Rhinology, 41, 16-20, 2003

Peak inspiratory flow rate is more sensitive than acoustic rhinometry or rhinomanometry in detecting corticosteroid response with nasal histamine challenge*

Andrew M. Wilson, Erika J. Sims, Fiona Robb, Wendy Cockburn, Brian J. Lipworth

Asthma & Allergy Research Group, Department of Clinical Pharmacology & Therapeutics, Ninewells Hospital & Medical School, University of Dundee, Dundee, Scotland, United Kingdom

SUMMARY

Nasal histamine challenge testing is a standard method of assessing upper airway hyperreactivity although there is still debate as to the best measure of response. The aim of the study was to evaluate peak nasal inspiratory flow rate (PIFR) as an endpoint during histamine challenge and compare this with rhinomanometry (Rhino) and acoustic rhinometry (AR). Twenty two patients with perennial allergic rhinitis (PAR) were enrolled into a 2-way randomised crossover study comparing placebo with intra-nasal mometasone furoate (MF) 200mg once daily, with laboratory measurements of PIFR, AR and Rhino being made during histamine nasal challenge after each 10-14 day treatment period. Patients also recorded their domiciliary nasal symptoms and PIFR on a daily basis. With nasal challenge testing using PIFR PC30 there was a significant ($p<0.05$) difference between MF and placebo but not with PC30 AR or PC175 Rhino. There was also significant ($p<0.05$) improvement in terms of domiciliary total nasal symptom scores but not domiciliary PIFR. In conclusion PIFR after nasal challenge with histamine is a sensitive test of response to treatment with intra-nasal corticosteroids in PAR.

Key words: histamine, nasal challenge, nasal inspiratory flow, allergic rhinitis

INTRODUCTION

Perennial allergic rhinitis (PAR) is an inflammatory condition of the nasal mucosa which results in significant impairment of the quality of life of sufferers (Juniper, 1998; Leynaert et al., 2000). Furthermore it is often under-diagnosed and under-treated. Inadequate management of allergic rhinitis is an important cause of poor asthma control, sinusitis and sleep disturbance (Craig et al., 1998; Settipane, 1999).

The disease severity of PAR is often assessed by symptom scoring. In previous studies we have also utilised domiciliary peak inspiratory flow rate as an objective measure of treatment response in seasonal allergic rhinitis (Wilson et al., 2000; Wilson et al., 2001b; Wilson et al., 2002a). These measures assess the consequences of nasal airway obstruction rather than the mucosal inflammation per se. Bronchial challenge testing can be used as a measure of hyperreactivity and has been shown to correlate with sputum eosinophils in the lower airways (Obase et al., 2001). Nasal challenge testing, which also correlates with nasal eosinophils (Romero and Scadding, 1992), has been used to examine the nose and the response is often assessed by determining the degree of nasal obstruction (Plavec et al., 1994; Malm et al., 2000).

Nasal obstruction can be measured objectively by rhinomanometry, acoustic rhinometry and nasal inspiratory flow. The most commonly used method is rhinomanometry (Giannico et al., 1996; Kanthawatana et al., 1997; Ferreira and Carlos, 1998), however acoustic rhinometry has been shown to be as sensitive to anterior (Scadding et al., 1994) and posterior rhinomanometry (Austin and Foreman, 1994) during nasal challenge tests. Indeed some authors prefer acoustic rhinometry as they feel it is easier to perform (Roithmann et al., 1975; Austin and Foreman, 1994; Miyahara et al., 1998). Peak inspiratory flow rate (PIFR) can also be used to assess the response to stimulus in terms of histamine challenge testing (Plavec et al., 1994) and Ganslmayer et al. (1999) has shown it to be as sensitive as acoustic rhinometry in nasal allergen challenge. However in the study by Ganslmayer et al. (1999), patients with allergic rhinitis were compared to healthy controls and no measure of treatment response was made.

* Received for publication: April 16, 2002; accepted: November 11, 2002

In order to evaluate the different methods of objectively assessing nasal obstruction during a histamine challenge in terms of assessing the response to treatment we performed a placebo-controlled study with intra-nasal mometasone furoate. We chose mometasone furoate as it is an example of a highly potent corticosteroid (Stellato et al., 1999) which has been shown to inhibit mucosal inflammation after nasal allergen challenge (Ciprandi et al., 2001). Furthermore it would not have been valid to use anti-histamine therapy in our study as this form of medication may have directly antagonized the effects of intra-nasal histamine and not given us an indication of the degree of nasal inflammation.

