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Evaluation of treatment response in patients with seasonal allergic rhinitis using domiciliary nasal peak inspiratory flow

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Summary

Background Measurement of domiciliary nasal peak inspiratory flow rate (PIFR) may have a role in the objective assessment of treatment response in seasonal allergic rhinitis (SAR).

Objective We wished to evaluate the relationship between domiciliary measurement of nasal PIFR and a variety of symptoms associated with rhinitis.

Methods Thirty-eight nonasthmatic patients, mean age (SEM) 30 years (1.4), with symptomatic SAR were evaluated in a placebo-controlled, single-blind, double-dummy, three way parallel group study. Patients received oral cetirizine 10 mg once daily and were randomized to receive, in addition, either: (i) intranasal mometasone furoate 200 μg ($n = 14$); (ii) oral montelukast 10 mg ($n = 11$); or (iii) placebo ($n = 13$). All treatments were given once daily for 4 weeks and were preceded by a 1 week placebo period. Domiciliary diary cards were used to record morning (am) and evening (pm) domiciliary nasal PIFR and symptom (nasal, eye, throat) scores and impact on daily activity. A total daily symptom score was then calculated from the sum of these separate symptom scores.

Results Baseline values for symptom scores and PIFR after placebo run-in were not significantly different when comparing the three groups. After 4 weeks of active treatment, there were significant ($P < 0.05$) improvements in nasal symptoms, total daily symptoms and PIFR with all treatments, with there being no significant confounding effect of pollen count, when analysed as a covariate. There were significant ($P < 0.01$) correlations for nasal symptom scores vs PIFRam ($r = -0.51$) and PIFRpm ($r = -0.56$), and similarly for daily activity vs PIFRam ($r = -0.42$) and PIFRpm ($r = -0.48$).

Conclusions These results suggest that domiciliary measurements of nasal peak flow correlate significantly with symptoms of seasonal allergic rhinitis and may therefore be a potentially useful objective short-term marker of treatment response.

Keywords: cetirizine, domiciliary, mometasone, montelukast, nasal peak inspiratory flow, seasonal allergic rhinitis, symptoms

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Introduction

The assessment of treatment response in patients with any disease process may be subjective or objective. For example, in asthma, the evaluation of treatment response is usually based on both subjective and objective parameters, typically symptoms and peak expiratory flow measurements [1]. The assessment of patients with allergic rhinitis has conventionally been by symptoms alone. Although this is adequate for some patients, a more objective marker of clinical efficacy would be useful, particularly when evaluating the effects of existing and new therapies.

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Nasal airflow obstruction is an important component of the allergic rhinitis syndrome [2]. It is possible to quantify this obstruction, usually in the laboratory setting, using rhinomanometry to measure nasal airway resistance. However, this requires expensive nonportable equipment together with staff skilled in its use and is therefore not applicable to routine domiciliary use. In clinical trials the measurement of forced nasal inspiratory volumes or flow rates are alternative ways of evaluating nasal obstruction.

Youlten [3] developed a portable peak nasal inspiratory flow meter in 1980. Since then, several studies [4,5] have compared it to rhinomanometry, in the setting of spot laboratory measurements, showing a good correlation with the added advantages of simplicity, portability and economy. There have, however, been no studies examining its use in the domiciliary setting in patients with allergic rhinitis.

Disease severity in seasonal allergic rhinitis (SAR) varies over a short-term basis. In view of this, domiciliary assessment of treatment response using nasal peak inspiratory flow (PIFR) measurement might be more informative, at least in the research setting, as a marker of treatment response, compared to one-off clinic measurements using rhinomanometry. Just as domiciliary peak expiratory flow measurement forms the cornerstone of asthma monitoring, we therefore wished to evaluate whether domiciliary nasal PIFR measurement might be a useful objective marker of treatment response in patients with allergic rhinitis. To make the study clinically relevant, we decided to study a group of symptomatic patients with SAR during the pollen season. In addition, in order to try to optimize the treatment response, we evaluated three different treatment regimes, although the study was not powered to discriminate efficacy between treatments. All treatment regimes included regular antihistamine, since our patients were symptomatic [2].

