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Oxymetazoline nasal spray three times daily for four weeks in normal subjects is not associated with rebound congestion or tachyphylaxis*

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SUMMARY

Topical decongestants are available over the counter and provide rapid relief of nasal obstruction for conditions of short duration, for example the common cold. Manufacturers' recommendations are that topical decongestants should not be used regularly for more than 1 week in view of the risk of rebound mucosal hyperaemia with persistent nasal obstruction and refractoriness to further effects of decongestants. For this reason we performed a randomised double-blind placebo-controlled trial in 30 normal adult subjects with 0.05% oxymetazoline nasal spray 2 sprays (0.1 ml/spray) to each nostril 3 times daily over an extended period of 4 weeks. Degree of nasal blockage was assessed before and after 4 weeks treatment and for 2 weeks following discontinuation of treatment. Outcome measures included diary symptom scores and measurements of nasal peak inspiratory flow, airway resistance (using posterior active rhinomanometry) and volume (using acoustic rhinometry). Nasal patency was assessed at baseline and 15 minutes after oxymetazoline challenge at each clinic visit. Results demonstrated no significant increases in subjective nasal blockage throughout the 6 weeks study period in either oxymetazoline - or placebo-treated subjects. No significant differences were observed between groups for baseline measurements of nasal peak inspiratory flow, airway resistance or volume at each clinic visit. A highly significant decongestant effect of oxymetazoline was observed at each clinic visit with changes in all 3 measurements for both treatment groups, again with no significant differences between groups. In summary, in normal subjects, we identified no significant nasal blockage or impaired decongestant response to oxymetazoline following 4 weeks treatment with oxymetazoline compared to matched placebo nasal spray.

Key words: oxymetazoline, rhinitis medicamentosa, acoustic rhinometry

INTRODUCTION

Topical nasal decongestants, including oxymetazoline nasal spray provide rapid relief from short-term nasal congestion. Current recommendations restrict use of topical decongestants to a maximum of 2 weeks (Lund et al., 1994) in view of the risks of prolonged use on the nasal mucosa. Repeated applications of decongestants in patients with pre-existing nasal disease cause prolonged vasoconstriction which may result in relative refractoriness to both endogenous catecholamines responsible for maintaining vascular tone as well as to applied agonists (Kully, 1945; Toohill et al., 1981). Rebound vasodilatation may occur with engorgement of the erectile venous sinusoids and the mucosa may become less drug responsive, so called "rhinitis medicamentosa" (Fox, 1931; Feinberg and Friedlaner, 1945; Lake, 1946; Proctor and Adams, 1968). However, the precise mechanism is unknown, not least because our information is based largely on animal studies which may not be applicable (Malm, 1973; Eccles and Wilson, 1974) to man. Also the mechanism may be different for the sympathomimetic amines (eg ephedrine) and the imidazoles (eg oxymetazoline). The histopathology of the condition is poorly understood and again largely based on animal studies

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(Ryan, 1947; Talaat et al., 1981; Elwany and Stephanos, 1983). One study in man identified a close association of plasma cells with degenerating autonomic and sensory nerve endings (Cauna and Cauna, 1974). The prevalence of the condition is controversial and is likely to be much higher within a specialist referral clinic (Mabry, 1982) than within a more general population of patients with underlying rhinitis (Toohill, 1981) and even less when decongestants are used by normal subjects (Petruson, 1981), for example for the relief of the common cold. We therefore undertook a double-blind placebo-controlled trial in 30 normal adult subjects to investigate the effect of topical oxymetazoline 2 x 0.1 ml nasal spray (0.5 mg/ml) to each nostril 3 times daily over an extended period of 4 weeks.

MATERIALS AND METHODS

Subjects

Thirty normal subjects aged 16-60 were recruited from the staff of the Royal Brompton Hospital and in response to an advertisement placed in the local newspaper. Inclusion criteria included: (1) A negative history of seasonal or perennial nasal symptoms other than occasional common colds. (2) Current non-smokers (ex-smokers for greater than 6 months duration with a total smoking history of less than 5 pack-years were eligible), [One pack year equals 20 cigarettes per day for one year or the equivalent (eg 10 cigarettes per day for 2 years)]. (3) Normal lung function (peak expiratory flow rate and FEV1 80-120% predicted normal values for age, height and gender). (4) Normal nasal anatomy on anterior rhinoscopy.

