

Effectiveness of 0.05% oxymetazoline (Vicks Sinex Micromist®) nasal spray in the treatment of objective nasal congestion demonstrated to 12 h post-administration by magnetic resonance imaging[☆]

S. Pritchard^{a, *}

Susan.Pritchard@nottingham.ac.uk

M. Glover^b

G. Guthrie^b

J. Brum^d

D. Ramsey^d

G. Kappler^d

P. Thomas^d

S. Stuart^c

D. Hull^c

P. Gowland^a

^aSir Peter Mansfield Magnetic Resonance Centre, School of Physics and Astronomy, The University of Nottingham, Nottingham, UK

^bDivision of Therapeutics and Molecular Medicine, University of Nottingham, UK

^cProcter & Gamble, Whitehall Lane, Egham, Surrey, UK

^dProcter & Gamble, Mason, OH, USA

*Corresponding author. Tel.: +44 0 115 95 14 747.

[☆]This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-No Derivative Works License, which permits non-commercial use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Introduction

This study aimed to assess the qualitative and quantitative utility of MRI imaging to illustrate the magnitude and duration of the effect of a standard 100 µg dose of oxymetazoline in a commercially available formulation that also contains aromatic oils.

Methods

This was a randomized, open label, single dose, parallel group study in 21 adult male and female subjects who reported moderate to severe nasal congestion due to acute upper respiratory tract infection or hay fever. MRI scans were acquired using a 3T Philips Achieva scanner with a 16 channel head receive coil. High resolution MRI scans of the nasal turbinates were obtained immediately prior to dosing (baseline) and at approximately 1, 8, 10, 11, and 12 h after dosing. The efficacy variables of primary interest were inferior turbinate total volume at 8 and 12 h post-dosing. The secondary efficacy variables analysed were inferior turbinate total volume at 1, 10, and 11 h post-dosing, middle turbinate total volume at 1, 8, 10, 11, and 12 h post-dosing.

Results

Changes from baseline volumes measured for the inferior and middle turbinates of subjects receiving the oxymetazoline formulation showed significant ($P < 0.05$) decreases at all times up to and including 12 h post-administration. No significant decreases from baseline were detected in subjects receiving a sham 'spray' (untreated control – spray bottles with no spray solution). Statistical ANCOVA results of inferior and middle turbinate volume indicated significant differences ($P < 0.05$) at all measurement points up to and including 12 h post-administration between the oxymetazoline treatment group and the untreated control with the only exception the middle turbinate volume at 10 h ($P = 0.0896$). The significant changes were likely to be clinically relevant though this was not measured in the study. No AEs were reported during this study and no other safety evaluations were made.

Conclusions

This study showed that MRI assessment of nasal congestion in human volunteers is a robust, repeatable and viable measurement technique. The application of a 100 µg Vicks Sinex Micromist® nasal decongestant (0.05% oxymetazoline solution) delivered a highly significant reduction in inferior and middle turbinate volumes compared with the application of a control, measurable by the MRI method up to and including a 12 h post-dose scan.

Keywords: Oxymetazoline; Long-lasting; Nasal turbinates; MRI; Volume measurement

1 Introduction

Oxymetazoline is an established imidazoline derivative which acts directly on alpha-adrenergic receptors in the arterioles of the nasal mucosa to decrease blood flow, leading to a reduction in the swelling of the nasal turbinates, and a consequent enlargement of the nasal lumen ([1] Chen et al., 1995; [2] Docherty, 1998; [3] Martindale, 1998). The rapid and direct topical action of this imidazoline class of decongestant has been determined via symptom scales (categorical or visual analogue scale [VAS]), and using objective methods such as the rhinomanometric measurement of nasal airway resistance (NAR) at the minimum cross-sectional area of the air passages via posterior or anterior rhinomanometry ([4] Cohen & Duffy, 1969; [5] Matson et al., 1978; [6] Kjaergaard et al., 2009; [7] Nathan et al., 2005).

