Name of Sponsor/Company
University of Dundee

Title of Study
A Proof of Concept Study into the Effects of Inhaled Extra-Fine and Standard Formulations of Beclomethasone Dipropionate and Oral Montelukast on Surrogate Markers of Small and Large Airway Inflammation in Asthma

Investigators
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Study centre(s)
Asthma & Allergy Research Group

Publication (reference)
MENZIES D, NAIR A, HOPKINSON P, McFARLANE L, LIPWORTH BJ. Differential anti-inflammatory effects of large and small particle size inhaled corticosteroids in asthma. Allergy 2007;62:661-667

Objectives
To establish whether EF-BDP preferentially suppresses alveolar inflammation over SF-BDP preparations, and to determine whether the LRA montelukast has additive effects upon this suppression over and above that conferred by ICS alone.

Methodology
A double-blind randomized crossover trial was undertaken comparing the anti-inflammatory effects of HFA-BDP (100 and 400 µg/day) and CFC-BDP (200 and 800 µg/day). Treatment with montelukast was evaluated as add-on to the higher dose of BDP.

Number of patients planned
30

Number of patients analysed
22

Diagnosis and main criteria for inclusion
Participants were required to have a physician diagnosis of persistent asthma, be receiving $\leq$ 1000 µg of BDP/day or equivalent, be a non-smoker and have a positive skin-prick reaction to at least one common aeroallergen. Participants were excluded if they had experienced a respiratory tract infection or had received oral corticosteroids within the 3 months prior to the date of trial enrolment

Test product dose

Arm A
200 µg CFC-BDP daily (2 weeks)
800 µg CFC-BDP daily (2 weeks)
800 µg CFC-BDP plus 10 mg montelukast once daily (1 week)

Arm B
100 µg HFA-BDP daily (2 weeks)
400 µg HFA-BDP daily (2 weeks)
400 µg HFA-BDP plus 10 mg montelukast once daily (1 week)

Duration of treatment
10 weeks (2 treatment periods of 5 weeks)

Reference therapy
None

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Primary Endpoint
CA_{NO}

Secondary Endpoints
Respiratory function (measured by IOS and methacholine challenge), sputum and blood eosinophils, ECP, CRP

Statistical methods
The SPSS software version 13 (SPSS Inc., Chicago, IL, USA) was used to perform the statistical analysis. An a priori power calculation revealed that 20 participants completing trial per protocol would give 80% power to detect a 15% reduction in exhaled nitric oxide levels with add-on montelukast, assuming a within-patient SD of 2 ppb and an α-error set at 0.05. Only data from participants who completed the trial per protocol were included in the final analysis. Distribution plots and the Shapiro–Wilk test were performed to evaluate the data for normality, and any non-Gaussian data underwent log transformation prior to analysis. Data were evaluated by an overall ANOVA with randomization sequence as a cofactor, followed by Bonferroni corrected pairwise comparisons with a two-tailed α-error set at 0.05.

Summary Conclusions

Results
Compared with baseline after withdrawal of usual asthma therapy, 100 μg of HFA-BDP significantly attenuated serum eosinophilic cationic protein levels (0.61-fold change, 95% CI 0.49–0.77; a 39% reduction, $P < 0.001$), but 200 μg of CFC-BDP did not (0.87-fold change, 95% CI 0.63–1.23; $P = 1$). A dose of 800 μg of CFC-BDP and 400 μg of HFA-BDP led to reductions in exhaled nitric oxide (0.57-fold change, 95% CI 0.44–0.73; a 43% reduction, $P < 0.001$ and 0.65-fold change, 95% CI 0.47–0.91; a 35% reduction, $P = 0.008$, respectively); and peripheral eosinophils (-74 cells/μl, 95% CI -146 to -2; $P = 0.020$ and -77 cells/μl, 95% CI -140 to -14; $P = 0.012$, respectively). Montelukast further reduced exhaled nitric oxide (0.81-fold change, 95% CI 0.66–0.98; $P = 0.028$) with 400 μg HFA-BDP and eosinophils (-44 cells/μl, 95% CI -80 to -8; $P = 0.012$) with 800 μg CFC-BDP, but not vice versa.

Conclusion
Chlorofluorocarbon beclometasone dipropionate and HFA-BDP have differential effects on pulmonary and systemic inflammation, which dictate the additive effects of montelukast.

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