J. Sleep Res. (2008) 17, 444–449 Sleep apnoea

doi: 10.1111/j.1365-2869.2008.00667.x

Does nasal decongestion improve obstructive sleep apnea?

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Accepted in revised form 27 March 2008; received 16 December 2007

SUMMARY Whether nasal congestion promotes obstructive sleep apnea is controversial. Therefore, we performed a randomized placebo-controlled cross-over trial on the effects of topical nasal decongestion in patients with obstructive sleep apnea syndrome (OSA) and nasal congestion. Twelve OSA patients with chronic nasal congestion (mean ± SD age 49.1 ± 11.1 years, apnea/hypopnea index 32.6 ± 24.5/h) were treated with nasal xylometazoline or placebo for 1 week each. At the end of treatment periods, polysomnography including monitoring of nasal conductance by an unobtrusive technique, vigilance by the OSLER test, and symptom scores were assessed. Data from xylometazoline and placebo treatments were compared. Mean nocturnal nasal conductance on xylometazoline was significantly higher than on placebo (8.6 ± 5.3 versus 6.3 ± 5.8 mL $s^{-1}Pa^{-1}$, $P < 0.05$) but the apnea/hypopnea index was similar (29.3 ± 32.5/h versus 33.2 ± 32.8/h, P = NS). However, 30–210 min after application of xylometazoline, at the time of the maximal pharmacologic effect, the apnea/hypopnea index was slightly reduced (27.3 ± 30.5/h versus 33.2 ± 33.9/h, $P < 0.05$). Xylometazoline did not alter sleep quality, sleep resistance time (33.6 ± 8.8 versus 33.4 ± 10.1 min, P = NS) and subjective sleepiness (Epworth score 10.5 ± 3.8 versus 11.8 ± 4.4, P = NS). The reduced apnea/hypopnea index during maximal nasal decongestion by xylometazoline suggests a pathophysiologic link but the efficacy of nasal decongestion was not sufficient to provide a clinically substantial improvement of OSA. ClinicalTrials.gov Identifier is NTC006030474.

KEYWORDS nasal resistance, obstructive sleep apnea, rhinitis, sleep quality

INTRODUCTION

Nasal obstruction is common, impairs sleep quality (Leger *et al*., 2006) and may predispose to snoring (Young *et al*., 2001) and the obstructive sleep apnea syndrome (OSA) (Young *et al*., 1997). In healthy subjects, experimental nasal occlusion has been shown to promote obstructive sleep apnea (Olsen *et al*., 1981). However, in patients with OSA treatment of nasal obstruction by topical decongestants (Braver *et al*., 1995; McLean *et al*., 2005) or corticosteroids (Kiely *et al*., 2004), external nasal dilators (Hoijer *et al*., 1992) and nasal surgery (Virkkula *et al*., 2006) has provided equivocal results (Kohler *et al*., 2007). The interpretation of these studies is hampered by the small number of patients involved and because the measurement of nasal resistance during sleep has not been feasible. This is because conventional techniques for measurement of nasal obstruction such as rhinomanometry or acoustic reflexion rhinometry require patient cooperation and wearing a nasal mask which makes them unsuitable for application during sleep. To overcome these drawbacks, we have recently developed an unobtrusive method for continuous side-selective monitoring of nasal airflow and conductance (Kohler *et al*., 2006). Studies based on this technique revealed that nasal conductance is highly variable over the course of a

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night suggesting that a single assessment of nasal patency performed during wakefulness before or after a sleep study cannot accurately predict the physiologic conditions during sleep (Kohler *et al*., 2006).

To better define the potential interactions among nocturnal nasal obstruction, sleep and breathing disturbances in patients with OSA and chronic nasal congestion, we performed a randomized, placebo-controlled study on the effects of topical nasal decongestion on nocturnal nasal conductance monitored continuously by the novel technique in relation to breathing patterns, sleep quality, and subjective perception of nasal obstruction. We hypothesized that xylometazoline, an imidazoline derivate, which attains its maximal effect between 30 and 210 min after nasal application (Hochban *et al*., 1999) would increase nasal conductance and lead to a transient, time-dependent improvement in breathing and sleep disturbances.

