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Evaluation of the dose-response relationship for intra-nasal oxymetazoline hydrochloride in normal adults

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Abstract *Objectives*: To evaluate the dose-response relationship of increasing doses of oxymetazoline compared with placebo in normal subjects, and to determine the sensitivities of rhinomanometry, acoustic rhinometry and symptoms in discriminating between differing doses of oxymetazoline in normal subjects.
Methods: The study had a randomized, double-blind, placebo-controlled, parallel group, dose-response design. One hundred and twenty-five healthy volunteers with no nasal obstruction were randomized to administration of a single intra-nasal dose of oxymetazoline (6.25 μg, 12.5 μg, 25 μg or 50 μg) or placebo to each nasal cavity. Nasal airway resistance (NAR) was measured by active posterior rhinomanometry. Total minimum cross-sectional area (tMCA) and volume (tVOL) were measured by acoustic rhinometry. Symptoms of congestion (CON) were assessed on a visual analogue scale.
Results: The two highest doses of oxymetazoline produced a significant decrease in NAR compared with placebo ($P = 0.015$) but not between placebo and 12.5 μg or 6.25 μg. There was a dose-response relationship for tVOL, which increased significantly after all doses compared with placebo ($P < 0.001$) and showed differences between 6.25-μg and 25-μg ($P < 0.014$) and 12.5-μg and 50-μg ($P < 0.05$) doses. tMCA increased compared with placebo after all treatments ($P = 0.028$), but there were no significant differences between any of the active doses. There were no significant changes in CON after any treatments compared with placebo.
Conclusions: tVOL shows a clear dose-response relationship for the range of doses of oxymetazoline administered. tVOL provides a sensitive and discriminatory measure of small nasal changes after low doses of oxymetazoline. NAR is able to discriminate between doses, but is less sensitive than tVOL and tMCA, requiring a higher threshold dose before significant changes are seen in nasal patency.

Key words Dose-response relationship · Acoustic rhinometry · Nasal decongestant

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Introduction

The sympathomimetic drug oxymetazoline hydrochloride is a nasal decongestant which causes vasoconstriction within the nasal airways. It acts as an alphaadrenergic 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 mucosal volume [1]. Nasal sprays and drops containing oxymetazoline hydrochloride are approved for over-the-counter (OTC) use in many countries for indications including the symptomatic relief of nasal and nasopharyngeal congestion associated with the common cold, hay fever and sinusitis.

Intra-nasal application of oxymetazoline has previously been demonstrated to have dose-dependent effects in reducing nasal mucosal blood flow measured by ^{133}Xe washout in healthy subjects and in subjects with acute rhinitis [1]. Dose-dependent effects of oxymetazoline application have also been shown to reduce nasal congestion, measured by anterior rhinomanometry and by symptom scores, in subjects with acute infectious rhinitis and objectively obstructed noses [2]. Posterior rhinomanometry is an established technique that measures nasal airflow and pressure and reproducibly determines nasal airway resistance (NAR) [3, 4]. Acoustic rhinometry maps nasal dimensions by detecting reflected sound waves along the nasal passage. Nasal patency can also be subjectively measured by the patient, but this may not correspond with objective measurements [5].

These measuring systems have not previously been used in normal subjects to assess the dose-response relationship for the effects of oxymetazoline hydrochloride on nasal function and structure. We have determined the effects of four different doses of topically applied oxymetazoline and matching placebo on nasal airway resistance and the acoustic rhinometric parameters of cross-sectional area and nasal volume. The aims of the study were to compare the sensitivity of these measurements in the detection of drug-related changes in the nasal airways, and to determine whether each measurement system was capable of discriminating between dose levels.

Methods

Subjects

The Royal Adelaide Hospital Research Ethics Committee approved the study protocol and all subjects gave informed written consent. The study was conducted according to the Declaration of Helsinki. Subjects were recruited by advertising within a university and teaching hospital. Eligible subjects were free of upper respiratory tract infection and symptoms of nasal congestion, and displayed no evidence of pharyngeal erythema, nasal obstruction or significant anatomical nasal deformity. Those subjects who had taken any medication that may have influenced nasal congestion or may have interacted with oxymetazoline were excluded.

