

A comparison of once daily fexofenadine versus the combination of montelukast plus loratadine on domiciliary nasal peak flow and symptoms in seasonal allergic rhinitis

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Summary

Background The combination of montelukast (ML) and loratadine (LT) has previously been shown to be superior to either drug alone in managing seasonal allergic rhinitis (SAR), whilst fexofenadine (FEX) has been shown to be better than LT as monotherapy.

Objectives We wished to compare ML + LT vs. FEX alone for effects on daily measurements (am/pm) of peak inspiratory flow (PIF) and symptoms.

Methods Thirty-seven patients with SAR (skin prick positive to grass pollen) were randomised into a single-blind, double-dummy placebo (PL)-controlled cross-over study during the grass pollen season, comparing 2 weeks of once daily treatment with (a) 120 mg FEX or (b) 10 mg ML + 10 mg LT. There was a 7–10 day placebo run-in and washout prior to each randomised treatment. The average of am/pm PIF (the primary outcome variable) was analysed. Patients recorded their symptom scores (from 0 to 3) twice daily, for nasal blockage, discharge, itching and sneezing with; total eye symptoms, ocular cromoglycate use, and daily activity. The total nasal symptom score was calculated as a composite (out of 24).

Results There were no significant differences between baselines after the run-in and washout placebos for any variables. There were significant ($P < 0.05$, Bonferroni) improvements in all symptoms and PIF compared to pooled placebo with both treatments for all end-points, but no differences between the two treatment regimes (as means and within-treatment 95% confidence intervals): PIF: PL 102 (98–107), FEX 111 (107–116), ML + LT 113 (109–118); total nasal symptoms: PL 7.4 (6.7–2.0), FEX 5.0 (4.3–5.7), ML + LT 4.0 (3.3–4.7).

Conclusions Once daily FEX as monotherapy was equally effective as the combination of once daily ML + LT in improving nasal peak flow and controlling symptoms in SAR. Further studies are indicated to assess whether ML confers additional benefits to FEX in SAR.

Keywords allergic rhinitis, leukotriene antagonist, antihistamine, fexofenadine, montelukast, loratadine, peak inspiratory flow

Submitted 6 November 2000; revised 6 April 2001; accepted 25 April 2001

Introduction

Allergic rhinitis is an inflammatory condition of the upper airways, which has an increasing incidence throughout the western world [1,2], and occurs in up to 20% of the population [3]. Although it does not have an associated mortality it causes distress and impaired quality of life to sufferers. This results in decreased productivity and potential absenteeism from work or schooling [4].

As histamine is a key mediator released from mast cells, antihistamines are considered to be the first-line therapy in

seasonal allergic rhinitis (SAR), particularly as they have a rapid onset and can be used on demand [5]. First generation antihistamines exhibited poor selectivity for H_1 receptors and had significant adverse effects including sedation and gastrointestinal upset. Newer antihistamines such as fexofenadine and loratadine do not cross the blood brain barrier and as a result have no clinically relevant sedation [6,7]. Although recent research has illustrated a beneficial effect of modern antihistamines on nasal blockage [8], it is generally considered that these drugs, as a class effect, are less effective against nasal congestion and blockage than against sneezing and itch [9,10]. This was shown in a study by Numata et al. [11] where the effects of mequitazine or pranlukast were evaluated, in patients with perennial allergic rhinitis, in terms of patients symptoms and response after nasal allergen challenge. The leukotriene receptor antagonist had no effect on sneezing whereas the antihistamine had no protection against nasal blockage during the nasal

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challenge. For this reason antihistamines have been combined with adrenoceptor stimulants [12] or leukotriene receptor antagonists [13].

Meltzer et al. [13] studied the effects of montelukast or loratadine alone or in combination for 2 weeks in patients with SAR. Neither drug when taken alone had a significant improvement in daytime nasal symptoms (the primary end-point), although there was a significant difference from placebo when drugs were used in combination. However no objective measurement of nasal airflow obstruction was evaluated. In another 4 week study there was a significant effect on nasal symptoms and nasal peak inspiratory flow (PIF) with cetirizine as monotherapy but no further benefit by adding in montelukast [8]. Furthermore, Simons et al. [14] showed significant suppression of cutaneous allergic responses with fexofenadine as monotherapy but no greater effect with the addition of montelukast.

