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Title of Study
A proof of concept study to evaluate differential tachyphylaxis of α1 and α2 adrenoreceptor mediated decongestant response to oxymetazoline and its acute reversal by corticosteroid in healthy volunteers

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Publication (reference)
VAIDYANATHAN S, WILLIAMSON P, CLEARIE K, KHAN F, LIPWORTH BJ. Fluticasone reverses oxymetazoline induced tachyphylaxis of response and rebound congestion. Am J Respir Crit Care Med 2010;182:19-24

Date of first enrolment	**Phase of development**
May 2008 **Date of last completed** May 2009	Phase IV

Objectives
We evaluated if tachyphylaxis can be reversed by intranasal fluticasone propionate, and the relative α1- and α2-adrenoceptor components of tachyphylaxis using the α1-antagonist prazosin.

Methodology
In a randomized, double-blind, placebo-controlled, crossover design, 19 healthy subjects received intranasal oxymetazoline, 200 mcg three times a day for 14 days, followed by the addition of fluticasone, 200 mcg twice a day for a further 3 days. At Days 1, 14, and 17, participants received a single dose of oral prazosin, 1 mg, or placebo with measurements made before and 2 hours later.

Number of patients planned
31

Number of patients analysed
19

Diagnosis and main criteria for inclusion
Male or female healthy volunteers; 18 to 65 years; no rhinitis or rhinosinusitis, negative skin prick test to common aeroallergens; normal ECG; normal BP with no postural hypotension; PNIF >100 L/min (best of 3); PNIF reversibility with oxymetazoline, 0.05% w/v 2 squirts in each nostril (20 min reading) > 20 L/min.

Test product dose
Oxymetazoline 0.05%, 2 squirts in each nostril t.d.s.
Prazosin 1mg (single dose at study visits)
Placebo to Prazosin (single dose at study visits)
Fluticasone Nasal Spray 50 mcg, 2 quirts each nostril b.i.d.

Duration of treatment
34 days (2 treatment periods of 17 days)

Reference therapy
N/A

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Primary Endpoint
Difference in peak PNIF response to incremental doses of OXY [i.e. as a dose response]

Secondary Endpoints
Domiciliary morning PNIF and TNS-4 pre and 20 minutes post OXY and before night dose
Active Anterior Rhinomanometry to measure airway resistance
Nasal oscillometric indices to measure resistance and reactance
Laser Doppler Flowmetry to measure nasal blood flow
Systolic, Diastolic blood pressure (lying and standing)
Withdrawals from study

Statistical methods
The study was powered at > 80% with an α-error of 0.05 (two-tailed) to detect a 10 L/min difference in PNIF between randomized treatments, with an estimated sample size of 16 participants assuming the within-subject SD to be 9.2 L/min. This was considered adequate to demonstrate tolerance to oxymetazoline. Each outcome was assessed for normality using the Shapiro-Wilk test and by visual inspection of histograms and Q-Q plots. Nonnormal data were logarithmically transformed. An overall analysis of variance was performed with subject, treatment, and sequence as cofactors followed by Bonferroni-corrected pair-wise comparisons with a two-tailed α-error set at 0.05. The DRC was analyzed using a two-way analysis of variance factoring in time in addition to the previously mentioned factors, to obviate multiple comparisons at several time points. All analyses were performed on a per-protocol basis using SPSS version 17 (SPSS Inc., Chicago, IL).

Summary Conclusions

Results
Outcomes evaluated were peak nasal inspiratory flow, nasal resistance, blood flow, and oxymetazoline dose–response curve (DRC). On Day 14 versus Day 1, inspiratory flow decreased (mean difference, 95% confidence interval) (-47.9 L/min; -63.9 to -31.9; $P < 0.001$) and the DRC shifted downward (24.8 L/min; 20.3–29.3; $P < 0.001$). On Day 17 versus Day 14, after fluticasone, inspiratory flow increased (45 L/min; 30–61; $P<0.001$) and the DRC shifted upward (26.2 L/min; 21.7–30.7; $P<0.001$). On Day 1, prazosin reduced inspiratory flow (-52.6 L/min; -19.2 to -86) compared with baseline. This effect was abolished on Day 14 (7.9 L/min; -41.3 to 25.5).

Conclusion
Oxymetazoline-induced tachyphylaxis and rebound congestion are reversed by intranasal fluticasone. Further studies are indicated to evaluate if combination nasal sprays of decongestant and corticosteroid are an effective strategy to obviate tachyphylaxis and rebound in rhinitis.

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