Exclusion criteria were as follows: (1) Current smokers. (2) Subjects taking concurrent medication. (3) History of use of topical or systemic nasal vasoconstrictors in the previous 6 months. (4) History of upper respiratory infection (including the common cold) in the preceding 4 weeks. (5) Previous history of hypertension, cardiovascular or other significant medical problems.

Study Design

The study was performed with the approval of the Royal Brompton Ethics Committee and the subjects' written informed consent. A randomised double-blind placebo-controlled design was employed. During a preliminary visit a history of possible nasal and chest symptoms was taken, peak expiratory flow rates and spirometry recorded and skin prick tests to common aeroallergens (house dust mite, grass pollen, cat fur, dog hair and histamine 10mg/ml) and control (diluent) were performed. Anterior rhinoscopy was performed to exclude any anatomical abnormalities including deflected nasal septum, nasal polyps or abnormally large inferior turbinates. Subjects were instructed to complete a diary card of nasal symptoms as follows: nasal blocking (scale 0-4) 0=no symptoms, 1=mild blockage, 2=moderate blockage, 3=severe blockage, 4=complete nasal blockage (Varney et al., 1992). Symptoms were recorded twice daily on waking and before retiring to bed. After instruction, nasal patency was then assessed by a) nasal inspiratory flow b) active posterior rhinomamometry and c) acoustic rhinometry (see below).

Subjects were asked to return after one week (visit 1). Diary cards were checked to ensure compliance. Repeat measurements of inspiratory flow, posterior active rhinometry and acoustic rhinometry were performed at baseline. Measurements were performed from 10 am – 4 pm at the same time of day as the preliminary screening visit. Patients for whom measurements of nasal patency varied by greater than 20% (coefficient of variation) in one or more of the three objective assessments were excluded. Thirty compliant subjects were randomised to receive oxymetazoline or matched placebo nasal spray. Both active and placebo sprays contained benzalkonium chloride (0.1%). The dose of oxymethzoline was 2 x 50 µg in 0.1 ml to each nostril taken three times daily. The allocation was performed according to a randomisation code in blocks of 8 (4/4) subjects. Subjects were supplied with 2 bottles and compliance checked by re-weighing at the end of 4 weeks treatment. Subjects then received 2 x 50 µg sprays of oxymetazoline nasal spray to each nostril. After 30 minutes subjective (scale 0-3) and objective measurements of nasal patency were repeated in the same order for each subject. Subjects were then instructed to take their nasal spray (oxymetazoline or placebo according to randomisation schedule) 2 sprays to each nostril on waking, at lunch-time and before retiring to bed. Diary cards were completed twice daily (as above) just before taking the nasal spray and subjects were instructed to discontinue their nasal spray 24 hours before subsequent visits.

Subjects returned for visit 2 after 4 weeks at the same time of day as visit 1. Subjects were asked to confirm that they had not taken their nasal spray in the preceding 24 hours. Diary cards were collected and checked for completion. Subjective (scale 0-4) assessment of nasal patency and 3 objective measurements of nasal patency were performed at baseline and repeated 30 minutes after oxymetazoline nasal spray 2 sprays to each nostril. Subjects continued to complete diary cards for a further 2 weeks (run out period) and returned for an identical assessment of nasal patency before and after an oxymetazoline challenge test (visit 3).

Nasal patency

Measurements of nasal patency were performed in an assigned room in a quiet area. Subjects were not distracted and were allowed to rest for a minimum of 20 minutes (ambient temperature 20°C +/– 3°C). No alcohol was permitted in the preceding 24 hours and no caffeine-containing drinks were allowed for a minimum of 2 hours. Subjects with upper respiratory infection were excluded.

a) Nasal peak inspiratory flow

Nasal peak inspiratory flow was measured using Youlten's nasal peak flow meter (Youlten, 1980). This represents a modi-

fied version of the Wright low range mini-peak flow meter enclosed in an air-tight casing to which an anaesthetic face mask is attached and through which air is indrawn through the nose to record the peak nasal airflow. The measurement is performed with the subject standing to enable him or her to produce a maximal inspiratory effort with the mask held gently but firmly over the face in order to obtain an air-tight seal. The first 2 readings are ignored. The next 5 readings are recorded after the subject has adapted to the instrument. The measurements are made in litres per minute. The result is recorded as the arithmetic mean value of the 5 readings.

