Pulmonary deposition of inhaled drugs

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Presenter Disclosures

**F.L.** has received in the last 5 years fees for lectures, advisory boards and reimbursements for attending meetings from the following pharma companies:

- AstraZeneca,
- Boehringer Ingelheim,
- CIPLA,
- Chiesi,
- Mundipharma,
- TEVA.

The content of this talk represents the personal opinion of the presenter and does not necessarily represent the views or policy of the A.O.U. Careggi.
The efficacy by which inhaled drug particles reach the target site in the lung is determined by:

- **Penetration** of the particles into the airways
- **Deposition** of the particles on the wall of the airways

"Deposition is the process by which an aerosol particle leaves the airstream and is retained on the epithelium”

Bisgaard H, O'Callaghan C, Smaldone GC. Drug delivery to the Lungs, 2002
Factors Influencing the Lung Deposition of Medical Aerosols

**Aerosol Characteristics**
- Particle size
- Particle density
- Particle charge
- Aerosol plume speed & duration
- Lipophilicity
- Hygroscopicity

**Patient Factors**
- Inhalation technique
  - Inspired volume
  - Inspiratory flow
  - Breath hold pause
- Airway disease & severity
- Device acceptance
- Compliance

*Labiris & Dolovich, Br J Clin Pharm 2003*
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*Labiris & Dolovich, Br J Clin Pharm 2003*
1: PARTICLE SIZE

But before we get started...

......

Some terms used to describe an aerosol
Aerosol particles can be considered small spheres with a *diameter* and a *density*.

**Mass Median Aerodynamic Diameter (MMAD)** is defined as the diameter at which 50% of the particles are larger and 50% are smaller.

**Geometric Standard Deviation (GSD)** is a measure of the spread of an aerodynamic particle size distribution.
**Monodisperse aerosol:** particles with the same size (GSD<1.2). Example: laboratory generated aerosols

**Polydisperse aerosol:** particles include a wide-range of sizes (GSD >1.2). Example: therapeutic medications range from 2-3

**Fine Particle Fraction (FPF):** The proportion of particles within the aerosol with MMAD <5 µm, or *fine particle dose* if expressed in absolute mass of drug in particle with MMAD<5 µm.
MMAD, GSD, FPF are the most frequently used terms to describe an aerosol.

A series of 8 stages reflecting the progressive decreasing in size of the airways.
What do we mean by dose?

- Inhaled dose
- Labeled Dose
- Emitted Dose
- Fine Particle Dose
Deposition: main mechanisms

- **Inertial transport (impaction):** large particles (6-10 μm); high flow velocity; mainly in the upper and large airways.

- **Gravitational transport (sedimentation):** small particles (0.5-6 μm); low flow velocity; time-dependent transport mechanism; mainly in the lung periphery lower generations where the velocity is low and airway is small.

- **Diffusional transport (diffusion):** very small particles (< 0.5 μm); low flow velocity; time-dependent transport mechanism; mainly in the alveoli due to long residence time.
Sedimentation takes time

✓ Sedimentation (under influence of the force of gravity) takes time and the stationary settling velocity decreases with the square of the diameter.

✓ The time necessary to fall a distance of 0.5 mm for a particle of:
  - 1 µm is 16.5 s
  - 2 µm is 4.2 s
  - 4 µm is 1.0 s
Relationship between the impaction parameter and the oropharyngeal deposition

Oropharyngeal deposition becomes higher when the flow rate is increased and the effect is greater for larger particles.

Inertial impaction in the larger airways depends on particle diameter ($D$) and particle flow rate ($\Phi$),

Sedimentation in the smaller airways depends on particle diameter ($D$) and particle residence time
Where do most inhaled aerosols deposit in the healthy human adult male respiratory tract?

«Respirable range»

Chrstyn, Allergy 1999
Reduce impaction by delivering particles with small MMADs

Patient with cystic fibrosis after inhalation of 7- and 3-μm radiolabelled carbenicillin aerosols

Gamma camera images of $^{99m}\text{Tc}$-labelled salbutamol monodisperse aerosols in one asthma patient.

Smaller Particles = Good Lung & Peripheral Deposition; Low Oropharyngeal Deposition
Small Particles = **High Total Lung Deposition**

- Central (C) + Intermediate (I) Zone
- Peripheral Zone (P)

**Small Particles = Better Peripheral Deposition**

- 1.5µm
- 3µm
- 6µm

Usmani, AJRCCM 2005
Small Particles = Low Oropharyngeal Deposition

O = Oropharyngeal

* p<0.05

Usmani, AJRCCM 2005
Small Particles = Exhaled less vs. *in vitro* data

% Deposition

<table>
<thead>
<tr>
<th>Deposition</th>
<th>0</th>
<th>20</th>
<th>40</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>L – Total Lung Deposition</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>O – Oropharyngeal</td>
<td>0</td>
<td>*</td>
<td>+</td>
<td>*</td>
</tr>
<tr>
<td>E – Exhaled</td>
<td>0</td>
<td>*</td>
<td>+</td>
<td>*</td>
</tr>
</tbody>
</table>