Materials and methods

Subjects

Forty patients aged 16–65 with symptomatic SAR [2] were initially recruited into the study. Two patients withdrew from the study during the placebo run-in prior to randomization, both because of upper respiratory tract infection. The remaining 38 patients were randomized into the study (Table 1). Inclusion criteria for the study were active nasal symptoms of rhinorrhoea, stuffiness and sneezing at the beginning of the run-in period, which were sufficient to require medical attention. All demonstrated a positive skin-prick test to at least one of the following pollen extracts: grass pollen ($n = 10$), weed pollen ($n = 0$), tree pollen ($n = 1$), grass and weed pollen ($n = 14$), grass and tree pollen ($n = 3$), weed and tree pollen ($n = 1$), grass and weed and tree pollen ($n = 9$). Thus, the majority ($n = 36$) of our patients were allergic to grass pollen. Patients were all nonsmokers with no history of other nasal or respiratory diseases and had normal spirometry, full medical examination, full blood count and biochemistry at initial screening. Approval for the study was obtained from the Tayside Medical Ethics Committee and all patients gave their written informed consent.

Design

The study had a randomized, placebo-controlled, single-blind, double dummy, three-way parallel group design. Patients were recruited during June-July 1998 when grass and pollen levels in Tayside are usually high. After a screening visit, symptomatic patients entered a minimum of 1-week placebo run-in period, having stopped their usual medication, followed by randomization to one of three active treatments.

During the placebo run-in period, each patient received two placebo tablets and a placebo nasal spray, each to be taken once daily in the morning. After run-in, patients began active treatment for 4 weeks with either (a) cetirizine hydrochloride 10 mg o.d. (as ZirtekTM, UCB Pharma, Watford, UK) and a placebo tablet and placebo nasal spray; (b) cetirizine hydrochloride 10 mg o.d. and an intranasal steroid, mometasone furoate 200 μg daily (as Nasonex^{TM}, 50 μg per actuation, Schering-Plough, Welwyn Garden City, UK) and a placebo tablet; (c) cetirizine hydrochloride 10 mg o.d. plus montelukast sodium 10 mg (as Singulair ^{TM}, Merck Sharp & Dohme Ltd, Herts, UK) and placebo nasal spray.

Table 1. Mean (SEM) data for patient characteristics at baseline after placebo run-in. There were no significant differences between treatment groups for any parameter

	Cetirizine	Cetirizine plus mometasone	Cetirizine plus montelukast
Age in years	30(2.5)	31(2.7)	31(2.4)
Sex (F/M)	10/3	9/5	7/4
Total daily symptom score	11.3(2.0)	10.0(1.8)	10.4(2.0)
PIFRam (L/min)	117(12)	103(8)	102(5)
PIFRpm (L/min)	115(12)	107(9)	117(7)

All medication was taken once daily at 8 a.m. each day and nasal sprays were always administered as two squirts into each nostril. Before the study and at each visit, all patients were given detailed instructions on how to use their nasal spray by an independent third party advisor and sprays were primed before use, according to manufacturer's instructions.

Patients attended the laboratory after 2 and 4 weeks of treatment, in order to check compliance tick charts and diary cards and to collect nasal peak flow data. An independent third party observer counted remaining tablets. In order to continue in the trial, patients were required to have taken more than 90% of the prescribed doses.

Measurements

Nasal peak inspiratory flow measurement

Patients measured peak nasal inspiratory flow at home, using a portable inspiratory flow meter (In-check^{TM}, Clement Clarke International Limited, Harlow, UK) with a purpose built facemask. Each patient used the same individual inspiratory flow meter throughout the study. Patients were instructed in how to use their inspiratory flow meter and technique was checked prior to the study and at each visit. Prior to testing, patients were instructed to blow their noses to expel secretions. All measurements were made in the sitting position, with a good seal round the facemask and patients inspired forcefully from residual volume to total lung capacity through their nose, with the mouth closed, according to manufacturer's instructions. Measurements were made twice daily, at approximately the same time each day $\pm$ 1 h, at 8 a.m. and 8 p.m., throughout the study. Three maximal inspiratory efforts were performed, the highest value being recorded by the patient. Technique for measuring nasal peak flow was checked at subsequent visits.

Symptom diary card

Patients recorded symptoms under four headings, i.e. nasal, eye, throat and daily activity score. Symptom scores were documented according to a 4-point scale with 0 representing no symptoms and 3 representing maximal symptoms. Under the heading of nasal symptoms, patients recorded 'runny nose', 'blocked/stuffy nose', 'itchy nose' and 'sneezing'. For eye symptoms, patients recorded 'itchy eyes', 'watery eyes' and 'red eyes'. Under the heading of throat symptoms, patients recorded 'tickly throat'. Patients were also asked to record how much their symptoms were interfering with their daily activity on an 11-point scale, with 0 representing no interference with daily activity and 10 representing maximal interference with daily activity.

