

Comparative in vivo bioactivity of modern H₁-antihistamines on AMP challenge in atopic asthma

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Background: Modern H₁-antihistamines differ in their in vitro binding affinity, but their comparative in vivo bioactivity in asthmatic airways is unknown.

Objectives: We compared clinically recommended doses of 3 H₁-antihistamines on airway hyperresponsiveness to AMP challenge (the primary outcome variable).

Methods: Sixteen atopic patients with mild-to-moderate asthma of whom 10 were receiving inhaled corticosteroid therapy (all had positive results to house dust mite on skin prick testing) were randomized in a double-blind, placebo-controlled, cross-over fashion to receive single doses of 5 mg of desloratadine, 180 mg of fexofenadine hydrochloride (FEX), 5 mg of levocetirizine dihydrochloride (LEV), or placebo, with AMP challenge performed 12 hours after dosing.

Results: All H₁-antihistamines demonstrated significantly greater ($P < .05$) geometric mean $\pm$ SEM AMP PC₂₀ values compared with that of placebo (86 ± 29 mg/mL): desloratadine, 189 ± 54 mg/mL; FEX, 176 ± 57 mg/mL; and LEV, 163 ± 48 mg/mL. Prechallenge forced expiratory flow at 25% to 75% of maximal lung volume (percent predicted) but not FEV₁ was significantly higher ($P < .05$) for all H₁-antihistamines compared with that of placebo ($53\% \pm 4\%$): desloratadine, $62\% \pm 4\%$; FEX, $62\% \pm 4\%$; and LEV, $59\% \pm 3\%$. There were no significant differences in either AMP PC₂₀ or lung function values among the H₁-antihistamines.

Conclusion: Single doses of H₁-antihistamines improved airway hyperresponsiveness and small-airways caliber to a similar degree. Data for in vitro binding affinity do not therefore translate into commensurate differences in in vivo bioactivity at clinically recommended doses. (*J Allergy Clin Immunol* 2003;111:337-41.)

Key words: H₁-antihistamines, desloratadine, fexofenadine, levocetirizine, adenosine monophosphate

Asthma and allergic rhinitis commonly coexist with histamine as a common mediator, producing smooth muscle contraction, vascular permeability, and associated inflammatory changes.¹ H₁-antihistamines are widely

Abbreviations used

AHR: Airway hyperresponsiveness

FEF₂₅₋₇₅: Forced expiratory flow at 25% to 75% of maximal lung volume

FEX: Fexofenadine hydrochloride

LEV: Levocetirizine dihydrochloride

used in the treatment of allergic rhinitis for alleviation of symptoms, such as nasal congestion, rhinorrhea, and sneezing. H₁-antihistamines might also improve airway hyperresponsiveness (AHR) to indirect-acting bronchoconstrictor stimuli, such as AMP or mannitol.^{2,3} This is especially relevant because AMP bronchial challenge has been shown to better correlate with allergic airway inflammation than a direct challenge, such as that with methacholine,⁴⁻⁶ which is associated with airway caliber. The effects of H₁-antihistamines on AMP occur through antagonism of histamine release from primed mast cells and might therefore be used as a suitable method for an in vivo bioassay of relative potency.

Modern H₁-antihistamines primarily consist of desloratadine, fexofenadine hydrochloride (FEX), and levocetirizine dihydrochloride (LEV). These drugs represent enantiomers or active metabolites of loratadine, terfenadine, and cetirizine, respectively. All modern H₁-antihistamines have been shown to exhibit anti-inflammatory activity that often surpasses that of their older predecessors.⁷⁻¹³ However, their relative effects on AHR to AMP challenge have not yet been studied. In addition, recent data suggest that FEX might paradoxically prolong recovery time after bronchial challenge with mannitol.³

We therefore elected to evaluate the effectiveness of the 3 different modern H₁-antihistamines desloratadine, FEX, and LEV at clinically recommended doses on AHR and recovery in patients with mild-to-moderate persistent atopic asthma by using AMP bronchial challenge.