METHODS

Patients

Successive patients diagnosed with OSA (defined by a complaint of excessive daytime sleepiness, an Epworth sleepiness score >8 (Bloch *et al*., 1999), and an apnea/hypopnea index >10/h) were included if they also suffered from chronic nasal congestion defined by a complaint of impaired nasal breathing that interfered with subjective sleep quality on at least three nights per week during at least the last 3 months (Young *et al*., 1997). Exclusion criteria were nasal surgery within the last 6 months, current treatment with nasal decongestants or topical steroids, sleep disorders other than obstructive sleep apnea, internal medical or psychiatric disorders that interfered with sleep. Two female and 10 male patients with a mean ± SD age of 49.1 ± 11.1 years gave informed consent. Their body mass index was 30.7 ± 5.1 kg/m^2, the apnea/hypopnea index was 32.6 ± 24.5 events/h and the Epworth score was 11.8 ± 4.5. The Ethics Committee of the University Hospital of Zurich approved the protocol.

Measurements

A medical history and a physical examination were performed. Patients completed the Epworth Sleepiness scale (Bloch *et al*., 1999) with the instruction to rate the average tendency to fall asleep during the 7 days corresponding to each treatment period. Subjective perception of nasal obstruction was assessed by a visual analogue scale extending from 0 (unimpaired nasal breathing) to 10 (completely obstructed nose).

Polysomnography was performed from approximately 10 p.m. to 6 a.m. according to standard guidelines (Bloch, 1997). Breathing patterns were monitored by calibrated respiratory inductive plethysmography (Bloch *et al*., 1997). Snoring was recorded with a miniature-microphone taped to the skin on the lateral aspect of the larynx. Recordings of nasal conductance over the course of the night were obtained by a novel unobtrusive technique developed at our laboratory (Kohler *et al*., 2005, 2006). The technique uses modified nasal cannula and small bore catheters inserted coaxially through the cannula into the epipharynx for side-selective measurement of nasal airflow and conductance in the left and the right nasal passage. The sum of the left plus right nasal conductance corresponds to total nasal conductance and its reciprocal value is total nasal resistance. The technique does not require a nasal or face mask and is therefore well suited to monitor nasal conductance during sleep.

Vigilance was assessed by the Oxford Sleep Resistance Test (OSLER) on four occasions over the course of the day following polysomnography (Bennett *et al*., 1997). Sleep resistance time was defined as the mean latency to seven missed signals from four trials.

Protocol

A randomized double-blind, placebo-controlled, cross-over block-design with two 1-week treatment periods separated by a 1-week washout period was used (Fig. 1). During the 1-week treatment periods, patients applied every evening either xylometazoline (0.1% solution, three drops, 0.15 mg) in each nostril, or an identically looking placebo (sodium chloride, 0.9% solution) according to the randomization. Assessments were performed at the end of each treatment period. The ClinicalTrials.gov identifier is NTC00630474.

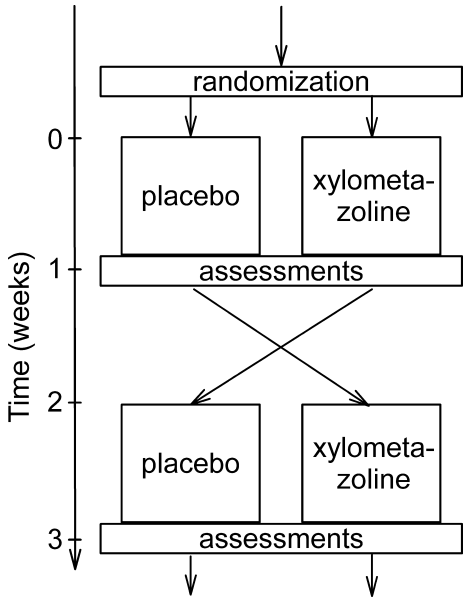

Figure 1. The study was designed according to a randomized, placebo-controlled cross-over protocol. After baseline evaluation, patients underwent a 1-week treatment with either xylometazoline or placebo, followed by a wash-out period of 1 week, and a 1-week treatment with the other drug. At the end of each treatment period assessments comprised polysomnography including nasal conductance monitoring, vigilance tests and symptom scores.