Unpublished Procter and Gamble studies of the duration of oxymetazoline's effect with rhinomanometry indicated that it was capable of reducing NAR for up to 12 h post-administration. NAR, describing as it does a minimum cross-sectional area, does not elaborate on overall volumetric changes of the nasal turbinates. Diagnostic methods such as computed tomography (CT) can help image the architecture of nasal passages, however, objective techniques which eliminate exposure to ionizing radiation e.g. magnetic resonance imaging (MRI) have been developed for use in the clinic and in research ([8] Kennedy et al., 2001).

MRI is a widely used medical imaging technique that generally detects the signal from the hydrogen nucleus in the water molecule, and the MRI signal depends on the physico-chemical environment of the water molecule. Thus MRI allows structures with a high water content to be clearly represented, for example the swollen mucosal lining imaged against the air of the patent nasal and sinus passages. MRI is also non-invasive, making it possible to use it to study dynamic changes purely in response to pharmacological treatments.

MRI has previously been used to image nasal patency from the nares to the oropharynx in healthy volunteers ([9] Lindemann et al., 2009) and to show short-term (to 40 min post-administration) effects of oxymetazoline in patients (unpublished Procter and Gamble pilot study with University of Nottingham). The authors postulated that the advanced MRI equipment and imaging techniques currently available would have the sensitivity to show decreases in turbinate volume at 8 and 12 h for subjects dosed with a single standard non-prescription dose of oxymetazoline. Consequently, the primary objective of this method development study was to evaluate the utility of MRI in demonstrating the nasal decongestant efficacy of Vicks Sinex Micromist® at 8 and 12 h after dosing, relative to a control.

2 Methods

2.1 Design

Clinical Trial Authorization was obtained from the Medicines and Healthcare Products Regulatory Agency prior to the start of the study in accordance with Part 3, Regulation 12 of the UK Statutory Instrument. This study was also conducted in accordance with applicable national laws and regulations; the ethical principles that have their origin in the Declaration of Helsinki; the International Conference on Harmonization (ICH E6) Guideline for Good Clinical Practice (GCP); the ethical requirements of Directive 2001/20/EC (as incorporated into British law). The trial was registered on the EU Clinical Trials Register, EudraCT Number: 2011-002443-10. All subjects gave written informed consent before entry into the study. The study was also approved by the Faculty of Medicine & Health Science, Medical School Research Ethics Committee, University of Nottingham. Clinical monitoring was provided by Research Pharmaceutical Services, Inc.

This was a randomized, open label, single dose, parallel group (treated vs untreated sham control) study in adult male and female subjects who were experiencing nasal congestion due to acute upper respiratory tract infection (URTI) or hay fever (seasonal allergic rhinitis). The study was conducted in October 2011–March 2012 at the Sir Peter Mansfield Magnetic Resonance Centre (SPMMRC) University of Nottingham, and subjects were recruited from the Nottingham, UK area. Personnel who

performed the MRI analyses were blinded to treatment. During the study an amendment was made and approved regarding the measurement of the small superior turbinates (see Section 2.5).

2.2 Subjects and treatment

The sample size for this study (20 subjects were planned; 21 subjects were evaluated) was based on logistical considerations. The mean difference between treatments that can be detected at a power of 80% was estimated for the primary comparisons using data from the previously unpublished Procter & Gamble sponsored pilot study at the University of Nottingham (2010). In this previous study, subjects who had nasal congestion due to the common cold received a single dose of either Vicks Sinex[®] (100 µg oxymetazoline) or a vehicle control and MRI scans of the nasal cavity were performed at baseline and 40 min post-dosing. Mean total volume of the inferior turbinates was found to be 8459 mm³ for the vehicle control and 4238 mm³ for Vicks Sinex[®] at 40 min post-dosing. The root mean square error from the analysis of covariance was 1475 mm³.