METHODS

Patients

Eligible patients had stable mild-to-moderate persistent asthma for at least 3 months before the study, and none had received a course of oral corticosteroids or antibiotics during this period. All patients were recruited from our asthma database and were required to exhibit a positive reaction to house dust mite and at least one

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TABLE I. Patient demographic details

Subject	Sex	Age (y)	FEV ₁ (L)	FEV ₁ (%)	FEF ₂₅₋₇₅ (L/sec)	FEF ₂₅₋₇₅ (%)	AMP PC ₂₀ (mg/mL)	SPP (n)	ICS	Dose (μg)	Second line
1	F	35	2.60	89	3.22	86	93	6		0	
2	F	50	2.17	87	1.74	54	30	4	BDP	200	
3	M	45	3.59	93	3.14	74	112	4	FP	500	
4	M	49	2.52	72	1.86	47	12	3		0	
5	F	26	2.52	90	2.56	65	22	4	BDP	800	
6	M	66	2.13	67	1.25	38	46	2	FP	500	SM
7	F	43	2.58	102	2.38	70	158	4		0	
8	M	26	3.95	90	3.45	69	113	4		0	
9	F	30	3.34	108	3.84	97	189	2		0	
10	M	39	2.65	71	2.33	54	162	3		0	
11	F	51	1.54	72	1.21	39	108	5	BUD	800	
12	F	58	1.75	102	1.86	67	35	5	BDP	50	
13	F	41	2.32	82	2.43	68	184	2	BDP	800	
14	M	54	2.7	68	1.45	36	191	3	FP	500	SM
15	F	51	2.22	84	2.25	69	124	3	FP	500	SM
16	F	46	2.13	78	1.74	51	30	3	BDP	400	SM, TH

SPP, Positive skin prick test response; ICS, inhaled corticosteroids; BDP, beclomethasone dipropionate; FP, fluticasone propionate; SM, salmeterol; BUD, budesonide; TH, theophylline.

other common aeroallergen on skin prick testing and to demonstrate hyperresponsiveness to AMP on bronchial challenge testing with a PC₂₀ value of less than 200 mg/mL.¹⁴ All patients provided informed consent, and the study was approved by the Tayside Committee on Medical Research Ethics.

Study design

The study was conducted in a randomized, double-blind, placebo-controlled, cross-over fashion. Patients receiving second-line controller therapy, such as long-acting β_2 -agonists or theophylline, had them stopped during a 1-week washout period before the study. None of the patients were receiving antihistamine therapy. Patients were randomized to receive a single dose of either 5 mg of desloratadine (Neoclarityn; Schering-Plough Ltd, Welwyn Garden City, United Kingdom), 180 mg of FEX (Telfast; Aventis Pharma Ltd, West Malling, United Kingdom), 5 mg of LEV (Xyzal; UCB Pharma Ltd, Watford, United Kingdom), or placebo. All tablets were encapsulated and were identical in external physical appearance. Patients took the study capsules at 10 PM and attended the department the next morning at 10 AM. There was a washout period of 1 week between each study visit.

Measurements

Skin prick testing. Skin prick testing was performed according to a standard protocol (Bencard Testing Solutions, Welwyn Garden City, United Kingdom) with extracts, including house dust mite, cat, dog, grass, tree, and weed pollen, in addition to a negative control. Results were read after 15 minutes, with a positive reaction being defined as a wheal diameter of at least 2 mm greater than that elicited by the negative control.

Spirometry. Spirometry was performed according to the American Thoracic Society criteria¹⁵ by using a Vitalograph compact spirometer (Vitalograph Ltd, Buckingham, United Kingdom) with a computer-assisted pneumotachograph head and pressure transducer. The spirometer was calibrated daily with a Vitalograph 1-L precision syringe.