Study design

The study had a randomized, double-blind, placebo-controlled, parallel-group design with five treatment groups comprising of placebo and four dose levels of oxymetazoline. A paper balance and assignment schedule was used to generate the randomization scheme for the study. Treatment was randomized in blocks of five. All treatments were packaged in identical spray units by the Royal Adelaide Hospital pharmacy and allocated by treatment number, and all investigators and subjects were blind to treatment allocation.

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 12 breaths was used where the coefficient of variation (CV) was less than 20%. Re-calibration against reference pressure and airflow meters was performed daily throughout the study. The pressure and flow measurements were linear in the range 0–300 Pa and 0–300 $ml \cdot s^{-1}$, respectively, on repeated static testing ($r > 0.998$). A disposable anti-viral filter (resistance 0.15 $Pa \cdot s \cdot cm^{-3}$) was placed in series between the subject and the rhinomanometer to comply with infection control 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 acoustic rhinometry. The mean accuracy [(observed – expected)/expected] of volume and cross-sectional area was 12% with a reproducibility (standard deviation/mean) of 12%.

The minimum cross-sectional area (MCA) of each nasal cavity between 22 mm and 54 mm from the anterior nares was recorded and the nasal volume between the MCA depth and 54 mm was recorded (VOL). The median of 3 replicate measurements was used. Intra-day CVs for reproducibility were 8% for NAR and 6% for VOL and MCA (assessed prior to the study, $n = 12$).

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 mm and 100 mm, respectively. The results were read as the distance in millimetres from zero.

Study medication

Treatment solutions consisted of 0.1%, 0.05%, 0.025% and 0.0125% oxymetazoline hydrochloride (Procter & Gamble UK) solution in 0.9% sodium chloride and placebo (sodium chloride 0.9%). The solution was delivered to the nasal cavity via a calibrated pipette delivering 50 µl (0, 6.25 µg, 12.5 µg, 25 µg or 50 µg of oxymetazoline per nostril) using a standard technique by a trained nurse. Subjects adopted a head-back posture for drug administration.

Study procedures

After successful screening, subjects were trained for a period of up to 30 min in rhinomanometry and acoustic rhinometry. A requirement for eligibility was an NAR at the completion of training of less than 0.4 $Pa \cdot s \cdot cm^{-3}$ (i.e. within the normal range for this laboratory). Eligible subjects were then randomized double-blind to treatment. Baseline NAR and acoustic rhinometry measurements were made at 0, 15, 30, 45 min and 60 min over a 1-h period prior to treatment administration. The subjective measurement of congestion was recorded at the 60-min time point, before any treatment was administered. After dosing with the test product, rhinomanometry, acoustic rhinometry and subjective assessments were performed over 120 min at 15, 30, 60, 90 min and 120 min. All adverse events (AEs) reported were documented.

Data analysis

Sample size estimates were calculated on the basis of data from a paper by Akerlund [2]. A group size of 25 was required to detect a 30% difference in the area under the concentration-versus-time curve (AUC) for NAR with a power of 80% and a significance level of 5%. Total volume (tVOL) and total minimum cross-sectional area (tMCA) were calculated by adding left and right VOL and left and right MCA, respectively. The total values were used for analysis to reduce any effects from the nasal cycle on the data. The mean of individual baseline data for each variable was calculated. Post-dose AUC was calculated for NAR, tMCA, tVOL and subjective scores (CON) for the period 15–120 min after dose by the trapezoidal method. NAR data were natural log-transformed prior to statistical analysis to normalize the data. Differences between mean AUCs were analysed using analysis of variance for all groups, with baseline as covariate (ANOVA, SPSS Version 8.0 for Windows). Pairwise comparisons of means between all groups were performed using ANOVA least-squares differences and 95% confidence intervals (CIs) were calculated for these differences.

