Name of Sponsor/Company
University of Dundee

Title of Study
Comparative Relative Lung Bioavailability of HFA-Seretide via spacer devices in healthy volunteers

Investigators
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Study centre(s)
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Publication (reference)
NAIR A, McKINLAY L, WILLIAMSON P, SHORT P, BURNS P, LIPWORTH B. Comparative lung bioavailability of fluticasone/salmeterol via breath actuated spacer and conventional plastic spacers. Eur J Clin Pharmacol 2011;67:355-63

Date of completion
30.12.2009

Objectives
To compare the in vivo relative lung bioavailability of HFA Seretide delivered via unprimed and unwashed Aerochamber Plus or Volumatic spacers, an integrated breath-actuated vortex Synchro-Breathe device and an Evohaler pMDI device using adrenal suppression and early fall in serum potassium (K) as surrogates for respirable dose

Methodology
Randomised double-blind, double-dummy crossover study. Single doses of placebo/Seretide 250 (total dose ex-valve fluticasone 2000 mcg/salmeterol 200 mcg) were administered via the devices. Overnight urinary cortisol/creatinine (OUCC) and serum K were measured at baseline and after each dose.

Number of patients planned
20 patients randomized to ensure at least 16 complete

Number of patients analysed
17

Diagnosis and main criteria for inclusion
Healthy volunteers, non-smokers, between the ages of 18 and 65 years.

Test product dose

Arm A	Arm B
8 puffs of Placebo pMDI via Volumatic	8 puffs of Seretide 250/25 µg via Volumatic
8 puffs of Placebo pMDI via Synchro-Breathe	8 puffs of Placebo via Synchro-breathe
8 puffs of Placebo via Aerochamber Plus	8 puffs of Placebo via Aerochamber Plus
8 puffs of Seretide 250/25 µg HFA via Evohaler Actuator	8 puffs of Placebo via Evohaler Actuator

Arm C	Arm D
8 puffs of Placebo via Volumatic	8 puffs of Placebo via Volumatic
8 puffs of Seretide 250/25 µg HFA via Synchro-breathe	8 puffs of Placebo via Synchro-breathe
8 puffs of placebo via Aerochamber Plus	8 puffs of Seretide 250/25 µg via Aerochamber Plus
8 puffs of placebo via pMDI Evohaler Actuator	8 puffs of Placebo via Evohaler Actuator

Duration of treatment
Treatment arms administered one per visit, with a 5 – 7 day washout period between visits.

Reference therapy
None

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Criteria for evaluation

Primary Endpoint
Overnight urinary cortisol creatinine ration (OUCC)

Secondary Endpoints
Change in serum potassium from baseline, and early morning urinary cortisol to creatinine ratio

Statistical methods
A sample size of 16 patients per protocol to completion was chosen to power the study at 80% in order to detect a 20% difference in the OUCC. Data sets were analysed for patients who completed the crossover study per protocol. All data were tested for normality prior to analysis. The OUCC data was log transformed, and K, heart rate, blood pressure data were analysed without transformation in view of its normal distribution. Comparisons were made using repeated measures General Linear Model (GLM) analysis of variance with Bonferroni correction for multiple comparisons, set with 95% confidence intervals (CIs) for differences. All effects were reported as being significant at $p < 0.05$ (twotailed), and violation of sphericity of within-subject effects was tested with the Mauchly's test. The analysis was carried out using SPSS ver. 15 (SPSS, Chicago, IL).

Summary Conclusions

Results
Significant suppression of OUCC and K occurred from baseline with the SB, AP and VM but not with the EH devices. The geometric mean fold suppression (95% confidence interval, p) was: EH, 1.59 (0.80–3.14, p=0.40); AP, 4.26 (3.01–6.02, p<0.001); VM, 3.11 (1.99–4.78, p<0.001); SB, 3.29 (2.04–5.24, p<0.001). For K, the arithmetic mean fall (mmol/l) (95% confidence interval; p) was: EH, −0.10 (−0.25–0.05, p=0.18); AP, −0.23 (−0.41 to −0.04, p=0.02); VM, −0.22 (−0.44 to −0.01, p=0.04); SB, −0.28 (−0.42 to −0.13, p=0.001).

Conclusion
The breath-actuated SB device was comparable to 'out of the box' small and large volume spacers and produced similar improvements in relative systemic lung bioavailability for fluticasone and salmeterol

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