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Particle Deposition and Small Airways In Asthma

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“Try this—I just bought a hundred shares.”
Disclosure Statement
Lanny J. Rosenwasser, MD

• RESEARCH STUDIES
  – Alcon, A-Z, GlaxoSmithKline, Genentech, Novartis
  – MBBH/MacArthur Foundation, National Institutes of Health

• CONSULTANT
  – Abbott Corp, Alcon, Alexion, Altana Pharmaceuticals, A-Z, Biogen Idec Corp, Genentech, GlaxoSmithKline, Merck, Novartis, Regeneron, Sanofi-Aventis

• SPEAKERS’ BUREAU
  – Alcon, Banyu Pharmaceuticals, Genentech,
  – Merck, Novartis
Characterization of aerosol output from various nebulizer/compressor combinations

Colin Reisner, MD; Rohit K. Katial, MD; B. Bucher Bartelson, PhD; Andrea Buchmeir, CCRC; Lanny J. Rosenwasser, MD; and Harold S. Nelson, MD

Figure 4. Mean percentage of particles in respirable range by nebulizer and flow rate. Percentage of particles in the respirable range (1 to 5 μm) was measured during continuous nebulization to the point where the nebulizer output fell 8-fold. AL = Airlife Misty Nebulizer; HD = Hudson Micromist; PB = Puritan Bennett Raindrop; PR = Pari LC Jet; and SL = Salter 8900.
The Disease Process in Asthma is Located in All Parts of the Bronchial Tree, Small Airways and Alveoli.
Small Airway Inflammation in Asthma: Background

- Inflammation and airway remodeling in asthma extends into the small airways (< 2 mm diameter).
- This small airway inflammation may contribute to difficult-to-control asthma.
Inflammation of Small Airways in Asthma

Q Hamid et al. J Allergy Clin Immunol 1997;100:44-51

Surgical lung specimens from 6 patients with asthma and 10 controls were examined. There was a similar inflammatory process present in the peripheral (< 2mm diameter) compared with the central airways.
Immunohistochemical Markers in the Large & Small Airways

Airways < 2 mm

Airways > 2 mm

A = asthmatics
C = controls

Hamid JACI 1997
Difficult-to-Control Vs. Stable Asthmatics

- There were no significant differences in lung function except increased closing volume and closing capacity in the difficult to treat asthmatics.
- “This is indicative of small airway pathology in these patients”
- “Delivery of anti-inflammatory medication to the small airways in this subgroup is of specific clinical relevance”.

AJRCCM 2000;161:1902-6
Andersen Sampler Simulates Human Respiratory System

<table>
<thead>
<tr>
<th>STAGE</th>
<th>Size Range</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAGE 0</td>
<td>11+</td>
<td>Oropharynx</td>
</tr>
<tr>
<td>STAGE 1</td>
<td>7.0-11.0</td>
<td>Oropharynx</td>
</tr>
<tr>
<td>STAGE 2</td>
<td>4.7-7.0</td>
<td>Oropharynx</td>
</tr>
<tr>
<td>STAGE 3</td>
<td>3.3-4.7</td>
<td>Trachea and primary bronchi</td>
</tr>
<tr>
<td>STAGE 4</td>
<td>2.1-3.3</td>
<td>Secondary bronchi</td>
</tr>
<tr>
<td>STAGE 5</td>
<td>1.1-2.1</td>
<td>Terminal bronchi</td>
</tr>
<tr>
<td>STAGE 6</td>
<td>0.65-1.1</td>
<td>Respiratory bronchioles</td>
</tr>
<tr>
<td>STAGE 7</td>
<td>0.43-0.65</td>
<td>Alveoli</td>
</tr>
</tbody>
</table>

Steroid Particle Size

<table>
<thead>
<tr>
<th></th>
<th>FP-Diskus</th>
<th>CFC-TAA</th>
<th>BUD-Turbuhaler</th>
<th>CFC-Flunisolide</th>
<th>CFC-BDP</th>
<th>CFC-FP</th>
<th>HFA-BDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass Median Diameter (μm)</td>
<td>5.4</td>
<td>4.5</td>
<td>4.0</td>
<td>3.8</td>
<td>3.5</td>
<td>2.4</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Adapted from Bensch and Newman. AJRCCM 2001;163(5)
A440 at ERS 200
Steroid Lung Deposition

Lung Deposition of HFA-ciclesonide

Lung Deposition of HFA-ciclesonide

Lung Deposition of HFA Inhaled Corticosteroids

Study Design

• Crossover design
• 9 healthy subjects aged 18-52 years
• Randomized to receive inhaled technetium-99m labeled
  - HFA-beclomethasone
  - CFC-fluticasone
  - CFC-beclomethasone