Fexofenadine, the active metabolite of terfenadine, has been shown to be clinically effective when given once daily [15], but without the potential cardiac complications of terfenadine [16]. Studies have reported comparable efficacy compared to cetirizine but whereas cetirizine showed significant drowsiness compared to placebo fexofenadine did not [17]. Recently, fexofenadine has been shown to have a greater effect on quality of life, nasal blockage and eye symptoms than loratadine in patients with SAR [18].

We therefore wished to compare fexofenadine given alone vs. loratadine combined with a leukotriene receptor antagonist (montelukast) in SAR, using domiciliary PIF as the primary outcome variable for objective on nasal airflow obstruction. In addition we also measured subjective effects on daily symptoms scores. Recent data has suggested that domiciliary PIF is a reliable measure of disease control in SAR [8,19].

Patients

Thirty-seven patients (mean (SE) age 37.0 (2.0) yrs), with symptomatic SAR according to current criteria [20], completed the study. All patients had a positive skin prick test to grass pollens; a present and past history of SAR requiring treatment. Eighteen patients were also skin prick-positive to tree pollen, 17 patients to weed pollen and 10 patients to grass, weed and tree pollen. Patients were excluded if they had a history of persistent asthma, a requirement for inhaled corticosteroids, or an FEV₁ less than 90% of predicted normal, a history of nasal polyps or aspirin sensitivity, occlusive septal deviation (> 50%) or a requirement for oral prednisolone or antibiotics within the preceding 6 months.

Prior to enrolling into the study, 12 patients were taking intranasal corticosteroids (beclomethasone dipropionate 200 µg bid *n* = 9, triamcinolone acetate 200 µg/day *n* = 1, fluticasone propionate 200 µg/day *n* = 2) and 12 were taking oral antihistamines (cetirizine 10 mg/day *n* = 5, loratadine 10 mg/day *n* = 6, chlorpheniramine 4 mg qid *n* = 1). 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. A doctors exemption certificate was obtained from the Medicine Control Agency (UK) for using montelukast in SAR.

Methods

The study was of a randomised, placebo-controlled, single-blind, double-dummy, cross-over design (Fig. 1). Patients were enrolled during June and July 2000 when grass pollen levels are usually high in Tayside. All treatment was withdrawn including intranasal steroids, nasal decongestants and antihistamines, from the beginning of the study. Patients were randomised to receive the following for 2 weeks, all given once daily at 0800 h: (a) Oral fexofenadine hydrochloride 120 mg once daily (as Telfast 120, Aventis Pharmaceuticals, Kent, UK) plus placebo tablet, or (b) Oral loratadine 10 mg once daily (as Clarytin, Schering-Plough, Hertfordshire, UK) plus oral montelukast 10 mg once daily (as Singulair, Merk Sharp & Dohme Ltd, Hoddesdon, Herts, UK). Prior to each treatment (run-in), and at cross-over, patients had a 7–10 day washout period with placebo tablets also taken once daily at 0800 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 masked 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.

Measurements

Nasal peak flow

Nasal inspiratory flow rate was measured using an In-check[®] peak inspiratory flow meter (Clement Clarke International Ltd,

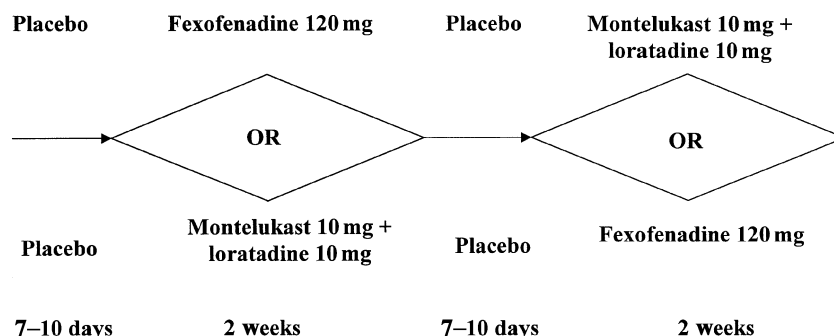


Fig. 1. Flow chart of the study.

Harlow, UK). After blowing their nose, patients inspired forcefully from residual volume to total lung capacity 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: 0800 h and 2000 h throughout the study and patients recorded the highest of three readings. Analysis was performed on the average daily value.

