geometric mean PD20FEV1 histamine values (μmol) were 0-52 (95% confidence interval 0-14–1-83) and 0-54 (0-12–2-38), compared with 22-9 (11-5–38-3) and 15-2 (6-47–35-6) after azelastine (p < 0-01 for both). LTC4 was on average 1000 times more potent than histamine in inducing bronchoconstriction. Azelastine did not inhibit the effect of inhaled LTC4; the geometric mean PD20FEV1 LTC4 (nmol) after a single dose and 14 days' treatment was 0-60 and 0-59 with placebo compared with 0-65 and 0-75 with azelastine. The PD35gGaw LTC4 was also unchanged at 0-66 and 0-73 for placebo compared with 0-83 and 0-74 for azelastine. Thus prolonged blockade of H1 receptors did not attenuate the response to LTC4, suggesting that histamine and LTC4 act on bronchial smooth muscle through different receptors. Four patients complained of drowsiness while taking azelastine but only one who was taking placebo and three patients complained of a bitter, metallic taste while taking azelastine.

Airway hyperresponsiveness to specific and non-specific stimuli is characteristic of bronchial asthma, though the mechanisms are unclear. It has been suggested that the sulphidopeptide leukotrienes (LT), derived from membrane arachidonic acid, may play a part in airway hyperresponsiveness in asthmatic patients.1-3 LTC4 and LTD4 are released in vitro and in vivo after allergen challenge4 and both are extremely potent bronchoconstrictors in man. Inhaled LTE4 has been reported to enhance airway responsiveness to inhaled histamine in patients with asthma.8

Azelastine hydrochloride is a phthalazino derivative (4-(p-chlorobenzyl)-2-(hexahydr0-1H-aze pin-4yl)-(2H) phthalazino) with prolonged antiallergic and antihistamine activity after oral administration.9,11 It inhibits release of mediators from mast cells in response to antigen, calcium ionophore, concanavalin A, and compound 48/80 and in this respect is from 100 to 1000 times more potent than sodium cromoglycate, theophylline, ketotifen, astemizole, and verapamil.10 It also inhibits the synthesis and release of leukotrienes from the rat peritoneal mast cell and is reported to modify leukotriene induced bronchoconstriction in guinea pigs.11,12 Recently azelastine has been shown to attenuate the early bronchoconstrictor response to allergen in asthmatic patients.13 The effect of azelastine on leukotriene induced bronchoconstriction in patients with asthma has not been studied.
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previously. We have examined the effect of a single dose (8-8 mg) and of two weeks' treatment (8-8 mg twice daily) with azelastine on the resting bronchomotor tone and histamine and LTC4 induced bronchoconstriction in patients with mild extrinsic asthma in a double blind, placebo controlled, crossover study.

Methods

We studied 10 patients (five of them women), mean age 32 (range 22-40) years, with mild extrinsic asthma and positive responses to skinprick tests with common inhaled allergens. None of the patients was taking oral corticosteroids, theophyllines, sodium cromoglycate, or antihistamine or anticholinergic drugs. Inhaled β agonists were stopped at least 12 hours before the test. The study was approved by the hospital ethics committee and informed written consent was obtained from each subject.

Patients received either 8-8 mg of azelastine twice daily or identical placebo for 14 days with a washout period of 14 days between treatments. Treatment was given double blind and in random order. The full blood count and serum urea and electrolyte concentrations were determined and liver function tests were carried out on their entry to the study and at the end of each treatment period. Airway response was assessed by measuring FEV1 with a dry wedge spirometer (Vitalograph, Buckingham) and specific airways conductance (sGaw) with a constant volume body plethysmograph (Fenyves and Gut, Basel, Switzerland). The best of three attempts was recorded for FEV1, and the mean of eight satisfactory manoeuvres for sGaw by on-line data acquisition.

Histamine inhalation challenge was carried out in seven patients three hours after medication on the first and the 14th day of each treatment period. After pretreatment and post-treatment baseline FEV1 had been recorded patients inhaled 10 breaths of phosphate buffered saline (control) from a Mefar 120 nebuliser (Mefar, Elettromedicali, Brescia, Italy) with a dosimeter set at a constant delivery time (1-0 s) and pressure (25 lb/in2, 172 kPa). The patient breathed from functional residual capacity to total lung capacity with a breath hold time of three seconds between inhalations. Patients proceeded to histamine challenge if the change in FEV1, after inhalation of buffered saline was less than 5%. Each subject inhaled 10 breaths of histamine diaphosphate dissolved in phosphate buffered saline in doubling concentrations (from 0-018 to 39-4 μmol) until the FEV1 had fallen more than 20% below the lowest FEV1 value after inhalation of buffered saline (control). The results, expressed as the cumulative dose producing a 20% fall in the FEV1 (PD20 FEV1), were obtained from the log dose-response curves.

