

Comparative effects of desloratadine, fexofenadine, and levocetirizine on nasal adenosine monophosphate challenge in patients with perennial allergic rhinitis

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Summary

Background There are no data directly comparing the relative efficacy of modern H₁-antihistamines in allergic rhinitis using nasal provocation challenge.

Objective We elected to study the comparative effectiveness of usual clinically recommended doses of desloratadine (DES), fexofenadine (FEX), and levocetirizine (LEV), on nasal adenosine monophosphate (AMP) challenge in patients with perennial allergic rhinitis (PAR).

Methods 16 patients with PAR were randomized in double-blind cross-over fashion to receive single doses of DES 5 mg, FEX 180 mg, LEV 5 mg, or placebo (PL), with nasal AMP challenge performed 12 h after dosing. Measurements of peak nasal inspiratory flow (PNIF) were made over 60 min after nasal AMP challenge.

Results Pre-challenge values (mean $\pm$ SEM) for PNIF (L/min) were not significantly different comparing all groups; DES (129 $\pm$ 9), FEX (128 $\pm$ 11), LEV (128 $\pm$ 13), and PL (128 $\pm$ 12). The maximum % PNIF fall from baseline over 60 min after nasal AMP challenge was significantly attenuated ($P < 0.05$) compared to PL (50 $\pm$ 4), with DES (32 $\pm$ 5), FEX (36 $\pm$ 4), and LEV (36 $\pm$ 4). The area under the 60-min time–response curve (%.min) was also significantly attenuated ($P < 0.05$) compared to PL (2110 $\pm$ 268), with DES (1126 $\pm$ 285), FEX (1225 $\pm$ 255), and LEV (1261 $\pm$ 194). There were no significant differences between the three H₁-antihistamines for any outcomes.

Conclusion DES, FEX, and LEV were equally effective in attenuating the response to nasal AMP challenge. However, further long-term studies will be required to study their comparative effects on nasal symptoms, quality of life, as well as on nasal inflammatory cells.

Keywords adenosine monophosphate, desloratadine, fexofenadine, H₁-antihistamine, levocetirizine, nasal challenge, peak nasal inspiratory flow, perennial allergic rhinitis

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Introduction

H₁-antihistamines are currently advocated for the treatment of allergic rhinitis with alleviation of nasal symptoms. Modern H₁-antihistamines such as desloratadine (DES), fexofenadine (FEX), and levocetirizine (LEV) represent the active enantiomeric metabolites of loratadine, terfenadine, and cetirizine, respectively. Although *in vitro* and *in vivo* data are available regarding the efficacy of these modern H₁-antihistamines, there has been no study to date directly comparing their relative efficacy in patients with allergic rhinitis. This is especially relevant given the significant differences in human H₁-receptor binding affinities of the H₁-antihistamines [1, 2].

Nasal provocation with adenosine monophosphate (AMP) is a novel method of assessing upper airway hyper-responsiveness and has been shown to be both sensitive and reproducible [3]. AMP acts indirectly via primed airway mast

cells causing the release of pro-inflammatory mediators and is therefore considered to be a useful surrogate for effects on airway inflammation [4]. In addition, peak nasal inspiratory flow (PNIF) has been shown to be more sensitive than acoustic rhinometry or rhinomanometry in evaluating responses related to nasal provocation challenge [5]. We therefore elected to study the comparative effectiveness of usual clinically recommended doses of DES, FEX, and LEV, on nasal AMP challenge using PNIF measurements in patients with perennial allergic rhinitis (PAR).

Methods

Patients

Eligible patients had a history of PAR without concomitant asthma and none had received a course of oral corticosteroids or antibiotics over a period of at least 3 months. All patients were recruited from our database and were required to exhibit a positive reaction to house dust mite on skin prick testing. Patients were also required to demonstrate a positive response

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to nasal AMP challenge at screening as defined by a maximal fall in PNIF of at least 20% from baseline over 60 min. The study was conducted out of the pollen season in order to obviate any potential confounding effects in patients who were skin prick positive to pollen. All patients gave 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 concomitant PAR therapy such as intranasal corticosteroids or H₁-antihistamines had them stopped during a 1-week wash-out period prior to screening, and for the entire duration of the study. Patients were randomized to receive a single dose of either DES 5 mg (Neoclaritin[®], Schering-Plough Ltd, Welwyn Garden City, UK), FEX 180 mg (Telfast[®], Aventis Pharma Ltd, West Malling, UK), LEV 5 mg (Xyzal[®], UCB Pharma Ltd, Watford, UK), or placebo (PL). All tablets were encapsulated by a third party and were identical in external physical appearance. Patients took the study capsules at 22:00 hours and attended the department the next morning at 10:00 hours. There was a washout period of 1 week between each study visit.

