Acoustic rhinometry compared with posterior rhinomanometry in the measurement of histamine- and bradykinin-induced changes in nasal airway patency

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- 1 Acoustic rhinometry is a relatively new method for objectively assessing nasal airway patency. In this paper we compare acoustic rhinometry with active posterior rhinomanometry.
- 2 Twenty normal healthy volunteers underwent nasal challenge with either histamine or bradykinin, 100 µg to 1000 µg, and responses were assessed by acoustic rhinometry. A further 20 subjects received identical nasal challenges and responses were assessed by active posterior rhinomanometry.
- 3 On a subsequent occasion, the subjects challenged previously with histamine, were given the selective H₁-receptor antagonist, cetirizine, 10 mg orally, 3 h before repeat nasal challenge with histamine, 100–1000 µg. Again, responses were assessed by active posterior rhinomanometry and acoustic rhinometry.
- 4 The acoustic reflection measurements and the nasal airway resistance measurements showed comparable, significant dose-related changes in nasal patency to both histamine and bradykinin. Pretreatment with cetirizine blocked the histamine-induced change in nasal patency as measured by both methods.
- 5 We conclude that acoustic rhinometry has a number of advantages over posterior rhinomanometry. It is quick to perform, requires minimal subject co-operation and gives a reliable objective, measurement of dose-related changes in nasal airway patency before and after pharmacological treatment.

Keywords histamine bradykinin nasal airway human acoustic rhinometry posterior rhinomanometry

Introduction

Nasal blockage is one of the symptoms of rhinitis. It is caused by oedema of the soft tissue of the nose, and by exudate and secretion which fills the airway. The ability to quantify this is of importance for the evaluation of rhinitis in the experimental situation, and also for the objective clinical assessment of upper airway diseases. Many methods for assessing nasal blockage have been described, such as rhinomanometry [1], nasal inspiratory peak flow [2], apparent nasal volume [3] and body plethysmography [4]. However, all these methods have some disadvantages. A high degree of subject co-operation is required and the methods can be time-consuming and often unsuitable for subjects with severely congested nasal airways. To date, no single method has gained general acceptance, which reflects the difficulty of obtaining reproducible and valid measurements of nasal

airway resistance. Thus, there is a requirement for a simple, non-invasive and reliable technique requiring minimal subject compliance.

More recently, the method of acoustic rhinometry has been introduced. This is based on acoustic reflection [5] and has previously been used for examination of the trachea [6] and the pharynx [7]. The method provides a two-dimensional picture of a cross-section of the nasal airway at a specified distance from the nostril. It requires relatively little subject co-operation and requires no airflow through the nose, so it can be used to obtain measurements from subjects with very congested nasal airways.

In this study we set out to assess the potential of acoustic rhinometry as a means of quantifying changes in nasal patency induced by histamine and bradykinin,

and to compare this technique with the established and frequently used method of active posterior rhinomanometry.

Methods

Subjects

For all studies, normal, healthy volunteers with an age range of 22–40 years were used. Subjects suffering from respiratory tract infections or experiencing any nasal symptoms were excluded. Subjects were taking no medication at the time of, or in the 2 weeks prior to the experiment. All subjects gave informed consent and the study was approved by the local Ethics Committee at University College London. Experiments were performed in conditions of constant temperature and humidity.

Posterior rhinomanometry

Active posterior rhinomanometry using a Mercury Electronics (Glasgow, UK) NR6D rhinomanometer was used to obtain measurements of nasal airways resistance (NAR). The instrument was programmed to calculate the resistance to airflow at a reference pressure of 75 Pa. The subject held a mask, with an airtight seal over the nose and mouth and breathed through the nose. Airflow was monitored by a pneumotachograph, and pressure within the oropharynx was monitored by a pressure transducer connected to a cannula placed over the tongue and held through sealed lips. The instrument was programmed to give the mean NAR over four breath cycles, and for each subject, three consecutive series of four breath cycles were used to calculate an overall mean of twelve breaths. Readings were only accepted if the coefficient of variation of the overall mean NAR for a subject was less than 20%.

