The nasal decongestant effect of xylometazoline in the common cold

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ABSTRACT

Background: *Xylometazoline is a nasal decongestant spray that constricts nasal blood vessels and increases nasal airflow, enabling patients with a blocked nose to breathe more easily. The purpose of this study was to characterize objectively and subjectively the decongestant and additional effects of xylometazoline in the common cold.*

Methods: *A double-blind, placebo-controlled, parallel group study was performed. Patients with a common cold (n = 61) were treated with xylometazoline 0.1% (n = 29) or placebo (saline solution; n = 32; 1 spray three times a day for up to 10 days). The primary objective was to determine the decongestant effect (nasal conductance); the secondary objectives were to determine the peak subjective effect (visual analog scale), duration of relief of nasal congestion, total and individual cold symptoms and general well-being (patients' daily diary), and adverse events (AEs).*

Results: *The decongestant effect of xylometazoline was significantly greater than placebo, as shown by the nasal conductance at 1 hour (384.23 versus 226.42 cm^3/s; $p \leq 0.0001$) and peak subjective effect (VAS, 20.7 mm versus 31.5 mm; $p = 0.0298$). Nasal conductance was significantly superior for up to 10 hours ($p = 0.0009$) and there was a trend in favor of xylometazoline for up to 12 hours (not statistically significant). Xylometazoline significantly improved total and some individual common cold symptoms scores ($p < 0.05$), leading to significantly greater patient general evaluation and satisfaction with treatment ($p < 0.05$). Nineteen AEs were reported: 8 with xylometazoline (all mild–moderate) and 11 with placebo (1 severe).*

Conclusion: *Xylometazoline is an effective and well-tolerated decongestant nasal spray that significantly relieved nasal congestion compared with placebo in the common cold and provided long-lasting relief with just 1 spray, helping patients to breathe more easily for a longer period of time.*

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Key words: Common cold, decongestant, nasal congestion, Otrivin, placebo effect, rhinomanometry, topical nasal decongestant, xylometazoline

Inflammation of the nasal mucous membrane leads to swelling and prolonged congestion of nasal blood vessels in both nasal passages. Nasal congestion impedes breathing, leads to accumulation of thick nasal mucus, causes a frequent desire to blow the nose, disturbs sleep, and causes snoring and apnea.[1] In short, nasal congestion can have a considerable negative impact on daily life.

There are many common causes of nasal congestion, including upper respiratory viral infections (common cold or influenza), allergic rhinitis, sinus infections/chronic sinusitis, vasomotor rhinitis, and overuse of some nasal sprays/drops. Of these, the common cold is one of the most prevalent causes, affecting adults around two to four times per year, and children (aged 2–6 years) around six times per year.[2] Nasal congestion has been identified as the most common symptom among common cold sufferers.[2] There is no marketed cure for the common cold and symptomatic therapy is the only treatment option for nasal congestion. To this end, numerous oral and topical over-the-counter decongestant drugs have been marketed for both adults and children.[3]

A well-known and commonly used decongestant is xylometazoline (Otrivin) nasal spray (Novartis Consumer Health, Parsippany, NJ), which is indicated for the symptomatic relief of nasal congestion due to common cold and allergy, either alone or in combination with ipratropium.[4,5] Xylometazoline is a sympathomimetic agent that causes constriction of nasal blood vessels and a reduction in NAR, with a subjective sensation of improved nasal airflow.[6] Otrivin has been marketed for a few decades and used by several million patients, suggesting it is an effective and safe topical decongestant. However, most studies have investigated its effect in healthy patients and only few trials have been performed in patients with a common cold.[7–9] Objective measures of its decongestant effect have not been commonly used in clinical trials, and studies report mainly subjective parameters. Furthermore, relief of other cold symptoms with the topical use of xylometazoline had not been investigated.

In an attempt to provide new knowledge about the benefits of treatment with xylometazoline (Otrivin) nasal decongestant spray (Novartis), this double-blind, randomized, placebo-controlled, parallel group, single-center study aimed to characterize the pharmacologic aspects of xylometazoline, using objective and subjective measurements, and to investigate its beneficial effects on exploratory variables such as sore throat, ear ache, sleep, tiredness, daily activities, and general well-being in patients with a common cold.

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Conflicts of interest: M. Eriksson, S. Garreffa, and S.C. Chen are employees of Novartis; the clinical trial was sponsored by Novartis

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METHODS

The study treated 61 patients from a single center (Cardiff University, Wales, U.K.) in March 2007. The trial was approved by the South East Wales Research Ethics Committee and all patients gave informed consent before the start of treatment.