AMP bronchial challenge. AMP bronchial challenge was performed as previously described by Tan et al.¹⁶ In brief, AMP was administered at 90-second intervals in doubling concentrations from 0.09 to 800 mg/mL until a 20% reduction in FEV₁ was recorded.

Spontaneous recovery. Spontaneous recovery after AMP

bronchial challenge was monitored with measurement of FEV₁ at 10-minute intervals for 60 minutes.

Statistical analysis

The study was powered at 80% with an α error set at .05 (2 tailed) to detect a one doubling dilution difference in AMP PC₂₀ (the primary outcome variable) between randomized treatments, with a sample size of 16 completed patients in a cross-over design. An overall ANOVA, followed by multiple-range testing with the Bonferroni correction, was performed. Data for AMP PC₂₀ were logarithmically transformed to normalize distribution, and analyses were performed with the Statgraphics statistical software package (STSC Software Publishing Group, Rockville, Md).

RESULTS

Patients

Patient demographic data are shown in Table I. Sixteen patients (10 female and 6 male patients) with a mean $\pm$ SEM age of 44 ± 3 years were enrolled, and all completed the study per protocol. Ten patients were receiving inhaled corticosteroid therapy, which remained unchanged throughout the study. The geometric mean AMP PC₂₀ value at recruitment was 75 ± 17 mg/mL, and the mean FEV₁ value was $85\% \pm 3\%$ of predicted value.

Airway hyperresponsiveness

Airway hyperresponsiveness data are shown in Figs 1 and 2. All H₁-antihistamines demonstrated significantly greater ($P < .05$) geometric mean AMP PC₂₀ values compared with those caused by placebo (86 ± 29 mg/mL): desloratadine, 189 ± 54 mg/mL (a 0.9 doubling dilution difference; 95% CI, 0.4-1.4); FEX, 176 ± 57 mg/mL (a 0.9 doubling dilution difference; 95% CI, 0.4-1.5); and LEV, 163 ± 48 mg/mL (a 0.8 doubling dilution difference; 95% CI, 0.2-1.5). There were no significant differences in AMP PC₂₀ values when comparing the H₁-antihistamines.

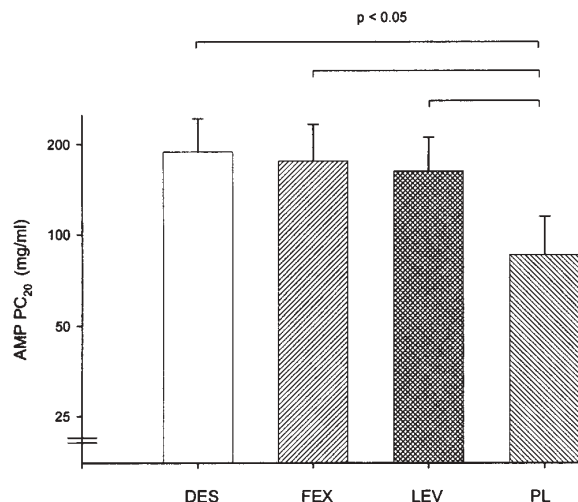


FIG 1. Geometric mean AMP PC₂₀ with geometric SEM, plotted on a log 2 scale to depict doubling dilutions. DES, Desloratadine; PL, placebo.

Spontaneous recovery

Data on spontaneous recovery are shown in Fig 3. The decrease in FEV₁ after AMP challenge as a percentage change from prechallenge baseline FEV₁ values were not significantly different in all 4 groups: desloratadine, 26% ± 2%; FEX, 26% ± 2%; LEV, 26% ± 1%; and placebo, 26% ± 1%. Recovery was significantly delayed compared with recovery after placebo for 20 minutes with all 3 H₁-antihistamines, for 40 minutes with FEX and LEV, and for 60 minutes with LEV alone. Recovery as area under the curve was delayed significantly ($P < .05$) with desloratadine (339% ± 54%.min) for 20 minutes compared with placebo (265% ± 41%.min), with FEX (618% ± 91%.min) for 40 minutes compared with placebo (439% ± 85%.min), and with LEV (783% ± 123%.min) for 60 minutes compared with placebo (559% ± 125%.min).

