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Effects of fexofenadine and desloratadine on subjective and objective measures of nasal congestion in seasonal allergic rhinitis

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Summary

Background *In vitro* studies have shown much higher H_1-receptor antagonist potency with desloratadine (DL) compared to fexofenadine (FEX), although it is unclear whether this has any clinical relevance on disease control parameters in seasonal allergic rhinitis (SAR), especially for nasal congestion.

Objective To compare the relative efficacy between presently recommended doses of DL and FEX on daily measurements of peak nasal inspiratory flow (PNIF) and nasal symptoms in SAR.

Methods Forty-nine patients with SAR were randomized into a double-blind, placebo-controlled cross-over study during the grass pollen season, comparing 2 weeks of once daily treatment with (a) 180 mg FEX or (b) 5 mg DL, taken in the morning. There was a 7–10 day placebo run-in and washout prior to each randomized treatment. Measurements were made in the morning (AM) and in the evening (PM) for PNIF (the primary outcome variable), nasal and eye symptoms. The average of AM/PM values were used for analysis.

Results There were significant ($P < 0.05$) improvements, compared to placebo, with FEX and DL, for PNIF, nasal blockage, nasal irritation, and total nasal symptoms, but not nasal discharge or eye symptoms. There were no significant differences between active treatments. Values for PNIF (L/min) for mean placebo baseline, mean difference from baseline (95% CI for difference) were 126, 10 (4–16) for FEX; and 122, 11 (4–17) for DL. The mean difference (95% CI) between FEX vs. DL was 1 L/min (−7–8). Values for total nasal symptoms (out of 12) were: 3.2, 0.7 (0.2–1.2) for FEX; and 3.4, 0.9 (0.3–1.5) for DL, and for nasal blockage (out of 3) were: 1.1, 0.2 (0.1–0.4) for FEX; and 1.2, 0.3 (0.1–0.5) for DL. The mean difference (95% CI) in total nasal symptoms and nasal blockage between FEX vs. DL was 0.1 (−0.6–0.8) and 0.1 (−0.2–0.3), respectively.

Conclusions Recommended once daily doses of fexofenadine and desloratadine were equally effective in improving nasal peak flow and nasal symptoms in SAR.

Keywords antihistamine, desloratadine, fexofenadine, nasal congestion, seasonal allergic rhinitis
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Introduction

Allergic rhinitis is a common inflammatory condition of the upper airways with a prevalence of between 9% and 42% [1], which is increasing in the western world [2]. Although rhinitis itself is not life-threatening, it is associated with other medical conditions such as asthma [3]. Furthermore, allergic rhinitis results in reduced quality of life [4], cognitive processing and psychomotor speed of sufferers [5]. This in turn results in decreased productivity at work with considerable cost to employers [6].

In a meta-analysis Weiner et al. reported that as a class, intranasal corticosteroids were more efficacious than antihistamines in allergic rhinitis, especially for their effect on nasal blockage in moderate to severe patients [7]. However in that analysis only first and second generation antihistamines were included, and it is unknown whether with more modern, third generation antihistamines, different results would have been found. Indeed, as histamine is an important mediator in allergic disease, antihistamines are considered to be the first-line therapy in seasonal allergic rhinitis [8, 9] particularly in young children as intranasal corticosteroids are difficult to administer [10]. Furthermore, antihistamines have a rapid onset and can be used on demand [11]. Recent guidelines recommend that the decision to use intranasal corticosteroids or antihistamines should be individualized, depending on the disease severity and the prevailing symptoms [12].

Fexofenadine, the active metabolite of terfenadine, and desloratadine, the active metabolite of loratadine, have been shown to be clinically effective and well tolerated when given once daily [13, 14]. It has been demonstrated that there is no significant change in QT_c interval when either fexofenadine or desloratadine were given in combination with azithromycin [15]. Both drugs have also been shown to be free from the daytime drowsiness which was associated with first generation antihistamines. In a meta-analysis, fexofenadine and loratadine

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were the least sedating antihistamines [16], whilst desloratadine has been reported to have no sedative effects in a review of this drug [14].

