Combining imaging techniques and CFD to model lung deposition in various age classes of the paediatric population

Deborah Bickmann

Lung Imaging in Inhaled Product Development
Contents:

- **Motivation:**
  Why modelling the paediatric dose to lung via *in-vitro* and *in-silico* methods?

- Experiences with adult models

- Exploring the paediatric anatomy and physiology

- Why to use paediatric models at an early stage of product development?

- Challenges in the lab

- Summary & Outlook
The individual dose to lung is the result of a complex interaction between patient, inhalation device and formulation!

**Patient**
- Age
- Anatomy & Morphology
- Handling

**Device**
- Air flow resistance
- Spray velocity, Nozzle / Mouthpiece geometry

**Formulation**
- MMAD, PSD, FPD
- Dispersing mechanism
- Manufacturing process

**Excipients**
- Physico-chemical properties

**Inhalation technique**
- Handling

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A big challenge for inhaled medications: The 90° bend of human mouth-throat

Scintigraphic pictures of particle deposition of 99MTc-labelled Tiotropium (T Meyer et al. / 2003)
Children use (in most cases) inhalation devices initially developed for adults!
Role for lung imaging (pre-clinical species or human tissue):
I. Understanding disease progression
II. Biomarker identification

Role for lung imaging (pre-clinical species):
I. Deposition in animals
II. Monitoring disease progression
III. Monitoring drug efficacy
IV. Biomarker identification

But: Scintigraphic deposition studies in children are in most countries seen as not appropriate!

Role for lung imaging (clinical studies):
I. Deposition in man
II. Monitoring disease progression
III. Monitoring drug efficacy
IV. Biomarker validation and monitoring
Ethical dilemma:

Efficient, safe and well-studied medications meeting the special needs of children!

Avoiding any risks during tests with children & minimizing the number of necessary clinical trials!

Performing realistic in vitro tests already at an early stage of development via artificial casts of children’s upper airway geometry and simulating their specific inhalation profile!

=> Tools: Clinical handling studies & MRI/CT scans of children
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First step: Can adult upper airway models really mimic the *in-vivo* conditions?

- Mouth-throat model + Respimat
- to pressurized air (+humidifier)
- to electronic lung
- to flow pump
- NGI
- Conditioning cabinet
Comparison to published scintigraphic in-vivo data revealed good agreement to our *in-vitro* results!

<table>
<thead>
<tr>
<th>Device</th>
<th>Lung dose for patients with very severe COPD</th>
<th>In-vitro data</th>
<th>Clinical data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spiriva HandiHaler:</td>
<td></td>
<td>15.05%</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Throat: 34.36%)</td>
<td>(Throat: 29%)</td>
</tr>
<tr>
<td>Respimat:</td>
<td></td>
<td>65.26%</td>
<td>53%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Throat: 34.81%)</td>
<td>(Throat 45%)</td>
</tr>
<tr>
<td>pMDI:</td>
<td></td>
<td>24.2%</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Throat: 56.62%)</td>
<td>(Throat 56%)</td>
</tr>
</tbody>
</table>

*Brand et al. (2007)*
Good agreement between *in-vitro* and *in-silico* data using an adult upper airway model.

CFD-Code: Fluent 6.3

Turbulence model: k-ω SST
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EU – Pediatric Regulation 1901/2006:

Regulation came into force on 26 January, 2007

• Pediatric Committee of the EMA (PDCO) established July 2007
  ➔ for the approval of new pharmaceuticals (or new indications / dosage forms) clinical studies for children have to be conducted (deferrals / waivers possible)!

Rewarding:
• 6 months SPC extension, PUMA
  (orphan drug: 2 years additional market exclusivity – 10 + 2)
Deposition data from adults cannot be extrapolated to children, because children have different...

