The effectiveness of oxymetazoline plus intranasal steroid in the treatment of chronic rhinitis: A randomised controlled trial

Torpong Thongngarm,[1] Paraya Assanasen,[2] Panitan Pradubpongsa[3] and Pongsakorn Tantilipikorn[2]

Summary

Background: **The recommended drug for moderate to severe chronic rhinitis is intranasal steroids (INS). However, nasal congestion could be refractory and need additional treatments.**

Objective: **We sought to explore the benefit of oxymetazoline (Oxymet) plus INS on nasal congestion without inducing rhinitis medicamentosa.**

Methods: **We performed a 6-week, randomised, double-blind clinical trial in 50 patients, 18 years of age or greater, with chronic rhinitis who had used INS and cetirizine and still had nasal congestion. Subjects were randomised to receive 2 sprays of 0.05% Oxymet in each nostril twice daily or placebo for 4 weeks. All patients received 2 sprays of budesonide (100 μg/spray) in each nostril twice daily and 10 mg cetirizine once daily from entry throughout the study. Nasal symptom scores, nasal peak inspiratory flow (NPIF) and Rhinoconjunctivitis Quality of Life (Rcq) scores were measured.**

Results: **Oxymet significantly reduced nasal congestion in subjects with chronic rhinitis compared with placebo on the day of 15-28 and 29-42. In subjects with allergic rhinitis, nasal congestion scores in the Oxymet group were significantly reduced compared with those in the placebo group on days 4-7, days 8-14, days 15-28 and days 29-42. In the Oxymet group, post hoc analysis showed that subjects with allergic rhinitis significantly improved their nasal congestion scores compared to non-allergic individuals (N, allergic/non-allergic = 18/7, $p < 0.05$). The combination of INS and Oxymet was not associated with rhinitis medicamentosa.**

Conclusions: **The combination of INS and Oxymet provides additional benefit compared to INS monotherapy in relieving nasal congestion in subjects with chronic rhinitis and allergic rhinitis without developing rhinitis medicamentosa.** ***(Asian Pac J Allergy Immunol 2016;34:30-7)***

Keywords: *intranasal steroid, nasal congestion, nasal peak inspiratory flow, oxymetazoline, rhinitis, rhinitis medicamentosa*

Introduction

Chronic rhinitis, including allergic and non-allergic types, is very common in Thailand and worldwide. The recommended drug for moderate to severe forms of chronic rhinitis is intranasal steroids (INS).[1] Despite the efficacy of INS in relieving all nasal symptoms, nasal congestion could occasionally be refractory to treatment as high as 40% of patients, resulting in the need for additional treatments.[2-3] The higher dose of INS for treating allergic rhinitis showed a slightly greater reduction in symptom score but did not reach statistical significance.[4] Therefore, patients who have already taken INS plus antihistamine and still have nasal congestion may finally undergo surgical treatment such as radiofrequency turbinoplasty or immunotherapy.

Oxymetazoline (Oxymet) is an imidazole derivative which directly acts on α-adrenergic receptors in the arterioles of the nasal mucosa. This leads to a decrease in the oedema of nasal turbinates. The duration of action of the drug is up to 12 hours, as shown by rhinomanometry and magnetic resonance imaging on nasal patency.[5-6] A recent study reported that Oxymet added to the effectiveness

From 1. Division of Allergy and Clinical Immunology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
2. Department of Otorhinolaryngology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
3. Division of Allergy and Clinical Immunology, Department of Medicine, Phramongkutklao Hospital, Bangkok, Thailand
Corresponding author: Torpong Thongngarm
E-mail: torallergy@gmail.com, torpong.tho@mahidol.ac.th
Submitted date: 8/4/2015
Accepted date: 29/6/2015

Downloaded from http://www.apjai-journal.org. For personal use only. No other uses without permission

of INS in the treatment of allergic rhinitis without the development of rhinitis medicamentosa.[3,7] However, the combination of INS and Oxymet has never been studied in patients with non-allergic rhinitis who commonly present with nasal congestion. In accordance with previous studies, Oxymet might be helpful to treat nasal congestion while INS prevents the development of rhinitis medicamentosa.[8-9] Thus, we hypothesised that the combination of high-dose INS and Oxymet would improve nasal congestion for patients with chronic rhinitis, both allergic and non-allergic, compared with INS alone without inducing rhinitis medicamentosa.

