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Title of Study
Comparative Lung Bioavailability of HFA-Seretide via Spacer Devices in Healthy Volunteers

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Publication (reference)
NAIR A, CLEARIE K, MENZIES D, MELDRUM K, McFARLANE L, LIPWORTH BJ. A novel breath-actuated integrated vortex spacer device increases relative lung bioavailability of fluticasone/salmeterol in combination. Pulmonary Pharmacology & Therapeutics 2009;22:305-310

Objectives
To compare the in vivo relative bioavailability to the lung of Hydrofluoroalkane (HFA) Seretide delivered via Synchro-Breathe; an optimally prepared 750 ml large volume plastic spacer, Volumatic; and conventional Evohaler pMDI.

Methodology
Randomised double blind, double dummy crossover design. Single doses of placebo or Seretide HFA 250 (total dose ex-valve: fluticasone 2000 mcg/salmeterol 200 mcg) were administered via Synchro-breathe, Volumatic and Evohaler. Overnight urinary cortisol creatinine (OUCC) and serum potassium (K) were measured at baseline and after each dose as systemic surrogates of relative respirable dose delivery for the fluticasone and salmeterol moieties, respectively.

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

Number of patients analysed
19

Diagnosis and main criteria for inclusion
Non-smoking, healthy adults between the ages of 18 and 65 years.

Test product dose

Arm A
8 puffs of Placebo pMDI via Volumatic
8 puffs of Placebo pMDI via Synchro-breathe
8 puffs of Seretide 250/25 µg pMDI Evohaler Actuator

Arm B
8 puffs of Placebo pMDI via Volumatic
8 puffs of Seretide 250/25 µg pMDI via Synchro-breathe
8 puffs Placebo pMDI via Evohaler Actuator

Arm C
8 puffs Seretide 250/25 µg pMDI via Volumatic
8 puffs Placebo pMDI via Synchro-breathe
8 puffs Placebo pMDI via Evohaler Actuator

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

Reference therapy
None

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Primary Endpoint
The primary endpoint was overnight urinary cortisol creatinine ratio.

Secondary Endpoints
Beta adrenoreceptor response (Heart rate, blood pressure, and serum potassium) as a surrogate for the lung bioavailability of the salmeterol moiety; and early morning urinary cortisol to creatinine ratio as another surrogate of the lung bioavailability of the fluticasone moiety.

Statistical methods
A sample size of 16 completed patients per protocol was chosen to power the study at 80% to detect a 20% difference in overnight urinary cortisol creatinine ratio. Data sets were analyzed for patients who completed the crossover study per protocol. All data were tested for normality prior to analysis. The OUCC data were log-transformed, and K data were analyzed 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 for differences. All effects are reported as being significant <0.05 (2-tailed) and violation of sphericity of within subject effects was tested with the Mauchly's test. The analysis was carried out using SPSS Version 13.

Summary Conclusions

Results

Significant suppression of OUCC and K occurred from baseline with Synchro-breathe and Volumatic but not Evohaler devices (geometric mean fold suppression, 95% CI, p and arithmetic mean fall mmol/L, 95% CI, respectively); Evohaler: 1.51(0.43–1.01), p = 0.06; Volumatic: 2.52(1.57–4.04), p < 0.001; Synchro-breathe: 2.66(1.57–4.49), p < 0.001(equating to 33.8%, 60.2% and 62.3% falls, respectively). For K, the falls for Evohaler were -0.09(-0.25 to 0.07), p = 0.69; Volumatic: -0.27(-0.46 to -0.08), p = 0.003; Synchro-breathe: -0.32(-0.53 to -0.11), p = 0.002 (equating to 2.2%, 6.8%, and 8.06% fall, respectively). There were no significant differences between Synchrobreathe and Volumatic.

Conclusion
The breath-actuated Synchro-Breathe device was comparable to an optimally prepared Volumatic spacer, and resulted in commensurate improvement in relative lung bioavailability for both fluticasone and salmeterol moieties compared to pMDI.

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