Subjects were otherwise healthy adults suffering from moderate to severe nasal congestion associated with upper respiratory tract infection or allergy. Subjects were excluded from the study if they were pregnant or nursing females, had a fever of greater than 38.1 °C, had a concurrent medical condition, a history of allergy or hypersensitivity or abnormal reaction to Vicks Sinex Micromist[®] or the following ingredients: oxymetazoline hydrochloride, levomenthol, sodium citrate dihydrate, tyloxapol, citric acid anhydrous, chlorhexidine gluconate solution, benzalkonium chloride solution, camphor, disodium edetate dihydrate, eucalyptol, sodium hydroxide.

Additional exclusion criteria included history of rhinitis medicamentosa or frequent nose bleeds, dependence on nasal, oral, or ocular decongestants, clinically significant nasal abnormality (e.g., deviated septum, ulcer, septal perforation, or polyp), use of any prescription or non-prescription medication likely to interfere with the study or having exercised within the past 6 h.

Subjects qualifying for inclusion provided a subjective assessment of their nasal congestion on an ordinal scale: absent (no sign/symptom evident), mild (sign/symptom clearly present, but minimal awareness; easily tolerated), moderate (definite awareness of sign/symptom that is bothersome but tolerable), severe (sign/symptom that is hard to tolerate). A score of moderate or severe was required for continuation.

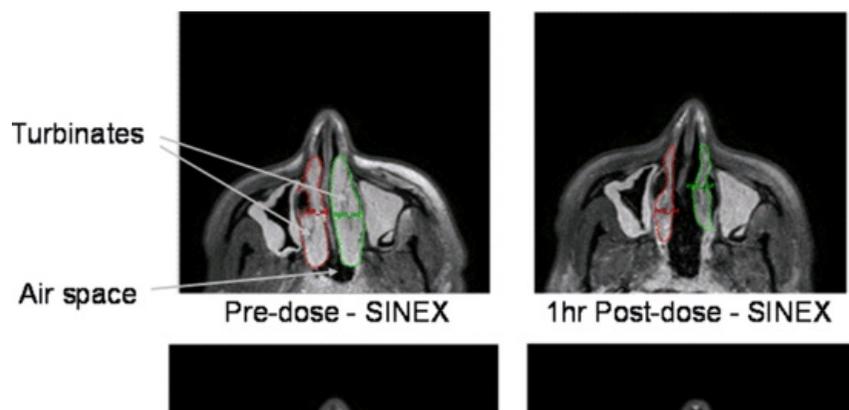
Qualifying subjects were randomized to either 0.05% oxymetazoline (commercially available Vicks Sinex Micromist[®] presented in trade pack) or untreated (sham) control treatment and allocated their test product. Subjects took a single dose of their assigned treatment as follows. While seated upright, and using their dominant hand, they administered 2 sequential sprays of their assigned treatment to each nostril during inhalation (each spray of Vicks Sinex Micromist[®] delivers approximately 50 µL giving a total dose of approximately 200 µL (100 µg oxymetazoline)). Subjects randomized to the sham control performed the same manoeuvre with an identical, empty bottle, administering 2 puffs of air to each nostril.

MRI scans were acquired using a 3T Philips Achieva scanner with a 16 channel head receive coil. After acquiring localization scans, a multislice fast spin echo sequence was acquired in axial sections covering all the sinuses. Seventy-six (76) serial sections of 1 mm thickness were acquired with pixel dimensions of 0.65 mm × 0.65 mm. The total scan time was 5 min, 30 s.

High resolution MRI scans of the nasal turbinates (inferior, middle, and superior) were obtained immediately prior to dosing (baseline) and at approximately 1, 8, 10, 11, and 12 h after dosing.

2.3 Volumetric measurements

The data sets were renamed according to a code to ensure that the person analysing the data (SP) was blinded to whether or not the subject had received treatment. All MRI data were analysed using a proprietary software package Analyze9 (Mayo Foundation, Rochester, MN). Each data set was manually segmented into regions identifying the nasal turbinates within each axial slice (Fig. 1) thereby creating a 3-dimensional map of these structures. Each map was saved for future reference and used to calculate the regional volume measurements within Analyze9. The results were then transferred to Excel to monitor the changes in the volumes as a function of time.