Results

One hundred and eighty-five subjects were screened and 60 were excluded. Common reasons for exclusion were anatomical nasal obstruction or deformity ($n = 28$), inability to train in rhinomanometry ($n = 19$) and the taking of excluded medication ($n = 5$). One hundred and twenty-five subjects were randomized to treatment and took the test product. Eight subjects were excluded from analysis (four due to prolonged training and four due to delay in treatment administration). The efficacy analysis was performed on the intention-to-treat (ITT)

data set, consisting of 117 subjects. The mean age of the ITT set was 25 years, range 18–49 years; M/F: 51/66 (Table 1). There were no serious AEs.

Baseline values of variables for each group are presented in Table 2. Mean values between groups showed some differences and this was allowed for in the statistical analysis of AUC, where baseline was a covariate. After treatment, groups given higher doses (50 μg and 25 μg) had lower mean NAR at all time points compared with baseline (Fig. 1). The placebo and 6.25-μg groups showed a rise in mean NAR after treatment. For tVOL, the mean values were lower at all time points after treatment in the placebo group, and increased consistently in all active groups (Fig. 2). A similar pattern was seen with tMCA (Fig. 3). Symptoms of congestion were minimal at baseline, and tended to decline after both active and placebo treatments (Fig. 4).

Calculated AUC values adjusted for baseline are shown in Table 3. Comparisons between groups for logNAR AUC values found no significant differences between placebo and either of the two lowest dose groups, but significant decreases in the 50-μg and 25-μg groups compared with the placebo group ($P = 0.005$ and $P = 0.015$, respectively; Table 4). Comparisons between active treatment groups revealed a significant decrease in logNAR AUC in the 50-μg group compared with the 6.25-μg group only ($P = 0.027$).

Analysis of post-dose AUCs of tVOL showed a significant increase in all active groups compared with placebo ($P < 0.001$ all groups). Between oxymetazoline groups, there was a significant increase in tVOL AUC between the 6.25-μg and 50-μg groups ($P < 0.001$), the 6.25-μg and 25-μg groups ($P = 0.014$), and between the 12.5-μg and 50-μg groups ($P = 0.049$).

For tMCA AUC, there were significant increases in all oxymetazoline groups compared with placebo ($P = 0.028$) but there were no significant differences between any of the active treatment groups. There was no significant change in CON AUC after any of the doses compared with placebo. Further pairwise comparisons were not performed on the CON data for this reason.

Table 1 Subject demographics of the intention-to-treat group

	Group					
	50 μg	25 μg	12.5 μg	6.25 μg	Placebo	Total
Number of subjects	23	24	21	25	24	117
Age (years, mean with range)	25 (18–43)	26 (18–44)	24 (18–39)	27 (18–49)	22 (18–33)	25 (18–49)
Gender (M/F)	8/15	15/9	7/14	9/16	12/12	51/66

Table 2 Baseline values for all efficacy variables in each treatment group (mean with SE). *NAR* Nasal airway resistance, *tVOL* total volume, *tMCA* total minimum cross-sectional area, *CON* symptoms of congestion

Group	NAR ($Pa \cdot s \cdot cm^{-3}$)	tVOL (cm^3)	tMCA (cm^2)	CON (mm)
Placebo	0.303 (0.015)	6.440 (0.242)	1.164 (0.056)	11.3 (3.4)
6.25 μg	0.314 (0.027)	5.821 (0.249)	1.059 (0.061)	8.8 (2.1)
12.5 μg	0.335 (0.032)	5.476 (0.267)	1.002 (0.047)	8.7 (1.9)
25 μg	0.311 (0.017)	6.358 (0.303)	1.136 (0.063)	16.3 (2.9)
50 μg	0.313 (0.020)	6.321 (0.291)	1.142 (0.061)	9.0 (1.7)

