CLINICAL RELEVANCE OF IN VITRO PARTICLE SIZING DATA

Steve Newman, PhD
Nottingham, UK
November 2006

EFFECT OF PARTICLE SIZE ON AEROSOL DEPOSITION
From Heyder et al 1996

![Graph showing deposition as a function of aerodynamic diameter](image-url)
MEAN (SD) FINE PARTICLE FRACTION (FPF) vs WHOLE LUNG DEPOSITION FROM THREE INHALERS
From Pitcairn et al 2005

CROMOLYN SODIUM DEPOSITION AND CLINICAL RESPONSE IN 8 ASTHMATIC PATIENTS
Mean and SD data from Laube et al 1998

<table>
<thead>
<tr>
<th></th>
<th>Slow Inhalation</th>
<th>Fast Inhalation</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole lung dep. (%)</td>
<td>11.8 (3.5)</td>
<td>8.6 (3.9)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Inner/outer lung ratio</td>
<td>3.1 (2.2)</td>
<td>5.3 (2.3)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Lung distribution skew</td>
<td>2.4 (0.4)</td>
<td>3.0 (0.4)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Fall in FEV₁ (after antigen challenge)</td>
<td>5.4 (4.2)</td>
<td>12.6 (11.0)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
PARTICLE SIZE / DEPOSITION / CLINICAL EFFECTS OF PHARMACEUTICAL AEROSOLS

AERODYNAMIC PARTICLE SIZE DISTRIBUTION → AEROSOL DEPOSITION → CLINICAL EFFECTS
PARTICLE SIZE / DEPOSITION / CLINICAL EFFECTS OF PHARMACEUTICAL AEROSOLS

AERODYNAMIC PARTICLE SIZE DISTRIBUTION

AEROSOL DEPOSITION

CLINICAL EFFECTS

What is the clinical significance of change or variability in APSD from an inhaler device?

What change in APSD is clinically relevant?

Four-fold change in inhaled steroid dose may be needed to detect a difference in response (Barnes et al 1998)

Widespread belief that for a drug with a wide therapeutic window, APSD can vary considerably without a clinically significant change in response

Do published literature studies support this belief?
AERODYNAMIC PARTICLE SIZE vs CLINICAL EFFECT

How does the APSD / clinical effect relationship vary between
- Different drug categories?
- Asthma vs. COPD?
- Different degrees of airflow obstruction?

What is the relevance of APSD data under the Quality by Design paradigm?

Would a better understanding of in vitro / in vivo correlations enable more clinically meaningful APSD specifications to be set?

DATA REVIEW

A review of published data linking APSD to clinical effect of inhaled drugs
- Instigated by IPAC-RS Cascade Impactor Working Group
- Joint review by Steve Newman and Kim Chan (University of Sydney)

Primary data set:
- Studies comparing two or more aerosols of different sizes from the same or similar pMDI or DPI

Secondary data set:
- Comparison of nebulizers with different APSDs
- Other pMDI or DPI data: e.g. CFC vs HFA pMDIs
- Monodisperse pharmaceutical aerosol studies
**PRIMARY DATA SET**

- Few published pMDI or DPI studies have been conducted to examine APSD / response relationship

- Five clinical studies in patients with asthma:
  - Bronchodilators 4; cromolyn sodium 1
  - pMDI 4; Turbuhaler DPI 1

- Single-dose and cumulative-dose designs

- All studies published between 1982 and 1991 in a range of medical and pharmaceutical journals

---

**FEV1 RESPONSE TO CUMULATIVE DOSES OF TERBUTALINE SULPHATE FROM TURBUHALER DPI IN 12 ASTHMATICS**

From Persson and Wiren 1989

**Mean (SD) FEV1 (L)**

- P<0.05

---

**Cumulative terbutaline dose, mg**

- FPD 90 µg
- FPD 40 µg
- FPD 5 µg
MEAN (SD) RESPONSE TO 250 µg TERBUTALINE SULPHATE FROM pMDI IN 10 ASTHMATICS
From Rees et al 1982

Note: Size fractions were those placed in pMDI, not APSD of emitted aerosol

EFFECT OF CHANGES IN pMDI ACTUATOR ORIFICE DIAMETER ON ALBUTEROL BRONCHODILATOR RESPONSE
From Evans et al 1992, available as abstract only

- 200 µg albuterol given to 19 asthmatics via pMDI actuators with orifice diameters 0.23, 0.40, 0.50 and 0.59 mm
- No data provided in abstract
- Qualitative results:
  - FPF differences statistically significant
  - Statistically significant differences in PEFR, but not FEV₁
  - PEFR differences not considered clinically significant
  - Andersen cascade impactor “…offers a guide to clinical response and does not predict it accurately”
PROBLEMS WITH PRIMARY DATA SET

- Only three of five studies were designed to investigate relationship between particle size and clinical effect
- Remaining two studies conducted for marketing purposes to show comparability between innovator and generic products
- Full details of APSD not provided (usually limited to FPD)
- Most studies used doses at or close to the top of the dose-response curve
- Studies used small patient groups (max. 19), and some were probably underpowered
- No inhaled corticosteroid data available

NEBULIZER STUDIES

- Eleven published studies have compared clinical responses to nebulized aerosols of different sizes
  - 8 used bronchodilators (X-over in up to 20 patients)
  - 3 used rhDNase (100+ patients randomized to parallel groups)
- APSD changes engineered by using different nebulizers, varying the compressed gas flow rate used to drive the nebulizer, or both
- Most studies unable to detect statistically significant or clinically significant changes in response
- Two studies showing greater response to smaller aerosols also varied the inhalation manoeuvre
FEV₁ RESPONSE TO CUMULATIVE DOSES OF ALBUTEROL FROM TWO NEBULIZERS IN 8 ASTHMATICS
Data from Johnson et al 1989

