Rhinology, 43, 291-295, 2005

Decongestant effects of nasal xylometazoline and mometasone furoate in persistent allergic rhinitis*

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SUMMARY

Thirty-six persistent allergic rhinitis (PAR) sufferers were studied, to both compare and correlate 15 minute response to nasal xylometazoline (XYLO) with 28 day response to nasal mometasone furoate (MF). 0.1% XYLO(1 spray each nostril) response was measured on two occasions, then a randomised double blind cross-over comparison of MF (200mcg daily) to placebo conducted. Outcomes were peak nasal inspiratory flow (PNIF), nasal forced inspiratory volume in one second ($nFIV_1$) and nasal blockage score (NBS) improvements.

Thirty-one participants completed per protocol. Within subject standard deviation for percentage improvement to XYLO was 26.0 for PNIF and 25.2 for $nFIV_1$. Median % improvement (95%CI) in PNIF for XYLO vs. MF was 20.0 (11.4 to 31.0) vs. 9.6 (3.2 to 15.8) and in $nFIV_1$ was 17.8 (10.0 to 28.1) vs. 3.3 (-4.3 to 19.1). XYLO effects were greater than MF ($p<0.05$) for PNIF, $nFIV_1$ and NBS. There was no significant correlation of MF to XYLO improvements in PNIF, $nFIV_1$ or NBS. In conclusion, acute reversibility to XYLO showed poor repeatability and XYLO reversibility is not predictive of decongestant response to nasal corticosteroid. XYLO was a stronger decongestant than MF but rhinitis medicamentosa still precludes any preference for long term XYLO therapy at this time.

Key words: rhinitis, persistent, mometasone, xylometazoline, allergy

INTRODUCTION

The use of topical nasal corticosteroids is recommended as the most effective therapy in persistent allergic rhinitis (PAR) [1]. In many cases of PAR the primary aim is symptomatic relief of nasal blockage, which may be more effectively achieved with decongestants.

The use of long term nasal decongestants is limited by development of rhinitis medicamentosa (RM). This is a syndrome of rebound hyperaemia which follows prolonged courses of nasal alpha-adrenergic agonists or imidazoline derivatives, characterised by tachyphylaxis and increased nasal congestion [2], hyperreactivity [3] and histological changes [4]. There is conflicting evidence on the underlying pathophysiology which may involve interstitial oedema, vasodilatation [5] or a combination of both. It is established that corticosteroids and topical decongestants have an additive effect, which may be evidence that nasal obstruction has elements of both oedema and vasodilatation, or that there is a synergistic effect of the drugs [6].

Decongestants are often avoided for fear of RM. In the UK they are used even less commonly than in other countries, particularly the oral preparations with lower risks of RM [2]. Treatment decisions include not only the risk of RM, but also potential systemic effects of steroid administration, tolerability, cost and efficacy – including effects on irritant symptoms and discharge which are likely to favour steroid use.

The vasoconstrictive effects of nasal corticosteroids are well established [7]. Likewise, blockage is better controlled by nasal corticosteroids than antihistamines. However, no studies have set out to make a specific comparison of decongestant effects of nasal steroids and alpha agonists. It seems intuitive that decongestants should be a stronger treatment for blockage symptoms.

The acute response to xylometazoline (XYLO) is used in outpatient practice to quantify the reversible component of nasal blockage. This is considered useful in predicting response to and necessity for surgery. It is possible that this same measure may mirror response to long term steroid use, in the same way that salbutamol response mirrors long term inhaled steroid response in the lower airways [8].

The present study compares and correlates the response over 15 minutes to nasal XYLO with the response over 28 days to nasal mometasone furoate (MF). Measurements include peak nasal inspiratory flow (PNIF), nasal forced inspiratory volume in 1 second (nFIV1) and a nasal blockage score (NBS).

* Received for publication: September 29, 2004; accepted: February 7, 2005

MATERIALS AND METHODS

Participants

Participants were identified from our own database of sufferers in the Dundee, Scotland area. They were required to have a PNIF of less than 100 L/min, an NBS of 2 or more out of 3, and a positive skinprick test to house dust mite. Rigid nasal endoscopy was conducted and participants with grade 2 or higher nasal polyps or more than 50% nasal septal deviation (50% reduction in expected cavity cross-sectional area) were excluded.

Study Design

The study was conducted in six visits to the research laboratory. All participants gave informed consent and the study was approved by the Tayside Committee on Medical Research Ethics.

At visit 1 a medical history was taken, skin prick tests were conducted to common aeroallergens, routine blood tests (FBC, U&E, LFT) were sent, and nasal endoscopy was conducted. Participants stopped their usual therapy with decongestants, antihistamines, antileukotrienes and nasal steroids, and arranged another visit 2 weeks later.