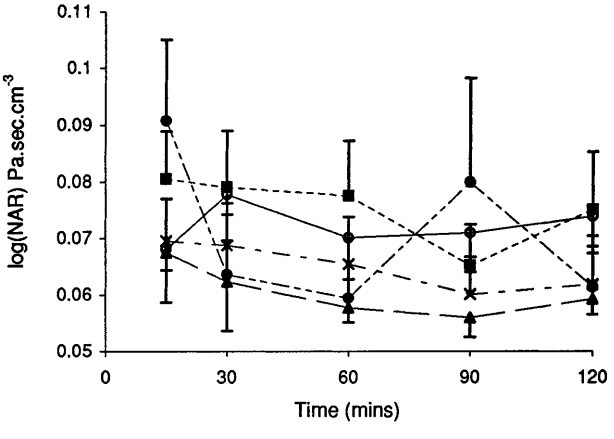

Fig. 1 LogNAR as change from baseline after oxymetazoline or placebo at times after dosing. *NAR* nasal airway resistance, -▲- 50 μg, - × - 25 μg, -●- 12.5 μg, – -■- – 6.25 μg, -○- placebo

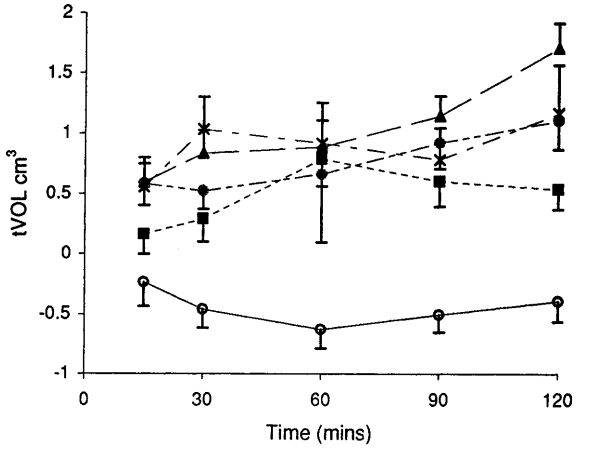

Fig. 2 tVOL as change from baseline after oxymetazoline or placebo at times after dosing. *tVOL* total volume, -▲- 50 μg, - × - 25 μg, -●- 12.5 μg, – -■- – 6.25 μg, -○- placebo

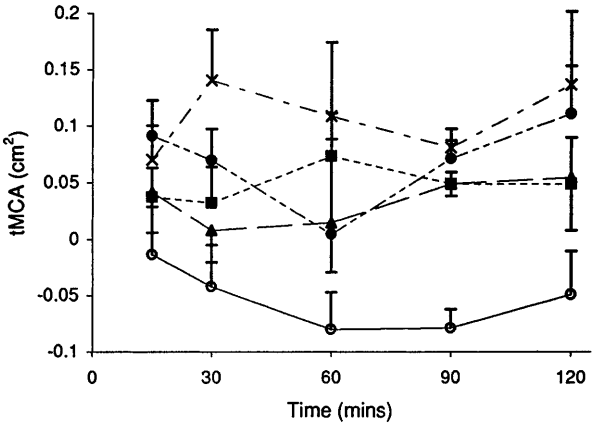

Fig. 3 tMCA as change from baseline after oxymetazoline or placebo at times after dosing. *tMCA* total minimum cross-sectional area, -▲- 50 μg, - × - 25 μg, -●- 12.5 μg, – -■- – 6.25 μg, -○- placebo

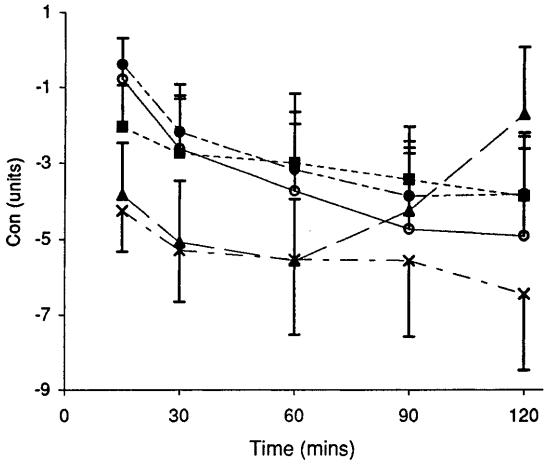

Fig. 4 CON as change from baseline after oxymetazoline or placebo at times after dosing. *CON* symptoms of congestion, -▲- 50 μg, - × - 25 μg, -●- 12.5 μg, – -■- – 6.25 μg, -○- placebo