Prenner et al. [17] showed statistically greater reduction in total seasonal allergic rhinitis symptoms with loratadine and more fexofenadine non-responders improved with loratadine than vice versa. However, Van Cauwenberge et al. [18] showed greater effect with fexofenadine on nasal blockage and quality of life than loratadine in a multicentre study in patients with seasonal allergic rhinitis. In a recent study there was no significant difference between fexofenadine and the combination of loratadine and montelukast for nasal blockage and peak inspiratory flow, with both being superior to placebo [19]. *In vitro* studies have shown much greater H_1 receptor potency with desloratadine compared to fexofenadine [20]. However it is unknown whether such differences in *in vitro* potency are associated with commensurate differences in clinical efficacy in allergic rhinitis.

We therefore wished to evaluate the clinical efficacy of recommended daily doses of fexofenadine (180 mg) and desloratadine (5 mg) on subjective and objective outcome measures in seasonal allergic rhinitis, especially for nasal congestion. We assessed domiciliary peak nasal inspiratory flow rate, as this has been shown to be a sensitive objective method of assessing nasal function [21, 22], as well as assessing domiciliary subjective nasal symptoms.

Patients

Forty-nine patients mean (SE) age 32 (1.6) years ($n = 28$ females), with symptomatic seasonal allergic rhinitis according to current criteria, completed the study. All patients were recruited from primary care and had a positive skin prick test to grass pollens, a present and past history of SAR requiring treatment. Ten patients were also skin prick-positive to tree pollen and 15 patients to weed pollen. Patients were excluded if they had an FEV_1 less than 80% of predicted normal or a requirement for inhaled corticosteroids greater than 400 μg per day of beclomethasone or equivalent. Exclusion criteria also included a history of nasal polyps or aspirin sensitivity, clinically relevant septal deviation (> 50%) at rigid nasal endoscopy, or requirement for oral prednisolone or antibiotics within the preceding 6 months.

The mean FEV_1 was 102% predicted (range 81–139% predicted) and five patients were receiving inhaled corticosteroids. Prior to enrolling into the study, 18 patients were taking intranasal corticosteroids (beclomethasone dipropionate 200 μg bid $n = 9$, mometasone furoate 200 μg/day $n = 4$, fluticasone propionate 200 μg/day $n = 5$) and 34 were taking oral antihistamines (cetirizine 10 mg/day $n = 7$, loratadine 10 mg/day $n = 20$, desloratadine 5 mg/day $n = 2$, fexofenadine 120 mg/day $n = 1$, chlorpheniramine 4 mg qid $n = 4$). All patients were non-smokers and had normal full blood count, biochemical profile and urinalysis. Approval for the study was obtained from the Tayside Medical Ethics Committee and all patients gave their written informed consent.

Methods

The study was of a randomized, placebo-controlled, double-blind, cross-over design. Patients were enrolled during June and July 2001 during the pollen season in Tayside. All treatments were withdrawn including intranasal steroids, nasal decongestants and antihistamines, from the beginning of the study. Patients were randomized to receive the following for 2 weeks all given once daily at 08.00 h: (a) oral fexofenadine hydrochloride 180 mg once daily (as Telfast 180, Aventis Pharma, West Malling, UK), or (b) oral desloratadine 5 mg once daily (as Neoclarytin, Schering-Plough, Welwyn Garden City, UK). Prior to each treatment (run-in), and at cross-over, patients had a 7–10 day washout period with identical placebo tablets also taken once daily at 08.00 h. Throughout the study, patients were permitted to use rescue treatment with ocular cromoglycate for eye symptoms up to four times per day.

The tablets were encapsulated in double-blind fashion and sealed in envelopes by a pharmacist along with instruction sheets at the beginning of the trial. All treatments were dispensed by a third party. A tablet count was made after each treatment period. Each subject received a simple tick chart as an aide to compliance. Data from patients with more than 90% compliance from the tablet count were considered to be evaluable. All patients who completed the study were 100% compliant as assessed by the tablet count of returned treatment packs.

Measurements

Peak nasal inspiratory flow An In-check™ peak nasal inspiratory flow meter (Clement Clarke International Ltd, Harlow, UK) was used. After blowing their nose, patients inspired forcefully with their mouth closed. All measurements were made while in the sitting position with a good seal around a purpose built soft facemask. Measurements were made at the same time each day at 08.00 h and 20.00 h throughout the study and patients recorded the highest of three readings. Analysis was performed on the average daily value.