% increase in FEV₁

P<0.02

3.3 µm

7.7 µm

cumulative albuterol dose, µg

FEV₁ RESPONSE TO CUMULATIVE DOSES OF IPRATROPIUM BROMIDE FROM TWO NEBULIZERS IN 8 ASTHMATICS
Data from Johnson et al 1989

% increase in FEV₁

NS

3.3 µm

7.7 µm

cumulative ipratropium bromide dose, µg
### Mean (SD) Changes in Pulse Rate After Inhalation of Albuterol or Ipratropium Bromide in 8 Asthmatics

From Johnson et al 1989

<table>
<thead>
<tr>
<th></th>
<th>3.3 µm</th>
<th>7.7 µm</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-albuterol</td>
<td>72.6 (4.8)</td>
<td>70.3 (5.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Post-albuterol</td>
<td>78.1 (4.8)</td>
<td>76.5 (4.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Pre-ipratropium</td>
<td>71.4 (6.2)</td>
<td>72.6 (4.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Post-ipratropium</td>
<td>75.8 (4.8)</td>
<td>77.8 (5.8)</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Nebulizer Characteristics and Spirometric Responses to Inhaled rhDNase in Two Groups of Over 300 CF Patients

Mean and range (or SD) data from Geller et al 1998

<table>
<thead>
<tr>
<th></th>
<th>Neb 1</th>
<th>Neb 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fine particle fraction (%)</td>
<td>83 (82-83)</td>
<td>51 (48-53)</td>
</tr>
<tr>
<td>Output (%)</td>
<td>36 (33-40)</td>
<td>46 (45-48)</td>
</tr>
<tr>
<td>Fine particle output (%)</td>
<td>30 (27-33)</td>
<td>23 (22-25)</td>
</tr>
<tr>
<td>Nebulization time (min)</td>
<td>1.5 (1.3-2.0)</td>
<td>9.1 (8.1-10.3)</td>
</tr>
<tr>
<td>% Δ FEV₁</td>
<td>4.3 (12.8)</td>
<td>2.5 (13.5)</td>
</tr>
<tr>
<td>% Δ FVC</td>
<td>2.6 (8.9)</td>
<td>1.2 (9.4)</td>
</tr>
</tbody>
</table>
PROBLEMS WITH NEBULIZER STUDIES

- The studies involved nebulizers, not “portable” inhalers (pMDIs and DPIs)
- Most studies were carried out to answer a practical question: what is the clinical response when different nebulizers are operated in different ways?
- Most studies provide very limited APSD data
- Difficult to assess APSD / response relationship because of confounding variables
  - Differences in nebulizer type, compressor, volume fill, nebulization time, drug concentration, inhalation manoeuvre
- Doses often high enough to reach the top of the dose-response curve
- Most of the studies were probably underpowered

RESPONSE TO INHALED BECLOMETHASONE DIPROPIONATE IN 323 ASTHMATIC PATIENTS
Mean and SE data from Busse et al 1999

% increase in FEV1 after 6 weeks

Qvar: MMAD 1.1 µm
CFC pMDI: MMAD 3.5 µm

Qvar 2.6 times more potent than CFC pMDI
PLUME CHARACTERISTICS OF pMDI SPRAYS
From Gabrio et al 1999

Maximum impact force (mN)

Minimum plume temperature (deg C)

PROBLEMS WITH CFC vs HFA pMDI COMPARISONS

- Difference in APSD may not be the only difference between the sprays
  - Other spray characteristics (e.g. impact force and spray temperature) may change as well

- Meta-analysis of > 50 studies comparing CFC pMDIs vs other inhalers (Hughes et al 1999)
  - Most studies underpowered and used inappropriately high drug doses
**MEAN BRONCHODILATOR RESPONSE TO MONODISPERSE ALBUTEROL AEROSOLS**

**FEV1 increase (%)**  
Zanen et al 1994

**FEV1 increase (mL)**  
Usmani et al 2005

---

**Zanen et al:** same effect in mild and severe asthmatics, and for albuterol, ipratropium bromide and combinations

---

**PROBLEMS WITH MONODISPERSE AEROSOL STUDIES**

- Results of similar studies from two major laboratories disagree about the nature of the relationship between particle size and clinical response to inhaled bronchodilators

- Difficult to extrapolate results of studies with stable monodisperse aerosols of a fixed size to heterodisperse and unstable aerosols emitted from inhaler devices
SOURCES OF VARIABILITY IN CLINICAL RESPONSE

APSD
(INHALER / IMPACTOR)

SOURCES OF VARIABILITY IN CLINICAL RESPONSE

APSD

PATIENT IN CLINICAL TRIALS
CONCLUSIONS - 1

- A range of published studies relate the APSD of pharmaceutical aerosols to therapeutic response – most data are at least 15 years old
- In the context of assessing the APSD / response link, most published studies suffer from design problems and often present very limited APSD data
- Most published studies were not conducted with the primary objective of examining the APSD / response relationship
CONCLUSIONS - 2

- Studies confirm that APSD influences therapeutic response to inhaled drugs
- Some evidence that the relationship between APSD and clinical effect may vary from product to product
- Even for well-established drugs, the change in APSD required for a clinically significant change in response cannot be deduced from public-domain information

CONCLUSIONS - 3

- Andersen cascade impactor “…offers a guide to clinical response and does not predict it accurately”
- Variability in clinical response depends partly on the inhaler and on the APSD, but much more upon the patient who uses the inhaler
- Trying to establish truly meaningful in vitro / in vivo correlations is challenging
ACKNOWLEDGEMENTS

- Review of data undertaken jointly with Kim Chan (University of Sydney)

- Thanks to members of the IPAC-RS Cascade Impactor Working Group for their help and support