LTC4 challenge was performed one hour after the histamine inhalation challenge (four hours after treatment) and when FEV1 readings had returned to within 5% of pretreatment baseline values. LTC4 (Miles Laboratories, Slough) was stored at −70°C in sealed ampoules until it was used, and appropriate dilution was made freshly with phosphate buffered saline (pH 7-4). The dilutions were kept in ice until immediately before they were placed in the nebuliser. LTC4 was inhaled in doubling concentrations (from 0-025 to 3-2 nmol), and FEV1 and sGaw were measured five, seven, 10, 15, and 20 minutes later.

PD20FEV1 and PD20sGaw (cumulative dose producing a 35% fall in sGaw) were obtained from log dose-response curves. The changes in FEV1 and sGaw at each time after placebo and after azelastine were compared by analysis of variance. Log PD20FEV1 and PD20sGaw were compared by analysis of variance and Student’s t test.

Results

The subjects’ mean (SEM) FEV1 was 87% (3-3%) predicted on entry to the study. There was no significant difference in the mean pretreatment baseline FEV1 and sGaw values on the four study days. FEV1 and sGaw were unchanged after a single dose and after 14 days’ treatment with placebo (table). After the single dose of azelastine mean FEV1 was 9-6% greater than after placebo (2-91 v 2-61 l) and mean sGaw 20% greater (1-4 v 0-95 s−1 kPa−1) at 3 hours, both changes being significant (p < 0-05). After 14 days’ azelastine, however, there was no significant difference in mean FEV1 and sGaw values before and after azelastine. The drug was a potent H1 receptor antagonist in the airways (table, fig 1). After a single dose and 14 days’ treatment with placebo the geometric mean PD20FEV1 (95% confidence interval) for histamine was 0-52 (0-14–1-83) and 0-54 (0-12–2-38) μmol. After a single dose of azelastine the geometric mean PD20FEV1 was 22-9 (11-55–38-30) μmol, a 45 fold increase over placebo values (p < 0-01). After 14 days’ treatment with azelastine the geometric mean PD20FEV1 was 15-2 μmol (6-47–35-6), a 28 fold increase over placebo values (p < 0-01). The difference in inhibition after a single dose and 14 days’ treatment was not significant.

In seven patients who underwent LTC4 and histamine challenges, LTC4 was about 1000 times more potent than histamine. Azelastine had no effect on LTC4 induced bronchoconstriction (table, fig 2). The geometric mean PD20FEV1 for LTC4 was 0-60 (95% confidence interval 0-19–1-97) and 0-59 (0-22–1-54) nmol after a single dose and 14 days’ treatment with placebo respectively, compared with 0-65 (0-25–1-70) and 0-75 (0-46–1-22) nmol after a single dose and 14
Effect of a single dose and of 14 days' treatment with azelastine and placebo on baseline respiratory function and the responses to inhalation challenge in patients with asthma

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Azelastine</th>
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<tbody>
<tr>
<td>Day 1</td>
<td>Day 14</td>
</tr>
<tr>
<td>FEV₁ (l); n = 10</td>
<td>FEV₁ (l); n = 10</td>
</tr>
<tr>
<td>Before drug</td>
<td>2.79 (0.16)</td>
</tr>
<tr>
<td>After drug</td>
<td>2.75 (0.17)</td>
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<tr>
<td>p value</td>
<td>NS</td>
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sGaw (s⁻¹ kPa⁻¹); n = 10

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<tr>
<th>Placebo</th>
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<tbody>
<tr>
<td>Day 1</td>
<td>Day 14</td>
</tr>
<tr>
<td>Before drug</td>
<td>0.81 (0.13)</td>
</tr>
<tr>
<td>After drug</td>
<td>0.85 (0.16)</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
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Responses to inhalation challenges (geometric mean (95% confidence interval))