b) Posterior active rhinomanometry

The method measures total nasal airway resistance which is the quotient of the pressure differential in the nose during inspiration or expiration and the flow. Measurements were undertaken at a constant pressure of 150 Kpascals, according to guidelines of the European Committee for standardisation of rhinomanometry (Dallimore and Eccles, 1977; Clement, 1984). Measurements were performed using a mercury electronic NR3 rhinomanometer linked to a microcomputer and a visual display unit. At least 30 minutes was allowed for the machine to "warm-up". The machine was calibrated before each subjects' measurement was recorded. The investigation was performed with the subject comfortably seated. A small, firm, polythene oral tube (3 mm in diameter and 6 cm in length) was held in the oral cavity resting on the tongue, in such a way as not to touch the roof of the mouth and held by closed lips in a stable position in order to detect pressure changes in the nasopharynx. Subjects were asked to avoid biting, excessive movement of the tube or blocking by the tongue in order to avoid instability with resultant poor recordings of pressure-flow curves. The oral tube was incorporated in an inflatable transparent face mask which was held lightly but firmly over the centre of the face in order to establish a good seal with the subject during normal quiet respiration. The machine recorded 4 readings and gave a mean value of the 4 recordings. Three consecutive mean values were taken provided they represented a coefficient of variation of less than 20%. The final reading was the arithmetic mean of 3 consistent mean values.

c) Acoustic rhinometry

Acoustic rhinometry represents a novel, quick, non-invasive and objective assessment of the volume and cross-sectional areas of the nasal cavities. The method was performed using a GM1 A1 acoustic rhinometer incorporated with an IBM computer and printer (Rajakulasingam et al., 1997). Measurements were performed on a seated subject using a snugly fitted nose piece applied to each nasal cavity in turn. The nose piece delivers from the rhinometer an acoustic signal "click" and the reflections of the click are received by a microphone, amplified, and analysed by the computer. Data is converted to an area-distance function and displayed by plotting cross-sectional areas on a logarithmic scale. Nasal volume was measured from 6.9 cm (representing the vestibule of the nose from the tip of the nose piece) to 14 cm.

Analysis of results

Outcome measures included: (1) Baseline nasal inspiratory peak flow, airway resistance and volume at each visit. (2) Change in nasal peak inspiratory flow, airway resistance and volume pre- to 30 minutes post-oxymetazoline at each visit. (3) Subjective and objective assessment by the same investigator at each visit before and after oxymetazoline. (4) Daily symptom diary card assessment throughout the 6 week study period.

Treatment effects (Wilcoxon, 1945; Edgington, 1980) were assessed between groups for these variables using the Wilcoxon rank sum test. Within subject comparisons were performed using the Wilcoxon matched-pairs signed-ranks test. It was not possible to plot or analyse subject diary symptom scores because the large majority were 0 (no blockage). Results were therefore presented in tabular form and analysed by the permutation test (Scadding, 1995).

RESULTS

Thirty normal subjects were randomised to receive either oxymetazoline (Wang and Bu Guo, 1991) or placebo (Wang and Bu Guo, 1991) nasal spray. The 2 groups were matched for gender, baseline lung function and atopic status (Table 1). Similarly, there were no significant differences between baseline measurement of nasal peak inspiratory flow, airway resistance and volume (Table 2). The median values (+/– quartiles) for nasal peak inspiratory flow, airway resistance and volume before and 30 min after oxymetazoline challenge are plotted in Figure 1. During each visit and for both oxymetazoline- and placebo-treated groups the median nasal peak flow and volume measurements increased whilst the median airway resistance values decreased. These changes were statistically significant for both treatment groups at all visits and for all variables (for nasal peak inspiratory flow all $p=<0.0001$ except for visit 1, oxymetazoline group where $p=0.003$. For airway resistance decreases were all significant $p<0.0001$, except visit 1, placebo group $p=0.003$, oxymetazoline group $p=0.005$. For nasal volume all $p<0.0001$ except visit 1, placebo group $p=0.026$ and visit 3, oxymetazoline group $p=0.01$). These changes after oxymetazoline challenge, represented 15-45% of baseline values for nasal peak inspiratory flow and acoustic rhinometry and 25-85% of baseline values for rhinomanometry (Tables 2 and 3). These differences indicate clinically significant decongestion for all parameters studied.