Acoustic rhinometry

Measurements of nasal cross-sectional area and volume were made by acoustic rhinometry using equipment supplied by 'gm' Instruments (Kilwinning, UK). The apparatus consists of a spark-source that produces the sound impulse, a microphone with amplifier for measurement of sound, a wave tube through which the acoustic pulse is transmitted to the anterior nares of the subject, and a computer for data acquisition and analysis. The spark generated is discharged between two electrodes placed in the end of the wave tube and an audible sound impulse is created. The acoustic pulse is propagated down the wave tube, passes the microphone and enters the nasal cavity via a 6 cm long plastic tube inserted into the wave tube. The wave forms reflected from the nasal structures pass back down the wave tube and are collected by the microphone. The free end of the tube was inserted a few millimetres into the anterior nares. Three sizes of tubes were available to ensure a tight-fit in the nostril of each subject. The data obtained were converted to an

area-distance function and was used to provide estimates of cross-sectional area and volume between various specified distances in the nasal cavity, and a minimum nasal cross-sectional area ($A_{\min}$). The measurement lasts less than 10 ms.

Nasal challenge

Nasal challenge was performed with a nasal pump spray (Perfect-Valois, UK Ltd) delivering 100 μ l per actuation, with a 98% degree of accuracy. The spray was placed in one nostril and activated once, then repeated in the other nostril. All solutions were at room temperature, and doses were controlled by varying the concentration of the solution. Fresh solutions of challenge agents were made daily from stock solutions stored at -20° C. Both histamine and bradykinin were dissolved in sterile saline (NaCl, 154 mM) to achieve a range of concentrations from 1 mg ml $^{-1}$ to 10 mg ml $^{-1}$.

Study design

On each occasion, subjects were first challenged with saline, then NAR measurements or acoustic reflection measurements were performed as described above, every 5 min over a 15 min period. The averaged data from all time points formed the baseline.

In the first study, ten subjects were given histamine, 100, 300 and 1000 μ g to each nostril, and NAR measurements were performed at 2, 5, 10, 15 and 20 min. Each subject had three doses in total, and NAR was allowed to return to baseline before proceeding with the next dose. At least 1 week later, subjects were given the selective histamine H_1 -receptor antagonist, cetirizine 10 mg, orally, 3 h before repeat histamine challenges of 100, 300 and 1000 μ g. NAR measurements were then made as before. A further 10 subjects were given histamine, 100, 300 and 1000 μ g to each nostril, and acoustic reflection measurements were performed at 2, 5, 10, 15 and 20 min. One week later, these subjects repeated the experiment in the presence of cetirizine, 10 mg, given orally 3 h before.

In another study, ten subjects were given bradykinin, 100, 300 and 1000 μ g per nostril and NAR measurements were made at 2, 5, 10, 15 and 20 min. Each subject had three doses in total, allowing NAR to return to baseline between each dose. This experiment was repeated in these subjects 1 week later using acoustic rhinometry to quantify nasal blockage. Again, measurements were made at 5 min intervals during the 20 min post-challenge period.

Materials

Histamine diphosphate was obtained from Sigma, Poole, UK. Bradykinin was obtained from Peninsula Labs, St Helens, Merseyside, UK. Cetirizine was a gift from UCB Pharma Ltd, Belgium.

Data analysis

To achieve comparability, the mean of the $A_{\min}$ values from acoustic rhinometry of the left and right nostrils

was calculated for each measurement taken because NAR measurements made by posterior rhinomanometry measure resistance for both nostrils together. Changes in NAR and in A min were expressed as the percentage change from saline control values to normalize the data. Responses to histamine and bradykinin were quantified for each dose as the *maximal* percentage change in both NAR and A min during the post-challenge measurements. All data were expressed as mean $\pm$ s.e. mean. Repeated measures analysis of variance (ANOVA) was used statistically to evaluate the responses to histamine and bradykinin. A probability value of $P < 0.05$ was considered significant.