Skin-prick testing

Patients withheld antihistamine medication for a minimum of 4 days prior to skin-prick testing. This was performed following a standard protocol (Bencard testing solutions, Welwyn Garden City, UK) using extracts including grass, tree and weed pollen in addition to positive and negative controls. Results were read after 10 min, a positive reaction being defined as a minimum wheal diameter of 3–5 mm, with erythema.

Pollen count measurement

Collection of data was local (Scottish Crop Research Institute, Dundee, UK) using a 7 day recording volumetric spore trap (Burkard Manufacturing Co Ltd, Hertfordshire, UK). Individual tree, grass and weed species pollen levels were summed daily to provide a total daily pollen score and this figure was used in subsequent analysis.

Data analysis

There were no previous studies examining the use of domiciliary nasal peak flow measurement to guide power calculations. Indeed, this was the rationale for the different treatment regimes in order to optimize potential response. Retrospective post hoc power calculation confirmed at least 90% power to detect a change of 15 L/min in nasal PIFR with our sample size. The primary end-points were considered to be nasal PIFR and combined nasal symptom score after 4 weeks of active treatment. For each day of the study, a total daily symptom score was calculated as the sum of each patient's individual symptom scores. For total daily symptom scores, daily activity scores and individual symptom scores, a mean for each week was calculated. The mean score for the week of the placebo run-in and for the week preceding each visit to the laboratory (i.e. weeks 2 and 4 of active treatment) were used for analysis purposes. Daily tree, grass and weed pollen level data were summed to provide a daily pollen score for each day of the study. Similarly, an average daily pollen score was calculated weekly.

Placebo and active treatments at both visits were compared by an overall multifactorial analysis of variance (MANOVA) using treatment, subject and time as factors for the analysis, followed by Bonferroni multiple range testing to obviate multiple pair-wise comparisons. Analysis of covariance was used to account for any possible changes in pollen count, with each of the treatments. The Bonferroni's multiple range test was set with 95% confidence intervals and hence any significant differences are by definition only reported at the $P < 0.05$ level (two-tailed). Least square regression analysis was used to assess the correlation between both morning and evening nasal PIFRs with nasal symptom scores as well as daily activity scoring. Data were analysed using a Statgraphics software package (STSC Software Group, Rockville, MD, USA) and SPSS version 7.5.2 software package (SPSS Inc, Woking, Surrey, UK).

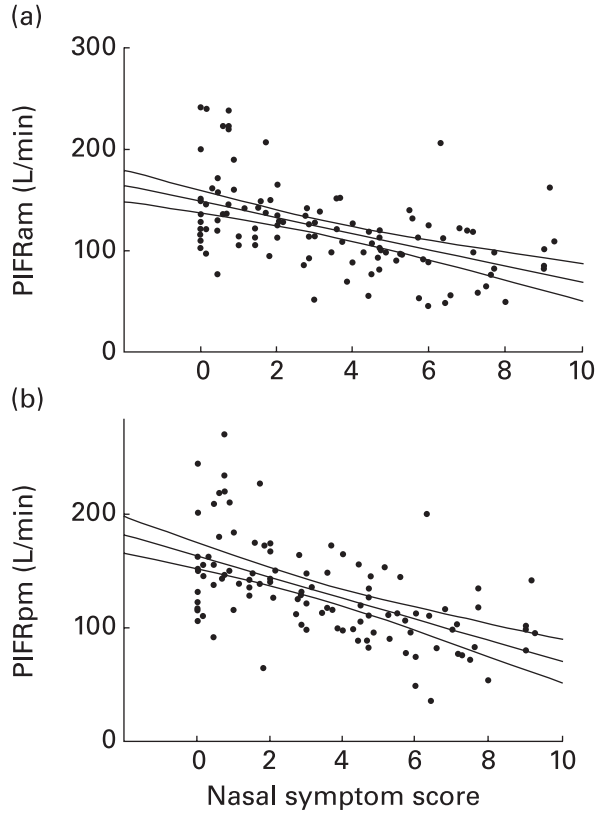

Fig. 1. Scatter plot of individual responses for nasal symptom score and (a) morning peak inspiratory nasal flow rate (PIFRam) (L/min) and (b) evening peak inspiratory flow rate (PIFRpm) (L/min). There was a significant ($P < 0.01$) correlation between nasal symptom score and PIFRam ($r = -0.51$), and PIFRpm ($r = -0.56$).