Table 2 summarises the results of a comparison between treatment groups of baseline measurements of nasal patency at each visit before oxymetazoline challenge. The results, expressed as median +/– ranges were not significantly different between the groups at baseline (visit 1) or following four weeks treatment with oxymetazoline (visit 2). There was a small sta-

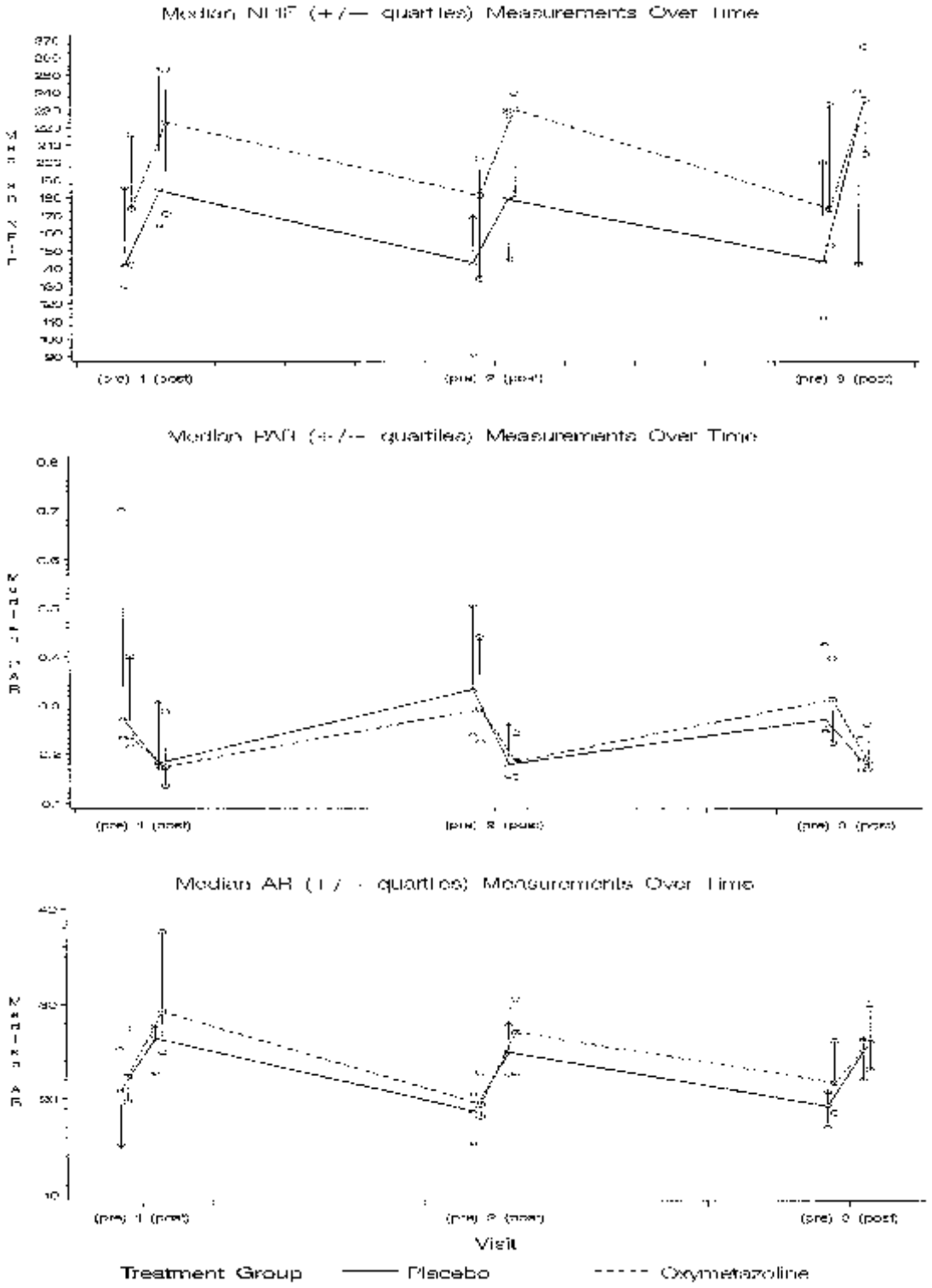

Figure 1. Median values (+/– quartiles) for nasal peak inspiratory flow (NPIF), airway resistance (PAR) and volume (AR) before and 30 minutes after oxymetazoline nasal spray at visit 1 (before treatment), visit 2 (after 4 weeks treatment) and visit 3 (2 weeks after stopping treatment). Open circles, broken lines represent patients treated with oxymetazoline (n=15), crosses refer to placebo treated group (n=15). For statistical comparisons see text.

tistically significant increase in median values for nasal inspiratory peak flow and volume in favour of the oxymetazoline group two weeks after stopping treatment. Within each treatment group measurements of all 3 variables were closely similar with no significant changes either during the four weeks treatment or following discontinuation of treatment.