Methods

We performed a 6-week, randomised, double-blind clinical trial in 50 patients, 18 years of age or greater, with chronic rhinitis. Chronic rhinitis including both allergic and non-allergic rhinitis was defined as having nasal symptoms at least 3 months or greater. Allergic rhinitis was defined as having nasal symptoms with the presence of specific IgE by positive skin prick testing or *in vitro* testing for relevant aeroallergens whereas non-allergic rhinitis showed no evidence of having specific IgE. Other causes of non-allergic rhinitis including drug-induced, hormonal and occupational factors were excluded. Written informed consent was obtained from all participants before enrolment. This study was approved by the institutional Review Board at Faculty of Medicine Siriraj Hospital, Mahidol University. The study was registered at http://Clinicaltrials.gov (#NCT01847131).

All patients had already been treated with budesonide (Bunase®, Okasa Pharma, India), 100 µg/spray or equivalent, using 2 sprays in each nostril once daily, and 10 mg cetirizine once daily for at least 2 weeks and still had nasal congestion. Eligible patients were examined by ENT doctors to exclude significant deviated nasal septum or other mechanical obstruction. Then, patients were instructed to record the severity of nasal congestion on a scale of 0 to 3 (0 = no symptom, 1= mild symptoms, 2 = moderate symptoms and 3 = severe symptoms). For 3 days prior to the baseline visit, the seven twice-daily instantaneous (NOW) diary scores[3] (b.i.d. + morning of the baseline visit day) for nasal congestion were required to be 1 or greater to make the patient eligible for randomisation.

The following patients were excluded from the study: patients with a history suggestive of cardiovascular, hepatic or renal diseases, pregnant or lactating women, patients taking oral or nasal decongestants within 7 days, patients treated with immunotherapy, patients with nasal polyps or significant deviated nasal septum and patients with a history of upper respiratory tract infection within 14 days. Skin prick test to aeroallergens was performed. Fifty patients were categorised into 2 groups, 25 in the interventional group and the other 25 in the control group.

Patients were sequentially randomised by patient code numbers generated by the research coordinator who was not directly involved in the process of randomisation. Therefore, investigators and other research assistants were blinded to the interventional drug or matched placebo (an identical placebo containing similar ingredients except for active drug). As shown in Figure 1, all patients received budesonide (Bunase®, Okasa, India), 100 µg/spray

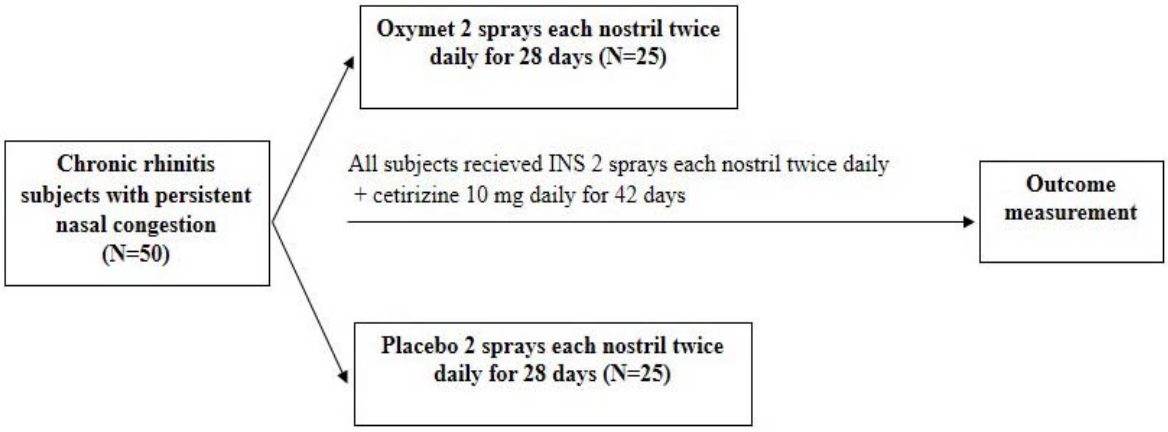

Figure 1. The diagram of study design and treatment regimens. Oxymet, oxymetazoline; INS, intranasal steroid