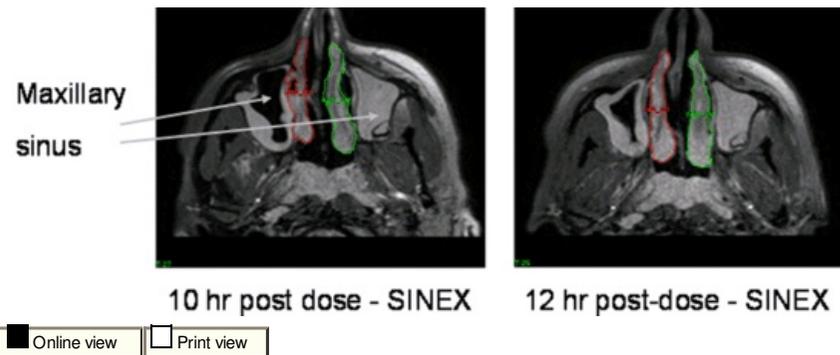


Fig. 1 Axial MRI images showing segmentation of inferior turbinates pre- and post-treatment.

2.4 Outcome measures

The efficacy variables of primary interest were inferior turbinate total volume at 8 and 12 h post-dosing. The secondary efficacy variables were 1) inferior turbinate total volume at 1, 10, and 11 h post-dosing, 2) middle turbinate total volume at 1, 8, 10, 11, and 12 h post-dosing, and superior turbinate total volume at 1, 8, 10, 11, and 12 h post-dosing.

Upon analysis of the first subjects (with treatment blinded to analyst), the identification and measurement of the superior turbinates proved difficult due to their small size and the problems in defining the demarcation of these structures from the ethmoid sinus structure above. Baseline volume measurements of the turbinates (in one volunteer where structures could be unequivocally identified) showed the following: Left inferior, 9873 mm³, Right inferior, 6400 mm³, Left middle, 2390 mm³, Right middle, 2994 mm³, Left superior, 100 mm³ and Right superior, 166 mm³. Subsequent assessment of repeatability gave errors of 1% in inferior turbinate volume measurement (i.e., ±100 mm³) and 10% in middle (i.e., ±300 mm³). This level of accuracy in the volume measurement of the middle turbinate, when compared with the size of the superior turbinate, and combined with the difficulty in even identifying the superior turbinate in some subjects was judged unacceptable and the protocol was duly amended. Consequently, measurements of the superior turbinates are not reported.

2.5 Statistical analyses

The primary and secondary analyses were tested using analysis of covariance where the relevant baseline was modelled as a continuous covariate and treatment was a fixed effect. Analysis of covariance (ANCOVA) was carried out separately on the primary and secondary endpoints data using the Mixed procedure of SAS version 9.2 (SAS Institute, Cary, NC, USA). The sample size considerations were calculated using less stringent criteria than the traditional ones. For evaluation of the data, traditional levels of significance (two sided test, *P*-values <0.05) were used.

3 Results

The safety population included all subjects who were randomized and the per-protocol (PP) population included all subjects in the safety population who had no major protocol violations. The PP population was determined prior to database finalization. There were no major protocol violations so the PP population included all subjects randomized and was identical to the safety population. Subject disposition is summarized in [Table 1](#).

Table 1 Demographic summary data.

Parameter	Control	Vicks Sinex Micromist
Statistic/category	(N = 10)	(N = 11)
Age (years)		
Mean (SE)	27 (3)	22 (3)
Median	23	19
Min	18	18
Max	54	50

Sex		
Female	3 (30%)	7 (64%)
Male	7 (70%)	4 (36%)

N = number of subjects within specified treatment. *n*(%) = number and percentage of subjects within specified parameter, treatment, and category.