Patients

Eligible patients were ≥18 years of age, with recent onset of nasal congestion associated with common cold. Included patients had a minimum nasal congestion score of 2 (moderate) according to a 4-point scale (0 = not present; 1 = mild; 2 = moderate; and 3 = severe); had cold symptoms of <36 hours duration before study entry; presented with a minimum of two common cold symptoms (runny nose, blocked nose, sore throat, and/or cough) on entry to the study; were male patients or a nonpregnant, nonlactating female patient; and were willing and able to undergo measurement of total nasal airway resistance (NAR) using active posterior rhinomanometry and score symptoms.

Main exclusion criteria included inability to abstain from smoking for 1 hour before and for the duration of each visit; NAR of <0.2 Pa/cm^3 per second at screening visit 1; history of perennial allergic rhinitis, unless recruited out of season; clinically significant abnormalities (*e.g.*, polyps and deviated septum); history of transsphenoidal hypophysectomy or rhinitis medicamentosa; bacterial sinusitis infection during the past 2 weeks before study entry; use of drugs (antibiotics, α-adrenergics, glucocorticosteroids, antidepressants, or monoamine oxidase inhibitors); use of any medication that may affect sleep as judged by the investigator; known hypersensitivity to xylometazoline or any of the excipients of Otrivin nasal spray; alcohol intake; and uncontrolled arterial hypertension. All chronic medications, except those mentioned as exclusion criteria, were allowed during the trial if kept at a constant dose but only additional paracetamol was allowed as rescue medication during the trial.

Procedure

Eligible patients were randomized in a 1:1 ratio and treated double-blind, with xylometazoline 0.1% (Otrivin), 1.0 mg/mL of F2 metered-dose nasal spray, or placebo (saline solution, Otrisal, Novartis). The nasal sprays devices were identical and delivered 0.14 g/actuation. Patients were stratified according to severity of nasal congestion as measured by posterior rhinomanometry during screening on the first study visit (NAR, 0.2–0.4 and >0.41 Pa/cm^3 per second).

On the first study visit, baseline data on age, gender, and common cold symptom scores were collected and patients were trained to measure NAR using active posterior rhinomanometry and instructed in the use of subjective scores. The first treatment dose (1 spray [0.14 g] in each nostril three times per day) was administered by the investigator and subsequently patient self-administered until the total common cold symptom score was recorded to be 0 or for a maximum of 10 days.

Primary Outcome. The primary outcome was the assessment of nasal congestion, using the objective method of rhinomanometry to determine total NAR to airflow. Measurements at baseline; 30 minutes; and 1, 6, 7, 8, 9, 10, 11, and 12 hours after treatment were done.

Secondary Outcomes. Several secondary outcomes were measured, using subjective or objective parameters: the time to onset of subjective relief of nasal congestion after administration of the nasal spray and the peak subjective relief of nasal congestion with a visual analog scale (VAS; 0 = nose completely clear and 100 = nose completely blocked) defined as the lowest VAS score. Subjective relief of nasal congestion was assessed by VAS every 5 minutes over a 30-minute period. The duration of relief of nasal congestion was defined as the last time point at which the value of $p < 0.05$ when comparing the least squares (LS) mean nasal conductance for each treatment at each time point. In addition, total and individual common cold symptoms (runny nose, blocked nose, sore throat, cough, sneezing, and ear ache) scores (4-point scale: 0 = not present, 1 = mild, 2 = moderate, 3 = severe) were recorded every day from day 1 of treatment in diaries. All adverse events (AEs) were reported throughout the study.

Exploratory Variables. For the purpose of gathering information on the benefits of topical decongestion in the common cold, some exploratory variables were also assessed: time to resolution of subjective measures of common cold symptoms; time to specific VAS improvement; subjective measures of sleep, tiredness, daily activities, and general well-being; and smell.

Statistical Analysis

The analysis of upper airway conductance at 1 hour was conducted by fitting an ANCOVA using treatment as a factor and the baseline NAR as a covariate. An analogous nonparametric ANCOVA was performed in support of the parametric procedure. The mean, standard deviation and 95% confidence limits were calculated for each of the treatment groups, without stratification.