Results

The coefficient of variation (CV) for mean A min values, under baseline conditions (saline), was calculated in order to provide information about the reproducibility of this parameter in comparison with others. For the subjects in the histamine study, the CV for the mean A min values was $5.7 \pm 2.5\%$ ($n = 10$), which was less than the CV for any of the other parameters measured by acoustic rhinometry. For NAR, the CV of the mean values under baseline conditions was $9.6 \pm 2.9\%$ ($n = 10$).

Histamine, 100–1000 μg in each nostril, produced a dose-related increase in NAR and a dose-related decrease in A min. Figure 1 is an example of an area-distance function provided by the acoustic rhinometer before and after challenge with histamine, 1000 μg , demonstrating that swelling and thus nasal blockage, occurs throughout the nasal mucosa following such a challenge. Figure 2 shows that histamine, 100, 300, 1000 μg per nostril, resulted in increases in NAR of 69.7%, 126.5% and 174.3% respectively (ANOVA, $P = 0.002$, $n = 10$), and Figure 3 demonstrates that over the same dose range, histamine produced dose-related decreases in A min of 27.8%, 36.1%, and 53.8% respectively (ANOVA, $P = 0.028$, $n = 10$).

Figure 1 Area-distance function of the right nasal cavity in one subject before and 2 min after intranasal administration of histamine, 1000 μg . The initial value for the minimum nasal cross-sectional area (A min) on the right was 0.32 cm^2 , changing to 0.1 cm^2 after histamine challenge.

After pretreatment with cetirizine, 10 mg, histamine 100, 300, 1000 μg per nostril, resulted in increases in NAR of 21.0%, 15.2% and 23.3% respectively, $n = 10$ (Figure 2), and decreases in A min of 3.0%, 19.6% and 11.8%, $n = 10$ (Figure 3). None of these responses to histamine in the presence of cetirizine, 10 mg was

Figure 2 Dose-response curve for histamine (●) and increased nasal airway resistance (NAR). The effect of histamine in the presence of cetirizine, 10 mg (▽) on NAR is also shown. The data are the means from 10 separate experiments for histamine and 10 experiments for histamine following treatment with cetirizine, 10 mg; vertical error bars represent s.e. mean. Control (saline) values for NAR were $0.366 \pm 0.027 \text{ Pa s cm}^{-3}$ for histamine and $0.392 \pm 0.033 \text{ Pa s cm}^{-3}$ for histamine/cetirizine.

Figure 3 Dose-response curve for histamine and histamine in the presence of cetirizine, 10 mg and decreased minimum nasal cross-sectional area (A min). ●, histamine; ▽, histamine in the presence of cetirizine, 10 mg. The data are the means from 10 experiments each and vertical error bars represent s.e. mean. Control (saline) values for A min were $0.462 \pm 0.019 \text{ cm}^2$ for histamine and $0.446 \pm 0.028 \text{ cm}^2$ for histamine in the presence of cetirizine, 10 mg.

statistically significantly different from measurements taken at baseline (saline challenge).

Subjects challenged with bradykinin 100, 300 and 1000 μg per nostril, all experienced an increase in nasal blockage. Figure 4 shows bradykinin-induced increases in NAR, of 48.1%, 86.2% and 186.4% respectively (ANOVA, $P = 0.020$, $n = 10$), and Figure 5 represents bradykinin-induced decreases in A_{min} . These were 16.4%, 28.7% and 49.3% respectively (ANOVA, $P < 0.0001$, $n = 10$).