At visit 2, after ensuring that usual medications had been discontinued, acute XYLO reversibility was assessed. This involved measurements of PNIF, $nFIV_1$ and NBS before and 15 minutes after administration of 1 spray of nasal 0.1% XYLO to each nostril. Participants returned after a minimum of 24 hours for visit 3 at which the XYLO reversibility assessment was repeated, and visit 4 arranged 24 or more hours later.

Visit 4 was used to establish a further baseline for PNIF, $nFIV_1$ and symptom scores prior to entry into a period of a randomised double blind crossover comparison of effects for MF nasal spray (100mcg to each nostril once daily) to an identical placebo each taken for consecutive 28 day treatments. The 200mcg MF is close to the plateau of the dose response curve [9]. No washout period was necessary given the length of the treatments.

Visits 5 and 6 followed the first and second 28 day crossover treatment periods respectively. At each of these visits the PNIF, $nFIV_1$ and NBS measurements were repeated.

Measurements

PNIF was taken as the best of three measurements using the In-Check® PNIF meter (Clement Clarke International Ltd, Harlow, UK). PNIF is a repeatable and objective measure of nasal airway obstruction [10, 11].

$nFIV_1$ was taken as the best of three measurements using an ML3535 handheld spirometer (Micro Medical Ltd, Rochester, UK). The spirometer sensor had been reversed and recalibrated for nasal measurements by the manufacturer as described by previous authors [12].

NBS was measured on an interval scale of 0, 1, 2 or 3 representing no symptoms, mild, moderate or severe symptoms respectively.

Statistical analysis

The study was powered (at >90%) to detect a 10 l/min difference in PNIF between groups. Analyses were performed using Minitab, Copyright© 2004, Minitab Inc. PA, USA and SPSS for Windows (v11) Copyright© 2004 (SPSS Inc. Chicago, IL, USA). Chi^2 tests were used for all NBS comparisons. All other data was tested for normality visually and with a Ryan-Joiner test. Improvements in PNIF and $nFIV_1$ all differed significantly from the normal, so were analysed using a 1-sample Wilcoxon test and Spearman's Rank correlation. Differences in improvements following MF or XYLO were normal in distribution, and were analysed by t-test.

RESULTS

Participant demographics

Thirty-six subjects aged 18 years and over with persistent allergic rhinitis were enrolled in the study. Thirteen men and 18 women with mean (SD) age of 39.2 (14.1) and 46.6 (10.8) years respectively completed per protocol. Demographics for completed participants analysed by sequence of treatment exposure showed no significant differences for age, sex, asthmatic status, antihistamine or nasal steroid use.

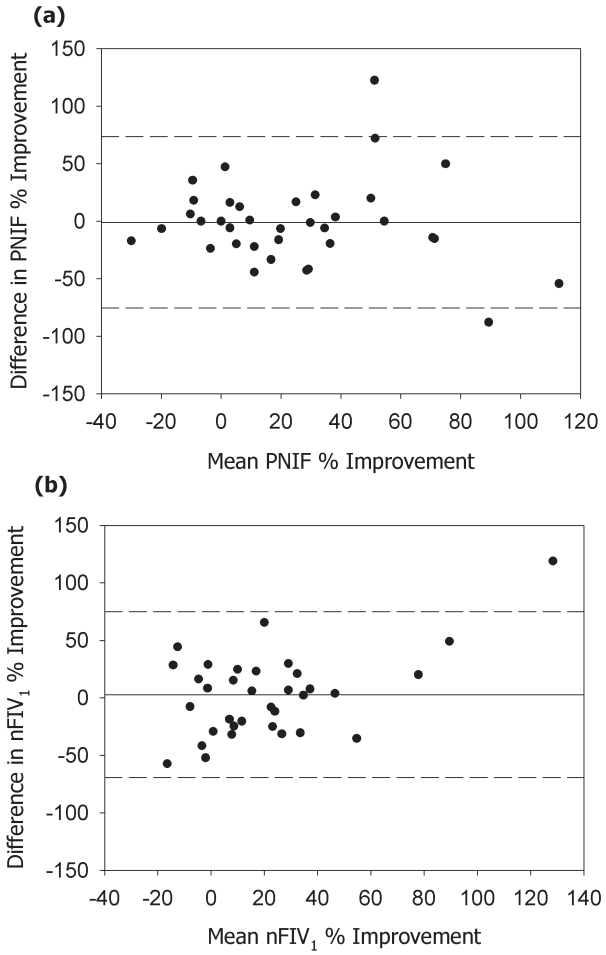

Figure 1. Altman Bland plots for (a) PNIF and (b) $nFIV_1$ response to XYLO at visits 2 and 3. Reference lines represent mean differences +/- 2 SD.