Time to onset of subjective relief of nasal congestion, time to subjective peak relief of nasal congestion, time to resolution of subjective measures of common cold symptoms, and time to 50 and 30 on the VAS were analyzed using Wilcoxon survival techniques. Peak relief of nasal congestion for each of the two treatment groups was compared by fitting an ANCOVA using treatment as a factor and the baseline NAR as a covariate. Duration of relief of nasal congestion was compared for each of the two treatment groups at each time point by fitting an ANCOVA using treatment as a factor and the baseline NAR as a covariate.

For each variable, the subjective measure of common cold symptoms was compared for each of the two treatment groups on each day by fitting an ANCOVA to the change from baseline using treatment as a factor and the baseline NAR as a covariate. Descriptive statistics for the subjective measures of sleep, tiredness, daily activities, general well-being, and smell and for the general questions on treatment were presented for each variable. For each variable, the two treatment groups were compared at each time point by fitting an ANCOVA to the change from baseline using treatment as a factor and the baseline NAR as a covariate. Treatment groups were compared for the VAS score at each time point by fitting an ANOVA using treatment as a factor and the baseline nasal conductance as a covariate.

The safety analysis included all patients who took at least one dose of study medication. The intent-to-treat (ITT) population included all randomized patients who were dispensed

the study medication and had at least one postbaseline efficacy assessment. The analysis of the ITT was considered the primary efficacy analysis.

RESULTS

Study Population

In total, 78 patients were screened for the study, of which 12 did not meet the inclusion criteria. Thus, 66 patients were randomized to the study but 5 were not dosed because they either did not return on day 1 of treatment ($n = 4$) or on returning were unable to reproduce the technique required for measurement of NAR ($n = 1$). Therefore, 61 patients (median age, 20 years) were subsequently dosed with the study treatment and completed the study. There were no significant differences between the groups with regard to the mean age, gender, and race of the patients or in the common cold scores or mean nasal congestion as measured by rhinomanometry (Table 1). All 61 patients were included in the ITT efficacy and safety analysis.

A total of 19 patients were not 100% compliant with treatment and missed one or more doses during the study, after day 1. None of these patients were excluded from the analysis, because the extent of noncompliance was not deemed to have a significant effect on the interpretation of the study results. In fact, the primary efficacy variable and all but one of the secondary efficacy variables were on day 1 in the clinic, when a single dose of nasal spray was administered by the investigator.

The mean number of doses taken in the xylometazoline group was 16.8 (range, 5–28), and in the placebo group the mean number of doses was 19.5 (range, 4–28). The variation in dosing was because of a variation in the duration of symptoms and the time taken by patients to reach a zero score. A total of 9 (31.0%) xylometazoline patients and 6 (18.8) placebo patients used concomitant rescue medication (paracetamol) during the study.

Primary Outcome

Upper Airway Conductance at 1 Hour. The decongestant effect of xylometazoline (Otrivin) was significantly greater than that of placebo, as shown by the LS mean upper airway conductance at 1 hour after treatment with xylometazoline (384.23 cm^3/s) compared with placebo (226.42 cm^3/s; LS mean difference, 157.82; $p \leq 0.0001$). Figure 1 illustrates the nasal conductance values up to 12 hours obtained after xylometazoline administration. The limit of a conductance of 250 cm^3/s illustrated in Fig.1 indicates a level, below which, patients are generally accepted as suffering from nasal congestion.[10]

Secondary Outcomes

Time to Onset of Subjective Relief of Nasal Congestion. The median time showed no significant difference between xylometazoline (1.7 minutes) and placebo solution (1.5 minutes).

Development of Subjective Relief of Nasal Congestion over the First 30 Minutes after Dosing. At all time points over the first 30 minutes after dosing, the LS mean VAS score was significantly lower after treatment with xylometazoline (range, 24.7–25.7 mm) compared with placebo (range, 35.8–36.7 mm; $p < 0.025$; Fig. 2).

Subjective Peak Relief of Nasal Congestion. Xylometazoline significantly improved nasal decongestion compared with placebo, as shown by the subjective measurement of peak relief of nasal congestion, which was significantly lower after administration of xylometazoline (LS mean, VAS, 20.7 mm) than after placebo (31.5 mm; $p = 0.0298$). This finding, which is based on subjective scoring of nasal congestion, supports the objective nasal conductance data (primary outcome).

Time to Subjective Peak Relief of Nasal Congestion. There was no significant difference between groups (median, 30 minutes in both groups).