Pooling data for histamine and bradykinin from each measurement technique but excluding the data in the presence of cetirizine, the correlation coefficient

Figure 4 Dose-response curve for bradykinin and increased nasal airway resistance (NAR). The data are the means from 10 separate experiments; vertical error bars represent s.e. mean except where they fall within the limits of the actual data point. Control (saline) values for NAR were $0.311 \pm 0.016 \text{ Pa s cm}^{-3}$.

Figure 5 Dose-response curve for bradykinin and decreased minimum nasal cross-sectional area (A_{min}). The data are the means from 10 separate experiments; vertical error bars represent s.e. mean. Control (saline) values for A_{min} were $0.467 \pm 0.034 \text{ cm}^2$.

(Spearman rank) for the relationship between the magnitude of change in A_{min} compared with the magnitude of the change in NAR was 0.943 ($0.01 < P < 0.05$).

Discussion

Our data show that it is possible to obtain reproducible dose-response relationships for histamine and bradykinin using acoustic rhinometry, and demonstrate for the first time, the effects of histamine and bradykinin on acoustically determined changes in nasal airway patency. Furthermore, measurements made by acoustic rhinometry have been compared with those made by the established method of posterior rhinomanometry.

Histamine and bradykinin were chosen for this comparative study because the effects of histamine on the nasal airway are well established [8, 9], as are those of bradykinin [10, 11]. Histamine- and bradykinin-induced changes in NAR are in agreement with previously established effects of these agents. Moreover, they correlate with the measurements obtained in this study by acoustic rhinometry. The histamine-induced changes in nasal patency have been shown to be inhibited by cetirizine, 10 mg and this is in accordance with other studies of the effect of H_1 -receptor antagonists on nasal blockage [12, 13].

In our acoustic reflection studies, the minimum nasal cross-sectional area (A_{min}) was used to express the results. The acoustic rhinometer was programmed to provide four measurements of nasal volume between different specified distances in the nasal cavity, and measurements of cross-sectional area at four defined distances into the airway. Nasal volume was found to be insensitive to drug-induced changes and the probable explanation for this is that changes in volume over a given distance in the nasal airway tend to be of lesser magnitude than changes in resistance to flow. Therefore an obstruction, such as might be caused by a small change in vascular tone, means that flow is affected and hence resistance changes, but such a vascular response does not cause the volume of the cavity to change appreciably. In contrast, our studies revealed that A_{min} is a more sensitive measurement, which is likely to reflect the fact that the limiting factor with respect to nasal resistance to airflow is the dimension of the narrowest part of the airway. The A_{min} values also exhibited more consistency under baseline conditions, as revealed from estimates of the coefficient of variation of the mean values.

Acoustic reflection measurements have previously been used to study airway area in the lower airways of human subjects, where the data proved to be accurate and reproducible [14]. Hilberg *et al.* [15], have since validated this technique for use on the nasal cavity; thus providing a simple and quick method requiring minimal subject input. In addition, acoustic rhinometry is not dependent on airflow through the nose, and is, therefore, suitable even for subjects with severely congested nasal airways. In contrast, rhinomanometry is time consuming, requires technical expertise, a high degree of subject co-operation and is impossible in subjects with severely

congested nasal airways. There are reports of failure rates of between 25% and 50% in the subjects examined by rhinomanometry [1, 16].

Acoustic rhinometry appears to be a useful technique in assessing the pharmacology of nasal patency and has a number of advantages over rhinomanometry. It should be pointed out, however, that acoustic rhinometry is essentially a measurement of anatomical dimensions of the nasal cavity whereas posterior rhinomanometry is a functional measurement based on pressure and flow in

the nasal cavity. It would seem that although rhinomanometry probably still has a place as a research tool, acoustic rhinometry is the more practicable of the two, and also has the distinct advantage of providing information about the precise distribution of resistance.

C.E.A. is in receipt of a SERC Case Award with Pfizer Central Research, Sandwich, Kent as the industrial sponsor. We are grateful to the volunteers who participated in these experiments.

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(Received 6 July 1993,
accepted 15 September 1993)