MATERIALS AND METHODS

Patients

Twenty-two patients with PAR, according to current criteria (Lund, 1994), (14 females), mean (SE) age 30.4 (2.0) years were recruited into the study. All patients had normal spirometry (mean FEV1 100 (1.8) % predicted), 13 patients were skin prick positive to grass, 20 to house dust mite, 13 to cat and 9 to dog. Four patients were taking intra-nasal corticosteroids (beclomethasone, fluticasone, budesonide and triamcinolone) but no patients were taking oral anti-histamines prior to enrolment into the study. Two subjects were taking as required inhaled bronchodilators but no subjects were taking inhaled corticosteroids. No subject had received oral corticosteroids or antibiotics for 6 months prior to the study. All subjects 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 performed as a single (investigator) blind, placebo controlled, crossover study. All treatment was withdrawn including intra-nasal steroids, nasal decongestants and anti-histamines, from the beginning of the study. Patients were randomised to receive the following for 10-14 days: A) 200μg intranasal aqueous mometasone furoate (as Nasonex, Schering-Plough, Herts, UK as 2 squirts of 50mg in each nostril) at 0800 hrs or B) Placebo nasal spray (2 squirts up each nostril) at 0800 hrs.

The nasal sprays 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. Each subject received a simple tick chart as an aide to compliance. Patients attended the laboratory after each treatment period. All measurements at the study visit were conducted at the same time of day for each patient.

Measurements

Nasal Histamine Challenge:

Patients had baseline measurements of nasal peak inspiratory flow rate, acoustic rhinometry and rhinomanometry. The above measurements were repeated 2 minutes after receiving a placebo nasal spray. Histamine was then administered via a nasal spray in doubling concentrations from 0.25mg/ml to 8mg/ml with the measurements repeated 2 minutes after each dose. The study was terminated on the request of the patient if the symptoms were severe or the physician if the patient had an unrecordable peak inspiratory flow rate or acoustic rhinometry value. Patients were then offered topical xylometazoline (Otrivine, Norvartis Consumer Health, West Sussex, UK) and observed until their symptoms of nasal blockage subsided.

Nasal Peak Inspiratory flow rate

Nasal inspiratory flow rate was measured using an In-check™ flow meter (Clement Clarke International Ltd, 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 facemask. The mean of 3 consecutive readings was recorded.

Rhinomanometry

Patients had measurements of nasal resistance by posterior rhinomanometry using a NR6 rhinomanometer (GM Instruments, Ashgrove, Kilwinning, UK) with on-line computerised integration of total nasal flow and pressure change in a subgroup of 13 patients. Total nasal flow was measured with patients breathing tidal volumes through a facemask with their mouths closed. Nasal pressure was measured by placing a pressure probe in the patients' mouth with their soft palate open to represent posterior nasal pressure changes. Flow rates were calculated at a nasal pressure of 150 Pa (Naito and Iwata, 1997). The pressure transducer and flow meter were calibrated weekly.

Acoustic rhinometry

Acoustic rhinometry was measured using an AI Executive acoustic rhinometer (GM Instruments, Ashgrove, Kilwinning, UK). A probe was inserted 0.5cm into each nostril such that a seal was obtained without distorting the nasal architecture. Patients were asked to hold their breath during the procedure and a probe-stand was used in order to ensure correct positioning of the probe (Wilson et al., 2001a). Measurements were made of the minimum cross sectional area (MCA) at the nasal valve (approximately 2 cm from nasal orifice).

Diary card data

Nasal Peak Flow:

Nasal inspiratory flow rate was measured using an In-check™ flow meter (Clement Clarke International Ltd, Harlow, UK) as described above. Measurements were made at the same time each day at 0800hrs throughout the study and patients recorded the highest of three readings.

Symptoms

Patients recorded their perennial allergic rhinitis symptoms on a daily basis under nasal symptoms as "runny nose", "blocked/-

stuffy nose", "itchy nose", and "sneezing". All symptoms were documented according to a four-point scale with zero indicating no symptoms and three indicating severe symptoms.

