Rhinology, 40, 66-68,2002

Short term repeatability and correlates of laboratory measures of nasal function in patients with seasonal allergic rhinitis*

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SUMMARY

The purpose of this study was to determine the variability of laboratory nasal function tests in 26 patients (18 female) with seasonal allergic rhinitis (SAR) (mean age 38.1 years). Their usual medication for SAR was withheld for 2 separate one week washout periods, separated by at least 2 weeks, in order to produce clinically significant nasal airflow obstruction. Measurements were made on both occasions for nasal nitric oxide (NO), nasal peak inspiratory flow (nPIF), oral PIF (oPIF), nasal forced inspiratory flow rate in 1 second ($nFIV_1$), oral FIV_1 ($oFIV_1$). The respective nasal-oral ratios for FIV_1 and PIF were also determined. The intra-individual coefficient of variation was: NO = 14%, $nFIV_1$ = 4%, $nFIV_1/oFIV_1$ ratio = 10%, nPIF = 8% and nPIF/oPIF ratio = 12%. Linear regression analysis showed significant ($p<0.05$) correlations between nPIF and $nFIV_1$ (R^2 =0.45) and between nPIF/oPIF and $nFIV_1/oFIV_1$ (R^2 = 0.20). In conclusion, there was a good correlation between the two methods of nasal inspiratory flow, although FIV_1 had a lesser degree of variability.

Key words: nasal inspiratory flow, allergic rhinitis, oral inspiratory flow, nasal nitric oxide

INTRODUCTION

Nasal obstruction is an important feature of seasonal allergic rhinitis (Lund, 1994; Lund, 1998) which can be measured by acoustic rhinometry and rhinomanometry. Both have been validated as sensitive measures (Fisher, 1997), however they are time consuming, involve expensive equipment and require trained personnel. Nasal inspiratory flow has been studied both in the laboratory (Gleeson et al., 1986; Holmstrom et al., 1990) and domiciliary setting (Wilson et al., 2000), and has been shown to have a good correlation with patients' rhinitis symptoms and treatment responses.

As peak nasal inspiratory flow rate is determined by both nasal obstruction and by the maximum negative pressure generated from the lower respiratory tract, methods of correcting for respiratory function have been developed. Taylor et al. (1973) and Larsen et al. (1992) have respectively developed nasal blockage and patency indices with close association to rhinometry (Larsen et al., 1990) and subjective response to surgery. We have suggested the use of the nasal-oral ratio of forced inspiratory volume in 1 second (FIV_1) (Oluwole et al., 1997) or peak flow (Wilson et al., 2001a) which have been shown to correlate well to patients symptoms and to the response to therapy.

Nasal nitric oxide (NO) is produced by an inducible nitric oxide synthase which is up regulated by inflammatory cytokines in the upper airways. Nasal NO is therefore elevated in patients with allergic rhinitis during the pollen season and is suppressed with topical corticosteroids (Kharitonov et al., 1997). Studies have therefore utilised nasal NO levels as a measure of response to treatment in patients with rhinitis (Baraldi et al., 1998; Wilson et al., 2001a; Wilson et al., 2001b). We wished to examine the repeatability of these measures in a laboratory setting.

MATERIALS AND METHODS

Patients

Twenty-six patients with seasonal allergic rhinitis (18 females), mean (SE) age 38.1 (±2.6) years were recruited into the study to completion. All completed patients had symptomatic seasonal allergic rhinitis (SAR) according to current criteria (Lund, 1994). Eight patients were taking intra-nasal corticosteroids (beclomethasone 200 μg/day n=7, fluticasone propionate 200 μg/day n=1) and 12 were taking oral antihistamines (loratadine 10mg/day n=7, cetirizine 10mg/day n=3, chlorpheniramine 16mg/day n=2). One patient was also taking ocu-

* Received for publication: September 5, 2001; accepted: December 6, 2001

lar cromoglycate. All patients had a positive skin prick test to grass pollens. 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 of an open labelled design. Patients were recruited during June and July 2000 when grass pollen levels are usually high in Tayside. Patients were asked to withhold their usual medication for SAR for 2 separate one-week washout periods in order to produce clinically significant symptoms. Each one-week period without treatment was separated by 2 weeks of their usual SAR treatment.

