The nasal airways response in normal subjects to oxymetazoline spray: randomized double-blind placebo-controlled trial

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Aims The effects of a single dose of oxymetazoline nasal spray on nasal patency have been compared with placebo using three separate measuring systems in normal subjects.

Methods The study was a placebo-controlled, randomised double-blind crossover trial. Subjects without ear, nose or throat disease and with resting nasal airways resistance >0.15 Pa s cm^{-3} were selected so that a fall in airways resistance could be detected. Nasal airways resistance (NAR) was measured by NR6–2 rhinomanometer. Acoustic rhinometry (SR-2000 rhinometer) provided the sum of the minimum cross-sectional areas (tMCA) and volume (tVOL) of the left and right nasal cavities. Symptoms of congestion were assessed on a visual analogue scale (CON, range 0–100). Measurements were made for 60 min before and for 120 min after bilateral administration of oxymetazoline nasal spray (0.9 mg) or placebo (0.9% saline). Crossover occurred 7–21 days later. Results for all measures were analysed as change from average baseline value by trapezoidal AUC, and statistical significance was tested by 2-way ANOVA.

Results NAR, tMCA, tVOL and CON did not change after placebo, but NAR and CON fell and tMCA and tVOL increased significantly at all timepoints after oxymetazoline. NAR_AUC, tVOL_AUC, tMCA_AUC were significantly different between placebo and oxymetazoline ($P<0.001$) as was CON_AUC ($P=0.012$). The day-to-day intraindividual repeatability of baseline NAR tMCA and tVOL was $<10\%$.

Conclusions Normal subjects can be used to detect the effects of nasally vasoactive drugs with a variety of complementary systems, with the advantages of easy subject recruitment and low variability.

Keywords: acoustic rhinometry, double-blind method, nasal airways, oxymetazoline, randomised clinical trial, rhinomanometry

Introduction

Posterior rhinomanometry is an established technique that measures nasal airflow and pressure and reproducibly determines nasal airways resistance (NAR) [1, 2]. Acoustic rhinometry maps nasal dimensions by detecting reflected sound waves along the nasal passage. Previous studies have shown a negative but nonlinear relationship between nasal cross sectional area measured by acoustic rhinometry and NAR [3]. Nasal patency can also be subjectively measured by the patient but this may not correspond with objective measurements [4].

Oxymetazoline is a topically applied nasal decongestant that has a vasoconstrictive effect on the nasal mucosal blood vessels thereby relieving symptoms of nasal congestion. It acts as an α-adrenergic agonist on receptors of the vascular smooth muscle, constricting the venous sinusoids within the nasal mucosa. This reduces blood flow through the nasal mucosa resulting in decreased nasal oedema and a reduced sensation of nasal congestion [5]. In patients with nasal obstruction, significant improvement in nasal patency after use of oxymetazoline and related compounds can be detected by both rhinomanometry and by patient subjective assessment [6]. These measuring systems have not been used in normal subjects to detect changes in nasal patency after oxymetazoline use.

Establishing relationships between different measuring systems may enable one measurement tool to be used as a predictor or as a replacement for another when assessing nasal patency. This is potentially useful when one tool is

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more suitable for a particular population or study design. The aims of this study were to assess the subjective and objective decongestant effects of oxymetazoline in normal subjects and to quantify the reliability, sensitivity, and relationships between three measuring systems in assessing this effect.

Methods

Subjects

The Royal Adelaide Hospital Research Ethics Committee approved the study protocol and all subjects gave informed written consent. Twenty healthy volunteers (14 female, 6 male, mean age 27.3 years) took part in the study. All subjects were free of upper respiratory tract infection and displayed no evidence of pharyngeal erythema, anatomic nasal obstruction or gross anatomical nasal deformity. They did not report any symptoms of abnormal nasal congestion. Those subjects who had taken any medication which may have influenced nasal congestion or may have interacted with oxymetazoline were excluded. Because some normal subjects have very low baseline NAR values from which a further reduction cannot be reliably discriminated, the subjects recruited had a minimal NAR requirement. All subjects had an initial total NAR of at least 0.15 Pa s cm^{-3}.