Symptoms

Patients recorded their SAR 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 four-point scale with 0 indicating no symptoms and 3 indicating severe symptoms. Patients were also asked to record how much their symptoms were interfering with their daily activity also on a four-point scale, with 0 representing no symptoms and 3 representing maximal symptoms. Recordings were made at 0800 h and 2000 h each day and the sum of the morning and evening symptoms were evaluated (i.e. out of 6). For statistical analysis eye symptoms were taken as the total of the morning and evening readings of the three ocular components (i.e. out of 18) and total nasal symptoms was taken as the composite of the four nasal components (i.e. out of 24).

Skin prick testing

Patients withheld antihistamine medication for four days prior to skin prick testing. This was performed following a standard protocol (Allerga pharma testing solution, Diagnostics 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 were collected locally (Scottish Crop Research Institute, Dundee, UK) using a seven-day recording volumetric spore trap (Burkard Manufacturing Co Ltd, Hertfordshire, UK) (Fig. 2) for total grass pollen. Pollen count was used as a covariate in the analysis to obviate for any variation in pollen count. Thus, falling pollen levels in August would not be a confounding factor in the analysis.

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 main end-point was domiciliary nasal inspiratory flow. The study was designed with $n = 30$ completed patients with at least 80% power in order to detect a 10-L/min change in nasal peak inspiratory flow [21]. For all domiciliary diary and pollen data, mean values for the last 5 days of the placebo and active treatment periods were analysed.

Overall comparisons between active treatments and placebos were made by multi-factorial analysis of variance using subject, treatment and period as factors. Having first shown no differences between placebo prior to each active treatment (i.e. run-in and washout baselines), subsequent comparisons were made using a pooled placebo and absolute values for each randomised treatment (i.e. as a group of three). The pollen count was used as a covariate to obviate any influence of pollen level on treatment response. This was followed by Bonferroni's multiple range testing (set at 95% CI) in order to obviate multiple pair-wise comparisons. Consequently comparisons are only denoted as being significant ($P < 0.05$, two-tailed) or not significant in order to not confound the overall alpha error. The analysis was performed using Statgraphics statistical software package (STSC Software Publishing Group, Rockville, MD, USA).

Results

Patient withdrawals

Forty-six patients were initially enrolled into the study with 37 completing the study as per protocol. Of the nine patients who withdrew from the study, four patients withdrew during the first placebo due to social or other commitments. Five patients withdrew during the study due to exacerbations of their SAR, three during the first placebo run-in phase and two during the second placebo washout phase.

Adverse effects

Ten patients documented an adverse effect during the study. One patient complained of a dry throat during both treatment

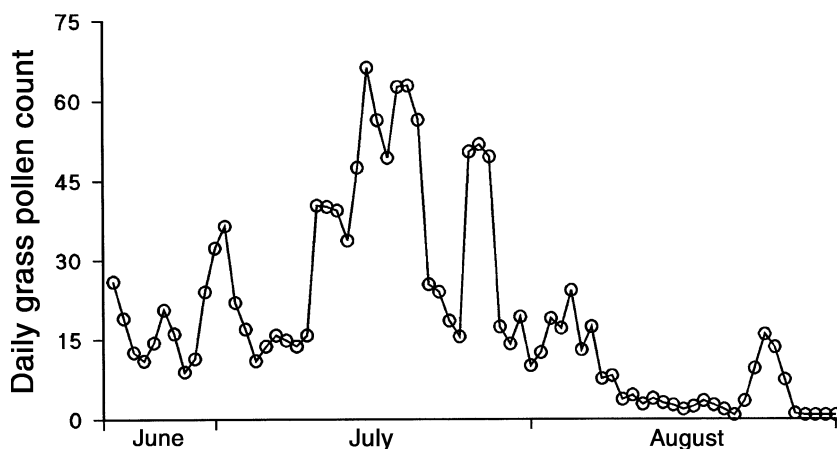


Fig. 2. Pollen counts for grass pollen (per m³) of the local area, as daily three point moving average, for the duration of the study (26 June–31 August 2000). The daily pollen count was factored into all analysis to ensure that variations in levels count would not confound the results.

and placebo periods. Three patients experienced tiredness or sleepiness with the combination therapy and two patients with fexofenadine although in most cases this was for a few days only. One patient complained of headache during the placebo period and another had a headache during the combination therapy. While receiving combination therapy one patient complained of diarrhoea and another complained of increased thirst.

Clinical end-points

There were no significant carry-over effects between run-in or washout placebo values for any of the end-points (Table 1). Consequently all comparisons were subsequently made compared to a pooled placebo. Pollen was factored into the analysis as a covariate in order to exclude the possibility of varying pollen counts influencing disease severity and outcome with different treatments.