Skin Prick Testing

Patients withheld anti-histamine medication for four days prior to skin prick testing. This 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 10 minutes, a positive reaction being defined as a minimum weal diameter of 3-5mm with erythema

Statistical analysis

Log-dose response curves were produced for each measurement. Provocation concentrations producing a pre-determined percentage change from base-line values were determined by interpolation of the curve. The required percentage changes were a 30% fall for nasal inspiratory flow rate, a 20% reduction in the acoustic rhinometry values of in nasal volume or minimal cross sectional area, and a 75% increase in nasal airways resistance. For diary card data the sum of nasal symptoms (Nasal symptoms) were used for analysis.

The effect of treatment response was assessed by comparing measurements after placebo and after mometasone furoate by a paired Student's T-test ($p<0.05$, two tailed). Nasal challenge data were analysed geometrically. A statistical analysis was performed using Microsoft Excel 97 (Microsoft, Seatle, USA).

RESULTS

There was significant improvement in total nasal symptoms (2.1 (0.3) vs. 2.9 (0.3)) with mometasone furoate compared to placebo. Domiciliary peak nasal inspiratory flow rate was greater with mometasone furoate (124.2 (7.4) l/min) than placebo (120.6 (9.0) l/min) but this was not statistically significant.

There was no significant difference between the provocative concentration required to cause a 20% reduction in the minimal cross sectional area acoustic for either the right or left nostril, or a 75% increase in nasal airways resistance for mometasone furoate compared to placebo. However there was a significant ($p<0.05$) difference between the concentration of histamine required to cause a 30% fall in peak inspiratory flow rate with mometasone compared to placebo (Figure 1).

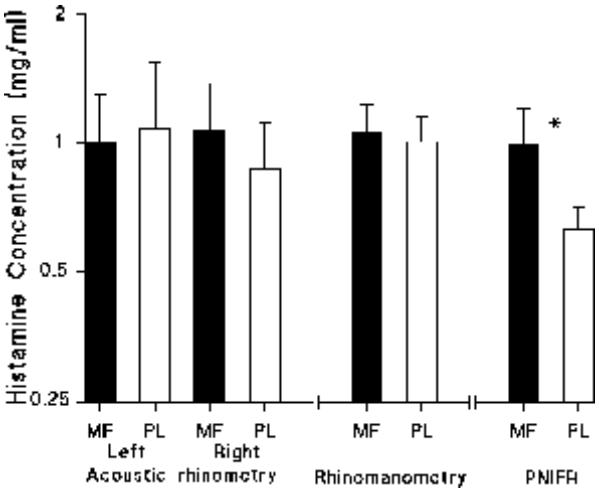

Figure 1. Geometric mean (SEM) provocative concentration of histamine (plotted on a log 2 scale to denote doubling dilution) required to cause a 20% fall in Minimal Cross Sectional nasal area with acoustic rhinometry (Acoustic Rhinometry), 75% increase in nasal airways resistance (Rhino) and a 30% fall in peak nasal inspiratory flow rate (PNIFR) for mometasone furoate (MF: solid bars) and placebo (P: open bars). Asterisk denotes significant ($p<0.05$) difference between treatments.

DISCUSSION

We have shown that short-term treatment with intra-nasal corticosteroid exhibited significant effects in perennial allergic rhinitis, which was evident for domiciliary nasal symptoms but not PIFR. In terms of the nasal histamine challenge test we found a significant difference between corticosteroid and placebo when PIFR was used as the measure of nasal obstruction but not when rhinomanometry or acoustic rhinometry were used. We have previously shown domiciliary peak nasal inspiratory flow rate to be more sensitive than laboratory measures of nasal obstruction (rhinomanometry or acoustic rhinometry)(Wilson et al., 2001b) and to correlate better with patients domiciliary symptoms(Wilson et al., 2001c). However in the present study these three measures were compared in the same setting, i.e. the response to histamine during a laboratory nasal challenge.

We elected to evaluate PIFR response to histamine challenge as this is a simple responsive test. Acoustic rhinometry and rhinomanometry, which are performed at tidal breathing, are regarded as sensitive measures of nasal obstruction (Fisher, 1997; Lund, 1998). Indeed the current guidelines on nasal challenge testing suggest that acoustic rhinometry is preferred to nasal inspiratory flow as an outcome measure during the test (Malm et al., 2000). However PIFR is measured in a manner which examines the system under dynamic stress rather than at baseline conditions i.e. maximal inspiratory flow rather than at tidal breathing.