Data analysis and statistics

The code of the medication was broken only after completion of data analysis. Sleep stages and arousals were scored according to standard criteria (Rechtschaffen and Kales, 1968; Sleep Disorders Atlas Task Force of the American Sleep Disorders Association EEG Arousals., 1992). An apnea/hypopnea was defined as a reduction of total nasal airflow by >50% for >10 s. Obstructive were differentiated from central apnea/hypopnea by asynchronous or paradoxical chest wall excursions during the event. Mean left, right and total nasal conductance during three consecutive breaths were computed every 15 min (Kohler *et al.*, 2006). A nasal cycle was defined as the time period between changes in left to right side predominance of nasal conductance or vice-versa. The amplitude of reciprocal changes in nasal conductance with nasal cycling was quantified by the coefficient of variation of the left/right nasal conductance ratio (Eccles *et al.*, 1996).

Data are summarized as means and SD. The main outcomes were nasal conductance, apnea/hypopnea index, nocturnal oxygen saturation, sleep efficiency, and Epworth score. Effects of xylometazoline versus placebo were evaluated by paired *t*-tests performed on data from entire nights and from the time of the expected maximal xylometazoline effect, i.e., 30–210 min after topical application (Hochban *et al.*, 1999). Statistical significance was assumed at $P < 0.05$. The study was powered with >70% to detect clinically relevant effects on outcomes defined as differences in the apnea/hypopnea index of 10/h, in mean oxygen saturation of 2%, in sleep efficiency of 12%, and in Epworth score of 2 points.

RESULTS

The effects of xylometazoline are summarized in Table 1. Mean nasal conductance on xylometazoline was significantly higher (by 70 ± 83%) compared with corresponding values of placebo (Fig. 2). Maximal nasal decongestion was achieved 90 min after beginning of the sleep studies with peak nasal conductance on xylometazoline of 11.09 mL $s^{-1}Pa^{-1}$ exceeding the corresponding value on placebo by 6.02 mL $s^{-1}Pa^{-1}$ (119%) ($P < 0.05$, Fig. 3). Side-selective analysis revealed that the number of nasal cycles defined by a switch in predominance of nasal conductance from one to the contralateral side was reduced by xylometazoline and the reciprocal changes in left-/right-sided nasal conductance were less pronounced (Table 1, Fig. 4). Despite the higher nasal conductance during the nights on xylometazoline, there was no significant difference in the apnea/hypopnea index (Fig. 2), the oxygen desaturation index, the sleep time spent with snoring nor in any of the variables reflecting sleep quality and there was no significant effect of xylometazoline on vigilance, subjective sleepiness and perception of impaired nasal breathing (Table 1). Visual analog scores of perceived nasal obstruction did not significantly correlate with objectively measured nasal conductance over the course of the night ($r = -0.33$, $P = 0.11$).

Table 1 Effects of xylometazoline on nocturnal breathing and sleep

	Xylometazoline	*Placebo*
Total nasal conductance entire night (mL $s^{-1}Pa^{-1}$)	8.6 ± 5.3*	6.3 ± 5.8
Total nasal conductance 30–210 min of night (mL $s^{-1}Pa^{-1}$)	9.8 ± 5.9*	5.8 ± 3.7
Nasal cycles per night†	1.8 ± 1.7*	4.6 ± 3.2
Variability of left/right nasal conductance ratio (Cvar, %)	54 ± 28*	130 ± 71
Apnea/hypopnea index entire night (1/h)	29.3 ± 32.5	32.2 ± 32.8
Apnea/hypopnea index 30–210 min of night (1/h)	27.3 ± 30.5*	33.2 ± 33.9
Oxygen desaturation index entire night (1/h)	26.1 ± 31.0	30.0 ± 31.0
Oxygen desaturation index 30–210 min of night (1/h)	23.8 ± 28.7*	30.1 ± 31.8
Snoring entire night (% of sleep time)	38 ± 18	38 ± 12
Snoring 30–210 min of night (% of sleep time)	42 ± 20	42 ± 15
Mean oxygen saturation (%)	94 ± 3	93 ± 3
Total sleep time (min)	341 ± 57	383 ± 29
Sleep efficiency (% sleep of time in bed)	86 ± 12	88 ± 6
Sleep stage III/IV (% total sleep time)	9 ± 8	7 ± 6
Sleep stage REM (% total sleep time)	10 ± 5	11 ± 5
Arousal index (events/h)	54 ± 12	56 ± 12
Supine body position (% of sleep time)	67 ± 30	71 ± 28
Sleep resistance time (OSLER test, min)	33.6 ± 8.8	33.4 ± 10.1
Epworth sleepiness score	10.5 ± 3.8	11.8 ± 4.4
Subjective perception of nasal obstruction‡	4.8 ± 2.2	5.6 ± 2.7