Nasal peak inspiratory flow rate

Fexofenadine alone and the combination of montelukast and loratadine significantly improved ($P < 0.05$) the average daily PIF, although there was no significant difference between the treatment regimes (Table 2). The mean difference (95% CI for difference) between the two treatment limbs was 2 L/min (6–10 L/min). The time profile of PIF as average daily values can be seen in Fig. 3, indicating that improvements in both treatment regimens had a rapid onset. Although not intended as the primary end-point for data analysis, the breakdown into morning and evening PIF illustrates the circadian variation (Fig. 4).

SAR symptoms

Both fexofenadine alone and the combination of montelukast and loratadine significantly improved ($P < 0.05$) all recorded

symptoms, although there was no significant difference between the treatment regimes (Table 2). This included total nasal symptoms (and the individual components), eye symptoms, rescue sodium cromoglycate usage and daily activity score. The mean difference (95% CI for difference) between the two treatment limbs for total nasal symptoms was 1.0 (–0.2–2.2). There was a fast onset on action of both treatments in terms of total nasal symptoms (Fig. 5).

Discussion

We have shown that monotherapy with once daily fexofenadine 120 mg and the combination of once daily 10 mg loratadine plus 10 mg montelukast both exhibited clinically relevant improvements in domiciliary PIF and SAR symptoms. Furthermore, there was no significant difference between the two treatment regimes in terms of peak inspiratory flow (the primary end-point) or subjective outcome variables.

We believe that our data are consistent with previous experiences from the literature. Loratadine in combination with montelukast, but not alone, was significantly more effective than placebo on symptoms in SAR [13]. However, cetirizine alone exhibited significant efficacy compared to placebo in SAR but there was no advantage of adding montelukast [8]. This lack of additive effect may reflect the greater efficacy of cetirizine than loratadine in SAR [22] and may suggest that adding in a leukotriene receptor antagonist to a more potent antihistamine might confer little additive benefit in SAR. It would therefore be interesting to see if there was any additive benefit of montelukast when given together with fexofenadine compared to fexofenadine alone in SAR.

There have been few studies comparing fexofenadine and loratadine in patients with SAR. Prenner et al. [23] showed

Table 1. Means (95% confidence intervals) for peak inspiratory flow (PIF), nasal blockage, nasal discharge, nasal itch, sneezing, total nasal symptoms, eye symptoms, rescue ocular sodium cromoglycate usage (cromoglycate), and effect of disease on daily activity (daily activity) for the placebo run-in and washout periods. There was no significant difference between the two placebos for any end-point

	PIF (L/min)	Nasal blockage (0–6)	Nasal discharge (0–6)	Nasal itch (0–6)	Sneezing (0–6)	Total nasal symptoms (0–24)	Eye symptoms (0–18)	Cromoglycate (per day)	Daily activity (0–3)
Run-in	99	2.9	1.7	1.8	2.0	8.1	4.5	0.9	1.4
Placebo	(95–104)	(2.6–3.2)	(1.5–2.0)	(1.6–2.1)	(1.8–2.2)	(7.2–8.9)	(3.9–5.1)	(0.7–1.1)	(1.2–1.7)
Washout	104	2.4	1.5	1.8	1.7	6.9	3.6	0.6	1.1
Placebo	(100–110)	(2.1–2.6)	(1.3–1.8)	(1.6–2.1)	(1.5–2.0)	(6.1–7.7)	(3.0–4.2)	(0.5–0.8)	(0.9–1.3)

Table 2. Means (95% confidence intervals) for peak nasal inspiratory flow rate (PIF), nasal blockage, nasal discharge, nasal itch, sneezing, total nasal symptoms, eye symptoms, rescue ocular sodium cromoglycate usage (cromoglycate), and effect of disease on daily activity (daily activity). There was a significant ($P < 0.05$) difference between all end-points and placebo, but not between fexofenadine and the combination of loratadine plus montelukast