Measurements

Posterior rhinomanometry (NR6–2 rhinomanometer, GM Instruments, Glasgow, UK) was used to measure NAR which was determined at a reference pressure of 75 Pa. The mean value of 8 breaths was used where the CV was less than 10%. Re-calibration against reference pressure and air flow meters was performed at regular intervals throughout the study. The pressure and flow channels were linear in the range 0–300 Pa and 0–300 ml s^{-1}, respectively, on repeated static testing ($r > 0.998$). A disposable antiviral filter (resistance 0.15 Pa s cm^{-3}) was placed in series between the subject and the rhinomanometer to comply with infection prevention requirements.

Acoustic rhinometry (SR-2000PC, SR Electronics, Lynge, Denmark) was used to obtain measurements of nasal area and volume. The acoustic rhinometer was internally calibrated before each set of measurements. In addition, a known fixed artificial cavity was measured using AR at different times during the study. The accuracy (observed/expected) of volume and cross-sectional area measurement was > 0.88, with an interday coefficient of variation of reproducibility of < 0.12. The minimum cross-sectional area (MCA) of each nasal cavity between 22 mm and 54 mm from the anterior nares, and the nasal volume between the MCA depth and 54 mm (VOL), were recorded. The median of three replicate measurements was used.

Subjective assessment of nasal congestion was recorded by the subject using a 100-mm visual analogue scale anchored by the descriptors 'nose completely clear' and 'nose completely blocked', representing values of 0 and 100 mm, respectively.

Study design

The study was performed as a randomised, double-blind, placebo-controlled crossover study. The randomization code was generated by an independent pharmacist using randomization tables. Baseline NAR and acoustic rhinometry measurements were made at 0, 15, 30, 45 and 60 min over a 1 h period prior to treatment administration.

Treatment consisted of a nasal spray containing either oxymetazoline 0.5 mg ml^{-1} solution (0.9 mg to each nostril) (Drixine^{TM}) or placebo (saline solution 0.9%) and was administered to each nostril in a standard technique. The dose of oxymetazoline used was the standard recommended dose in nonprescription preparations. Rhinomanometry, acoustic rhinometry measurements and subjective assessment were performed over 120 min at 15, 30, 45, 60, 90 and 120 min after dosing.

Subjects were given placebo and active treatments on different study days and returned between 7 and 21 days later for the crossover arm of the study.

Data analysis

A sample size of 20 subjects per arm was calculated to be sufficient to enable detection of a drug effect of 3.1 AUC_NAR units at a power of 80% and a significance level of 5%.

Total volume (tVOL) and total minimum cross-sectional area (tMCA) were calculated by summing left and right VOL and left and right MCA, respectively. The total values were used for analysis to reduce any effects from nasal cycling on the data. AUC was calculated for NAR, tMCA, tVOL and subjective scores (CON) measurements post treatment (as mean changes from baseline for 2 h after treatment). AUC was analysed for drug effect using analysis of variance (ANOVA, SPSS Version 7.5 for Windows). Ninety-five percentage confidence intervals were calculated for all variables. Correlations between tMCA, tVOL, NAR and CON changes from baseline on active therapy were calculated. Intra-individual reproducibility was calculated as coefficient of variation (CV, s.d./mean). Results in text are expressed as mean $\pm$ s.d.

Results

The baseline values of all the efficacy variables were similar on both study days. Baseline values for placebo and oxymetazoline visits, respectively, were for NAR; 0.39 ± 0.11 and 0.41 ± 0.10: for tMCA; 1.09 ± 0.24 and 1.08 ± 0.21 cm^2 and for tVOL; 6.41 ± 1.10 and 6.64 ± 1.19 cm^3. The day to day intraindividual reproducibility of baseline NAR, tMCA and tVOL. was $<10\%$.