Cvar = coefficient of variation = SD in percent of mean value.
Values are mean ± SD, $n = 12$ patients.
*$P < 0.01$, versus placebo.
†Seven patients on xylometazoline and 10 on placebo had nasal cycling.
‡Assessed by visual analog scale with 0 = unimpaired nasal breathing, and 10 = completely obstructed nose.

An analysis of the time period of the expected maximal effect of xylometazoline, i.e. 30 to 210 min following application of the drug (Hochban *et al.*, 1999) revealed a significant reduction in apnea/hypopnea and in oxygen desaturations by xylometazoline compared with placebo (Table 1). The time-dependent effect of xylometazoline was further explored by a multiple regression analysis with the hourly apnea/hypopnea index over the course of the night as the dependent variable and the drug (xylometazoline or placebo), nasal conductance and elapsed time as the independent variables. This analysis revealed that xylometazoline was associated with a significant reduction of the apnea/hypopnea index (β-coefficient −1.2, 95% confidence interval −0.08 to −2.33, $P = 0.04$) when controlled for the elapsed time over the course of the night and nasal conductance.

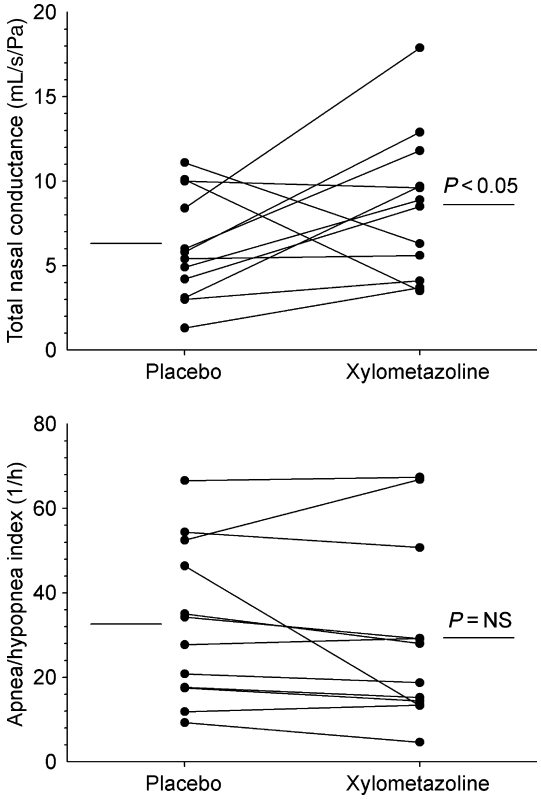

Figure 2. Individual (circles) and mean values (horizontal lines) of mean nocturnal nasal conductance (upper panel) and apnea/hypopnea index (lower panel) in 12 patients during treatment with xylometazoline and placebo.

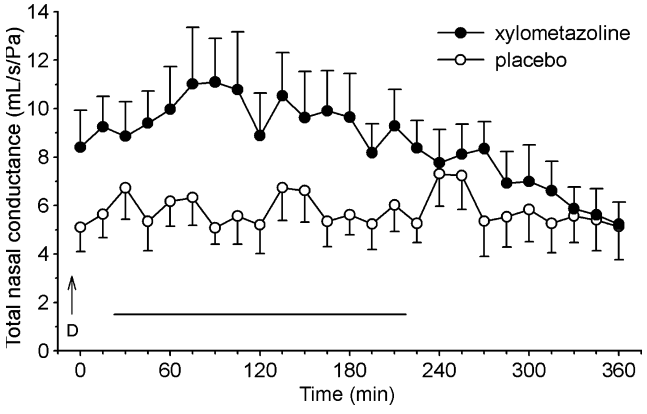

Figure 3. Time course of nasal conductance measured by the novel unobtrusive technique over the course of nocturnal sleep studies during xylometazoline and placebo treatment (group means, SE; $P < 0.05$ for comparison of xylometazoline versus placebo nights). The arrow (D) indicates drug application, time 0 = lights-off. The horizontal line represents the period of the expected maximal decongestive effect of xylometazoline.