Measurements

Nasal Nitric Oxide

Patients had a measurement of nasal nitric oxide using an integrated, LR2000 clinical, real-time, nitric oxide gas analyser with an accuracy of 2ppb NO and a response time of 2 seconds (Logan Research, Rochester, UK) using the procedures described by Kharitonov et al. (1997). Three measures of nitric oxide were taken and the results were analysed as the mean and the maximum of the three values. The analyser was calibrated weekly using a cylinder of nitric oxide at concentration of 108ppb.

Nasal and Oral Forced Inspiratory Volume in 1 second

Nasal and oral forced inspiratory and flow rates were measured using a modified *Microloop* spirometer (Micromedical Ltd). As described by Oluwole et al. (1997) the manufacturer had reversed the position of the swirl plate and vane of a standard spirometer to make it suitable for measurements of inspiratory flow. 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.

Peak Nasal and Oral Inspiratory Flow rate

Nasal inspiratory flow rate was measured, in a similar manner, using an In-check™ flow meter (Clement Clarke International Ltd, Harlow, UK). With the use of an independent adapter, patients also recorded their peak oral inspiratory flow using the same device.

Statistical Analysis

The values for nPIF and $nFIV_1$ were analysed along with their respective nasal oral ratios. Within subject variability was calculated from the mean sum of squares of intra-individual variation (SD2) from a one way ANOVA. The coefficient of variation was then calculated from (SD/global mean) x 100, and the 95% confidence interval was calculated as 2SD, which represents the size of change in an individual required to represent a true treatment response, i.e. in order to exclude biological variability for repeated measures. Least squares linear regression analysis was used to assess the correlation between nasal peak inspiratory flow rate and nasal FIV_1 and also between nPIF/oPIF and $nFIV_1/oFIV_1$. The analysis was performed using a Statgraphics statistical software package (STSC Software Publishing Group, Rockville, MD, USA).

RESULTS

Mean values, intra-individual coefficient of variation, and the size of change in an individual subject required to represent a true drug response with 95% confidence are shown in the Table 1. There was a significant correlation between nPIF and $nFIV_1$ ($R2=0.45$, $p<0.0001$) and between nPIF/oPIF and $nFIV_1/oFIV_1$ ($R2=0.20$, $p<0.001$).

Table 1. Mean values (mean), intra-individual coefficient of variation (CV), and the size of change in an individual subject required to represent a true drug response with 95% confidence (response). This in terms of average and maximal nasal nitric oxide (NO), nasal forced inspiratory volume in 1 second ($nFIV_1$), ratio between nasal and oral FIV^1 ($nFIV_1/oFIV_1$), nasal peak inspiratory flow (nPIF) and ratio between nasal and oral PIF (nPIF/oPIF) in patients with seasonal allergic rhinitis.

	NO average	NO max	$nFIV_1$	$nFIV_1$/ $oFIV_1$	nPIF	nPIF/ oPIF
Mean	947	1074	1.6	0.61	115	0.72
CV	14%	15%	4%	10%	8%	12%
Response	222	252	0.15	0.13	19	0.19

DISCUSSION

We have shown that there was a good correlation between the two methods of inspiratory flow. However forced inspiratory volume in 1 second had a lesser degree of variability. The coefficient of variation was similar when assessing either the average or maximal nasal nitric oxide level as was the change required to have a statistically significant change in response to treatment. Using this data it is possible to show biologically relevant treatment responses with nPIF if a difference in 19 l/min is used, or 0.15 l if assessing $nFIV_1$. These volumes can then be used for the purpose of power calculations for clinical trials.

Studies have shown significant improvements in treatment response by using nasal nitric oxide as an endpoint. For example, we have previously shown that treatment with topical budesonide resulted in a statistically significant reduction in nasal NO compared to placebo, which amounted to 369 ppb (95% CI: 15 to 723) (Wilson et al., 2001a). This was associated with statistical improvements in seasonal allergic symptom

scores and nPIF. These results are in keeping with the required intra-individual change of 250ppb described here to represent a true treatment response.

Although clinical studies demonstrate the efficacy of specific treatment in population samples, it is evident that in the real life setting that individual patients differ in their response to treatments. Therefore when faced with a patient in the clinic it is useful to know objectively as well as subjectively whether a satisfactory response has been achieved. Nasal peak inspiratory flow rate and $nFIV_1$ are measures that are relatively simple to perform and can be offered as rapid assessments at out-patient rhinology clinics along with symptom scores. Using the data from this study it is possible to determine what will represent a true treatment response.

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