Downloaded from http://www.apjai-journal.org. For personal use only. No other uses without permission

or equivalent, using 2 sprays in each nostril twice daily and continued 10 mg cetirizine once daily. Patients in the interventional group received an additional 0.05% Oxymet nasal spray (Oxymet®, Greater Pharma, Thailand), with 2 sprays in each nostril twice daily for 4 weeks, whereas patients in the control group received placebo for 4 weeks. After 4 weeks, all patients discontinued Oxymet or placebo and continued INS and cetirizine at the same dosage for 2 more weeks. After randomisation, participants were instructed to complete diaries of daily symptoms and recorded nasal peak inspiratory flow (NPIF). The severity of nasal congestion, sneezing and anosmia was recorded in the morning and evening on a 0 to 10 visual analogue scale (0 = no symptoms and 10 = the most severe symptoms). NPIF was measured in litres per minute with "In Check®" portable inspiratory flow meter (Clement Clarke International Ltd, UK). Subjects obtained NPIF 3 times and the best flow performed among the 3 values was recorded every morning and evening. Subjects returned to clinic on days 3, 7, 14, 28 and 42 for a review of their symptom diaries and NPIF record, completion of Rhinoconjunctivitis Quality of Life Questionnaire (Rcq),[10] and replacement of medications.

Statistical analysis

The sample size of 25 patients per group was needed when 5% type I error and 20% type II error were accepted. The data analysed by descriptive statistics were summarised using mean, standard deviation, frequency and percentage. Kolmogorov-Smirnov test was used to test the data distribution. For normally distributed variables, we used Student's t-test to compare mean of continuous data and Chi-square test to compare the proportion of categorical data between two groups. The data of daily nasal symptom scores were collected on days 3, 7, 14, 28 and 42 according to clinic visits. To minimise the variation of daily nasal symptom score, analysis was performed by using the summation of data at the intervals of days 1-3, 4-7, 8-14, 15-28 and 29-42. Square root transformation of mean nasal symptom scores and NPIF were applied to adjust the data to a normal distribution. Then, the slope of the graphs between the two groups was compared. To examine possible rebound nasal congestion, the paired t-test was used to compare square root of the mean nasal congestion score in the Oxymet group between the last day of treatment (Day 28) and the end of the study (Day 42). To confirm that there was no significant rebound effect, we also compared the data between the first day of treatment (Day 1) and the last day after cessation of therapy (Day 42). ANCOVA with post hoc analysis (Bonferroni test) was performed to compare two regression slopes for the relationship between baseline clinical outcome (covariate) and clinical point. Repeated measurement analysis of variance was undertaken to compare mean changes of Rcq scores during 4 visits. The level of statistical significance was set at p-value ≤ 0.05. SPSS version 18.0 software (IBM® SPSS® Statistics Server, New York, United States) was used for data analyses.

Result

Fifty subjects with chronic rhinitis were recruited into the study. Both groups were comparable at the entry for age, gender, skin test sensitivity and baseline nasal congestion scores (Table 1).

Analysis of subjects with chronic rhinitis (N=50)

After the mean nasal congestion scores were transformed to the square root numbers, Oxymet significantly reduced nasal congestion compared with placebo on days 15-28 and 29-42 (p = 0.034 and 0.038, respectively) as shown in Figure 2. Oxymet also significantly reduced sneezing and anosmia compared with placebo on days 15-28 (p = 0.042 and p = 0.008, respectively).

Table 1. Baseline characteristics.

Variables	Oxymet (N=25)	Placebo (N=25)	p-value
Gender, male (%)	4 (16.0)	4 (16.0)	1
Age, years, mean ± SD	38.6 ± 12.5	37.5 ± 11.5	0.752
Positive SPT, n (%)	18 (72.0)	16 (64.0)	0.544
Dust mites, n (%)	16 (64.0)	14 (56.0)	0.564
Cat, n (%)	6 (24.0)	5 (20.0)	0.733
Dog, n (%)	4 (16.0)	3 (12.0)	1
Molds, n (%)	5 (20.0)	2 (8.0)	0.417
Grasses, n (%)	11 (44.0)	9 (36.0)	0.564
Baseline nasal congestion scores, mean ± SD	1.73 ± 0.54	1.78 ± 0.64	0.752

SD, standard deviation; SPT, skin prick testing; n, number of positive skin test;

Oxymet, oxymetazoline; Dust mites include *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*; Molds include *Alternaria, Aspergillus* and *Penicillium*; Grasses include Bermuda and Johnson.