To evaluate the effect of nasal conductance on breathing disturbances, data were rearranged to compare nights with the individually higher versus the lower mean nocturnal nasal conductance, irrespective of whether they corresponded to a

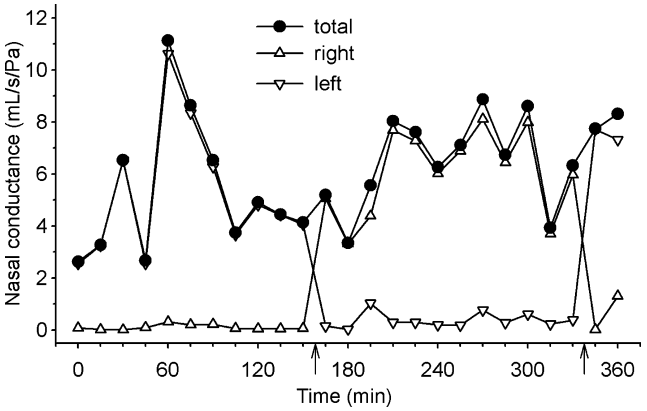

Figure 4. Side-selective nasal conductance over the course of a night's sleep in a patient on placebo. Values of the left and the right nasal conductance are displayed along with their sum, the total nasal conductance. The switches from left- to right-sided predominance of conductance and vice-versa (arrows) identify the end of two nasal cycles.

xylometazoline or a placebo night. This analysis revealed a lower apnea/hypopnea index of 27.9 ± 25.0 events/h during nights with the higher nasal conductance ($9.7 \pm 6.6 mLs^{-1}Pa^{-1}$) compared to an apnea/hypopnea index of 34.2 ± 25.0events/h during nights with the lower mean nasal conductance (5.2 ± 3.5 mL $s^{-1}Pa^{-1}$) ($P < 0.05$, both instances).

DISCUSSION

We performed a randomized, placebo-controlled, double-blind trial on the effects of the nasal decongestant xylometazoline on nocturnal breathing and sleep in patients with the obstructive sleep apnea syndrome (OSA) and a chronically congested nose. While topical application of xylometazoline induced a major increase in nasal conductance of 70% it did not significantly reduce the mean apnea/hypopnea index during the entire night nor did it improve snoring, sleep quality or daytime sleepiness (Table 1). However, monitoring of nasal conductance over the course of the night by a novel unobtrusive technique confirmed that during the period of maximally improved nasal conductance by xylometazoline the number of apneas/hypopneas and of oxygen desaturations was reduced. This corroborates the pathophysiologic link between impaired nasal breathing and obstructive sleep apnea. Since the improvement in sleep-related breathing disturbances by xylometazoline was modest and of marginal clinical relevance our data suggest that nasal decongestion by pharmacologic means is not an effective treatment for OSA patients with chronic nasal congestion.

The few randomized studies evaluating the effect of topical nasal drug treatment on nocturnal breathing disturbances in patients with OSA have provided variable results (Kohler *et al*., 2007). Kerr and coworkers (Kerr *et al*., 1992) studied 10 OSA patients during two successive nights on oxymetazalone in combination with a vestibular stent and placebo, respectively. They observed no change in the apnea/hypopnea index nor in sleep efficiency, and an only minor reduction in the

arousal index with nasal decongestion and vestibular stenting despite a considerable reduction in nasal resistance measured by posterior rhinomanometry before and after polysomnography. McLean and coworkers (McLean *et al*., 2005) compared oxymetazoline applied twice over the course of a night in combination with an external nasal-valve dilator strip with placebo in 10 OSA patients with severe nasal obstruction. Nasal resistance measured by posterior rhinomanometry before and after sleep studies was significantly reduced and this was associated with a modest drop in the apnea/hypopnea index by a mean of 12 events/h, an improved sleep efficiency and an increase in slow wave and REM sleep. Kieley and coworkers (Kiely *et al*., 2004) treated 13 OSA patients with rhinitis during 4 weeks with the intranasal corticosteroid fluticasone propionate. This resulted in a modest reduction of nasal resistance of 9% and a decrease in the apnea/hypopnea index by a mean of 7 events/h compared with placebo. The changes in the apnea/hypopnea index were correlated with the changes in nasal resistance induced by the treatment (Kiely *et al*., 2004).