Ganslmayer et al. (1999) have previously shown the sensitivity of PIFR as an outcome measure during allergen challenge. Despite being more variable in normal volunteers, PIFR was as sensitive as AR during challenge testing as all patients with allergic rhinitis had a positive test and both correlated well to the patients' symptoms. However that study did not evaluate response to treatment. Mastalerz et al. (1997) have used domiciliary peak inspiratory flow and lysine-aspirin nasal challenge

to assess treatment response to fluticasone. They showed beneficial effects in terms of domiciliary peak inspiratory flow and nasal challenge when assessed by acoustic rhinometry.

Unlike upper airway challenge testing, where there is a standard cut-off for change in response i.e. 20% fall in FEV1, there does not seem to be a standard for nasal challenge testing. In this study we employed the following threshold values which we have previously used as these were associated with significant symptoms: a 30% fall in peak inspiratory flow, a 20% fall in acoustic rhinometry, and a 75% increase in nasal airway resistance with rhinomanometry. The use of 30% fall in peak inspiratory flow is in keeping with that used by Plavec et al. (1994) also with histamine nasal challenge testing which had been shown to be significant in a pilot study.

We have previously performed a study which evaluated the response of 2 weeks of intra-nasal mometasone furoate in terms of domiciliary PIFR and symptoms scores (Wilson et al., 2001b). In that study there was a significant improvement peak inspiratory flow and total nasal symptoms. This is in contrast to our present study, as there was no significant improvement with domiciliary PIFR. The previous investigation was also a placebo-controlled study and enrolled 22 patients with SAR. It may be that there is a quicker treatment response with SAR when compared to PAR, as patients are less likely to have the same degree of chronic late phase mucosal inflammation.

PIFR is a relatively straightforward test to perform although it is effort dependent. We have shown that when it is used as a outcome measure during nasal challenge testing, it is more sensitive than other measures as a significant difference in PC_{30} was detected with mometasone that was in keeping with the domiciliary symptom response. This would greatly simplify the nasal challenge procedure. Further studies are now required to evaluate the use of this procedure further with other provocation stimuli such as AMP and mannitol.