Comparison of lung deposition in the same subject

Leach CL et al. Am J Respir Crit Care Med 2000; 16 (3): A34
Conclusions

- HFA-BDP is evenly distributed throughout the lungs and therefore reaches all sites of inflammation
- CFC-fluticasone is deposited primarily in the large and intermediate airways
- CFC-BDP is deposited almost exclusively in the large airways
Hydrofluoroalkane-134a Beclomethasone or Chlorofluorocarbon Fluticasone: Effect on Small Airways in Poorly Controlled Asthma

Study Design

Randomized, Open Label, Parallel Group

Asthma not controlled on med-high dose ICS

Randomization

Visit 1
Day 1

Visit 2
Week 6

Visit 3
Week 12

CFC-FP 220 mcg am
N=(10)

HFA-BDP 160 mcg twice daily
N= (20)

CFC-FP 220 mcg am
N=(10)

110 mcg pm

### Study Design

#### Endpoints

<table>
<thead>
<tr>
<th>Screening Period</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Bronchodilator</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spirometry</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Closing volume</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-Bronchodilator (albuterol x 2 Puffs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spirometry</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plethysmography</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Results: Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>HFA-BDP (20)</th>
<th>CFC-FP (9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV$_1$</td>
<td>59%</td>
<td>55%</td>
</tr>
<tr>
<td>FEV$_{25-75}$</td>
<td>33%</td>
<td>28%</td>
</tr>
<tr>
<td>RV</td>
<td>196%</td>
<td>205%</td>
</tr>
<tr>
<td>CV (L)</td>
<td>0.51</td>
<td>0.57</td>
</tr>
<tr>
<td>CV/VC</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>ICS (med/high)</td>
<td>5/15</td>
<td>3/6</td>
</tr>
<tr>
<td>Albuterol P/D</td>
<td>4</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>p &lt; 0.05</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma score</td>
<td>4</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>p = .11</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Exacerbations

- During the blinded period 5/20 subjects receiving HFA-BDP and 0/10 receiving CFC-FP experienced exacerbations treated with prednisone.

- Subjects were tested at least one month following their last prednisone.

- Post-treatment parameters in these 5 subjects fell within +/- one SD of those of the other 15 HFA-BDP subjects.
# Results: Pulmonary Function

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HFA-BDP</th>
<th>CFC-FP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>p</td>
</tr>
<tr>
<td>CV (L)</td>
<td>.51</td>
<td>.44</td>
<td>.57</td>
</tr>
<tr>
<td>CV/VC</td>
<td>18</td>
<td>14.2</td>
<td>(.02)</td>
</tr>
<tr>
<td>RV%</td>
<td>196</td>
<td>184</td>
<td>(.05)</td>
</tr>
<tr>
<td>FEV₁ Post Br Dil</td>
<td>67.6</td>
<td>71.9</td>
<td>(.02)</td>
</tr>
<tr>
<td>FEF₂₅₋₇₅ (post)</td>
<td>42.5</td>
<td>51</td>
<td>(.002)</td>
</tr>
</tbody>
</table>
Patients on HFA-BDP showed significant improvement in FEF25-75% pre-bronchodilator (P=0.0016) and post bronchodilator (P=0.0014).
There was no significant change in FEF25-75% pre-bronchodilator and post-bronchodilator in the CFC-fluticasone (CFC-FP) group.

Small Airway Patency
Closing Volume/Vital Capacity (CV/VC)
Pre-bronchodilator

Patients on HFA-BDP showed a significant decrease of 3.74% in pre-bronchodilator closing volume/vital capacity (CV/VC ratio (P=0.0214).

The CFC-fluticasone (CFC-FP) group recorded a mean increase of 3.0% (P=0.24).

Small Airway Patency
Closing Volume/Vital Capacity (CV/L)
Pre-bronchodilator

Mean (SE) pre-bronchodilator Closing Volume.

- Patients on HFA-BD trended toward a mean decrease in closing volume.
- Patients on CFC-Fluticasone trended towards an increase in closing volume.

# Results: Diary & Peak Flows

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HFA-BDP</th>
<th>p(B)</th>
<th>CFC-FP</th>
<th>p(BvF)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pre</td>
<td>post</td>
<td>pre</td>
<td>post</td>
</tr>
<tr>
<td>AM-PEF</td>
<td>303</td>
<td>333</td>
<td>(.04)</td>
<td>300</td>
</tr>
<tr>
<td>Phlegm</td>
<td>2</td>
<td>.14</td>
<td>(.05)</td>
<td>0</td>
</tr>
<tr>
<td>Albuterol use</td>
<td>4</td>
<td>.28</td>
<td>(.02)</td>
<td>.4</td>
</tr>
</tbody>
</table>
Conclusions

In patients with moderate to severe persistent asthma who were not adequately controlled on medium to high doses of inhaled corticosteroids.

The addition of HFA-BDP provided greater effects than the addition of a similar dose of CFC-FP on small airway parameters.
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