NAR, tMCA, tVOL and CON did not change after placebo (Figures 1–4). NAR and CON after oxymetazoline were lower than after placebo at all timepoints over the 2 h post dosing (Figures 1, 4). There was an increase in tVOL and tMCA at all timepoints after dosing after active (Figures 2, 3).

The AUCs for NAR and CON were significantly lower for oxymetazoline than placebo ($P<0.001$, $P=0.012$, respectively), and were higher for both tMCA ($P<0.001$) and tVOL ($P<0.001$) (Table 1).

Correlations between individuals for changes in all variables after active treatment were calculated. There were no significant correlations between any variables including between tMCA and tVOL. Mean correlations within individuals were also calculated for efficacy variables after oxymetazoline treatment. There was a highly significant correlation between tMCA and tVOL ($r=0.82$). There were negative correlations between NAR and tMCA and tVOL which were higher than those seen for interindividual correlations but did not reach statistical significance.

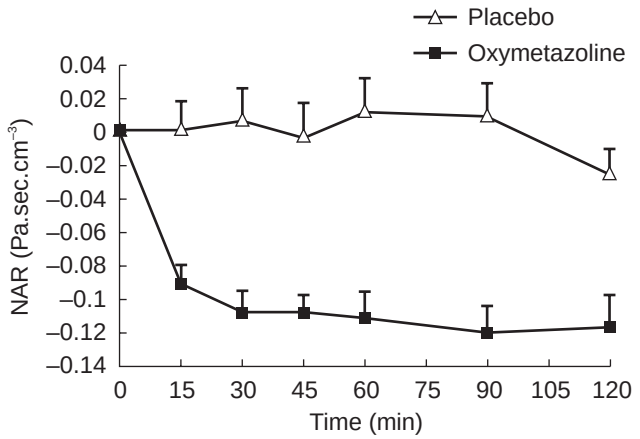

Figure 1 NAR change from baseline at times after dosing of placebo or oxymetazoline (0.9 mg) (mean SE).

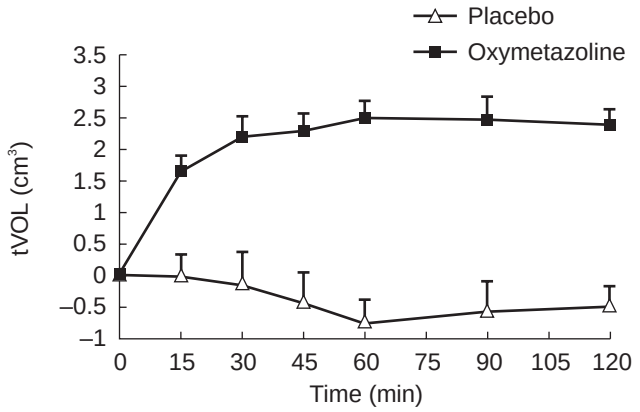

Figure 2 tVOL change from baseline at times after dosing of placebo or oxymetazoline (0.9 mg) ($\pm$s.e. mean).

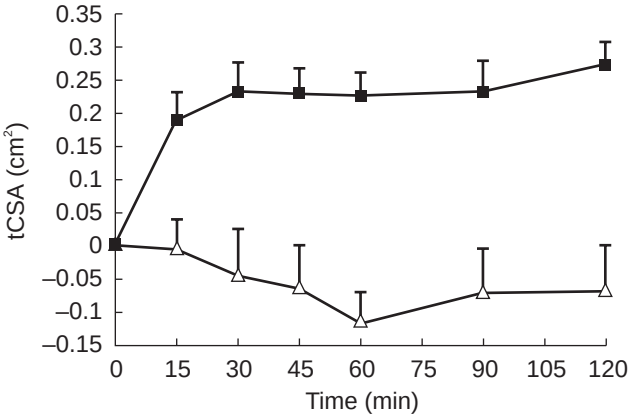

Figure 3 tCSA change from baseline at times after dosing of placebo (△) or oxymetazoline (0.9 mg, ■) ($\pm$s.e. mean).