REFERENCES

1. Austin CE, Foreman JC (1994) Acoustic rhinometry compared with posterior rhinomanometry in the measurement of histamine- and bradykinin-induced changes in nasal airway patency. Br J Clin Pharmacol 37: 33-37.
2. Ciprandi G, Tosca MA, Passalacqua G, Canonica GW (2001) Intranasal mometasone furoate reduces late-phase inflammation after allergen challenge. Ann Allergy Asthma Immunol 86: 433-438.
3. Craig TJ, Teets S, Lehman EB, Chinchilli VM, Zwillich C (1998) Nasal congestion secondary to allergic rhinitis as a cause of sleep disturbance and daytime fatigue and the response to topical nasal corticosteroids. J Allergy Clin Immunol 101: 633-637.
4. Ferreira MB, Carlos AG (1998) Anterior rhinomanometry in nasal allergen challenges. Allergie et Immunologie 30: 295-297.
5. Fisher EW (1997) Acoustic rhinometry. Clin Otolaryngol Allied Sci 22: 307-317.
6. Ganslmayer M, Spertini F, Rahm F, Terrien MH, Mosimann B, Leimgruber A (1999) Evaluation of acoustic rhinometry in a nasal provocation test with allergen. Allergy 54: 974-979.
7. Giannico R, Oliveira CA, Sole D, Naspitz CK (1996) Non-specific nasal provocation in children with chronic allergic rhinitis. J Invest Allergol Clin Immunol 6: 110-116.
8. Juniper EF (1998) Rhinitis management: the patient's perspective. Clin Exp Allergy 28 (Suppl 6): 34-38.
9. Kanthawatana S, Maturim W, Fooanant S, Manorot M, Trakultivakorn M (1997) Evaluation of threshold criteria for the nasal histamine challenge test in perennial allergic rhinitis. Asian Pac J Allergy Immunol 15: 65-69.
10. Leynaert B, Neukirch C, Liard R, Bousquet J, Neukirch F (2000) Quality of life in allergic rhinitis and asthma. A population-based study of young adults. Am J Respir Crit Care Med 162: 1391-1396.
11. Lund V (1998) Allergic rhinitis-making the correct diagnosis. Clin Exp Allergy 28 (Suppl 6): 25-28.
12. Lund VJ (1994) International consensus report on the diagnosis and management of rhinitis. International rhinitis management working group. Allergy 49 (Suppl 19): 1-34.
13. Malm L, Gerth VW, Bachert C (2000) Guidelines for nasal provocations with aspects on nasal patency, airflow, and airflow resistance. International Committee on Objective Assessment of the Nasal Airways, International Rhinologic Society. Rhinology 38: 1-6.
14. Mastalerz L, Milewski M, Duplaga M, Nizankowska E, Szczeklik A (1997) Intranasal fluticasone propionate for chronic eosinophilic rhinitis in patients with aspirin-induced asthma. Allergy 52: 895-900.
15. Miyahara Y, Ukai K, Yamagiwa M, Ohkawa C, Sakakura Y (1998) Nasal passage patency in patients with allergic rhinitis measured by acoustic rhinometry: nasal responses after allergen and histamine provocation. Auris, Nasus, Larynx 25: 261-267.
16. Naito K, Iwata S (1997) Current advances in rhinomanometry. Eur Arch Oto-Rhino-Laryngol 254: 309-312.
17. Obase Y, Shimoda T, Mitsuta K, Matsuo N, Matsuse H, Kohno S (2001) Correlation between airway hyperresponsiveness and airway inflammation in a young adult population: eosinophil, ECP, and cytokine levels in induced sputum. Ann Allergy Asthma Immunol 86: 304-310.
18. Plavec D, Somogyi-Zalud E, Godnic-Cvar J (1994) Modified method of nonspecific nasal provocation with histamine for routine use. Annals of Allergy 72: 321-328.
19. Roithmann R, Shpirer I, Cole P, Chapnik J, Szalai JP, Zamel N (1975) The role of acoustic rhinometry in nasal provocation testing. Ear, Nose, & Throat Journal 76: 747-750.
20. Romero JN, Scadding G (1992) Eosinophilia in nasal secretions compared to skin prick test and nasal challenge test in the diagnosis of nasal allergy. Rhinology 30: 169-175.
21. Scadding GK, Darby YC, Austin CE (1994) Acoustic rhinometry compared with anterior rhinomanometry in the assessment of the response to nasal allergen challenge. Clin Otolaryngol 19: 451-454.
22. Settipane RA (1999) Complications of allergic rhinitis. Allergy Asthma Proc 20: 209-213.
23. Stellato C, Atsuta J, Bickel CA, Schleimer RP (1999) An in vitro comparison of commonly used topical glucocorticoid preparations. J Allergy Clin Immunol 104: 623-630.
24. Wilson AM, Dempsey OJ, Sims EJ, Coutie WJ, Patterson MC, Lipworth BJ (2000) Evaluation of treatment response in patients with seasonal allergic rhinitis using domiciliary nasal peak inspiratory flow. Clin Exp Allergy 30: 833-838.
25. Wilson AM, Fowler SJ, Martin SW, White PS, Gardiner Q, Lipworth BJ (2001a) Evaluation of the importance of head and probe stabilisation in acoustic rhinometry. Rhinology 39: 93-97.
26. Wilson AM, Orr LC, Sims EJ, Lipworth BJ (2001b) Effects of monotherapy with intra-nasal corticosteroid or combined oral histamine and leukotriene receptor antagonists in seasonal allergic rhinitis. Clin Exp Allergy 31: 61-68.
27. Wilson AM, Sims EJ, Orr LC, Coutie WJ, White PS, Gardiner Q, Lipworth BJ (2001c) Effects of topical corticosteroid and combined mediator blockade on domiciliary and laboratory measurements of nasal function in seasonal allergic rhinitis. Annals of Allergy, Asthma, & Immunology 87: 344-349.

28. Wilson AM, Orr LC, Coutie WJ, Sims EJ, Lipworth BJ (2002) A comparison of once daily fexofenadine versus the combination of montelukast plus loratadine on domiciliary nasal peak flow and symptoms in seasonal allergic rhinitis. Clin Exp Allergy 32: 126-132.

Prof B J Lipworth
Asthma & Allergy Research Group
Department of Clinical Pharmacology & Therapeutics
Ninewells Hospital & Medical School
University of Dundee
Dundee DD1 9SY
Scotland, United Kingdom

Tel: `+44 - 1382-632983 (direct) 632180 (sec)
Fax: +44 - 1382-632983 (direct) 644972 (sec)
E-mail : b.j.lipworth@dundee.ac.uk

ANNOUNCEMENT