### Anatomy
- different upper airway geometry (not only smaller)
- large ratio of tongue to oral cavity
- the respiratory zones (terminal bronchioles, alveoles) are growing till the age of eight years in number, later in size
- glottis and subglottis aren’t fully developed at birth

### Behaviour
- < 3 yrs are often unable to adopt a prescribed breathing pattern
- motor skills are impaired
- a lot of children become upset and distressed
  => a short application time is recommended!

**Breathing pattern**
- lower inspiratory flow and volume
- shorter inhalation time
- < 2 yrs preferred nose breathing
- high breathing frequency
- depending on kind of disease, mood (relaxed/quiet vs anxious/stressed), body size and device used

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Subglottis of a 2-month (left side) and a 10-month old child (right side).
Workflow:

Patient geometry data → idealized model → CAD → STL-output

DICOM medical data

Segmentation → simplification, approximation, im-/export

Pharmaceutical ingredient

Inhalation flow profiles

Inhaler

Inhalation flow profiles → rapid prototyping / CNC manufact. / Laboratory bench testing → Mesh generation / Computational Fluid Dynamics (CFD)
Analyzing 78 MRI and CT scans of children aged 3 days to five years reveals a high anatomical diversity!

And clinical handling studies of inhalation profiles do also!
Analyzing 78 MRI and CT scans of children aged 3 days to five years reveal a high anatomical diversity!
Realistic models of children’s extrathoracic airways for in vitro inhaler testing.

V = 0.0398 L
V = 0.0245 L
V = 0.0148 L
V = 0.0112 L

for comparison: adult model V = 0.079 L

Age 4-5 yrs
Age 3-4 yrs
Age 2-3 yrs
Age 1-2 yrs

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In the wonderland of spacer devices – which one to choose?
Different types of spacers / valved holding chambers lead to different throat deposition and dose to lung.

Results using throat model and flow profiles
a) single breath Respimat and
b) 5 breaths with spacers of a 5 year-old child.

Can Pediatric Throat Models and Air Flow Profiles Improve Our Dose Finding Strategy?
Herbert Wachtel, Deborah Bickmann, Jorg Breitkreutz, Peter Langguth
Deposition results using our realistic child’s model (age 2-3 yrs) show good correlation with in vivo data!

Link to scintigraphic deposition data of Wildhaber et al. (1999) in six 2 year-old children using the same pressurized Metered Dose Inhaler (albuterol) and valved holding chamber (AeroChamberPlus with facemask).
Computational Fluid Dynamics (CFD) studies provide an impressive insight on the different flow fields.

- The child’s model shows:
  - higher particle velocities (narrow laryngeal region & trachea)
  - more vortices (jolted pharyngeal region)

resulting in a higher amount of particle deposition!

Inhalation flow rate:
20 L/min

CFD-Code:
Fluent 6.3
k – \( \omega \) SST turbulence model
Good agreement between \textit{in-vitro} and \textit{in-silico} results using the paediatric anatomical model.

![Graph showing particle throat deposition related to the delivered dose for Child (5yrs)](image)

- **Experiment**
- **Simulation**

- **CFD-Code**: Fluent 6.3
- **Turbulence model**: k-\(\omega\) SST

Experimental data with constant flow rates as well as CFD simulations were conducted using the Respimat Soft Mist Inhaler.
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The analytical challenge – where is the drug in these numerous parts?
Further issues:

• Finding appropriate CT / MRI scans of children, especially infants

• Harmonized paediatric upper airway models for better comparison reasons?

=> Under discussion in the ISAM paediatric networking group (which age classes, extension to the first bifurcations of the lung?)

• Improved turbulence models for better resolution of the complex flow in the human upper airways

• Standardized inhalation profiles?
In vitro and in silico modelling of inhaler performance in children via paediatric throat models based on CT and MRI scans help:

• to understand the special needs of infants, toddlers and pre-school children for a successful pulmonary treatment.

• to design appropriate inhalation devices for children’s special anatomy/physiology & enhanced compliance.

• to support dose finding strategies for inhaled medications while preventing children being exposed to investigational medicinal products (plus saving time & costs).
Acknowledgement

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