The fate of inhaled drugs

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Why Used Inhaled Therapy?

Drug is delivered directly to site of action

Spahan JD, Szefler SJ  Pediatric Respiratory Medicine 2008
Oral vs Inhaled therapy

Fundamental differences

- Lungs have evolved to exclude foreign material

- Even if you take the medication you may not derive any benefit

*Compliance x 2*

regimen compliance

device compliance

[competence + contrivance]
Inhaled Therapy for Pulmonary Disease

Speed of Onset

Therapeutic Index

Large luminal dose

Poorly absorbed drugs

Inhaled Therapy for Systemic Therapy

Very Large surface area
Inhaled Therapy

Device / Formulation

Drug

Therapeutic effect

[Diagram showing various devices and formulations related to inhaled therapy]
Inhaled Therapy - ISAM

Drug

Device
Anatomy
Physiology

Disease
Fate of drug

Inter-subject variation

Adverse Effects

Formulation issues
Availability
Cost
Target

Inter-subject variation
Age dependent

Generalised
Variable
Progressive
Sources of Variability in Lung Dose

Therapeutic effect

Drug

Device

Formulation issues

Availability

Cost

Target

Inter-subject variation

Age dependent

How controlled?

Adverse Effects

Compliance

Competence

Contrivance

Variable
Basic Principles

Lungs have evolved to exclude foreign material

Defences
Airways anatomy
Cough
Mucociliary clearance

Deposition
Impaction
Sedimentation
Brownian motion
Energy Is Required for Aerosolisation

Jet nebuliser  compressed air

pMDI  CFC / HFA

Dry powder  patient
## Lung Dose Variability - Healthy Adults

<table>
<thead>
<tr>
<th>Device</th>
<th>Intra-subject CV%</th>
<th>Urinary Salbutamol (μg)</th>
<th>‘Most efficient’</th>
</tr>
</thead>
<tbody>
<tr>
<td>pMDI</td>
<td>50.1 % [27-146.8]</td>
<td>5.4 [0.69-17.6]</td>
<td></td>
</tr>
<tr>
<td>pMDI+HC</td>
<td>31.7 % [20.1-87]</td>
<td>11.6 [2.2-35.9]</td>
<td>7</td>
</tr>
<tr>
<td>Breath Actuated</td>
<td>33.4 % [10.5-61.9]</td>
<td>8.8 [2.2-13.2]</td>
<td>2</td>
</tr>
<tr>
<td>Accuhaler/Discus</td>
<td>39.6 % [12.4-75.2]</td>
<td>9.6 [4.1-14.7]</td>
<td>3</td>
</tr>
<tr>
<td>Turbohaler</td>
<td>42.4 % [21.0-73.8]</td>
<td>7.5 [2.6-17.6]</td>
<td>1</td>
</tr>
</tbody>
</table>

*Everard et al. J Aerosols Med*
450 Mill. Alveoli
Surface Area of 150 m²
Diameter ¥¼ mm
Gasex-change Area 80-90%
‘Bacterial Chest Infections’
Drug Delivery is Non-Uniform
Distribution of Aerosol Deposition

John Fleming, Southampton

Martonen 2003
Does Breathing Pattern Matter?
Impact of Disease - Asthma
Fate of Deposited Particles

- Luminal Mucus Layer (rapidly cleared)
- Adherent Mucus Layer (slowly cleared)

Epithelia

Images A, B, and C show various structures and processes related to the fate of deposited particles.
Mucociliary Clearance & Absorption
Becker RHA 2006

Borgstrom 1992
Poor control vs Exacerbation

Reddel H Lancet 1999
Biofilms

I
II
III
IV
V

substratum

I: monolayer
II: 12 μm max. thickness
III: 30 μm max. thickness
IV: 80 μm max. thickness
V: 80 μm max. thickness
Bacterial Bronchitis
inc CF, bronchiectasis, COPD
COPD and Insulin
Inhaled Therapy

Drug

Device

Anatomy

Physiology

Disease

Fate of drug

Formulation issues
Availability
Cost
Target

Inter-subject variation
Age dependent

Generalised
Variable
Progressive

Adverse Effects

Therapeutic effect
We are taking on the forces of evolution, pathogens and disease [& regulators!]

Aerosol are best used in healthy individuals

Intervene early while you can effectively

Asthma is relatively easy