The cited studies differ from our own investigation in several ways. We applied the nasal decongestant alone rather than in combination with a mechanical device as in two of the previous studies (Kerr *et al*., 1992; McLean *et al*., 2005), and we used one single dose of xylometazoline at the beginning of the night only rather than a repeated application of oxymetazoline as performed by McLean and coworkers (McLean *et al*., 2005). A further difference relates to the assessment of nasal patency which was performed with conventional posterior rhinomanometry during wakefulness in the previous studies (Kerr *et al*., 1992; Kiely *et al*., 2004; McLean *et al*., 2005) while we employed a novel unobtrusive technique (Kohler *et al*., 2006) to measure nasal conductance repeatedly during sleep (Fig. 3). It allowed us to track the changes in nasal conductance over the course of the night simultaneously with the sleep-related breathing disturbances rather than measuring nasal resistance before or after the sleep studies. Since nasal conductance measured at the beginning of a night differs from subsequent measurements during sleep by an average of 26% (Kohler *et al*., 2006) rhinomanometry performed during wakefulness may not accurately reflect the physiologic conditions during sleep.

By assessing nasal conductance repeatedly over the course of the night, a time-dependent effect of xylometazoline on breathing disturbances was demonstrated (Table 1). According to our hypothesis, apneas/hypopneas were predominantly reduced in the time period of the maximal expected pharmacologic effect of xylometazoline (Hochban *et al*., 1999). A multiple regression analysis further confirmed a significant effect of xylometazoline on apnea/hypopnea, i.e., a reduction of breathing disturbances, if the elapsed time since administration of the drug was taken into account. These findings and the lower apnea/hypopnea index during nights with higher compared with lower mean nocturnal nasal conduction are consistent with a pathophysiologic link between obstructive sleep apnea and impaired nasal ventilation. Since even a maximal pharmacologic increase in nasal conductance attained 30–210 min after application of xylometazoline was associated with a relatively small reduction in the apnea/hypopnea index from 33.2 to 27.3 events/h (Table 1) impairment of nasal breathing seems to have an only minor effect on pharyngeal obstruction in patients with obstructive sleep apnea. This may be related to opening of the mouth allowing a greater fraction of oral ventilation to prevent excessive inspiratory pharyngeal pressure swings in severe nasal obstruction (McLean *et al*., 2005).

Side-selective monitoring of nasal conduction revealed that xylometazoline not only increased the mean nasal conductance during sleep but also reduced the number of nasal cycles and the variability of reciprocal changes in left/right nasal conductance (Table 1, Fig. 4). A potential explanation of this novel finding is that the natural variation in autonomic vasomotor control of the nasal mucosa was reduced or abolished by the strong sympathomimetic effect of xylometazoline in our patients with chronic nasal congestion who might have had an exaggerated nasal cycling while treated with placebo similar to what has been observed in patients with upper respiratory tract infection (Eccles *et al*., 1996).

The lack of a significant correlation between the subjectively perceived impairment of nasal breathing and measured nasal conductance suggests that perception of nasal congestion does not only depend on nasal airflow but on other, yet unknown factors as well.

In conclusion, this is the first study that investigated effects of topical nasal decongestion on breathing disturbances in OSA patients with chronic nasal congestion using a novel unobtrusive technique that tracked nasal conductance over the course of nocturnal sleep. Since the reduction of apnea/hypopnea by xylometazoline was only modest and not associated with improved sleep quality or daytime alertness, despite a considerable increase in nasal conductance, our data suggest that pharmacologic treatment of nasal obstruction has a clinically limited efficacy in improving sleep-disordered breathing in OSA patients with impaired nasal breathing.

ACKNOWLEDGEMENTS

This research is supported by Swiss National Science Foundation, Hartmann-Müller Stiftung, Zurich, and Lung Ligue of Zurich, Switzerland.

DISCLOSURE STATEMENT

There is no conflict of interest for any of the authors.

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