Nasal Conductance. Nasal conductance values for xylometazoline ranged from 383 cm^3/s at 30 minutes to 265 cm^3/s at the 12th hour postdose. At 10 hours, the LS mean nasal conductance with xylometazoline (300.44 cm^3/s) was statistically significant greater than with placebo (229.92 cm^3/s; LS mean difference, 70.52 cm^3/s; $p = 0.0009$) and there was a trend in favor of xylometazoline for up to 12 hours (not statistically significant). Xylometazoline provided long-lasting, effective relief of nasal congestion, as shown by the objective nasal conductance data (Fig. 1).

Subjective Measures of Total and Individual Common Cold Symptoms. Compared with placebo, xylometazoline significantly improved the total common cold symptom score on day 1 of treatment (xylometazoline 25.71 versus placebo 35.79; $p = 0.0221$) and significantly improved individual common cold symptoms on day 1 (blocked nose, sore throat, and ear ache), day 2 (blocked nose), day 5 (runny nose), and day 10 (runny nose) of treatment ($p < 0.05$).

Table 1 **Baseline characteristics**

	Otrivin 0.1% ($n = 29$)	**Placebo ($n = 32$)**
Sex female, *n* (%)	18 (62.1)	20 (62.5)
Age (yr), mean (±SD)	20.0 (1.6)	20.9 (5.2)
Race, *n* (%)		
White	28 (96.6)	29 (90.6)
Oriental	1 (3.4)	2 (6.3)
Other	0 (0)	1 (3.1)
Mean predose nasal congestion, Pa/cm^3 per s (±SD)	0.319 (0.113)	0.354 (0.128)
Mean predose nasal conductance, cm^3/s (±SD)	251.86 (91.86)	235.66 (71.09)

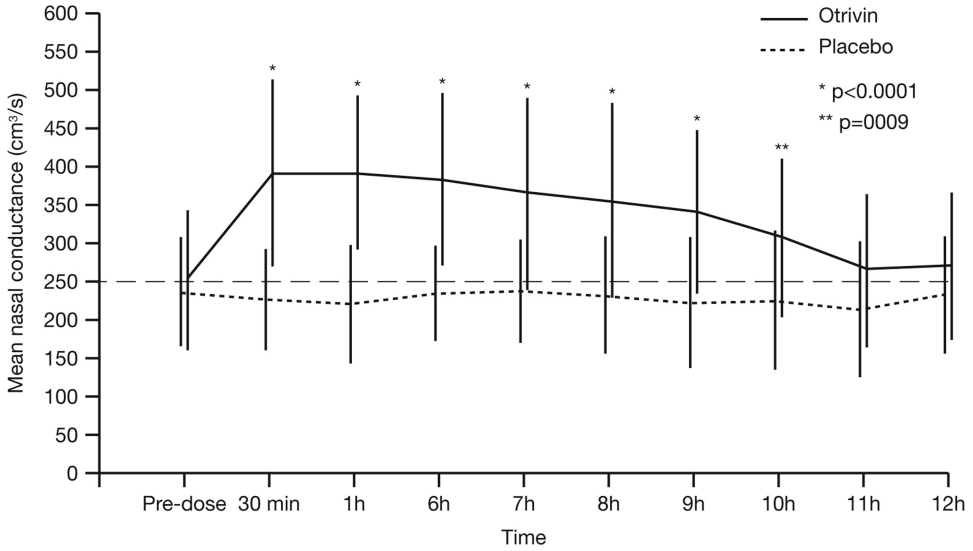

Figure 1. Extent and duration of relief from nasal congestion (expressed using nasal conductance values) after administration of xylometazoline (Otrivin) compared with placebo (saline solution). The dotted line at a conductance of 250 cm^3/s indicates a lower limit of conductance below which patients are generally considered to be suffering from nasal congestion.[10]