The mean age (SE) of subjects enrolled was comparable between the 2 treatment groups (27 (3) years in the control group; 22 (3) years in the oxymetazoline (0.05%) group). Both male and female participants were enrolled and most (>90%) were Caucasian. More female participants were enrolled in the Vicks Sinex Micromist® group (64%) than male (36%) and more male participants were enrolled in the control (70%) than females (30%). At baseline the mean Peak Nasal Inspiratory Flow (PNIF) rate (SE) was similar between the 2 groups (90 (10) L/min in the control group; 89 (10) L/min in the oxymetazoline (0.05%) group). All subjects in both groups described their nasal congestion as “moderate”. No AEs were reported during this study and no other safety evaluations were made.

Descriptive statistics for inferior and middle turbinate volumes at baseline are shown in [Table 2](#). The results from the analysis of covariance for both turbinates are shown in [Table 3](#) and [Figs. 2 and 3](#).

Table 2 Descriptive statistics of baseline characteristics.

Parameter visit statistic	Control (<i>N</i> = 10)	Vicks Sinex Micromist (<i>N</i> = 11)
Inferior turbinate volume		
Mean (SE)	14,281 (924)	14,510 (845)
Median	14,951	14,546
Min–max	9676–17,667	9577–20,488
Middle turbinate volume		
Mean (SE)	4520 (496)	4057 (392)
Median	5039	4539
Min–max	2262–6580	1705–6110
Peak nasal inspiratory flow rate		
Mean (SE)	90 (10)	89 (10)
Median	88	90
Min–max	40–150	50–170
Nasal congestion severity		
Moderate	10 (100%)	11 (100%)

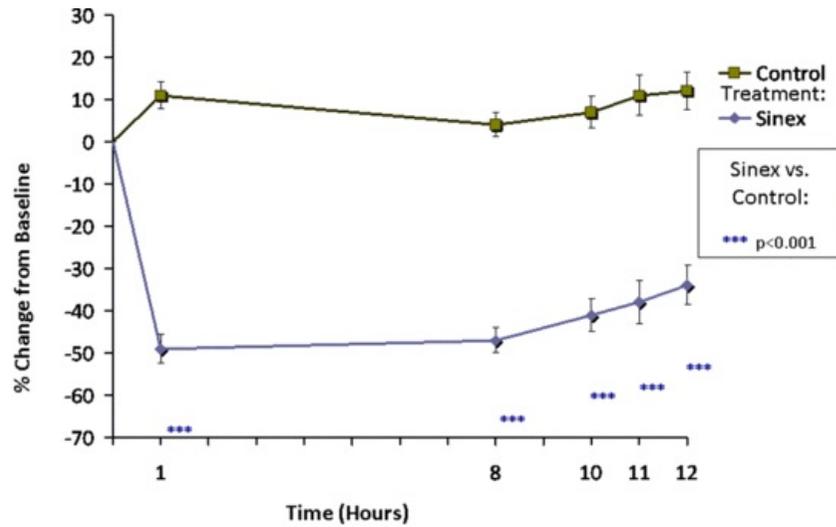
N = number of subjects within specified treatment group.

Table 3 Analysis of covariance of inferior and middle turbinate volume (mm³).

Parameter	Time	Adjusted mean (SE)		Vicks Sinex Micromist – control		% Difference vs control
		Vicks Sinex Micromist	Control	Adjusted mean		
		(<i>N</i> = 11)	(<i>N</i> = 10)	(SE)	<i>P</i> -value	
Inferior turbinate volume	1 h	7191 (493)	15,695 (517)	–8504 (714)	<0.0001	–54%
	8 h	7473 (430)	14,758 (451)	–7285 (623)	<0.0001	–49%
	10 h	8337 (557)	15,255 (585)	–6918 (808)	<0.0001	–45%
	11 h	8757 (728)	15,857 (764)	–7099 (1056)	<0.0001	–45%

	12 h	9358 (661)	16,055 (693)	-6697 (958)	<0.0001	-42%
Middle turbinate volume	1 h	3156 (192)	3956 (202)	-800 (281)	0.0107	-20%
	8 h	3399 (202)	4445 (212)	-1046 (295)	0.0023	-24%
	10 h	3710 (270)	4418 (284)	-708 (395)	0.0896	-16%
	11 h	3559 (262)	4505 (275)	-946 (383)	0.0237	-21%
	12 h	3671 (246)	4590 (258)	-920 (359)	0.0196	-20%

Statistical model includes terms for treatment group, and baseline score.