Downloaded from http://www.apjai-journal.org. For personal use only. No other uses without permission

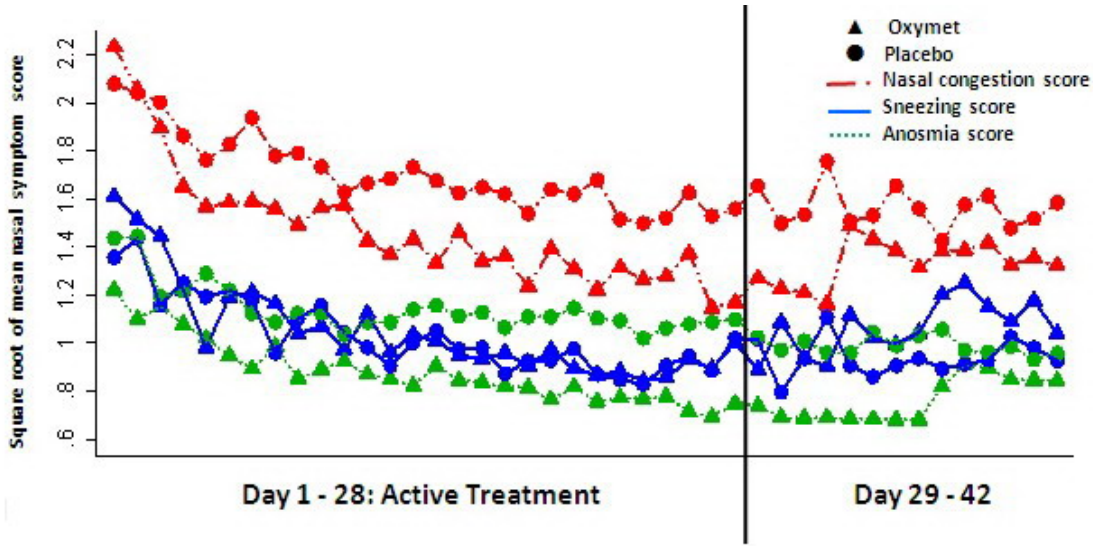

Figure 2. Daily nasal symptom scores in subjects with chronic rhinitis (N=50) during the 4 weeks of active treatment and the 2 weeks of follow-up period after cessation of therapy. Data are displayed as square root of the means. Compared with placebo, Oxymet significantly reduced nasal congestion score on the day of 15-28 and 29-42 (p = 0.034 and p = 0.038 respectively), sneezing and anosmia score on the day of 15-28 (p = 0.042 and p = 0.008 respectively).