Measurements

Skin prick testing Skin prick testing was performed following a standard protocol (Bencard Testing Solutions, Welwyn Garden City, UK) using extracts including house dust mite, cat, dog, grass, tree, and weed pollen in addition to a negative control. Results were read after 15 min, a positive reaction being defined as a weal diameter of at least 3 mm greater than the negative control.

Nasal endoscopy A significant degree of nasal septal deviation of more than 50% and the presence of nasal polypsis were excluded by nasal endoscopy using a rigid 30° Hopkins[®] Telescope (Karl Storz Endoscopy Ltd, Slough, UK).

PNIF All patients received appropriate instructions and were required to demonstrate good technique in recording their PNIF using the In-Check[®] PNIF meter (Clement Clarke International Ltd, Harlow, UK) at the initial screening visit. The technique was then further reassessed and reinforced, prior to each nasal AMP challenge, at each study visit.

Nasal AMP challenge Nasal AMP challenge was performed as previously described [6]. In brief, patients received a single dose of AMP (400 mg/mL) administered via a pump actuator spray device as two squirts per nostril. The response to nasal AMP challenge was recorded with measurements of PNIF at 1.5, 5, 10, 20, 30, 40, 50, and 60 min.

Statistical analysis

The study was powered at 80% with α -error set at 0.05 (two-tailed) in order to detect a 25% difference in the maximum % PNIF fall from baseline over 60 min (the primary outcome) between randomized treatments, with a sample size of 16 completed patients in a cross-over design. We also calculated the area under the 60-min time-response curve (AUC) as the

secondary outcome. An overall analysis of variance followed by multiple range-testing with Bonferroni correction set at 95% confidence interval (CI) was performed using Statgraphics[®] statistical software package (STSC Software Publishing Group, Rockville, MD, USA). In order not to confound the overall α -error, results were quoted as being either significant ($P < 0.05$) or not on the basis of the Bonferroni test.

Results

Patients

Patient demographic data are shown in Table 1. Sixteen patients (seven male patients and nine female patients) with mean $\pm$ standard error of mean age of 38 ± 4 years were enrolled and all completed the study per protocol.

Nasal AMP challenge

Nasal AMP challenge data are shown in Figs 1 and 2. Pre-challenge values for mean PNIF (l/min) were not significantly different comparing all groups; DES (129 ± 9), FEX (128 ± 11), LEV (128 ± 13), and PL (128 ± 12). There was no significant difference in the maximum % PNIF fall from baseline over 60 min comparing screening (49 ± 4) and PL (50 ± 4). The co-efficient of variation for the reproducibility of the nasal AMP challenge was 7.6%.

The maximum % PNIF fall from baseline over 60 min after nasal AMP challenge was significantly attenuated ($P < 0.05$) compared to PL (50 ± 4), with DES (32 ± 5): 95% CI for difference (2–34), FEX (36 ± 4): 95% CI for difference (1–27), and LEV (36 ± 4): 95% CI for difference (2–26). The AUC (%.min) was also significantly attenuated ($P < 0.05$) compared to PL (2110 $\pm$ 268), with DES (1126 $\pm$ 285): 95% CI for difference (19–1947), FEX (1225 $\pm$ 255): 95% CI for difference (71–1699), and LEV (1261 $\pm$ 194): 95% CI for

Table 1. Patient demographic details

Subject	Sex	Age (years)	SPP	Treatment
1	M	35	G, HDM, D, C	Cetirizine 10 mg PRN
2	F	42	G, W, HDM	Fluticasone 100 µg OD
3	F	48	HDM, D, C	Budesonide 100 µg BD
4	F	80	HDM, D	Mometasone 200 µg OD
5	M	25	G, T, HDM, C	Loratadine 10 mg PRN
6	M	33	G, W, HDM, D, C	Cetirizine 10 mg PRN
7	M	40	G, HDM, D, C	Cetirizine 10 mg PRN
8	M	27	G, T, W, HDM, C	Loratadine 10 mg PRN
9	F	41	HDM, C	Fluticasone 100 µg OD
10	M	44	G, HDM	Cetirizine 10 mg PRN
11	F	37	HDM, D	Fexofenadine 180 mg PRN
12	F	46	G, HDM	Fluticasone 100 µg OD, cetirizine 10 mg PRN
13	M	22	G, W, HDM, C	Loratadine 10 mg PRN
14	F	26	G, T, HDM, C	Cetirizine 10 mg PRN
15	F	19	G, T, W, HDM, C	Loratadine 10 mg PRN
16	F	43	HDM, D, C	Mometasone 200 µg OD

