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Title of study
A Proof of Concept Study to Assess the Steroid Sparing Effect of Combined Nasal and Inhaled Corticosteroid in Patients with Asthma and Persistent Rhinitis

Investigators
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Study centre(s)
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Publication (reference)
NAIR A, VAIDYANATHAN S, CLEARIE K, WILLIAMSON P, MELDRUM K, LIPWORTH BJ. Steroid sparing effects of intranasal corticosteroids in asthma and allergic rhinitis. Allergy 2010;65:359-367

Date of last completed
06.08.2008

Objectives
To determine if the treatment of the nose with intranasal steroid makes a difference to airway hyper-responsiveness and lower airway inflammation (i.e. does the use of intranasal steroid provide a steroid sparing effect in terms of the dose of inhaled steroid for the lower airway?)

Methodology
Twenty-five participants were randomized to receive two weeks of 100 µg/day (Low dose) or 500 µg/day (High dose) of inhaled fluticasone propionate both with intranasal placebo; or inhaled fluticasone 100 µg/day with intranasal fluticasone 200 µg/day (Combined) in a double-blind cross-over fashion.

Number of patients planned
30 patients recruited to ensure 24 complete per protocol

Number of patients analysed
25

Diagnosis and main criteria for inclusion
Males and females, 18–65 years, asthmatic, $FEV_1 \geq 60\%$, ≤1000 µg BDP equivalent, perennial allergic rhinitis, positive skin prick test to at least one perennial aeroallergen, methacholine $PC_{20} < 4$ mg/ml.

Test product dose
Arm A
1 puff of inhaled Fluticasone Evohaler 50 µg twice a day (Total dose 100 µg) and 1 puff of inhaled Placebo twice a day with placebo nasal spray2 squirts each nostril once a day.
Arm B
1 puff of inhaled Fluticasone Evohaler 50 µg twice a day (Total dose 100 µg) and 1 puffs of Placebo twice a day with nasal fluticasone (Flixonase®) 50ug 2 squirts each nostril once a day (i.e. total daily dose 200ug) .
Arm C
1 puff of inhaled Fluticasone Evohaler 250 µg twice a day (Total dose 500 µg) and 1 puff of inhaled placebo twice a day with placebo nasal spray 2 squirts each nostril once a day.

Duration of treatment
6 weeks (3 treatment periods of 2 weeks)

Reference therapy
None

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Primary Endpoint
Dose response between inhaled Fluticasone 100 µg and Fluticasone 500µg (both with intranasal placebo) vs inhaled Fluticasone 100µg and nasal Fluticasone 200ug on Methacholine bronchial hyperresponsiveness (as the PC20 threshold value)

Secondary Endpoints
Spirometry and asthma diary cards (Symptoms, am PEF and reliever use), Juniper asthma quality of life, Juniper mini rhinoconjunctivitis questionnaire, Exhaled nitric oxide (tidal and alveolar), nasal diary cards (Total Nasal Symptom Scores and Peak Nasal Inspiratory Flow), Nasal NO, Blood Eosinophils, Blood Siglec 8 antibody level, Serum Eosinophil Cationic protein(ECP), Salivary ECP, Spirometry, Lung Impulse oscillometry (IOS), Nasal IOS and Overnight Urinary Cortisol Creatinine Ratio (OUCC).

Statistical methods
SPSS version 14 (SPSS Inc., Chicago, IL, USA) was used to carry out the statistical analysis. A sample size of 24 completed patients was estimated to give 80% power to detect a one doubling-dilution shift (minimal important difference) in methacholine PC_{20} value (primary endpoint) assuming a 0.84 within-patient SD for this outcome. Datasets were analysed for patients who completed the crossover study per protocol. Data were assessed for normality using visual inspection, Q–Q plots and with previous consideration for literature, and if appropriate non-Gaussian data was logarithmically transformed prior to analyses. Comparisons were made using an overall repeated measures ANOVA (adjusted for baselines) with Bonferroni correction for multiple comparisons ($P < 0.05$, two tailed) and subject, treatment and sequence as factors.

Results
Low dose fluticasone produced a shift of 1.20 doubling-dilutions (95% CI, 0.63, 1.77); Combined fluticasone, 1.79 doubling-dilutions (95% CI, 0.77, 2.80) and high dose fluticasone, 2.01 doubling-dilutions (95% CI, 1.42, 2.61) in methacholine PC_{20} from respective baselines. There was a significant difference between high and low doses: 0.82 doubling dilutions (95%CI, 0.12, 1.50) but not between combined and low dose 0.58 doubling dilutions (95% CI, –0.78, 1.95). Combined treatment alone produced improvements in peak nasal inspiratory flow ($P < 0.001$), rhinitis quality of life ($P = 0.004$) and nasal NO ($P = 0.01$); reduced blood eosinophil count ($P = 0.03$), and serum eosinophil cationic protein ($P = 0.02$). All treatments significantly improved tidal NO, FEV_1 and asthma quality of life.

Conclusion
High-dose fluticasone was superior to low dose fluticasone for methacholine PC20, demonstrating room for further improvement. Combined treatment was not significantly different from low dose fluticasone and we could not demonstrate a steroid sparing effect on methacholine PC20. Combined treatment alone produced improvements in upper airway outcomes and suppressed systemic inflammation but not adrenal function.

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