	PIF (L/min)	Nasal blockage (0–6)	Nasal discharge (0–6)	Nasal itch (0–6)	Sneezing (0–6)	Total nasal symptoms (0–24)	Eye symptoms (0–18)	Cromoglycate (per day)	Daily activity (0–3)
Placebo	102 (98–107)	2.6 (2.4–2.90)	1.6 (1.4–1.8)	1.8 (1.6–2.0)	1.8 (1.6–2.0)	7.4 (6.7–8.0)	4.0 (3.5–4.6)	0.8 (0.6–0.9)	1.3 (1.1–1.5)
Fexofenadine	111 (107–116)	2.0 (1.8–2.3)	0.8 (0.6–1.1)	1.1 (0.9–1.3)	1.1 (0.8–1.3)	5.0 (4.3–5.7)	2.5 (2.0–3.1)	0.3 (0.2–0.5)	0.7 (0.5–0.9)
Montelukast + loratadine	113 (109–118)	1.6 (1.4–1.9)	0.5 (0.3–0.8)	1.0 (0.8–1.2)	0.9 (0.7–1.1)	4.0 (3.3–4.7)	1.8 (0.3–2.4)	0.3 (0.2–0.5)	0.5 (0.3–0.8)

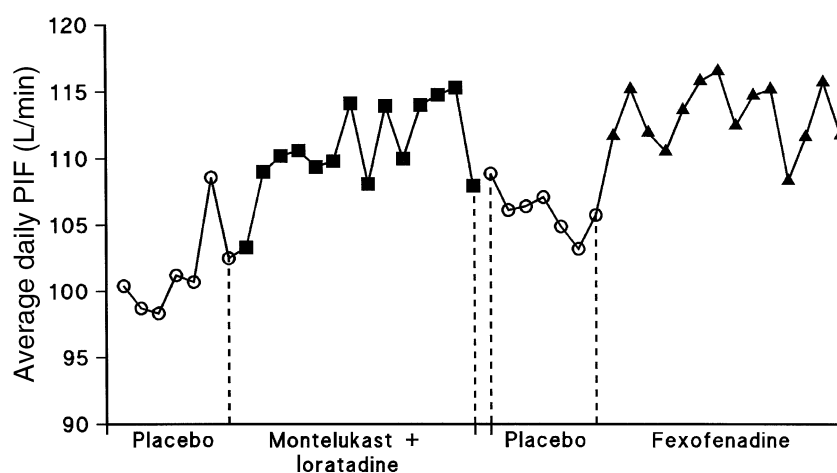


Fig. 3. Average daily peak inspiratory flow (the primary end-point) for the placebo period prior to fexofenadine (open circles), active treatment with montelukast and loratadine (solid squares), the placebo period prior to fexofenadine (open circles) and active treatment with fexofenadine (solid triangles) in litres per minute. Patients, in balanced blocks, were given the active treatments in random order so that half of the patients received fexofenadine prior to montelukast and loratadine.

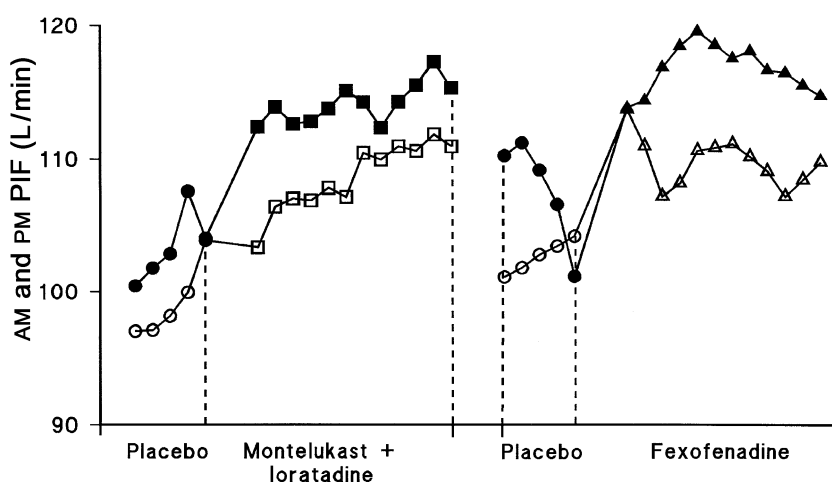


Fig. 4. Breakdown of daily peak inspiratory flow (as morning and evening values) to show the diurnal variation (L/min). For clarity data are represented as daily three day point moving averages. (Circles represent placebo, squares represent montelukast and loratadine, triangles represent fexofenadine, solid symbols represent evening values, open symbols represent morning values).