Participant withdrawals

Five participants withdrew; one due to perceived side effects of the nasal spray, three were unable to attend as planned, and one had suffered a myocardial infarction.

Adverse events

The myocardial infarction occurred in a participant taking placebo, nearly two months after XYLO use, and 3 weeks after MF use. We have concluded that it was coincidental. Headache was more common in the placebo treated limb of the cross over section ($p<0.05$) but numbers were very small. There were no other statistically significant differences in adverse events by treatment exposure (including upper respiratory tract infections, epistaxis and conjunctivitis).

XYLO reversibility

The within subject standard deviation (sw) was calculated from the paired measurements (for visits 2 and 3) of percentage improvements in PNIF and $nFIV_1$. This was 26.0 for PNIF, and 25.2 for $nFIV_1$. Altman Bland plots [13] were produced (Figure 1).

Improvements in Objective and Subjective measures (Figure 2)

All XYLO related PNIF and $nFIV_1$ improvements (Table 1) were calculated from the mean of each individual's measurements at visits 2 and 3. PNIF and $nFIV_1$ were expressed as percentage improvements, and NBS as absolute improvements. MF and placebo related improvements (Table 2) were expressed in the same way for data obtained at visits 5 or 6 relative to the baseline measurement at visit 4.

Comparisons of decongestant effects

PNIF was 13.4% (95% CI 1.9 to 24.9%, $p<0.05$) greater following XYLO than MF.

$nFIV_1$ was 11.5% (95% CI 0.5 to 22.7%, $p<0.05$) greater following XYLO than MF.

Mean NBS was 0.23 units ($p<0.01$) lower following XYLO than MF.

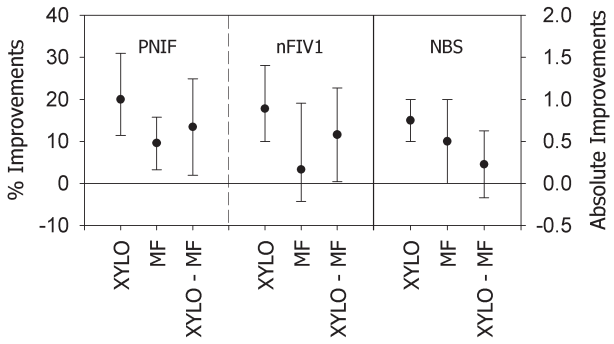

Figure 2. Median and 95%CI improvements in PNIF, $nFIV_1$ and NBS following XYLO and MF, with Mean difference and 95%CI for XYLO vs. MF.

Table 1. XYLO induced improvements in PNIF and $nFIV_1$ at visits 2 and 3, with comparisons between visits.

	Median	95% CI
Visit 2 PNIF % Improvement	21.5	11.1 to 33.3
Visit 3 PNIF % Improvement	20.8	9.2 to 35.4
Difference	-3.0	-12.7 to 8.1
Visit 2 $nFIV_1$ % Improvement	20.5	11.2 to 29.8
Visit 3 $nFIV_1$ % Improvement	18.2	8.0 to 29.5
Difference	-0.1	-11.0 to 13.6
Visit 2 NBS Improvement	0.5	0.5 to 1
Visit 3 NBS Improvement	0.5	0.5 to 1
Difference	0.0	0 to 0.5

Table 2. MF and placebo induced improvements in PNIF, $nFIV_1$ and NBS.

		Median	95% CI
MF	PNIF % Improvement	9.6	3.2 to 15.8
MF	$nFIV_1$ % Improvement	3.3	-4.3 to 19.1
MF	NBS Absolute Improvement	0.5	0 to 1
PL	PNIF % Improvement	-2.5	-10.0 to 6.7
PL	$nFIV_1$ % Improvement	-2.4	-10.1 to 7.9
PL	NBS Absolute Improvement	0	-0.5 to 0

Correlation of decongestant effects for XYLO and MF

Response to MF showed no significant correlation with response to XYLO when measured with PNIF, $nFIV_1$, or NBS (Table 3, Figure 3).

DISCUSSION

The present study shows that in PAR, the acute decongestant response to XYLO is greater than the chronic decongestant response to MF for subjective and objective outcomes of nasal airflow obstruction. This was evident in comparing absolute improvements in NBS, and relative improvements in PNIF and $nFIV_1$.

The repeatability of the acute response to XYLO was surprisingly poor for both PNIF and $nFIV_1$ outcomes. One possible explanation may be the relatively low dose (1 spray each side) used, potentially on the steep part of the dose response curve for vasoconstriction. With a higher dose (e.g. 2-4 sprays each side) on the plateau of the dose response curve, the vasoconstrictor response achieved might have been maximal and more consistent than we observed.