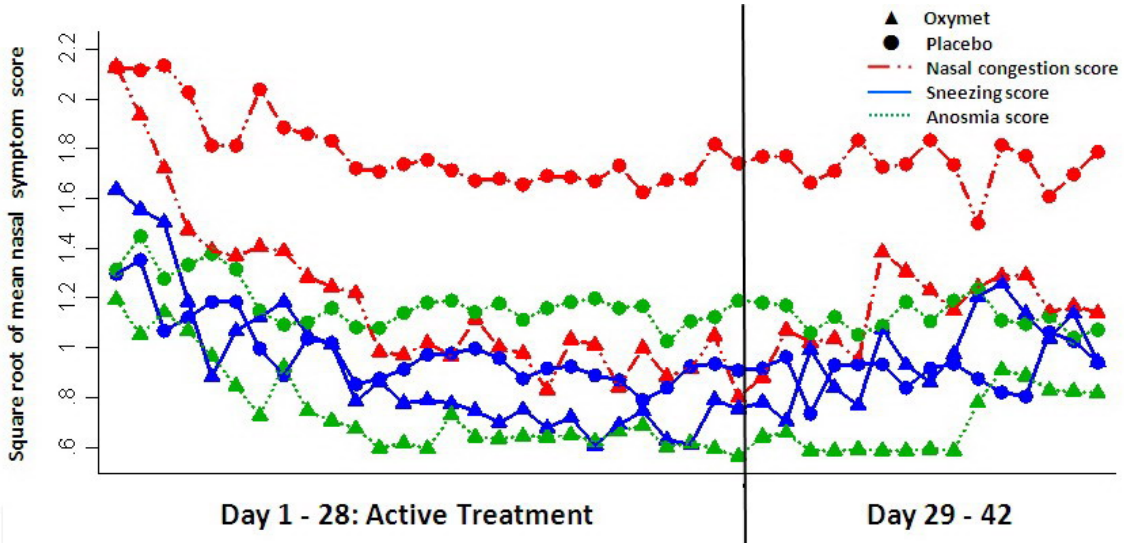

Figure 3. Daily nasal symptom scores in subjects with allergic rhinitis (N = 34) during the 4 weeks of active treatment and the 2 weeks of follow-up period after cessation of therapy. Data are displayed as square root of the means. Compared with placebo, Oxymet significantly reduced nasal congestion score on the day of 4-7, 8-14, 15-28 and 29-42 (p = 0.028, 0.007, 0.001 and 0.006 respectively) and anosmia score on the day of 4-7, 8-14, 15-28 and 29-42 (p = 0.023, 0.007, 0.003 and 0.036 respectively).

There was no statistically significant difference of NPIF between Oxymet and placebo groups. Both treatment groups led to a significant decrease in the overall domain of Rcq, suggesting a significant clinical improvement. However, there was no significant difference in Rcq scores between both treatment groups at any of the time points.

Analysis of subjects with allergic rhinitis (N=34)

Nasal congestion scores in the Oxymet group significantly improved compared to those in the placebo group on days 4-7, 8-14, 15-28 and 29-42 (p = 0.028, 0.007, 0.001 and 0.006, respectively) as shown in Figure 3. Anosmia scores in the Oxymet group significantly improved compared to those in

Downloaded from http://www.apjai-journal.org. For personal use only. No other uses without permission

the placebo group on days 4-7, 8-14, 15-28 and 29-42 (p = 0.023, 0.007, 0.003 and 0.036, respectively). Sneezing scores were not significantly different between the two groups.

There was no statistically significant difference of NPIF between the Oxymet and placebo groups. There was a significant improvement in Rcq scores from the baseline in each treatment group. However, no significant difference in Rcq scores was found between the groups.

Analysis of subjects with non-allergic rhinitis (N=16)

There was no statistically significant difference of nasal symptom scores, NPIF and Rcq between the Oxymet and placebo groups.

Subgroup analysis with post hoc test

Analysis was performed to compare four groups of subjects with allergic or non-allergic rhinitis receiving either Oxymet or placebo, as shown in Tables 2a, 2b and 2c. A significant difference in nasal congestion scores was found on days 8-14 and 15-28 with post hoc analysis showing the difference between Oxymet/Allergic vs Oxymet/Non-allergic ($p < 0.05$) and Oxymet/Allergic vs Placebo/Allergic ($p < 0.05$). A significant difference in anosmia scores was found on days 8-14 and 15-28 with post hoc analysis showing the difference between Oxymet/Allergic vs Placebo/Allergic ($p < 0.05$). No significant difference in sneezing scores was found among the four groups.

Analysis of possible rebound nasal congestion

When all subjects with chronic rhinitis in the Oxymet group were analysed, the mean nasal congestion score between day 28 and day 42 showed no significant difference. Nasal congestion score significantly improved at the end of the study (Day 42) compared to the first day of treatment ($p < 0.001$).

The numbers of adverse events were comparable in both groups, as shown in Table 3. No life-threatening adverse events were found.

Discussion

The authors showed a greater effect of the combination of INS and Oxymet on nasal congestion score compared to INS monotherapy. Each group revealed a significant improvement in nasal congestion and Rcq scores at the end of the study compared to baseline, suggesting that no evidence of rhinitis medicamentosa was observed. In subjects with allergic rhinitis, the combined INS and Oxymet worked to a greater extent from the first week of treatment throughout the study compared to those with chronic rhinitis which involved both allergic and non-allergic types. In the Oxymet group, post hoc analysis showed that subjects with allergic rhinitis significantly improved nasal congestion score compared to non-allergic individuals.