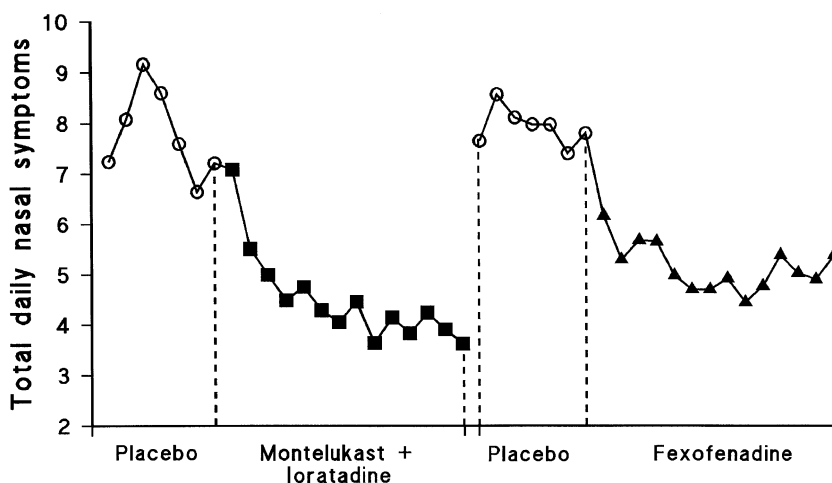


Fig. 5. Total daily nasal symptoms (units out of 24). Legend as Fig. 2.

statistically greater reduction in total SAR symptoms with loratadine and more fexofenadine non-responders improved with loratadine than vice versa. However, this is in contrast to a study assessing the inhibition of weal and flare response by antihistamines, which showed fexofenadine to be more potent than loratadine [24]. Van Cauwenberge et al. [18] also showed

fexofenadine to be superior to loratadine in controlling eye symptoms, nasal congestion and impact on quality of life.

It is interesting that fexofenadine was better at controlling nasal congestion as we found a significant improvement in nasal blockage with fexofenadine compared to placebo, and no significant difference when compared to the combination of

loratadine and montelukast. This finding is contrary to previous findings with older antihistamines, where nasal blockage was thought not to be controlled by these drugs [11]. However, it is recognized that the newer antihistamines have extensive anti-inflammatory effects, for example, on eosinophil recruitment and adhesion molecule synthesis [25]. In other words they are capable of attenuating the late- as well as early-phase allergic response as do leukotriene receptor antagonists [26].

In keeping with our findings on nasal blockage we found significant improvements with both treatments in terms of PIF. Nasal inspiratory flow has been studied both in the laboratory setting [27,28] and in the domiciliary setting [8]. In the latter study [8], PIF was shown to have good correlation with patients' rhinitis symptoms and treatment response. Furthermore, it has recently been suggested that patients symptoms correlate more closely to domiciliary peak inspiratory flow rate than snapshot laboratory measures of either acoustic rhinometry or rhinomanometry [19]. Domiciliary measures of nasal function have also been shown to be more sensitive than laboratory measures in assessing treatment response in patients with allergic rhinitis [29]. This is perhaps not surprising as repeated measurements are likely to be more sensitive than a single measurement, and are analogous to the use of domiciliary peak expiratory flow in asthma compared to the measurement of airways resistance or spirometry.

In order to ensure that this cross-over study was conducted during peak pollen levels it was designed to have relatively short treatment periods. However it can be seen from the time profile of average daily values throughout the study (Figs 3 and 4) that the onset of action of both treatments was rapid. Near maximal effects occurred within 2 days for SAR symptoms and PIF. In this respect the data suggests that both fexofenadine and loratadine have an onset of action within a few hours [16,30].

It can also be seen, however, from the time profile of pollen levels than the pollen season was rather brief this year in our area. For this reason it was imperative that pollen counts were factored as covariates into all of the analysis. In this way we can be sure that falling pollen counts towards the end of the study would not influence the results. Furthermore, as this study was of a cross-over design, the lower pollen counts at the end of the study would have affected both treatment groups similarly. We factored in grass pollen count rather than total pollen count as, although some patients were also responsive to tree and weed pollen, only ten patients had positive skin prick testing to all three pollens.

It should be noted that neither treatment regimes resulted in significant adverse events. In particular only a few patients commented on short-term lethargy. In this respect both fexofenadine and loratadine have been shown to be non-sedating antihistamines [6].

In conclusion, we have shown that fexofenadine alone or the combination of loratadine plus montelukast are beneficial in managing SAR without significant adverse effects. Furthermore, there was no significant difference between fexofenadine given alone and loratadine combined with montelukast. Further studies are now required to investigate whether the addition of montelukast confers additional benefits to fexofenadine in patients with seasonal allergic rhinitis.

Acknowledgement

The authors would like to thank Aventis Pharmaceuticals, Collegeville, USA for their financial support with this study.

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