We do not believe that the inherent variability of PNIF or $nFIV_1$ was a major factor in the observed degree of variability of response to XYLO, as we have previously shown that for PNIF and $nFIV_1$ the within subject coefficient of variation for repeated measures is 8% and 4% respectively [10]. Also, we have previously found that in response to nasal MF in intermittent allergic rhinitis, measuring PNIF response is more sensitive than other outcomes such as acoustic rhinometry or rhinomanometry [11].

Although the magnitude of response was significantly greater with XYLO than MF, alpha agonists are unlikely to replace

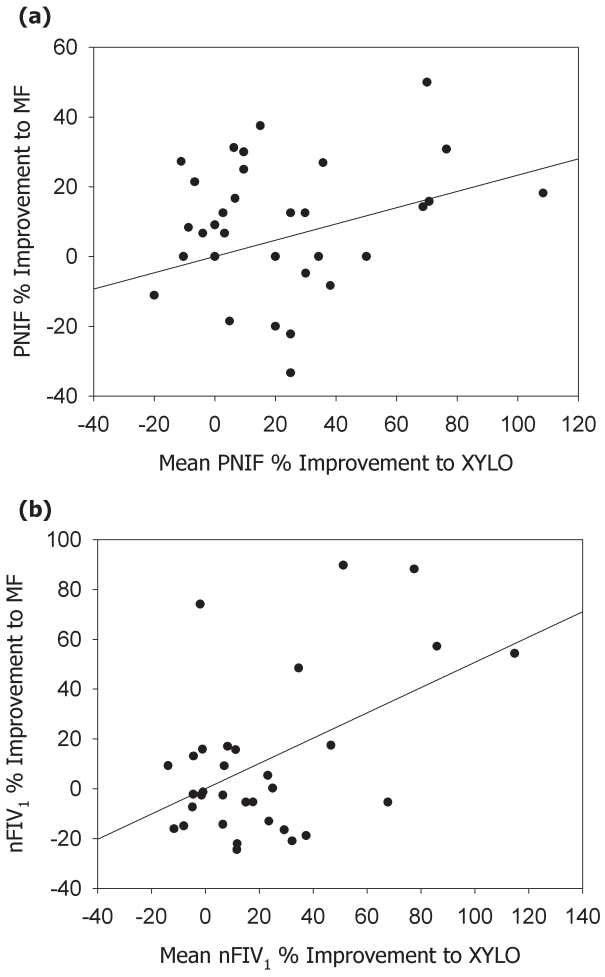

Figure 3. Scatter plots of MF against XYLO % improvements for (a) PNIF and (b) $nFIV_1$ with lines of best fit through the origin.

nasal steroid use even in patients for whom blockage is the foremost symptom. Nasal corticosteroids have beneficial effects aside from decongestion in PAR due to their broad spectrum of anti-inflammatory activity, namely improvement in itch, sneeze, discharge cough and olfaction [14-17]. Perhaps even more importantly, alpha agonist use is limited by RM and tachyphylaxis during chronic dosing [18]. As such, we do not currently recommend prolonged use of alpha agonists.

As mentioned in the introduction, there may be synergistic effects of corticosteroids and topical decongestants [6]. In addition to vasoconstriction, glucocorticosteroids are known to upregulate alpha adrenoreceptor expression [19]. These effects deserve further study, and may be analogous to combination inhaler use in asthma, where a corticosteroid (e.g. fluticasone propionate or budesonide) is given with a long acting beta-2 agonist (e.g. salmeterol or formoterol) resulting in a synergistic response [20, 21].

It is established that intranasal corticosteroids are effective in the treatment of RM [5, 22, 23], and in asthma corticosteroid administration can prevent tachyphylaxis and subsensitivity following chronic beta-2 agonist use [24]. It may be that concomitant nasal steroid use can prevent or reduce tachyphylaxis and RM associated with chronic alpha agonist use in a similar manner.

Table 3. Correlations of improvements following MF & XYLO.

	Spearman's ρ	p-value
PNIF	0.144	0.431
$nFIV_1$	0.252	0.165
NBS	0.294	0.103

There was no correlation seen between acute decongestant response to XYLO and chronic decongestant response to MF. Thus, in clinic situations, there seems little point in routinely assessing XYLO reversibility to predict the response to MF. Beyond this, xylometazoline reversibility testing is commonly used as a measure of mucosal verses structural nasal blockage to predict response to surgical intervention. Our study was not designed to directly assess this application, but such a poorly repeatable test is unlikely to be usefully predictive.

In conclusion, XYLO is unsurprisingly a stronger decongestant than MF, further studies are indicated for therapeutic combinations of alpha agonists and nasal corticosteroids, and XYLO reversibility as a measure has poor repeatability and does not predict MF response.

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