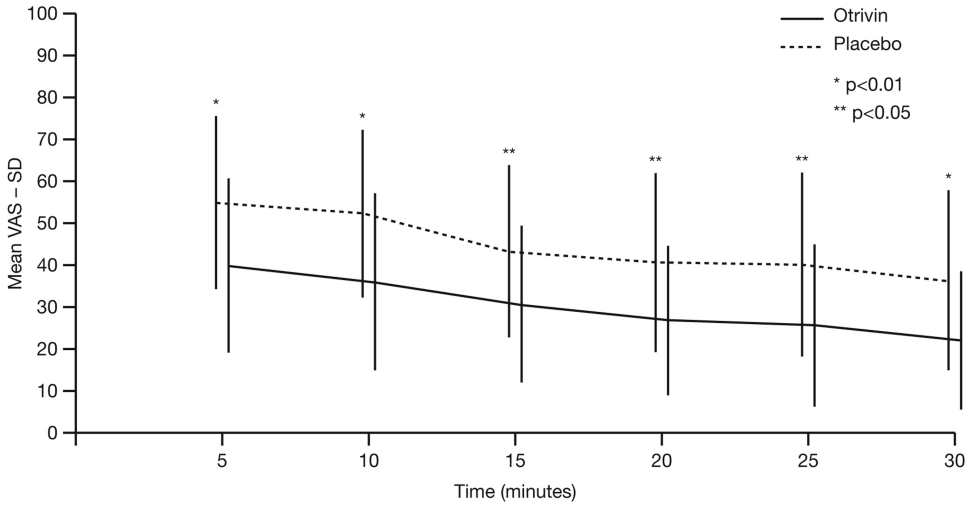

Figure 2. Development of subjective relief of nasal congestion over the first 30 minutes (mean visual analog score (VAS) ± SD) after dosing with xylometazoline (Otrivin) compared with placebo (saline solution).

Exploratory Variables

Some exploratory variables showed significant difference in favor of xylometazoline. The median time to reach a score of VAS 50 was shorter with xylometazoline (5 minutes) compared with placebo (10 minutes; $p = 0.0472$), and a similar result was observed when examining the time to reach a score of VAS 30 ($p = 0.0199$). Patient's overall assessment of treatment favored xylometazoline against placebo ($p < 0.05$). Other variables did not show significant separation between groups.

Safety Results

Results showed that both xylometazoline and placebo were well tolerated. In total, 19 AEs were reported during the study, with slight higher occurrence in the placebo group ($n = 11$) than the xylometazoline group ($n = 8$; Table 2). The most frequently occurring AEs were headache (five events) and dysmenorrhoea (three events). In the xylometazoline group, all AEs were mild to moderate and were not considered drug related. In the placebo group, one patient reported headache and sore eyes, which were considered to be severe events but not drug related.

DISCUSSION

The efficacy investigations, which include both objective and subjective measures, showed the clinically significant decongestant effect of xylometazoline. The primary objective measure of efficacy (upper nasal airway conductance at 1 hour after treatment) showed that xylometazoline was significantly better than placebo at relieving nasal congestion ($p \leq$

Table 2. **Adverse events (AEs) experienced during the study**

	Otrivin 0.1% (*n*, %)	Placebo (*n*, %)
Patients studied		
Total no. of patients	29 (47.5)	32 (52.5)
Total no. with AEs	7 (24.1)	9 (28.1)
Body system affected		
Eye disorders	0	1 (3.1)
Gastrointestinal disorders	1 (3.4)	1 (3.1)
Infections and infestations	1 (3.4)	0
Musculoskeletal and connective tissue disorder	0	2 (6.3)
Nervous system disorder	1 (3.4)	5 (15.6)
Reproductive system and breast disorder	3 (10.3)	0
Respiratory, thoracic, and mediastinal disorder	2 (6.9)	2 (6.3)
AEs		
Headache	1 (3.4)	4 (12.5)
Period pain	3 (10.3)	0
Epistaxis	1 (3.4)	1 (3.1)
Cough	1 (3.4)	1 (3.1)
Backache	0	1 (3.1)
Cystitis	1 (3.4)	0
Migraine	0	1 (3.1)
Nausea	0	1 (3.1)
Neck ache	0	1 (3.1)
Sore eyes	0	1 (3.1)
Toothache	1 (3.4)	0

0.0001) and confirmed a clear difference in magnitude of effect between xylometazoline and placebo. In addition, unlike placebo, one dose of xylometazoline improved and maintained nasal conductance to levels that were statistically significant at 10 hours ($p = 0.0009$) and there was a trend in favor of xylometazoline for up to 12 hours (not statistically significant). The magnitude of the increase in nasal conductance observed in this study 1 hour after treatment with xylometazoline (53%), is similar to the 48% reduction in nasal resistance reported in a previous study,[4] and much greater than the decrease in NAR after treatment with an oral decongestant such as pseudoephedrine (10%).[11]

The objective data were supported by the subjective measures of relief, which were performed using VAS ratings, accepted as an appropriate method of assessing subjective relief of nasal obstruction.[12] The assessment of subjective parameters is particularly relevant because it is an improvement in the patient's perception of the relief of their symptoms, which is the ultimate aim of treatment. The results of this study showed xylometazoline provided subjective relief of nasal congestion that was felt within 1.7 minutes and led to significantly less severe symptoms at every time point ($p \leq 0.02$) thereafter, resulting in a peak subjective relief of nasal congestion that was significantly greater than observed with placebo ($p = 0.0298$) at 30 minutes postdose.