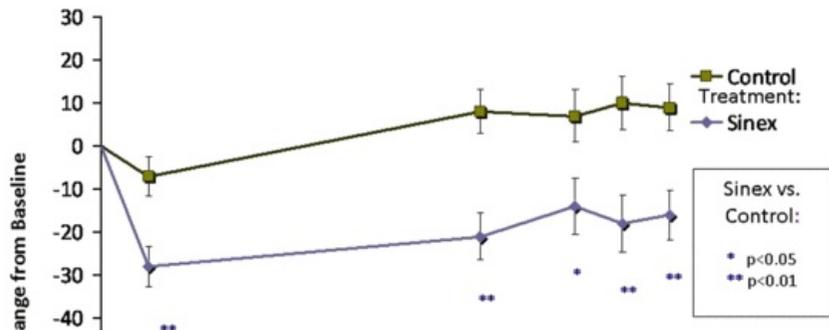


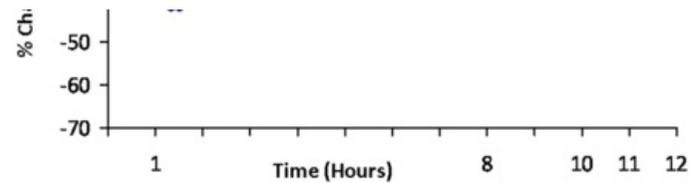
- Post-baseline values are adjusted means based on statistical model including baseline volume and treatment.

- Two tailed p-value comparing Sinex vs. Control: *** significant at $p < 0.001$.

Online view Print view

Fig. 2 Percentage change from baseline of inferior turbinate volumes (\pm SE) calculated from MRI images taken at 0, 1, 8, 10, 11 and 12 h post-administration of 100 μ g Vicks Sinex Micromist[®] and control. Baseline is an unadjusted mean and post-baseline values are adjusted means based on statistical model including baseline and treatment.





- Post-baseline values are adjusted means based on statistical model including baseline volume and treatment.

- Two tailed p-value comparing Sinex vs. Control: * significant at $p < 0.05$ and ** significant at $p < 0.01$.

Online view Print view

Fig. 3 Percentage change from baseline of middle turbinate volumes (\pm SE) calculated from MRI images taken at 0, 1, 8, 10, 11 and 12 h post-administration of 100 μ g Vicks Sinex Micromist[®] and control. Baseline is an unadjusted mean and post-baseline values are adjusted means based on statistical model including baseline and treatment.

Results for the inferior turbinates of patients in the control group indicate a mean volume at 12 h post-administration of 16,055 (SE 693) mm^3 , slightly increased to that assessed at baseline 14,281 (SE 924) mm^3 indicating a small, natural change in nasal congestion occurred over the test period ($P = 0.0282$).

Results for the inferior turbinates of patients in the Vicks Sinex Micromist[®] treatment group indicate an average volume at 12 h post-administration of 9358 (SE 661) mm^3 , which is considerably less than the baseline value of 14,510 (SE 845) mm^3 indicating that the turbinate volume shrinkage is still evident at this time point ($P < 0.0001$). Additionally, inferior turbinate volumes, post-administration were less than baseline for all subjects in this group.

Results for the middle turbinates of patients in the control group had similar but less pronounced trends compared to those for the inferior turbinates. In the control group the adjusted mean volume at 12 h post-administration was 4590 (SE 258) mm^3 , similar to that assessed at baseline 4520 (SE 496) mm^3 , again indicating that little natural change in nasal congestion occurred over the test period as anticipated ($P = 0.2409$).