Results

Correlations

There were significant ($P < 0.01$) correlations for nasal symptoms vs PIFRam ($r = -0.51$) and PIFRpm ($r = -0.56$), total daily symptoms vs PIFRam ($r = -0.39$) and PIFRpm ($r = -0.46$) and daily activity vs PIFRam ($r = -0.42$) and PIFRpm ($r = -0.48$) (Fig. 1). For the individual nasal symptom of nasal stuffiness, there was a significant correlation with PIFRam ($r = -0.36$) and PIFRpm ($r = -0.37$).

Treatment effects

For nasal symptoms and PIFRpm, there were significant ($P < 0.05$) improvements compared to placebo, for all treatment groups after four weeks of treatment. This was mirrored for effects on total daily symptoms, which also showed significant decreases in all three groups. After four weeks, there was only a statistically significant ($P < 0.05$) improvement for PIFRam in the mometasone group (Table 2).

Eye symptoms exhibited a fall in all three groups, although this was only significant ($P < 0.05$) in the mometasone and montelukast groups. Likewise, there were improvements in throat symptoms and daily activity scores for all groups, but was only significant in the cetirizine and mometasone groups. There was no significant difference between different groups for any of the measured parameters.

Pollen data

Total pollen levels tended to fall during the course of the study but no statistically significant differences were noted between the level of exposure encountered by each treatment group (Fig. 2). Furthermore, the effects of each treatment on measured end-points were significantly independent of the pollen count, when the latter was factored into the analysis as a covariate.

Discussion

Our study is the first to have used domiciliary PIFR measurements in the assessment of treatment response patients with allergic rhinitis. We have demonstrated a significant correlation between improvements in nasal symptoms and peak inspiratory flow. Interestingly we also found a significant, although weaker, correlation with total seasonal allergic rhinitis symptom score and daily activity. The implication of our findings is that measurement of peak nasal inspiratory flow in the domiciliary setting may prove to be a valuable objective tool in assessing treatment response.

Studies have shown a good relationship between rhinomanometry and nasal inspiratory peak flow in volunteers and patients after nasal challenge tests [4–6]. Hellgren *et al.,* [7] also studied a group of 21 patients with seasonal allergic rhinitis and 20 healthy controls, challenged with histamine, showing that PIFR was more sensitive in detecting nasal obstruction than both rhinomanometry and acoustic rhinomanometry. Indeed, Jones *et al.,* [8] showed anterior rhinomanometry had a closer correlation with peak inspiratory nasal flow rate than with posterior rhinomanometry.

Other studies have shown that rhinomamometry is more sensitive than peak inspiratory nasal flow rate at detecting changes in response to histamine challenge [9] in patients with mild seasonal allergic rhinitis. This is probably because rhinomanometry measures nasal resistance by simultaneously measuring pressure and flow whereas peak inspiratory flow rate only measures air flow. Indeed our finding of a significant correlation between peak inspiratory flow rate and symptoms in relatively mild patients might suggest that domiciliary peak inspiratory flow rate may be even more relevant in patients with severe disease.

We wished to assess the correlation between domiciliary

Table 2. Mean (SEM) data for effect of treatment on domiciliary nasal peak flow and symptom scores. Asterisk represents significant difference compared to placebo baseline, after 2 weeks or 4 weeks of each active treatment. (*$P<0.05$, **$P<0.01$, ***$P<0.001$)

	Cetirizine			Cetirizine plus mometasone			Cetirizine plus montelukast		
	Placebo	2 weeks	4 weeks	Placebo	2 weeks	4 weeks	Placebo	2 weeks	4 weeks
Nasal flow									
PIFRam (L/min)	117 (13)	129 (13)	137 (16)	103 (8)	132** (12)	136** (13)	102 (5)	119 (13)	123 (12)
PIFRpm (L/min)	115 (12)	140** (13)	146** (14)	107 (9)	143** (14)	144** (17)	117 (7)	138 (13)	144* (13)
Symptoms									
Total	11.3 (2.1)	6.5 (1.4)	4.3** (1.4)	10.0 (1.8)	3.4*** (1.2)	2.1*** (1.1)	10.4 (2.0)	6.8** (1.5)	5.5** (1.2)
Nasal	5.3 (0.8)	3.5** (0.7)	2.5** (0.8)	4.8 (0.7)	1.8*** (0.6)	1.1*** (0.6)	5.2 (0.8)	3.1*** (0.7)	2.6*** (0.5)
Eye	2.4 (0.5)	1.2 (0.4)	1.0 (0.4)	1.6 (0.4)	0.6** (0.3)	0.4** (0.2)	2.1 (0.6)	1.2 (0.4)	0.9* (0.3)
Throat	1.1 (0.3)	0.3** (0.1)	0.1** (0.1)	1.1 (0.2)	0.6 (0.3)	0.4** (0.3)	0.7 (0.2)	0.5 (0.2)	0.2 (0.1)
Daily activity	3.5 (0.7)	2.1 (0.5)	1.1** (0.4)	2.6 (0.6)	0.7*** (0.3)	0.5*** (0.3)	2.4 (0.6)	2.0 (0.5)	1.8 (0.5)