Xylometazoline also significantly decreased common cold symptom scores compared with placebo, with a significant decrease in the total common cold symptom score on day 1 of treatment ($p = 0.0221$) and significantly decreased individual common cold symptoms on day 1 (blocked nose, sore throat, and ear ache), day 2 (blocked nose), day 5 (runny nose), and day 10 (runny nose) of treatment ($p < 0.05$).

It is not unexpected to observe relief of earache and sore throat. The Eustachian tube from the middle ear opens up in the back of the nasal cavity, *i.e.*, in the nasal mucosa containing the venous sinuses that xylometazoline constricts. The vasoconstrictor effect of xylometazoline therefore may aid ventilation to the middle ear and relieve earache. Nasal congestion also causes mouth breathing that dries and irritates the throat. By relieving nasal congestion and allowing patients to breathe through the nose, xylometazoline can provide relief from sore throat. In studies on sore throat pain, patients with nasal obstruction are excluded because of this issue.[13] These results indicate that xylometazoline can help to reduce symptoms in the early phases of common cold, especially if the patient suffers from ear ache or sore throat.

In this study, placebo treatment caused an improvement in the subjective scores for nasal decongestion. Placebo reduced the severity of subjective nasal congestion over the first 30 minutes after dosing. The subjective relief of nasal congestion associated with placebo treatment has been previously reported in a similar study on nasal decongestants.[11] However, in the present study, the subjective relief experienced with placebo was significantly lower than that with xylometazoline at all time points.

This study also showed that there was no significant difference in the time to peak subjective relief of nasal congestion after use of saline solution versus xylometazoline. Nevertheless, at this point (30 minutes), xylometazoline resulted in a significantly greater peak subjective effect compared with the saline solution placebo ($p = 0.0298$) and thus confirmed superior relief from nasal congestion.

It was observed that there was no significant difference between the groups in the time to resolution of subjective measures of common cold symptoms. However, other results in this study showed that the use of a nasal decongestant may reduce the severity of cold symptoms.

No differences were noted in the assessment of exploratory end points such as sleep, tiredness, daily activities, general well-being, and smell. The study was neither designed nor powered to statistically evaluate these parameters; therefore, the results are of limited value. Nevertheless, most of the general questions were rated significantly better with xylometazoline than with the placebo both on day 1 and on the last visit of the treatment period. The time to specific subjective VAS improvement was significantly shorter in the patients using xylometazoline compared with those using placebo and xylometazoline patients reached both VAS 50 ($p = 0.047$) and VAS 30 ($p = 0.02$) twice as fast as the placebo patients.

As expected from the long history of safety, this study confirmed that xylometazoline (Otrivin) was well tolerated and did not lead to any drug-related or serious AEs. Two events (headache and sore eyes) were reported by one patient and were considered to be severe, but these were reported after administration of the placebo. All other events were mild or moderate in severity and were not suspected to be related to the study medication. The most frequently occurring AEs were headache (five events) and dysmenorrhoea (three events).

Prolonged use of a topical nasal decongestant medicine may be associated with rebound nasal congestion and rhinitis medicamentosa.[14] In this study, subjects were instructed to use the nasal spray three times a day until the resolution of all common cold symptoms or for a maximum of 10 days. Mean exposure of 16.8 doses with a range of 5–28 doses indicates that most subjects used the treatment for around 5–6 days. If this period of treatment had resulted in nasal rebound or other nasal symptoms indicative of rhinitis medicamentosa, then the subjects would have noted this in their symptom diaries. None of the subjects made any report of symptoms that could indicate rhinitis medicamentosa. This agrees with other studies where subjects have been exposed to topical decongestants for up to 10 days without showing this side effect.[15]

CONCLUSIONS

This double-blind, randomized, placebo-controlled trial confirms that xylometazoline (Otrivin nasal spray) is a highly effective and well-tolerated topical nasal decongestant in patients with common cold. Objective and subjective measures indicate that the decongestant effect of xylometazoline is rapid and long-lasting, resulting in significant relief of nasal congestion with just one spray, helping patients to breathe more easily for a longer time. Patients' overall satisfaction of treatment was confirmed. Rebound nasal congestion and symptoms of rhinitis medicamentosa were not observed in any patients and the most common AEs were headache and dysmenorrhoea.

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