LTC₄ (nmol); n = 10

<table>
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<th>Placebo</th>
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<tr>
<td>Day 1</td>
<td>Day 14</td>
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<tr>
<td>PD₂₀FEV₁</td>
<td>0.60 (0.19 to 1.97)</td>
</tr>
<tr>
<td>PD₃₅sGaw</td>
<td>0.66 (0.27 to 1.65)</td>
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<tr>
<td>p value*</td>
<td>NS</td>
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Histamine (μmol); n = 7

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<tbody>
<tr>
<td>Day 1</td>
<td>Day 14</td>
</tr>
<tr>
<td>PD₂₀FEV₁</td>
<td>0.52 (0.14 to 1.83)</td>
</tr>
<tr>
<td>p value*</td>
<td>&lt;0.01</td>
</tr>
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</table>

*In the comparison with placebo.

sGaw, specific airways conductance; LTC₄, leukotriene C₄; PD₂₀FEV₁, provocative dose causing a 20% fall in FEV₁; PD₃₅, provocative dose causing a 35% fall in sGaw.

Fig 1 Individual and geometric mean (—) PD₂₀FEV₁, histamine values after treatment with placebo (P) and azelastine (AZ). PD₂₀FEV₁—provocative dose causing a 20% fall in FEV₁.

Fig 2 Individual and geometric mean (—) PD₂₀FEV₁ and PD₃₅sGaw leukotriene C₄ values after treatment with placebo (P) and azelastine (AZ). PD₂₀FEV₁—provocative dose causing a 20% fall in FEV₁; PD₃₅sGaw—provocative dose causing a 35% fall in specific airways conductance.

Four patients taking azelastine complained of drowsiness and three patients complained of a bitter taste. There was no significant period effect (analysis of variance).
Terfenadine and astemizole are specific H₁ receptor antagonists and lack anticholinergic and antiserotonin activity. These drugs have been shown to modify exercise and allergen induced bronchoconstriction in patients with asthma. In addition to H₁ receptor antagonism, many antihistamines at high concentrations have the capacity in vitro to stabilise mast cells and ketotifen falls into this class. Ketotifen, however, offers no greater protection against the immediate response to inhaled antigen than can be attributed to its capacity to block histamine.

Astemizole has also been reported to attenuate the early component (2–15 min) of the bronchoconstrictor response to antigen challenge. The protective effect of azelastine in the immediate asthmatic response to allergen inhalation reported by Ollier et al can also be explained by its potent H₁ receptor blocking activity.

The time course of the bronchoconstrictor response to leukotrienes and histamine differ in vivo and in vitro in man: leukotrienes have a slow onset of action, which is more prolonged and persistent than that of histamine. After histamine the peak response is reached within 4–8 minutes of inhalation whereas with leukotrienes the response is slower, reaching a peak at 20 minutes. Recently Arm et al have shown that inhaled LTE₄ can enhance histamine responsiveness in asthmatic patients but not in normal subjects. Holroyde et al and Barnes et al, using the specific leukotriene antagonists FPL 55712, FPL 59257, and L 49923, have shown that the drugs will effectively inhibit LTC₄ and LTD₄ mediated airway responses without modifying histamine responsiveness in normal subjects. H₁ receptor blocking drug did not inhibit leukotriene induced bronchoconstriction and our results with azelastine in this respect are consistent with these observations. Leukotrienes and histamine act independently on the bronchial smooth muscle through specific receptors and studies in animal lung tissues have identified a site specific for LTC₄ and LTD₄. It has been suggested that there may be heterogeneity of leukotriene receptors in view of the very different molar ratios of LTC₄, LTD₄ and LTE₄ required to elicit identical biological effects in different tissues, and because the rank order of potency for the leukotrienes in contracting guinea pig tracheal spirals differs from that for contraction of parenchymal strips. Drugs may vary in their ability to block responses according to their different receptor affinities. FPL 55712 was found to have a higher affinity for the LTD₄ receptor, which is consistent with its more effective antagonism of the LTD₄ induced contractile response of lung parenchymal strips. The differences between the effects in animals and in patients with asthma of azelastine, sodium cromoglicate, and the calcium channel blocker...
verapamil\textsuperscript{16} on leukotriene induced bronchoconstriction may be related to species differences and to the lack of a good animal model that can mimic human asthma. Further studies are required to elucidate the role of azelastine and similar compounds in asthma.

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