Table 1. Baseline clinical data of subjects.

	Placebo (n=15)	Oxymetazoline (n=15)
Age (yr) median (± interquartile range)	30(25-37)	32(25-38)
Gender male/female (m/f)	(5m:10f)	(9m:6f)
Atopic status (atopic (A)/non-atopic (NA)	1A/14NA	2A/13NA
FEV1 % predicted (median ± quartiles)	106(91-114)	103(96-112)

Table 2. Comparison between treatments (placebo n=15 and oxymetazoline n=15) for baseline nasal peak inspiratory flow, airway resistance and volume (median ± range) at each visit.

		Visit 1 (before treatment)	Visit 2 (after 4 weeks treatment)	Visit 3 (2 weeks after stopping treatment)
nasal peak inspiratory flow (litres/min)	placebo	142(95,240)	143(71,252)	144(96,239)
	oxymetazoline	174(110,298)	181(106,273)	174(67,248)*
nasal airway resistance (Kpa)	placebo	0.27(0.20,0.89)	0.33(0.19,0.79)	0.27(0,1)
	oxymetazoline	0.24(0.13,1.03)	0.29(0.20,0.56)	0.31(0.17,0.65)
nasal volume (cc)	placebo	20.8(10,33)	18.8(11,24)	19.3(13,25)
	oxymetazoline	22.3(17,39)	19.5(16,32)	21.8(17,33)**

Rank sum test for placebo v oxymetazoline comparisons *p=0.044 **p=0.023 all other comparisons have p>0.05

Table 3. Comparison between treatments {placebo (n=15) and oxymetazoline (n=15)} for changes (from pre- to 30 min post-challenge with oxymetazoline) in nasal peak inspiratory flow, airway resistance and volume (median ± range) at each visit.

		Visit 1 (before treatment)	Visit 2 (after 4 weeks treatment)	Visit 3 (2 weeks after stopping treatment)
nasal peak inspiratory flow (litres/min)	placebo	34(5,125)	49(3,88)	49(14,132)
	oxymetazoline	42(-13,83)	44(-17,113)	44(3,101)
nasal airway resistance (Kpa)	placebo	-0.12(-0.71,0.16)	-0.09(-0.42,0.04)	-0.09(-0.32,-0.01)
	oxymetazoline	-0.08(-0.66,0.12)	-0.09(-0.33,0.03)	-0.08(-0.27,-0.01)
nasal volume (cc)	placebo	6.1(-10.7,12.1)	6.1(2.5,12.0)	6.5(0.6,11.1)
	oxymetazoline	6.1(0.8,15.3)	4.6(1.7,13.9)	4.1(-4.8,11.0)

Comparisons between treatment groups for the changes (from pre- to 30 minute post-challenge with oxymetazoline) in nasal peak flow, airway resistance and volume at each visit are summarised in Table 3. In agreement with the comparisons of baseline variables, these comparisons did not indicate any statistically significant difference between treatments at each visit in the response to oxymetazoline challenge.

Subjects symptoms of early morning and evening nasal blockage were recorded on diary cards daily throughout the 6 week study period on a scale 0 (no blockage), 1 (mild), 2 (moderate) and 3 (severe nasal blockage) and 4 (complete nasal obstruction). Median values for both treatment groups at all time points were 0 (no nasal blockage) (Table 4). Changes from before treatment start to weeks 1-4 demonstrated no significant

changes for either group although there was possibly a trend for more patients to develop mild (and occasionally moderate) nasal blockage within the placebo treated group. However when the changes from before treatment start to weeks 1-4 during treatment were compared there were no significant differences between treatment groups. Similarly, there was no difference between the groups when the changes from the end of treatment (week 4) to weeks 5 and 6 were compared.