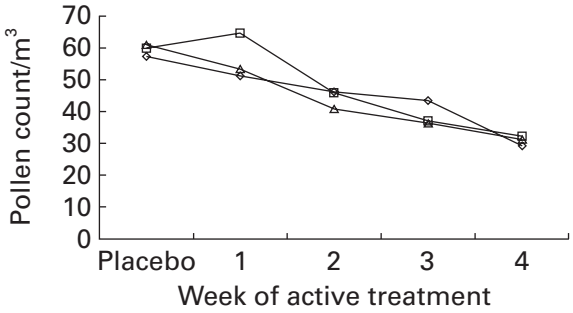

Fig. 2. Average weekly pollen count (count/m^3) for cetirizine alone (diamond), cetirizine plus mometazone furoate (square) and cetirizine plus montelukst (triangle) for placebo week and each week of active treatment. There was no significant difference between the treatment groups for the average pollen count.

nasal PIFR measurement and nasal symptom response. We therefore sought to optimize nasal symptom reduction in our patient group. Antihistamines are known to be extremely effective in seasonal allergic rhinitis [10], with rapid onset of action. Cetirizine, a second-generation antihistamine, has been shown to provide greater reduction in symptoms in patients with seasonal allergic rhinitis, compared to loratadine [11]. Indeed, it is used as the first choice antihistamine in our own rhinology clinic practice. We therefore elected to use cetirizine in all three treatment groups since our patients were symptomatic and we wished to optimize treatment response. We did not include a group receiving placebo alone as we felt it unethical to leave these symptomatic patients for 5 weeks without treatment. We did however, include an initial 1-week placebo run-in period in order to establish a true baseline in all three groups.

This study was not designed to compare differences in efficacy between the active treatments. Given that our patients had mild to moderate symptoms, together with cetirizine's proven efficacy [11–13], it is perhaps not surprising that the addition of mometasone or montelukast failed to provide additional clinical efficacy. Indeed, if anything, the patients who received cetirizine alone tended to have slightly more severe parameters after the initial run-in period although they fared as well as the other two groups who also received identical treatment with corticosteroid or leukotriene antagonist. However, both intranasal corticosteroids and leukotriene receptor antagonists have been shown to be efficacious in the treatment of seasonal allergic rhinitis [14–18]. It is possible that the saline placebo nasal spray may have improved some of our patients' symptoms but since no significant difference between treatments was observed, we do not believe this had an important effect.

The pollen counts in Dundee during the study were

relatively low, which presumably reflects the level of symptoms our patients reported. In addition, we were concerned that some of the reduction on patients' symptoms might have been influenced by variation in pollen counts during the study. We therefore factored pollen into the analysis as a covariate and there were no significant effects on symptom scores and nasal PIFR. Moreover, there were no significant differences in pollen counts between the three treatments and hence this was not a factor in determining the treatment response in each group. It was also evident that all three groups were relatively well matched for severity in terms of overall symptoms and PIFR after the initial placebo run-in period.

There is a considerable degree of day to day variation in the symptoms and nasal airflow in patients with allergic rhinitis, possibly due to the changes in daily pollen count and amount of exposure. For this reason, assessing treatment response in terms of nasal airflow on weekly laboratory visits will be too insensitive and daily measurements would seem to be more appropriate. The situation is similar to that of asthma, where daily peak flow measurements are more helpful than intermittent spot measurements.

In conclusion, our data supports the potential use of nasal peak flow in assessing short-term objective treatment response in patients with seasonal allergic rhinitis. Further studies are now indicated to evaluate its use in patients with more severe nasal obstruction. The use of domiciliary nasal peak flow over longer periods in perennial allergic rhinits would also seem to warrant further investigation, perhaps using allergen challenge as a model.

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