Results for the middle turbinates of patients in the Vicks Sinex Micromist[®] treatment group indicate a volume at 12 h post-administration of 3671 (SE 246) mm^3 , less than the baseline value of 4057 (SE 392) mm^3 indicating that the turbinate volume shrinkage is still evident at this time point ($P = 0.0238$). All adjusted mean middle turbinate volumes, post-administration were less than baseline in this group.

Statistical ANCOVA results of inferior and middle turbinate volume are summarized in Table 3 and graphically displayed for all time points via percent change from baseline in Figs. 2 and 3 respectively. Statistical analysis of these findings indicated significant differences ($P < 0.05$) at all measurement points up to and including 12 h post-administration between the active treatment group and the sham control with the only exception in the middle turbinate volume at 10 h ($P = 0.0896$). The percent change from baseline ANCOVA P -values in Figs. 2 and 3 are consistent with the ANCOVA results presented in Table 3 with one exception, the middle turbinate volume at 10 h is significant ($P < 0.05$) when analyzed using percent change from baseline.

4 Discussion

MRI is widely used in clinical medicine, but is increasingly being used to measure physiology. The increased sensitivity provided by high field (3T) scanners can be used to provide images with high spatial resolution making it possible to quantify and monitor dynamic changes in sinus volumes with high sensitivity.

Topical oxymetazoline is a commonly used decongestant therapy that has long been available without prescription. It is formulated in Vicks Sinex Micromist[®] along with aromatic oils and aloe vera for improved aesthetics. The aromatic oils are not likely to have contributed to the effects detected here as they have been shown to provide only a subjective sensation of nasal decongestion ([10] Eccles, 1987) Oxymetazoline is widely recognized as a fast and effective therapy with a good record of safety in use. Its duration of efficacy is variously reported as between 8 and 12 h ([11] Martindale, 2013).

The use of quantitative MRI in this study has demonstrated, objectively, the effects of oxymetazoline for longer periods than previously reported in the literature. At all time points after treatment, the changes in both inferior and middle turbinate volumes were statistically smaller following treatment with Vicks Sinex Micromist[®] compared with control. The changes in nasal patency observed in this study suggest that the product may provide relief of nasal congestion for up to 12 h post-dose in patients suffering from URTI or allergic rhinitis and suggest the possibility of recommending a twice daily posology for this medication.

There are some limitations to this study. Firstly, there were no subjective evaluations of efficacy. Subjective responses to 12 h have been shown previously (unpublished observations), indicating that the objective effects are clinically relevant. It therefore warrants further research to confirm the subjective effects. Secondly, the study was unblinded to all except the technician conducting the image analyses. This is not judged to be a significant limitation as the

MRI scans were objective and not readily open to unconscious or indeed conscious bias. Thirdly, the absolute volumes measured were subject to operator bias through decisions made when choosing the areas to delineate for volume calculations; however the technician was blind to the treatment group of patients so this bias would have been the same for both treatment groups and thus will not have changed the overall results observed.

As oxymetazoline is recognized as both a long-lasting and a fast-acting agent it is recommended that future work in this area should include an estimation of the absolute speed of action.

This study showed that MRI assessment of nasal congestion in human volunteers is a robust, repeatable and viable measurement technique which should compare favourably with the current gold standard subjective data. Existing rhinomanometric techniques provide data only at the point of measurement rather than the global view afforded by the MRI data. MRI clearly showed the anatomy of the nasal and sinus structures in all subjects and enabled the accurate sequential measurement of the volumes of engorged nasal soft tissue associated with the turbinate structures in the nose and is these structures that influence the degree of congestion felt.

The application of a 100 µg Vicks Sinex Micromist® nasal decongestant delivered a highly significant reduction in inferior and middle turbinate volumes compared with the application of a non-active control. This change between treatments was significant at all but one post-dose measurement up to and including the final 12 h post-dose scan confirming 12 h efficacy. These data support the notion of twice daily dosing as appropriate for this product.