A clinical examination and subjects subjective nasal blockage scores were also recorded before/after oxymetazoline challenge during clinic visits 1-3. In general, patients reported either no nasal blockage or mild blockage at baseline and subjective improvement after oxymetazoline with no significant differences either within or between treatment groups during the 3 visits (data not shown). Similarly, clinical examination did not demonstrate any significant changes in the appearance of the nasal mucosa, in particular no significant bleeding or changes suggestive of rhinitis medicamentosa for either treatment group.

DISCUSSION

In normal subjects 4 weeks treatment with oxymetazoline nasal spray did not induce any subjective symptoms of nasal blockage nor changes in nasal peak inspiratory flow, airway resistance or volume when compared with a matched group of subjects treated with placebo nasal spray containing diluent and preservative alone. Similarly, there was no change in the immediate response to oxymetazoline challenge following prolonged treatment with oxymetazoline. These results suggest that oxymetazoline nasal spray when used by normal subjects in conventional doses for up to 4 weeks is unlikely to be associated with clinically significant rebound congestion or tachyphylaxis to the effects of oxymetazoline.

The strengths of our study include the randomised blinded design with multiple objective and subjective measures of assessment, with each subject acting as his/her own control. Objective tests were validated by findings of less than 20% variability at baseline. The 2 weeks "run off" period was included to allow detection of any delayed or long lasting effects of oxymetazoline following discontinuation. Importantly, the results of this study in normal subjects may not be assumed to apply to patients with pre-existing nasal disease, in whom typically rhinitis medicamentosa may indeed occur following prolonged treatment with decongestants (Toohill et al., 1981; Mabry, 1982). In individual patients the characteristic clinical syndrome of severe nasal congestion, poor response to decon-

Table 4. Distribution of weekly subjective scores for nasal blockage AM (left) and PM (right).

Treatment Group								
		Morning					Evening	
		Score	Placebo	Oxymetazoline		Score	Placebo	Oxymetazoline
	Start	None	12 (80%)	13 (87%)	Start	None	12 (80%)	15 (100%)
		Mild	3 (20%)	2 (13%)		Mild	3 (20%)	0
	Week 1	None	10 (67%)	10 (67%)	Week 1	None	12 (80%)	13 (87%)
		Mild	5 (33%)	5 (33%)		Mild	2 (13%)	2 (13%)
						Moderate	1 (7%)	0
	Week 2	None	8 (53%)	13 (87%)				
		Mild	6 (40%)	2 (13%)	Week 2	None	8 (53%)	15 (100%)
During		Moderate	1 (7%)	0	During	Mild	5 (33%)	0
Treatment					Treatment	Moderate	2 (13%)	0
	Week 3	None	8 (53%)	13 (87%)				
		Mild	6 (40%)	2 (13%)	Week 3	None	9 (60%)	13 (87%)
		Moderate	1 (7%)	0		Mild	4 (27%)	2 (13%)
						Moderate	2 (13%)	0
	Week 4	None	9 (60%)	11 (73%)				
		Mild	4 (27%)	4 (27%)	Week 4	None	10 (67%)	14 (93%)
		Moderate	2 (13%)	0		Mild	5 (33%)	1 (7%)
After	Week 5	None	10 (67%)	13 (87%)	After	Week 5	None	9 (60%)	12 (80%)
Treatment		Mild	2 (13%)	2 (13%)	Treatment		Mild	5 (33%)	3 (20%)
		Moderate	3 (20%)	0			Moderate	1 (7%)	0
	Week 6	None	10 (67%)	12 (80%)		Week 6	None	10 (67%)	14 (93%)
		Mild	5 (33%)	3 (20%)			Mild	5 (33%)	1 (7%)

gestants, the appearances of erythema and mucosal swelling following prolonged decongestant use is well recognised. Toohill recognised a 1% incidence in his practice over a 10-year period during which patients had been using decongestant medication for an average of 21.4 months, the shortest period being one month (Toohill et al., 1981). In contrast, Mabry identified rhinitis medicamentosa in 52 out of 100 consecutive patients presenting with nasal obstruction (Mabry, 1982). However, the diagnosis cannot be made on the basis of decongestant overuse plus nasal obstruction alone since the majority of patients will have nasal obstruction due to other causes. Both mucosal changes *and* impaired response to topical decongestants are required for a convincing diagnosis (Scadding, 1995). In this controlled study in normal subjects we investigated the possibility of rebound congestion and poor response to decongestants following prolonged decongestant use. Thus, in contrast to so-called rhinitis medicamentosa in patients with pre-existing nasal disease, we identified no subjective nor objective evidence of either criteria within the sensitivity of the methods that we employed.