Discussion

The primary aim of this study was to establish the dose-response relationships in several nasal parameters for oxymetazoline hydrochloride in normal subjects. A large double-blind randomized study was conducted for this purpose in a study group whose demographics were typical of a young adult population. The 6.25-μg group was different to the placebo group for tVOL and tMCA at baseline, but this was corrected for adequately in the statistical analyses.

The data has been analysed to determine the sensitivity of the measuring systems in detecting the effects of a low dose of oxymetazoline compared with placebo. Furthermore, the ability of these systems to discriminate between different doses of oxymetazoline is considered. The sensitivity of the equipment used in this study was demonstrated in its ability to detect a significant change in the respective variables after a low dose of oxymetazoline (i.e. 50% or less of the usual decongestant dose). This is in contrast to the absence of significant changes in congestion in all of the oxymetazoline groups compared with placebo. This finding highlights the important role of objective measurement systems to detect any drug effect in normal subjects.

Both acoustic measures, tVOL and tMCA, were sufficiently sensitive to detect a significant change in nasal dimensions after the lowest dose of oxymetazoline (6.25 μg) compared with placebo, and for tVOL maximal changes were seen after 25 μg oxymetazoline. The highly significant *P* values of the tVOL AUC compared with the tMCA AUC may indicate that tVOL is able to detect a lower threshold drug dose than tMCA. The lowest dose of oxymetazoline used in this study (6.25 μg) is one eighth of that recommended [6]. Support for the occurrence of a pharmacological effect after a low dose of oxymetazoline comes from work by Bende [1]. A significant reduction in mucosal blood flow was found in healthy subjects and patients with acute rhinitis with doses of oxymetazoline as low as 1 μg when administered directly onto the inferior turbinate. Furthermore, a 10-μg dose was effective at producing 50% of the maximum response observed with higher doses.

The relative lack of sensitivity of rhinomanometry in detecting changes in NAR after low doses of oxymetazoline may be due to the high patency of the normal nasal airway. Thus a large change in nasal dimensions would be required to achieve a significant change in NAR (such as that seen between placebo and 25 μg oxymetazoline).

Several other studies support our findings. Akerlund demonstrated a dose-response relationship to oxymetazoline using rhinomanometry in subjects with acute rhinitis [2]. In that study, the lowest dose used (10 μg per nasal cavity) did not change NAR significantly from placebo at any time point, while the next lowest dose (25 μg) reduced NAR significantly compared with placebo after 180 min only. We have recently

Table 3 Post-dose AUC values (adjusted for baseline) for all efficacy variables (mean with SE). *AUC* Area under the concentration-versus-time curve, *NAR* nasal airway resistance, *tVOL* total volume, *tMCA* total minimum cross-sectional area, *CON* symptoms of congestion

Group	logNAR AUC $\log Pa \cdot s \cdot cm^{-3} \cdot h$	tVOL AUC $cm^3 \cdot h$	tMCA AUC $cm^2 \cdot h$	CON AUC $mm \cdot h$
Placebo	−0.492 (0.023)	9.84 (0.29)	1.815 (0.55)	13.2 (3.5)
6.25 μg	−0.514 (0.022)	11.40 (0.28)	2.003 (0.054)	11.5 (3.6)
12.5 μg	−0.524 (0.024)	11.79 (0.31)	1.998 (0.060)	10.0 (3.8)
25 μg	−0.570 (0.22)	12.41 (0.29)	2.110 (0.055)	18.2 (3.6)
50 μg	−0.583 (0.23)	12.65 (0.29)	1.995 (0.056)	11.9 (3.6)