Symptoms Patients recorded their seasonal allergic rhinitis symptoms under nasal symptoms as 'runny nose', 'blocked nose', 'itchy nose' and 'sneezing'; and under eye symptoms as 'itchy eyes', 'watery eyes' and 'red eyes' in the morning and evening. All symptoms were documented according to a 4-point scale with 0 indicating no symptoms and three indicating severe symptoms. Recordings were made at 08.00 h and 20.00 h each day. For data analysis, the averages of the morning and evening values were used. Eye symptoms were taken as the total of the three ocular components (out of 9), nasal irritation was taken as the sum of itch and sneeze (out of 6), total nasal symptoms was taken as the composite of the four nasal components, i.e. itch, sneeze, blockage, discharge (out of 12).

Skin prick testing Patients withheld antihistamine medication for four days prior to skin prick testing. This was performed following a standard protocol (Allergopharma testing solution, Diagenics Ltd, Notts, UK) using extracts including grass, tree and weed pollen in addition to a positive (histamine) and negative control. Results were read after 10 min, a positive reaction being defined as a weal diameter of 3 mm greater than negative control.

Pollen count measurement Data was collected locally (Scottish Crop Research Institute, Dundee, UK) using a 7-day recording volumetric spore trap (Burkard Manufacturing Co

Ltd, Hertfordshire, UK) for total grass pollen. Pollen count was used as a covariate in the analysis to obviate for any variation in pollen count.

Adverse events At the end of each placebo and active treatment phase patients were asked to describe any adverse symptoms or events that they experienced.

Statistical analysis The primary outcome variable was the average of AM/PM domiciliary peak nasal inspiratory flow (PNIF) for comparison between randomized treatments. The study was designed with $n = 30$ completed patients with at least 80% power in order to detect a 10-L/min change in peak nasal inspiratory flow. For all domiciliary diary and pollen data, mean values for the last 5 days of the non-randomized placebo and active treatment periods were analysed.

Overall comparisons between active treatments and placebo were made by analysis of variance using subject, treatment and sequence as factors. The pollen count was used as a covariate to obviate any influence of pollen level on treatment response. This was followed by multiple range testing (set at 95% CI using Bonferroni's correction), so as not to confound the overall alpha error. Consequently, comparisons are only denoted as being significant ($P < 0.05$, two-tailed) or not significant. The analysis was performed using Statgraphics statistical software package (STSC Software Publishing Group, Rockville, MD, USA).

Results

Patient withdrawals

Fifty-seven patients were initially enrolled into the study with 49 completing the study as per protocol. Of the nine patients who withdrew from the study, five withdrew during the first placebo period. One because of viral infection, three because of withdrawal of consent, and one because of acute sinusitis. One patient withdrew during the second placebo period due to social reasons and one patient withdrew during the desloratadine first active treatment study due to exacerbations of their seasonal allergic rhinitis. One patient completed the study but failed to return the diary card data therefore the data were not available.

Adverse effects

There were no major adverse events. Twenty-one spontaneously reported minor adverse effects were documented during the study. The total number of adverse effects during placebo prior to fexofenadine was $n = 7$, during placebo prior to desloratadine was $n = 4$, during fexofenadine $n = 6$, during desloratadine was $n = 4$. There was no difference between the active treatments and in particular no reports of increased drowsiness, dry mouth or blurred vision. (Table 1).

Table 1. Number of spontaneously reported minor adverse effects during the study. There was no difference between the two treatments. There were no major adverse events during the study

	Placebo prior to FEX	FEX	Placebo prior to DL	DL
Drowsiness	1	0	2	1
Headaches	1	3	1	0
Stomach upset	2	0	0	2
Sore tongue	0	0	1	0
Urinary frequency	1	0	0	0
Sinus pain/earache	1	1	0	0
Tightness of chest	1	0	0	0
Worse control	0	1	0	0
Skin rash	0	1	0	1
Total	7	6	4	4

Peak nasal inspiratory flow

For the primary outcome variable, there were no significant differences between the placebos prior to each randomized treatment, nor were there any differences between randomized treatments for PNIF. There were significant improvements in PNIF with both randomized treatments, compared to placebo baseline, amounting to a 10 (95% CI 4–16) L/min difference with FEX, and 11 (4–17) L/min difference with DL. The difference between DL vs. FEX was 1 (−7–8) L/min. (Tables 2, 3 & 4).