Oxymetazoline is an α-agonist which directly decreases the oedema of nasal turbinates with duration of action up to 12 hours. Although Oxymet has strong decongestant effects, updated guidelines recommend limiting its use to a few days at most because of concerns of tachyphylaxis and rebound congestion.[1,11-12] However, evidences are inconsistent regarding the potential risk of tachyphylaxis with long-term topical decongestant use. Watanabe et al. reported that the use of 0.05% oxymetazoline, using 2 sprays in each nostril 3 times daily, for 4 weeks was not associated with rebound congestion or tachyphylaxis, whereas Yoo et al. showed that use of once nightly Oxymet for 4 weeks did not lead to rhinitis medicamentosa.[13-14] However, Graf et al. demonstrated that rhinitis medicamentosa developed after the use of Oxymet 3 times daily for 4 weeks.[15] Evidence has shown that the concomitant use of INS with Oxymet can prevent Oxymet-induced rhinitis medicamentosa.[3,7-8] In addition, after rhinitis medicamentosa has already developed, INS remains the effective treatment.[9] Therefore, combining INS and Oxymet is intriguing for clinical use since it holds decongestant and anti-inflammatory activities as well as preventing rhinitis medicamentosa. The decreased oedema of the nasal mucosa will also facilitate the access of INS. We conducted the present study using Oxymet twice daily concomitantly with high-dose budesonide and hypothesised that high-dose INS would prevent rhinitis medicamentosa and probably improve nasal symptoms of patients in the placebo group.

In patients with chronic rhinitis who still have residual symptoms despite using INS and oral antihistamine, the guidelines recommend the addition of leukotriene antagonists.[1,11] However, the efficacy of leukotriene antagonists is rather modest, particularly in patients with refractory nasal congestion.[16] In patients with moderate to severe persistent allergic rhinitis whose symptoms have not improved within 2-4 weeks after using INS and oral antihistamine, the guideline recommends increasing the dose of INS.[11] Our study showed that high-dose INS significantly improved nasal congestion, suggesting that an increased dose of INS could be

Downloaded from http://www.apjai-journal.org. For personal use only. No other uses without permission

Table 2a. The summation of mean nasal congestion scores of subjects with chronic rhinitis.

Day	Oxymet (n=25)				Placebo (n=25)				p of β
	Allergic (n=18)		Non-allergic (n=7)		Allergic (n=16)		Non-allergic (n=9)		
	Mean of sqrt	95% CI	Mean of sqrt	95% CI	Mean of sqrt	95% CI	Mean of sqrt	95% CI	
Day 1-3	1.99	1.46-2.53	2.41	1.44-3.38	2.15	1.59-2.71	1.94	1.19-2.69	0.950
Day 4-7	1.55	1.14-1.95	2.13	0.98-3.27	1.98	1.39-2.58	1.78	0.85-2.70	0.134
Day 8-14	1.26	0.82-1.70	2.39†	1.48-3.30	1.81‡	1.22-2.41	1.71	0.85-2.57	0.015*
Day 15-28	1.06	0.62-1.49	2.22†	1.25-3.19	1.74‡	1.12-2.36	1.54	0.61-2.48	0.006*
Day 29-42	1.34	0.96-1.73	1.75	0.75-2.76	1.76	1.15-2.38	1.42	0.40-2.44	0.112

*Significant p-value among 4 groups < 0.05, Post hoc analysis: comparison of the regression slopes between †Oxymet/Allergic vs Oxymet/Non-allergic ($p<0.05$) and ‡Oxymet/Allergic vs Placebo/Allergic ($p<0.05$).

Table 2b. The summation of mean anosmia scores of subjects with chronic rhinitis.

Day	Oxymet (n=25)				Placebo (n=25)				p of β
	Allergic (n=18)		Non-allergic (n=7)		Allergic (n=16)		Non-allergic (n=9)		
	Mean of sqrt	95% CI	Mean of sqrt	95% CI	Mean of sqrt	95% CI	Mean of sqrt	95% CI	
Day 1-3	1.19	0.46-1.92	1.23	-0.21-2.67	1.37	0.66-2.08	1.45	0.12-2.77	0.990
Day 4-7	0.97	0.37-1.57	1.24	-0.05-2.52	1.31	0.59-2.03	1.07	-0.25-2.39	0.187
Day 8-14	0.75	0.22-1.28	1.48	0.35-2.61	1.14†	0.41-1.87	1.07	-0.24-2.37	0.026*
Day 15-28	0.67	0.14-1.20	1.22	0.10-2.34	1.16†	0.45-1.88	1.01	-0.24-2.25	0.013*
Day 29-42	0.78	0.22-1.35	0.93	-0.08-1.93	1.16	0.45-1.86	0.76	-0.29-1.81	0.183

*Significant p-value among 4 groups < 0.05, Post hoc analysis: comparison of the regression slopes between †Oxymet/Allergic vs Placebo/Allergic ($p<0.05$).