Lung function

Lung function data are shown in Fig 4. Prechallenge FEV₁ (percent predicted) was not significantly different when comparing all 4 groups: desloratadine, 86% ± 3%; FEX, 85% ± 4%; LEV, 83% ± 3%; and placebo, 80% ± 4%. Prechallenge forced expiratory flow at 25% to 75% of maximal lung volume (FEF₂₅₋₇₅; percent predicted) was significantly higher ($P < .05$) for all H₁-antihistamines compared with placebo (53% ± 4%): desloratadine, 62% ± 4% (mean difference, 9%; 95% CI, 2%-15%); FEX, 62% ± 4% (mean difference, 9%; 95% CI, 1%-16%); and LEV, 59% ± 3% (mean difference, 6%; 95% CI, 1%-10%). There were no significant differences in FEF₂₅₋₇₅ values among the H₁-antihistamines.

DISCUSSION

Our results show that single doses of H₁-antihistamines significantly improved AMP PC₂₀ and FEF₂₅₋₇₅ values compared with placebo in atopic patients with

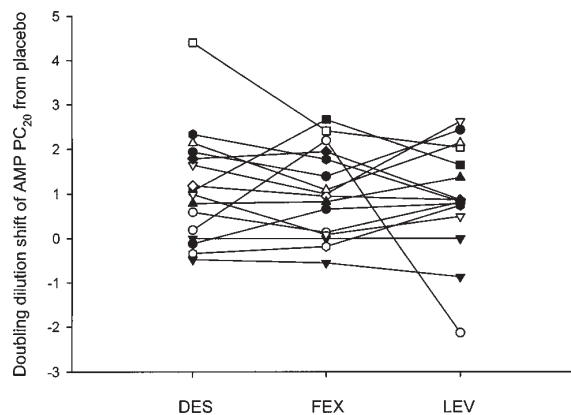


FIG 2. Scatter plot for individual AMP PC₂₀ values as doubling dilution shift from placebo. DES, Desloratadine.

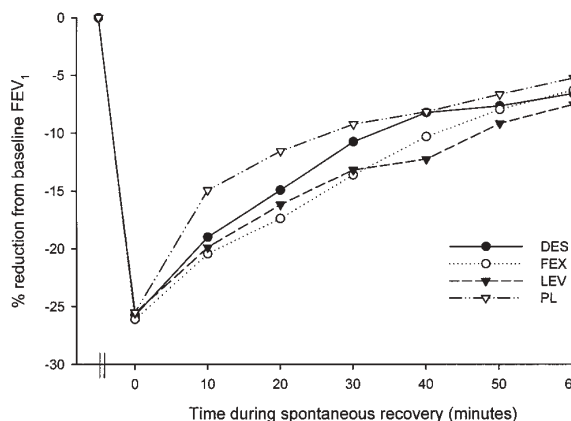


FIG 3. Time profile of spontaneous recovery after AMP challenge as a percentage mean reduction from baseline prechallenge FEV₁. Recovery was significantly delayed compared with recovery after placebo for 20 minutes with all 3 H₁-antihistamines, for 40 minutes with FEX and LEV, and for 60 minutes with LEV alone. DES, Desloratadine; PL, placebo.

mild-to-moderate persistent asthma. However, spontaneous recovery after AMP bronchial challenge was significantly delayed with all H₁-antihistamines.

AHR and inflammation are thought to be important hallmarks of asthma. AMP, when used as a bronchoconstrictor stimulus, acts by releasing inflammatory mediators from primed mast cells and has been shown to be more sensitive to changes in acute airway inflammation compared with direct-acting bronchial stimuli, such as methacholine.⁴⁻⁶ The response of AMP to more closely reflect the acute inflammatory processes involved in allergic airways disease justified its use in our study as a surrogate marker of inflammation. After single doses of the H₁-antihistamines, AMP PC₂₀ values significantly improved by approximately one doubling dilution, reflecting their potential for anti-inflammatory activity in asthma. Inspection of the scatter plot in Fig 2 shows considerable interpatient variability in the propensity for improving AMP-induced AHR.