1.5µm

3µm

6µm

* *

* p<0.01
+ p<0.05

Usmani, AJRCCM 2005
2. Aerosol plume speed & duration
Respimat: aerosol characteristics


Respimat may reduce the need of hand-breath coordination!
**Particle size distribution for Respimat**

<table>
<thead>
<tr>
<th>Fine particle range (µm)</th>
<th>Proportion of emitted dose (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.4</td>
<td></td>
</tr>
<tr>
<td>0.4–&lt;0.7</td>
<td></td>
</tr>
<tr>
<td>0.7–&lt;1.1</td>
<td></td>
</tr>
<tr>
<td>1.1–&lt;2.1</td>
<td></td>
</tr>
<tr>
<td>2.1–&lt;3.3</td>
<td></td>
</tr>
<tr>
<td>3.3–&lt;4.7</td>
<td></td>
</tr>
<tr>
<td>4.7–&lt;5.8</td>
<td></td>
</tr>
<tr>
<td>5.8–&lt;9.0</td>
<td></td>
</tr>
<tr>
<td>9.0–&lt;10.0</td>
<td></td>
</tr>
<tr>
<td>&gt;10.0</td>
<td></td>
</tr>
</tbody>
</table>

\(~ 45\% in the range 0.7-3.3\)

Andersen cascade impactor data

Zierenberg B. J Aerosol Med 1999
Lung Deposition of Fenoterol and Flunisolide Delivered Using a Novel Device for Inhaled Medicines

Comparison of RESPIMAT With Conventional Metered-Dose Inhalers With and Without Spacer Devices

Stephen P. Newman, PhD; Joanne Brown, BSc; Karen P. Steed, MPhil; Sandra J. Reader, PhD; Heinrich Kladders, PhD

![Graph showing lung deposition comparison between Respimat and pMDI + spacer](image)

*CHEST 1998; 113:957-63*
Drug delivery to the lungs with Respimat is more efficient than with HFA-pMDI, even in patients with poor inhaler technique.
3. Airway disease & severity
Total deposition of particles is increased in patients with obstructive airway disease, and correlates with FEV₁.
Regional deposition patterns is affected by airway obstruction with a shift of particles deposition from lung periphery towards proximal airways.
Particles deposition is less uniform with enhanced focal distribution («hot spots») of deposited particles with increasing dose of metahcoline (MCh).
Small Particles (MMAD 1.5μm) Achieve Consistent Lung Deposition in Varying Airflow Obstruction

De Backer, JAMPDD 2010

Scintigraphic images show consistency in lung deposition in different disease groups
4: BREATHING PATTERN & INHALATION MANOEUVRÉ
Breathing pattern hardly affects the shape of the deposition curve, but it can shift the curve up and down affecting deposition values across the entire range of particle size.
Total respiratory tract deposition of fine micrometer-sized particles in healthy adults: empirical equations for sex and breathing pattern
Chong S. Kim¹ and Shu-Chieh Hu²

*J Appl Physiol* 101: 401–412, 2006;

Particles 3 and 5 μm: total deposition increases by rising VT;

Particles 1 μm: total deposition unaffected by VT increases;

Particles 1-5 μm: total deposition increases by rising both VT and f;
Deposition shifts to larger airways when the flow rate is increased

Inhaled volume: 0.7 L; simulation for 5 μm particles
Breathing maneuvers affect deposition within the lung compartment

- Inspiration: 12 L/min
- Particle MMAD = 1.5\(\mu\)m

- Inspiration: 60 L/min
- Particle MMAD = 1.5\(\mu\)m

Slow inspiratory flow rates increase lung deposition for pMDI and nebulized aerosols

Laube BL. J Aerosol Med 1996; 9 Supplement: S-77-S-91
What the pulmonary specialist should know about the new inhalation therapies

ERS/ISAM TASK FORCE REPORT Eur Respir J 2011; 37: 1308–1331

Crucial differences between device types

**MDI**
- Shaking (+/-)
- Actuation
- Coordinated with inspiration, except
  - BAI
  - MDI + Spacer
- Slow inhalation

**DPI**
- Device preparation
- No actuation, i.e. no need to coordinate
- No manipulation during inhalation
- Fast inhalation from the beginning
Lung deposition of small-particle aerosol under coordinated and dis-coordinated conditions

N=7 asthmatics, FEV₁ 91% pred.