Competing interests

At the time of conducting this study J. Brum, D. Hull, G. Kappler, D. Ramsey, S. Stuart and P. Thomas were full-time employees of The Procter & Gamble Company and were Procter & Gamble share-holders. P. Gowland received a grant from the Procter & Gamble Company for leading the clinical study.

Study involvement

P. Gowland and D. Hull were responsible for study design and publication drafting. S. Pritchard and P. Thomas were responsible for study execution with P. Thomas also advising on design and S. Pritchard performing the MRI scans and subsequent analyses. D. Ramsey was responsible for statistical analyses and advice on design. J. Brum (Study Medical Monitor) and G. Kappler advised on design and G. Kappler was responsible for Data Management. M. Glover and G. Guthrie were the on-site study physicians. All attributed authors participated in the development and/or review of this manuscript.

Acknowledgements

We would like to thank all subjects who volunteered for this study. We also acknowledge with thanks the contributions of the study's CRA, Kym Teale, Research Pharmaceutical Services, Inc., for clinical monitoring.

References

[1]

K.S. Chen, S.S. Bharaj and E.C. King, Induction and relief of nasal congestion in ferrets infected with influenza virus, *Int J Exp Pathol* **76**, 1995, 55–64.

[2]

J.R. Docherty, Subtypes of functional α_1 - and α_2 -adrenoceptors, *Eur J Pharmacol* **361**, 1998, 1–15.

[3]

Martindale, The extra pharmacopoeia, 29th ed., 1998, London Pharmaceutical Press; London.

[4]

B.M. Cohen and E.P. Duffy, Physiological and clinical estimates of the relief of nasal flow obstruction in allergic rhinitis; effects of a topical decongestant (oxymetazoline), *J Asthma Res* **7** (2), 1969, 65–73.

[5]

C.J. Matson, A.N. Welter and D.C. Kvam, An experimental non-invasive animal technique for measuring nasal airway resistance: adrenergic and antihistaminic agents, *Arch Int Pharmacodyn Ther* **232**, 1978, 68–78.

[6]

T. Kjaergaard, M. Cvanarova and S.K. Steinsvag, Nasal congestion index: a measure for nasal obstruction, *Laryngoscope* **119** (8), 2009 Aug, 1628–1632.

[7]

B.A. Nathan, B. Eccles, B.H. Howarth, S.K. Steinsvag and A. Tosić, Objective monitoring of nasal patency and nasal physiology in rhinitis, *J Allergy Clin Immunol* **115** (2), 2005, S442–S450.

R.A. Nathani, R. Eccles, P.H. Howarth, S.K. Steinsvag and A. Trogias, Objective monitoring of nasal patency and nasal physiology in rhinitis, *J Allergy Clin Immunol* **15** (3), 2005, 5442–5459.

[8]

D.W. Kennedy, W.E. Bolger and S.J. Zinreich, *Diseases of the sinuses: diagnosis and management*, 2001, B.C. Decker Inc.; Hamilton, Ontario, 136–138.

[9]

J. Lindemann, E. Tsakiropoulou, V. Vital, T. Keck, R. Leiacker, S. Pauls, et al., Influence of the turbinate volumes as measured by magnetic resonance imaging on nasal air conditioning, *Am J Rhinol Allergy* **23** (3), May/June 2009, 250–254.

[10]

R. Eccles, B. Lancashire and N.S. Tolley, The effect of aromatics on inspiratory and expiratory nasal resistance to airflow, *Clin Otolaryngol Allied Sci* **12** (1), 1987 Feb, 11–14.

[11]

Martindale. The complete drug reference. http://www.medicinescomplete.com/mc/martindale/current/2093-v.htm?q=oxymetazoline&t=search&ss=text&p=1#_hit [accessed 01.05.13].

Queries and Answers

Query: Please check the journal title in Ref. [5] and correct if necessary.

Answer: This is correct

Query: Please confirm that given names and surnames have been identified correctly.

Answer: These are correct