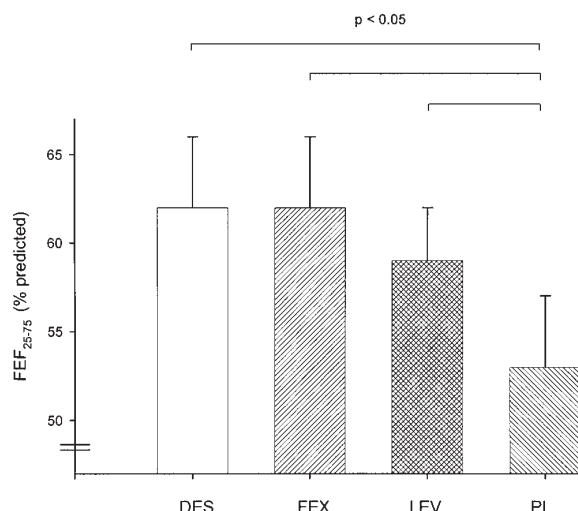


FIG 4. Mean FEF₂₅₋₇₅ (percent predicted) with SEM. DES, Desloratadine; PL, placebo.

The improvement in prechallenge lung function with the H₁-antihistamines was observed with FEF₂₅₋₇₅ but not with FEV₁. This is likely to be due to FEF₂₅₋₇₅ being a more sensitive indicator of changes in small-airways caliber. The bronchodilatory effects were surprising, especially in view of the response to just single doses of H₁-antihistamines. Moreover, it is noteworthy that the improvements in AMP PC₂₀ values for FEV₁ observed with the H₁-antihistamines were not merely due to improvements in airway geometry per se because the prechallenge FEV₁ values were not significantly different among all 4 groups. Thus the higher PC₂₀ value was likely to have reflected the mast cell-stabilizing effects of the H₁-antihistamines as such. Our patients were all allergic to house dust mite on skin prick testing, which would have resulted in mast cell priming and possibly explained the significant response observed with the H₁-antihistamines.

It is prudent to note that if we had not measured prechallenge FEF₂₅₋₇₅ as an outcome in our study, then the modest but significant effects of H₁-antihistamines on airway caliber would have been missed. Although FEF₂₅₋₇₅ is considered to be more sensitive to changes in small-airways caliber than FEV₁, it is not specific. Our patients had more room for potential improvement in airway caliber in terms of the percent predicted impairment of prechallenge FEF₂₅₋₇₅ compared with FEV₁. Whether this reflects a real effect of H₁-receptor antagonism in small airways is uncertain. We measured FEV₁ response to AMP challenge, which was sensitive to detect changes in airway caliber caused by mast cell-mediated histamine release.

There were differences in the way the H₁-antihistamines affected recovery compared with placebo in that LEV prolonged recovery the longest (ie, 60 minutes), and desloratadine had the shortest effect in delaying recovery (ie, 20 minutes), whereas FEX was intermediate in delaying recovery (ie, 40 minutes). These differences on recovery are difficult to explain because there were no differences in their respective PC₂₀ threshold values. A

similar prolongation of recovery has been reported after mannitol challenge with FEX.³ It is likely that the apparent delay in recovery is due to administering a higher dose of AMP (as PC₂₀ value) after H₁-antihistamine administration as opposed to placebo, which in turn results in a greater release of cysteinyl leukotrienes from mast cells and consequent bronchoconstriction. In this respect we have previously shown that spontaneous recovery after AMP challenge was shortened with the addition of a leukotriene receptor antagonist (ie, montelukast to desloratadine), despite a higher concomitant PC₂₀ value when compared with that produced by placebo.¹⁷ This serves not only to demonstrate that prolonged recovery is a leukotriene-mediated phenomenon but also an artifact of the process of bronchial challenge testing, whereby one has to administer a higher dose of AMP to produce the same degree of decrease in FEV₁. In other words, if patients received a fixed dose of AMP, one would expect to see a shortened recovery time with H₁-antihistamines compared with placebo. In real life, of course, this phenomenon of delayed recovery with H₁-antihistamines would not occur in the presence of a fixed dose of allergen or other such bronchoconstrictor stimuli.