Table 2c. The summation of mean sneezing scores of subjects with chronic rhinitis.

Day	Oxymet (n=25)				Placebo (n=25)				p of β
	Allergic (n=18)		Non-allergic (n=7)		Allergic (n=16)		Non-allergic (n=9)		
	Mean of sqrt	95% CI	Mean of sqrt	95% CI	Mean of sqrt	95% CI	Mean of sqrt	95% CI	
Day 1-3	1.63	1.03-2.23	1.45	0.40-2.49	1.26	0.79-1.73	1.58	0.77-2.39	0.161
Day 4-7	1.20	0.76-1.65	1.43	0.49-2.36	1.19	0.74-1.65	1.51	0.70-2.31	0.602
Day 8-14	1.03	0.61-1.46	1.56	0.79-2.33	0.99	0.53-1.45	1.32	0.36-2.28	0.533
Day 15-28	0.87	0.49-1.25	1.54	0.79-2.29	1.01	0.60-1.41	1.09	0.05-2.13	0.247
Day 29-42	1.15	0.81-1.50	1.26	0.26-2.26	0.99	0.58-1.41	1.12	0.05-2.20	0.293

Data are displayed as square root of the means. β, slope of the square root regression line between groups; p, p-value; sqrt, square root of the mean; CI, confidence interval

particularly effective in the short-term. This was consistent with a previous study showing that high-dosed fluticasone propionate improved symptom scores and nasal airflow in patients with allergic rhinitis.[4] In more severe cases, our study showed that combined Oxymet and high-dose INS could provide additional benefits. Subjects with allergic rhinitis in our study yielded a greater response to the combined INS and Oxymet compared with those with chronic rhinitis, probably because INS is theoretically effective to treat allergic rhinitis and only subtypes of non-allergic rhinitis including vasomotor rhinitis and NARES (non-allergic rhinitis with eosinophilia syndrome).[1] In the Oxymet group,

Downloaded from http://www.apjai-journal.org. For personal use only. No other uses without permission

Table 3. The numbers of adverse events

Adverse events	Oxymet group	Placebo group
Nasal discomfort	5	6
Headache	1	3
Insomnia	1	0
Numbness at lips or tongue	1	1
Epistaxis	0	1

Oxymet, oxymetazoline; Nasal discomfort includes burning sensation and dryness

post hoc analysis showed that subjects with allergic rhinitis significantly improved nasal congestion score compared to non-allergic individuals. This implied that nasal congestion in non-allergic patients was more refractory to treat compared with allergic individuals. Regarding the evaluation for rebound congestion, we compared nasal congestion scores on day 1 vs day 42 as well as day 28 vs day 42. If rhinitis medicamentosa developed in Oxymet group, we would have expected the outcome to be worse compared to the placebo group and to return to baseline after 2 weeks of no treatment. This outcome was not observed.

Both treatment groups significantly improved Rcq scores compared with the baseline but there was no significant difference between the two groups. The difference in NPIF between both groups did not reach statistical significance. This is probably due to the disconcordance between patient perception of symptoms and the measurement of Rcq scores as well as NPIF.[17] In accordance with the Cochrane handbook, the process of randomisation using patient code numbers potentially leads to a risk of bias. Therefore, we minimised this issue by cautiously blinding research assistants, investigators, subjects and using well-matched placebo. Further studies with larger numbers of subjects and longer period of follow-up are needed to evaluate Rcq scores, NPIF and the possible rebound congestion or other adverse events.

In summary, the combination of INS and Oxymet provided the advantage beyond INS monotherapy in relieving nasal congestion in subjects with chronic rhinitis. Subjects with allergic rhinitis appeared to have a greater response to the combination compared with those with chronic rhinitis. In the Oxymet group, subjects with allergic rhinitis significantly improved nasal congestion score compared to non-allergic individuals. In addition, the combination of INS and Oxymet was not associated with rhinitis medicamentosa.

Acknowledgements

This study was funded by Siriraj Research Development Fund from Faculty of Medicine Siriraj Hospital, Mahidol University. We would like to thank Ms. Khemajira Karaketklang for the contribution to statistical analysis, and Ms. Orathai Theankeaw and Ms. Aree Jameekornrak for their contribution to data collection and research assistance. We also acknowledge Greater Pharma, Thailand for supplying matched oxymetazoline and placebo nasal sprays.