Seasonal allergic rhinitis symptoms

There were no significant difference between the placebo values prior to each treatment nor was there any difference between randomized treatments for any of the subjective symptoms. There were significant improvements in most outcomes with both randomized treatments compared to placebo, apart from nasal discharge and eye symptoms.

Discussion

We have shown that presently recommended once daily doses of fexofenadine (180 mg) and desloratadine (5 mg) were equally effective in improving domiciliary PNIF (the primary outcome) and seasonal allergic rhinitis symptoms apart from nasal discharge. Thus, differences in *in vitro* potency between desloratadine and fexofenadine were not associated with commensurate differences in objective or subjective clinical outcomes of nasal congestion. Further studies are required to investigate whether the difference in potency might translate into clinically meaningful effects in subjective symptoms using recommended doses, with a larger sample size or with more severe blockage in patients with perennial allergic rhinitis. Another possibility to investigate relative *in vivo* efficacy might be to perform a dose–response study using nasal provocation challenge, although it would not be clinically relevant to look at higher than recommended doses used in the present study. Although we found significant improvements in subjective and objective outcomes in our patients, we did not measure effects on quality of life, which is important in terms of what these changes mean for patients in everyday real life.

Previous studies have shown good clinical efficacy in terms of seasonal allergic rhinitis symptoms with both fexofenadine and desloratadine [13, 14, 23–28]. Furthermore, both drugs have been reported to have clinically significant improvements in terms of subjective nasal blockage [18, 29–31]. In a previous study in 37 patients with seasonal allergic rhinitis there was also a significant mean improvement in peak nasal inspiratory flow rate of 9 L/min with fexofenadine 120 mg per day [19]. In

Table 2. Mean values for placebo baseline prior to fexofenadine (95% CI for mean) and mean difference from baseline with fexofenadine (95% CI for difference) for average of AM/PM values for: peak nasal inspiratory flow (PNIF, L/min), nasal blockage (units: out of 3), nasal discharge (units: out of 3), nasal irritation (units: out of 6), eye symptoms (units: out of 9), total nasal symptoms (units: out of 12). Asterisk denotes significant ($P < 0.05$) difference between active treatment vs. placebo

Measure	Placebo (mean)	CI for placebo	FEX (mean)	CI for FEX	Difference FEX vs. placebo	CI for difference
PNIF	126	(122–130)	136	(132–140)	10	(4–16)*
Nasal blockage	1.1	(1.0–1.2)	0.9	(0.8–1.0)	0.2	(0.1–0.4)*
Nasal discharge	0.6	(0.5–0.7)	0.5	(0.4–0.6)	0.1	(0.0–0.2)
Nasal irritation	1.4	(1.3–1.6)	1.1	(0.9–1.3)	0.4	(0.1–0.7)*
Eye symptoms	1.2	(1.0–1.5)	0.9	(0.7–1.2)	0.3	(0.0–0.6)
Total nasal symptoms	3.2	(2.9–3.5)	2.5	(2.2–2.8)	0.7	(0.2–1.1)*

Table 3. Mean values for placebo baseline prior to desloratidine (95% CI for mean) and mean difference from baseline with desloratadine (95% CI for difference) for average of AM/PM values for: peak nasal inspiratory flow (PNIF, L/min), nasal blockage (units: out of 3), nasal discharge (units: out of 3), nasal irritation (units: out of 6), eye symptoms (units: out of 9), total nasal symptoms (units: out of 12). Asterisk denotes significant ($P < 0.05$) difference between active treatments vs. placebo