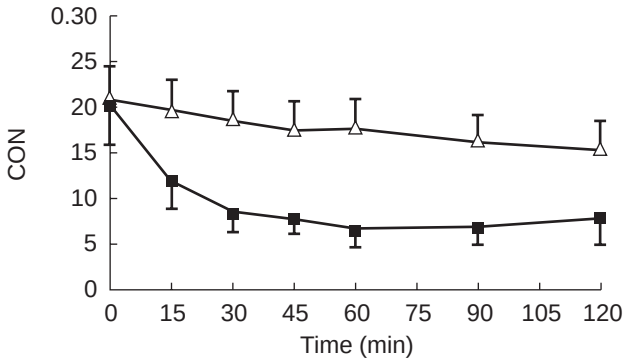

Figure 4 CON change from baseline at times after dosing of placebo (△) or oxymetazoline (0.9 mg, ■) ($\pm$s.e. mean).

Table 1 AUCs for efficacy variables (change from baseline over 2 h) after dosing with placebo and oxymetazoline (0.9 mg). Values expressed as $\pm$s.e. mean.

Efficacy variable	*Placebo*	*Oxymetazoline*
LogNAR (Pa s cm^{-3} h)	0.3 (−1.9, 2.6)	−11 (−14, −7)
tMCA (cm^2 h)	−7.4 (−14, −1)	−23 (13, 34)
tVOL (cm^3 h)	−49 (−98, −1)	239 170, 307)
CON (Units h)	− 5 (−10, 0)	−19 (−29, −9)

Discussion

Rhinomanometry and acoustic rhinometry measurements were reproducible in this study as shown by the high

within-individual reproducibility of measurements, similar to those seen in other studies [7, 8].

A vasoconstrictor effect of oxymetazoline in normal volunteers has been shown with significant changes from baseline in all of the objective variables measured (NAR, tMCA, tVOL). This is the first time significant changes in these variables have been observed in normal subjects after oxymetazoline, although comparable changes in tMCA have been observed with a similar topical decongestant phenylephrine [9].

In normals, baseline NAR values can be very low thereby making it difficult to detect a significant fall in NAR. The approach used in this study of selecting normal volunteers with a minimum NAR, but within the normal range, optimized the ability to detect a fall in NAR.

Baseline CON symptoms are low in these subjects, but this study found a significant fall in CON after oxymetazoline spray in parallel with changes in the objective measures.

Between individuals, nonsignificant correlations were found between tMCA, NAR and CON measurements, which suggest that measurements from one system do not predict the values of those from another. From these results we conclude that these measurements of airways function and structure cannot be regarded as surrogates for each other, and changes in airways resistance or symptoms of congestion cannot be inferred from changes in acoustic rhinometry measurements or *vice versa*.

There are several possible reasons which suggest why variables from different measurements do not significantly correlate with each other. NAR measured by rhinomanometry is a well-validated objective standard. Validation studies of acoustic rhinometry in cadavers showed that volume assessment using acoustic rhinometry is accurate [10], however, tMCA measured in normals demonstrated statistically significant but low correlation with CT measurements ($r < 0.2$) [11]. Acoustic rhinometry measurements are reproducible *in vivo* and *in vitro* but are not well validated against other assessments of nasal airways dimensions. CON symptoms may be affected by sensory changes as well as changes in NAR [4].

A nasal cycle consisting of reciprocal changes in resistance (and dimensions) in each nasal airway over 1–3 h is seen in some normal volunteers [12]. The variability associated with this phenomenon is conventionally minimized for acoustic measures by the summation of values for both sides. However, this correction may not adequately predict changes in airways resistance (which is proportional to an inverse power of the cross-sectional area) during the cycle. Thus the nasal cycle may also contribute to the low correlation between different objective measures.

The success of the design used in this study with its easy subject recruitment and low variability within measures suggests this study design would be useful for future studies which involve validation of measuring systems or testing efficacy of nasally active drugs.

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