References

1. Wallace DV, Dykewicz MS, Bernstein DI, Blessing-Moore J, Cox L, Khan DA, et al. The diagnosis and management of rhinitis: an updated practice parameter. J Allergy Clin Immunol 2008;122:S1-84.
2. Ratner PH, Hampel F, Van Bavel J, Amar NJ, Daftary P, Wheeler W, et al. Combination therapy with azelastine hydrochloride nasal spray and fluticasone propionate nasal spray in the treatment of patients with seasonal allergic rhinitis. Ann Allergy Asthma Immunol 2008;100:74-81.
3. Meltzer EO, Bernstein DI, Prenner BM, Berger WE, Shekar T, Teper AA. Mometasone furoate nasal spray plus oxymetazoline nasal spray: short-term efficacy and safety in seasonal allergic rhinitis. Am J Rhinol Allergy 2013;27:102-8.
4. Meltzer EO, Orgel HA, Bronsky EA, Furukawa CT, Grossman J, LaForce CF, et al. A dose-ranging study of fluticasone propionate aqueous nasal spray for seasonal allergic rhinitis assessed by symptoms, rhinomanometry, and nasal cytology. J Allergy Clin Immunol 1990;86:221-30.
5. Eskiizmir G, Hircin Z, Ozyurt B, Unlu H. A comparative analysis of the decongestive effect of oxymetazoline and xylometazoline in healthy subjects. Eur J Clin Pharmacol 2011;67:19-23.
6. Pritchard S, Glover M, Guthrie G, Brum J, Ramsey D, Kappler G, et al. Effectiveness of 0.05% oxymetazoline (Vicks Sinex Micromist(R)) nasal spray in the treatment of objective nasal congestion demonstrated to 12 h post-administration by magnetic resonance imaging. Pulm Pharmacol Ther 2014;27:121-6.
7. Baroody FM, Brown D, Gavanescu L, DeTineo M, Naclerio RM. Oxymetazoline adds to the effectiveness of fluticasone furoate in the treatment of perennial allergic rhinitis. J Allergy Clin Immunol 2011;127:927-34.
8. Ferguson BJ, Paramaesvaran S, Rubinstein E. A study of the effect of nasal steroid sprays in perennial allergic rhinitis patients with rhinitis medicamentosa. Otolaryngol Head Neck Surg 2001;125: 253-60.
9. Vaidyanathan S, Williamson P, Clearie K, Khan F, Lipworth B. Fluticasone reverses oxymetazoline-induced tachyphylaxis of response and rebound congestion. Am J Respir Crit Care Med 2010;182:19-24.

Downloaded from http://www.apjai-journal.org. For personal use only. No other uses without permission

10. Bunnag C, Leurmarnkul W, Jareoncharsri P, Ungkanont K, Tunsuriyawong P, Kosrirukvongs P, et al. Development of a health-related quality of life questionnaire for Thai patients with rhinoconjunctivitis. Asian Pac J Allergy Immunol 2004;22:69-79.
11. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy 2008;63 Suppl 86:8-160.
12. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol 2010;126:466-76.
13. Watanabe H, Foo TH, Djazaeri B, Duncombe P, Mackay IS, Durham SR. Oxymetazoline nasal spray three times daily for four weeks in normal subjects is not associated with rebound congestion or tachyphylaxis. Rhinology 2003;41:167-74.
14. Yoo JK, Seikaly H, Calhoun KH. Extended use of topical nasal decongestants. Laryngoscope 1997;107:40-3.
15. Graf P, Juto JE. Decongestion effect and rebound swelling of the nasal mucosa during 4-week use of oxymetazoline. ORL J Otorhinolaryngol Relat Spec 1994;56:157-60.
16. Esteitie R, deTineo M, Naclerio RM, Baroody FM. Effect of the addition of montelukast to fluticasone propionate for the treatment of perennial allergic rhinitis. Ann Allergy Asthma Immunol 2010;105:155-61.
17. Baraniuk JN. Subjective nasal fullness and objective congestion. Proc Am Thorac Soc 2011;8:62-9.

Downloaded from http://www.apjai-journal.org. For personal use only. No other uses without permission