Measure	Placebo (mean)	CI for placebo	DL (mean)	CI for DL	Difference DL vs. placebo	CI for difference
PNIF	122	(118–127)	133	(129–137)	11	(4–17)*
Nasal blockage	1.2	(1.1–1.4)	0.9	(0.8–1.1)	0.3	(0.1–0.5)*
Nasal discharge	0.6	(0.5–0.7)	0.6	(0.5–0.7)	0	(−0.1–0.2)
Nasal irritation	1.6	(1.4–1.8)	1.0	(0.8–1.2)	0.6	(0.3–0.9)*
Eye symptoms	1.4	(1.0–1.8)	1.0	(0.6–1.4)	0.4	(-0.2–1.0)
Total nasal symptoms	3.4	(3.1–3.8)	2.6	(2.2–3.0)	0.9	(0.3–1.5)*

this respect, it is recognized that both fexofenadine and desloratadine have effects on adhesion molecule synthesis [32, 33] which may modify eosinophil recruitment into the tissues and in turn nasal congestion. Our patients had relatively mild nasal blockage and so the response to treatment was relatively modest. Nonetheless, for patients with seasonal allergic rhinitis the decongestant effects of antihistamines are probably sufficient, whereas for perennial allergic patients where blockage is often more severe, a nasal corticosteroid would be indicated [12].

We have previously shown that repeated measures of domiciliary peak nasal inspiratory flow reflects nasal blockage and combined seasonal rhinitis symptoms [34]. Indeed it may be more representative of symptom response to treatment than the spot laboratory measures of acoustic rhinometry and rhinomanometry, which are clearly more expensive and time-consuming to perform [21, 22]. In previous studies it was possible to detect a treatment response with intranasal corticosteroid using serial domiciliary peak nasal inspiratory flow but not with spot laboratory measures, which indicates the greater sensitivity of this measure [22, 35]. This is analogous to the situation in asthma where serial measures of domiciliary peak expiratory flow rate are more sensitive than a spot laboratory measure of airways resistance or spirometry. Although peak nasal inspiratory flow is simple to perform, the patient still requires education and re-enforcement as with any other technique-dependant manoeuvre. For this reason, we checked the patient's technique at each visit and therefore can be reasonably sure that the results are valid. We were surprised that neither drug significantly affected eye symptoms, given that antihistamines are particularly effective in this respect [12]. Indeed in a previous study of seasonal allergic rhinitis with a lower dose of fexofenadine (120 mg) we observed significant improvements in eye symptoms and reductions in ocular cromoglycate usage [19].

Table 4. Difference between FEX vs. DL (95% CI for difference) for average of AM/PM values for: peak nasal inspiratory flow (PNIF, L/min), nasal blockage (units: out of 3), nasal discharge (units: out of 3), nasal irritation (units: out of 6), eye symptoms (units: out of 9), total nasal symptoms (units: out of 12). None of the differences were significant

Measure	Difference FEX vs. DL	CI for FEX vs. DL
PNIF	1.0	(-7–8)
Nasal blockage	0.1	(-0.2–0.3)
Nasal discharge	0.1	(-0.1–0.2)
Nasal irritation	0.1	(-0.3–0.5)
Eye symptoms	0.1	(-0.5–0.7)
Total nasal symptoms	0.1	(-0.6–0.8)

The pollen counts can be variable in Tayside as a result of the changeable weather conditions. For this reason we felt that it was important to factor pollen count into the analysis so that we could be sure improvements in symptoms or peak flow would be due to the treatment response rather than changing pollen counts. The study was of a randomized cross-over design with equal numbers of patients starting with each active treatment, so varying pollen counts would have affected both treatments to

the same extent. Indeed there were no significant differences when comparing the placebo values at baselines prior to each of the randomized treatments.

It should be noted that neither treatment resulted in significant adverse events. In particular only a few patients commented on transient drowsiness. We did not ask patients specifically about anti-cholinergic symptoms but nobody reported adverse effects of dry mouth or blurred vision with either treatment. This is despite suggestions translated from *in vitro* data that desloratadine may exhibit anti-cholinergic activity at therapeutic doses [36].

In conclusion, we have shown that both fexofenadine and desloratadine were equally effective in improving nasal peak flow and seasonal allergic rhinitis symptoms. Differences in *in vitro* potency were not associated with commensurate differences in clinical outcome measures of nasal congestion. Larger scale studies are now required to investigate how these treatments compare in patients with more severe disease activity who have perennial allergic rhinitis, as well as evaluating effects on quality of life.

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