M, male; F, female; SPP, skin prick positive; G, grass; HDM, house dust mite; D, dog; C, cat; W, weed; T, tree; OD, once daily; BD, twice daily; PRN, as required.

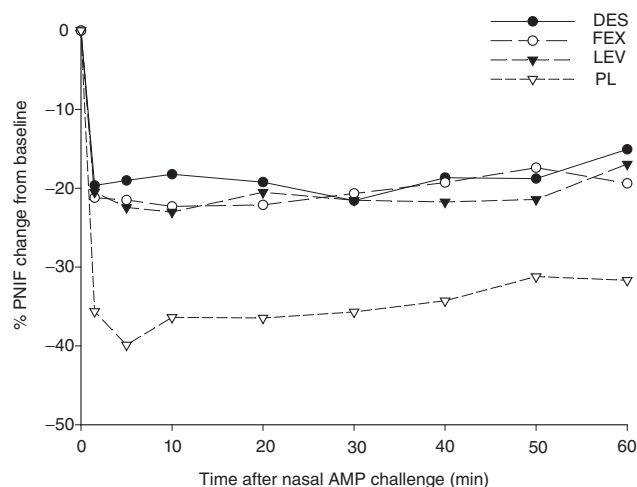


Fig. 1. Time-response profile over 60 min for % peak nasal inspiratory flow (PNIF) change from baseline after nasal adenosine monophosphate (AMP) challenge.

difference (121–1577). There were no significant differences between the three H_1 -antihistamines for either the maximum or AUC response.

Discussion

Our results showed that conventional doses of modern H_1 -antihistamines, DES, FEX, and LEV, all attenuated the response to nasal AMP provocation, compared to PL. There were no differences in efficacy comparing the individual H_1 -antihistamines suggesting that at clinically recommended doses, differences in *in vitro* binding affinities do not translate into differences in *in vivo* efficacy.

DES has been shown to have a 200-fold [1] and 50-fold [2] greater binding affinity *in vitro* compared to FEX and cetirizine, respectively. As the milligram dose of FEX (180 mg) is 36-fold greater than that of DES (5 mg), this would in part explain the similar *in vivo* efficacy despite the difference in *in vitro* binding affinities. However, as the milligram doses for DES and LEV were the same (5 mg), the lack of difference in clinical efficacy does not relate to the relative *in vitro* binding affinities. We had considered performing a dose ranging study, but decided to use standard recommended doses instead, as we felt this was more clinically relevant.

Modern H_1 -antihistamines are thought to exert anti-inflammatory effects through various mechanisms. DES has been found to down-regulate pro-inflammatory signals from human monocytes [7] and inhibit T helper cell Th2 cytokines from human leukocytes [8]. FEX has been shown to inhibit exocytosis and the release of pro-inflammatory mediators such as β -glucuronidase and interleukin (IL)-6 from human lung macrophages [9, 10]. FEX has also been found to reduce intercellular adhesion molecule ICAM-1 expression from epithelial cells and fibroblasts [11], in addition to attenuating eosinophil-induced release of IL-8, ICAM-1, and granulocyte macrophage-colony stimulating factor from human nasal epithelial cells [12]. Furthermore, tumour necrosis factor- α -stimulated cell activation is inhibited by FEX [13]. LEV has been shown to inhibit eotaxin-induced eosinophil transendothelial migration through both dermal and lung micro-