Because the challenges were performed at 12 hours after drug administration, it is conceivable that the differences in recovery might be related to the duration of action of the H₁-antihistamines, although we would have expected commensurate differences in PC₂₀ values to have also occurred. Whether this might explain possible differences in receptor binding half-time requires further evaluation.

H₁-antihistamines have been demonstrated to exert anti-inflammatory activity in vitro. Desloratadine has been shown to exert effects on human monocytes, leading to downregulation of proinflammatory signals,¹⁸ and on human leukocytes by means of inhibition of T_H2 cytokine secretion, which is involved in the inflammatory process.¹⁹ FEX has been shown to inhibit TNF- α -stimulated epithelial cell activation in vitro at physiologically relevant concentrations, and it has been suggested that such activity in vivo would be anticipated to influence airway inflammation.²⁰ The anti-inflammatory properties of LEV have been demonstrated through its effects on both histamine- and cytokine-induced upregulation of eotaxin by endothelial cells²¹ and on modulation of inflammatory responses of human neutrophils.²² Although the mechanisms by which H₁-antihistamines exert their effects have been delineated by Leurs et al,²³ demonstrating that H₁-antihistamines interact with H₁-receptors as inverse agonists and not as antagonists of the effects of histamine, there are clearly other mechanisms, as demonstrated above, by which H₁-antihistamines exert their anti-inflammatory activity beyond and above mere interaction with H₁-receptors.

In vitro desloratadine has been shown to bind to the human H₁-receptor with a 200-fold greater affinity compared with FEX²⁴ and a 50-fold greater affinity compared with cetirizine.⁹ However, the differences observed in vitro with different modern H₁-antihistamines, especially with regard to affinity or potency, do not appear to

translate to in vivo bioactivity or efficacy as evidenced by the nonsignificant differences observed in both AMP PC₂₀ and FEF₂₅₋₇₅ values when comparing the H₁-antihistamines, as previously suggested by Waldman.²⁵ We have previously demonstrated that there were no differences observed between 5 mg of desloratadine and 180 mg of FEX taken for 2 weeks by patients with seasonal allergic rhinitis on either symptoms or peak nasal inspiratory flow measurements.²⁶ It is prudent to point out that the milligram dose of FEX used in the study is 36-fold higher compared with that of desloratadine, which might in part overcome differences in in vitro potency. On the other hand, the milligram dose of LEV was the same as for desloratadine, despite a 50-fold difference in in vitro binding affinity. Moreover, the doses used might well be on top of the dose-response curve for clinical efficacy. However, the H₁-antihistamines in the study were chosen to reflect standard recommended doses used in everyday clinical practice. One could perhaps argue for the study to be conducted with much lower doses to correspond with the steep part of the dose-response curve, although this would not be clinically relevant to currently prescribed doses.

It would therefore seem that modern H₁-antihistamines might have a potential role in the treatment of persistent atopic asthma because they improve both AMP PC₂₀, a surrogate marker of inflammation, and FEF₂₅₋₇₅, an indicator of small-airways caliber. Further studies with chronic dosing are indicated to evaluate noninvasive markers of inflammation, such as sputum or serum eosinophils and eosinophil cationic protein, circulating vascular adhesion molecules, and exhaled nitric oxide. Furthermore, long-term studies are indicated to assess whether there is potential for the additive effects of modern H₁-antihistamines to inhaled corticosteroids in asthma, as has been shown with leukotriene receptor antagonists.

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