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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

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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.

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

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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 mm^3 for the vehicle control and 4238 mm^3 for Vicks Sinex® at 40 min post-dosing. The root mean square error from the analysis of covariance was 1475 mm^3.

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.