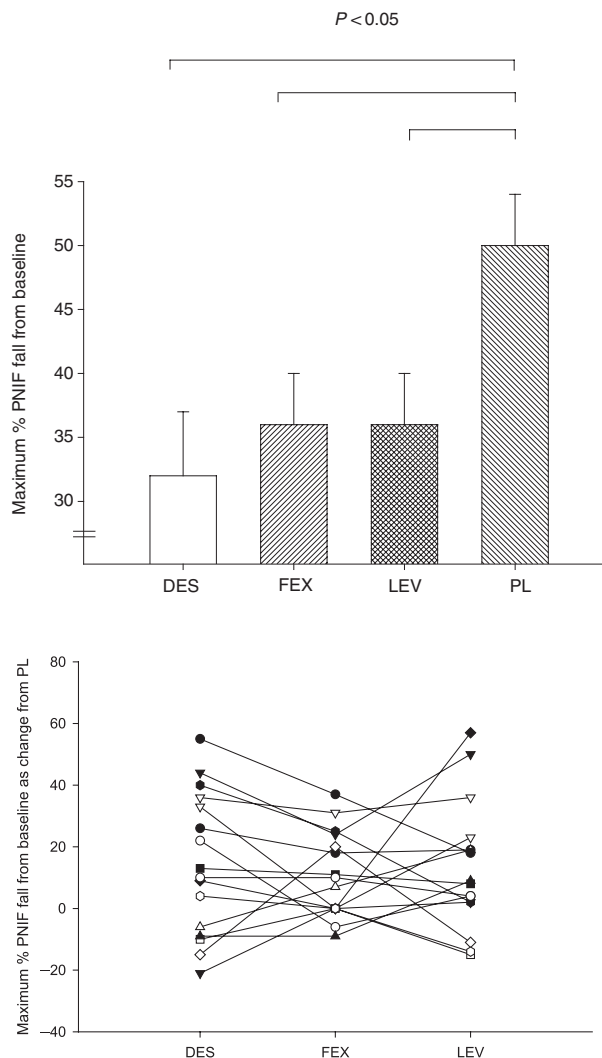


Fig. 2. Mean values for the maximum % peak nasal inspiratory flow (PNIF) fall from baseline over 60 min, with SEM (top). Individual data for the maximum % PNIF fall from baseline over 60 min, as change from placebo (PL), showing desloratadine (DES), fexofenadine (FEX), and levocetirizine (LEV) values, joined for each individual (bottom).

vascular endothelial cells [14], in addition to modulating inflammatory responses in human neutrophils [15] and inhibiting both histamine- and cytokine-induced up-regulation of eotaxin by endothelial cells [16].

We believe this to be the first study to evaluate the comparative *in vivo* efficacy of DES, FEX, and LEV in patients with allergic rhinitis. Previous comparative data have shown DES 5 mg and FEX 180 mg to be equally effective in improving PNIF and nasal symptoms in patients with seasonal allergic rhinitis (SAR) [17]. However, studies comparing FEX with loratadine offer conflicting results. In one SAR study, loratadine was found to have a better therapeutic response compared to FEX [18], while in another study the converse was true, with FEX being superior in relieving symptoms and nasal congestion as well as improving quality of life [19]. Furthermore, while FEX was found to be equally effective as cetirizine in a large multi-centre allergic rhinitis trial [20], the latter was shown to have a longer duration of action in another SAR study [21]. It is also important to note that we were careful to conduct our study out of the pollen season in order

to limit any potential confounding effects in patients who were skin prick positive to pollen.

A previous meta-analysis, which focussed on lung function parameters concluded that H₁-antihistamines were not effective in asthma [22]. However, it is appreciated that lung function is rather distant from the underlying inflammatory process, and consequently it is also important to evaluate the effects of H₁-antihistamines on surrogate inflammatory markers. We have recently shown that in asthmatics receiving chronic dosing with FEX 180 mg compared to either montelukast 10 mg or PL, as add-on therapy to inhaled corticosteroids, resulted not only in improvement in airway hyper-responsiveness to AMP, but also improvements in surrogate inflammatory markers such as exhaled nitric oxide and peripheral blood eosinophil count, as well as in asthma diary outcomes such as domiciliary peak expiratory flow and salbutamol rescue use [23]. Moreover, in another chronic dosing study comparing FEX 180 mg, montelukast 10 mg and PL, we have shown that the observed effects on nasal AMP challenge in PAR were accompanied by commensurate improvements in nasal symptoms [24]. In the present study, we used nasal AMP more as a surrogate test for assessing relative bioactivity *in vivo*, rather than comparing clinical efficacy, which would have needed a longer period of treatment looking at clinically relevant outcomes such as symptoms and quality of life.

In conclusion, it would seem that DES, FEX, and LEV are equally effective in attenuating the response to nasal AMP challenge. However, further long-term studies will be required to study their comparative effects on nasal symptoms, quality of life, as well as on nasal inflammatory cells.

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