Table 4 Comparisons of AUC data for efficacy variables at different doses of oxymetazoline, adjusted for baseline. Data are expressed as lower and upper 95% CIs (P value) of the change from placebo (or lower dose). *CIs* Confidence intervals, *NAR* nasal airway resistance, *tVOL* total volume, *tMCA* total minimum cross-sectional area

Group	Compared to	logNAR [log(Pa · s · cm^{-3} · h)]	tVOL (cm^3 · h)	tMCA (cm^2 · h)
Placebo	6.25 μg	−0.082, 0.041 (P = 0.5)	0.755, 2.367 (P < 0.001)	0.034, 0.342 (P = 0.017)
	12.5 μg	−0.097, 0.034 (P = 0.336)	1.091, 2.802 (P < 0.001)	0.020, 0.345 (P = 0.028)
	25 μg	−0.140, −0.015 (P = 0.015)	1.770, 3.380 (P < 0.001)	0.141, 0.449 (P < 0.001)
	50 μg	−0.154, −0.028 (P = 0.005)	1.997, 3.624 (P < 0.001)	0.024, 0.336 (P = 0.024)
6.25 μg	12.5 μg	−0.075, 0.053 (P = 0.74)	−0.443, 1.214 (P = 0.358)	−0.164, 0.153 (P = 0.946)
	25 μg	−0.005, 0.118 (P = 0.07)	0.210, 1.818 (P = 0.014)	−0.046, 0.261 (P = 0.169)
	50 ug	−0.132, −0.008 (P = 0.027)	0.438, 2.061 (P < 0.001)	−0.163, 0.147 (P = 0.918)
12.5 μg	25 μg	−0.111, 0.019 (P = 0.165)	−0.223, 1.480 (P = 0.147)	−0.049, 0.274 (P = 0.170)
	50 μg	−0.124, 0.006 (P = 0.076)	0.006, 1.722 (P = 0.049)	−0.166, 0.161 (P = 0.975)
25 μg	50 μg	−0.076, 0.049 (P = 0.673)	−0.578, 1.049 (P = 0.567)	−0.271, 0.041 (P = 0.146)

demonstrated in normal volunteers that nasal oxymetazoline produces a significant increase in tVOL and tMCA and a decrease in NAR [7]. A single dose of xylometazoline has been found to produce a less marked change in healthy volunteers than in subjects with nasal congestion [8].

The tVOL measurements had better ability to discriminate between different doses of oxymetazoline in normal subjects than either tMCA or NAR measurements. tVOL was able to detect a dose ratio (i.e. the ratio of the higher:lower doses) of 4:1 (between both 6.25 μg:25 μg and 12.5 μg:50 μg). Although unable to detect changes in NAR after the two lower doses of oxymetazoline, rhinomanometry systems of measurement were able to detect a dose ratio of 8:1 (between 6.25 μg:50 μg). In comparison, tMCA, although sensitive to low doses of oxymetazoline, was unable to discriminate between any of the doses used in this study (i.e. unable to detect a dose ratio of 8:1). Two separate studies in normal subjects have found that acoustic rhinomanometry is able to detect the acute response to a single dose of a topical decongestant and an oral decongestant [9, 10]. In both cases, there were significant changes in tVOL but not tMCA. This observation is in agreement with the findings of a dose-response effect in tVOL but not tMCA in the present study.

The findings of this study suggest that a lower dose of oxymetazoline hydrochloride than that recommended by manufacturers may be sufficient for maximum effect. However this study only measured the immediate effects of oxymetazoline for no longer than 2 h post dosing; the duration of action of the recommended dose of oxymetazoline is likely to be longer, which would benefit the consumer. However in clinical or experimental cases, where a 2-h period of decongestion is sufficient, a lower than normally prescribed dose of oxymetazoline may be adequate to achieve maximal decongestion, as measured by both rhinomanometry and acoustic rhinometry.

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