Deposition (% emitted dose)

- Lung
- Oropharynx

Leach et al J Aerosol Med 2005
Small Particles = **Less Affected by Inhalation Flow**

**FAST**: >60 litres/min

**SLOW**: 30-60 litres/min

- **1.5µm**
- **3µm**
- **6µm**

30µg dose

% Total Lung Deposition (TLD)

* p<0.05

**SLOW** Inhalation is better

Usmani, AJRCCM 2005
Inhalation flow rate can affect clinical outcomes

- Patients with stable, mild-to-moderate asthma (n=12)
- Monodispersed salbutamol aerosols of three different diameters

![Graph showing ΔFEV1 (mL) for different aerosol diameters with p values](Usmani et al. Am J Respir Crit Care Med 2005; 172:1497–504)
Crucial differences between device types

**MDI**
- Shaking (+/-)
- Actuation
- **Coordinated** with inspiration, except
  - BAI
  - MDI + Spacer
- **Slow** inhalation

**DPI**
- Device preparation
- No actuation, i.e. no need to coordinate
- No manipulation during inhalation
- **Fast** inhalation from the beginning
Powder formulations are always agglomerated (particles 1–5 μm)

Adhesive mixtures

Soft (spherical) agglomerates/pellets

Each inhalation should be as fast as you can from the start and for as long as possible.
DPI OPERATING PRINCIPLE

Inspiratory Force → Flow & Pressure → De-aggregation → Fine Particle Mass

Airflow Generated By Patient’s Inspiratory Effort

Turbulent Energy: $\sqrt{P} = Q \times R$

Q = Inhalation Flow
R = Inhaler resistance

“..for an inhaler with a low resistance you need a very high inhalation flow whereas for a higher resistance you need a low inhalation flow…”

Chrystyn et al. Am J Respir Crit Care Med 2001
Inhaler resistance and the corresponding flow to achieve 4 kPa pressure drop
"..with a low resistance inhaler you need a higher inhalation flow than with a high resistance inhaler."

Modified from Al-Showair et al Respir Med 2007; P. Krüger et al ERS meeting 2014
DPI Lung Dose Alters with Inhalation Flow

In vitro data do not necessarily correlate with clinical effectiveness.
Mean delivered ICS fine particle fraction (FPF) as function of kPa (*in vitro*)

<table>
<thead>
<tr>
<th>DPI</th>
<th>Resistant</th>
<th>Flow rate (4 kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(kPa⁰.⁵.min.L⁻¹)</td>
<td>(L/min)</td>
</tr>
<tr>
<td>Turbuhaler</td>
<td>0.0340</td>
<td>58.8</td>
</tr>
<tr>
<td>NEXThaler</td>
<td>0.0339</td>
<td>59.0</td>
</tr>
<tr>
<td>Ellipta*</td>
<td>0.0286</td>
<td>72.5</td>
</tr>
<tr>
<td>Diskus</td>
<td>0.0293</td>
<td>73.3</td>
</tr>
<tr>
<td>Elpenhaler</td>
<td>0.0273</td>
<td>68.3</td>
</tr>
</tbody>
</table>

# data from 1;* data from 2

In vitro data do not necessarily correlate with clinical effectiveness.

Similar results for β₂-agonist

Adapted from:
2. Grant A et al. *JAMPDD* 2015.
Let’s classify DPIs

Inhalation flow dependent
High - intermediate resistance
- Turbuhaler®
- Diskus®

Inhalation flow dependent
Low resistance
- Pulvinal®
- Jethaler®
- Easyhaler®

Inhalation flow independent
High-intermediate resistance
- Novolizer®
- Cyclohaler®
- Aerolizer®

Inhalation flow independent
Low resistance
- Handihaler®
- Diskhaler®
- Aerohaler®
- Clickhaler®
- Spinhaler®
- Gyrohaler®

Pictures from ADMIT homepage
With Diskus the central and peripheral deposition decreases when the flow is increased.

With Novolizer the central and peripheral deposition remains fairly constant at all flow rates.
NEXThaler, an innovative dry powder inhaler delivering an extrafine fixed combination of beclometasone and formoterol to treat large and small airways in asthma

Massimo Corradi†, Henry Chrystyn, Borja G Cosio, Michal Pirozynski, Stelios Loukides, Renaud Louis, Monica Spinola & Omar S Usmani
†University of Parma, Department of Clinical and Experimental Medicine, Parma, Italy
SUMMARY

- The advantages of pulmonary delivery of aerosolized therapeutic drugs have resulted in many classes of drugs and inhalers now available for this route of delivery.

- However, there are many challenges to optimizing delivery of aerosolized drugs by the pulmonary route.

- Be aware of the effect of particle size on pulmonary aerosol deposition.

- Understand the need for specific inhalation maneuvers to optimize pulmonary delivery of therapeutic medications with available devices.
THANKS FOR YOUR KIND ATTENTION

Questions?

That’s a great question!!
Come to think of it, I’m not sure what it is I was trying to tell you
Total respiratory tract deposition of fine micrometer-sized particles in healthy adults: empirical equations for sex and breathing pattern

Chong S. Kim¹ and Shu-Chieh Hu²  J Appl Physiol 101: 401–412, 2006;
Total respiratory tract deposition of fine micrometer-sized particles in healthy adults: empirical equations for sex and breathing pattern

Chong S. Kim\textsuperscript{1} and Shu-Chieh Hu\textsuperscript{2} \hspace{1em} J Appl Physiol 101: 401–412, 2006;
Regional deposition patterns is altered with increasing severity of airway obstruction

Laube BL et al  *Respiratory Care* 2005