Previous open studies have shown similar results in normal subjects (Petruson, 1981; Åkerlund and Bende, 1991; Yoo et al., 1997). However, our results are at variance with a series of studies by Graf and colleagues. In two studies of 8 and 9 subjects topical use of oxymetazoline (0.5 mg/ml) (Graf and Juto, 1994) and xylometazoline (1.0 mg/ml) (Graf and Juto, 1995a) three times daily respectively resulted in rebound swelling of the nasal mucosa as detected by symptoms of nasal stuffiness and by the technique of rhinostereometry. They further demonstrated that once daily oxymetazoline induced comparable rebound nasal congestion, increased symptoms of nasal blockage and increased histamine responsiveness (Graf et al., 1995b). The group also provided evidence that benzalkonium chloride, the preservative commonly used with oxymetazoline (as in the present study) may exacerbate rebound congestion and nasal stuffiness when results were compared with oxymetazoline in the absence of the preservative (Graf et al., 1995c). The group further performed a placebo-controlled study in 30 healthy subjects. Three groups of subjects received oxymetazoline only, benzalkonium chloride only and placebo nasal spray for 28 days. Oxymetazoline nasal spray increased nasal stuffiness but not mucosal swelling whereas benzalkonium chloride spray increased nasal mucosal swelling but did not induce stuffiness (Graf and Hallen, 1996). It seems likely from these results that benzalkonium chloride alone may cause a minute change of nasal swelling but this change may not appear to be clinically apparent.

There are several reasons which may account for the differences between the studies of Graf and our own results. Firstly, unlike Graf we did not include a placebo- only group without containing benzalkonium. Secondly, different outcome measures were employed. Our subjects recorded nasal blockage as absent, mild, moderate, severe or complete, whereas Graf employed a visual analogue scale. Thirdly, we employed 3 objective measures of nasal congestion, none of which provided any evidence of rebound congestion or impaired response to oxymetazoline challenge. It is likely that the technique of rhinostereometry employed by Graf may be a more sensitive marker of the effects of vasoconstrictors in the nasal mucosa although the clinical relevance of these subtle changes detected requires further evaluation. A further study in which rhinostereometry and the methods employed in the current study are compared as well as a comparison of visual analogue scores and diary subjective evaluations in the same placebo controlled trial may cast light on these differences. The several methods used to assess nasal patency (nasal peak inspiratory flow, rhinomanometry, acoustic rhinometry and rhinostereometry) may not always correlate closely with each other. It has been recommended that the combination of measurements of both acoustic rhinometry and rhinomanometry may provide the most reliable objective information on nasal patency (Hirschberg, 2002; Numminen et al., 2002). To our knowledge this is the first trial of the possible adverse effect of prolonged use of nasal decongestants in either patients or normal volunteers that compares these methods.

The possible harmful effects of benzalkonium chloride, a widely used preservative in nasal sprays requires careful consideration. In vitro studies suggest that benzalkonium chloride may induce ciliary dysfunction (Batts et al., 1989). Benzalkonium chloride may occasionally provoke bronchoconstriction (Miszkiel et al., 1988). An electronmicroscopic study of bronchial biopsies following prolonged use of benzalkonium chloride demonstrated no significant changes (Braat et al., 1995). Graf and colleagues suggested that benzalkonium may exacerbate rhinitis medicamentosa (Hallen and Graf, 1995). In our study (Table 4) there was a trend for an increase in the number of subjects complaining of mild/moderate nasal blockage during 4 weeks treatment with placebo (containing benzalkonium chloride but not oxymetazoline). However these changes were not significant either within or between the groups studied, and were not accompanied by changes in any of the objective parameters.

In summary, topical nasal oxymetazoline when used at a dose of 100 μg 3 times daily over an extended period of 4 weeks was not associated with either subjective or objective changes of rebound nasal congestion or impaired responsiveness to oxymetazoline. We cannot exclude from our design that the preservative benzalkonium alone may induce nasal congestion in a small population of subjects. Further studies are required involving subjects with both acute and chronic forms of rhinitis in order to assess any possible side effects of oxymetazoline on the inflamed nasal mucosa in these patient groups. Nonetheless our results suggest that in a large majority of normal subjects nasal decongestants may be safely used for up to 4 weeks with a low potential for clinically significant adverse events on the nasal mucosa.

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