Use of Target Tissue Concentrations in PK-PD Modeling of Inhaled Drugs

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IQ DMPK Leadership Group  31 May 2017
What’s On?

- Lung as target organ
- Benefit of inhalation: core business of RIA IMed Göteborg
- Asthma treatment: Bronchodilators and Glucocorticoids (GCs)
- PBPK modeling of pulmonary delivered drugs
- Linking regional exposures to receptor occupancy for GCs
- Bronchodilators translational lung PKPD

Ulrika Tehler (Introduction), Elin Boger (PBPK) & Douglas Ferguson (Bronchodilator Modeling)
The Lungs

Heterogeneous organ

Thoracic region
Generation 0-8
Surface area: 290 cm²

Bronchiolar region
Generation 9-15
Surface area: 2400 cm²

Peripheral region
Generation 16-24
Surface area: ~100 m²

Large absorptive surface with small aqueous volume and highly permeable membrane in the peripheral region

Local treatment of respiratory diseases such as COPD and Asthma minimizes systemic side-effects, improves dose-potency and enables fast onset of action.

Pulmonary delivery offers a route to rapid systemic absorption, e.g. general anesthetics and analgesics.
Rationale for Inhaled Drug Delivery

Employ the inhaled route of delivery to develop efficacious and safe treatments of respiratory diseases.
Inhaled vs Oral Dosing

Distinctive features related to local treatment

- **Oral Dosing**
  - Dose
  - Clearance
  - Other tissues
  - Effect + Adverse effect

- **Inhaled Dosing**
  - Delivered Dose
  - Effect and local adverse effect
  - Other tissues
  - Systemic circulation
  - Adverse effect
  - Clearance

- An *ideal inhaled medicine*: (1) delivers the drug to lung with low variability; (2) retains the drug at target to obtain desirable duration; (3) shows rapid clearance from system and; (4) no oral bioavailability
Inhaled Drug Delivery:
*Lung selective drug exposure?*

Typical data from inhalation studies in drug discovery

Split between $C_{\text{lung}}$ and $C_{\text{p}}$

- Solid drug, non-specific tissue binding…
  → Interpretation is difficult

$C_{\text{lung}}$ – Total lung concentration of drug

$C_{\text{p}}$ – Total plasma concentration of drug
Inhaled Drug Delivery: Receptor occupancy - a biomarker for lung-selectivity

Receptor occupancy is driven by the free drug concentration at the target site

\[ RO_{\text{lung}} \] – Receptor occupancy in the lung
\[ RO_{\text{systemic}} \] – Receptor occupancy in a reference organ for systemic exposure
Inhaled Drug Delivery:
Receptor occupancy - a biomarker for lung-selectivity

Receptor occupancy is driven by the free drug concentration at the target site

\( \text{Concentration after inhalation} \)

\( \text{Receptor occupancy after inhalation} \)

\( RO_{\text{lung}} \) – Receptor occupancy in the lung

\( RO_{\text{systemic}} \) – Receptor occupancy in a reference organ for systemic exposure
# Lung Targeting Case Studies: Glucocorticoid vs Bronchodilator Drugs

**Pharmacology, potency and physical chemical props:**

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<tr>
<th>Anti-inflammatory</th>
<th>Drugs</th>
<th>Functional Potency (nM)</th>
<th>Solubility (µM)</th>
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<td>Fluticasone Propionate</td>
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<td>0.4</td>
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<td>Formoterol</td>
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<td>600</td>
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**Anti-inflammatory**

- **Glucocorticoids** bind cytosolic glucocorticoid receptor

**Bronchodilating**

- β₂-agonists bind membrane bound β₂ adrenoreceptor

**LOW SOLUBLES**

- Budesonide
- Fluticasone Propionate
- Fluticasone Furoate

**HIGH SOLUBLES**

- Salbutamol
- Formoterol
- Salmeterol
Lung retention drivers: tissue binding, lysosomal trapping vs slow dissolution

Pharmokinetic lung profiles after pulmonary delivery

**Bronchodilators**
- Basic and highly soluble
- $\text{LogD}_{74} < -1.5$ for Salbutamol & Terbutaline
- $\text{LogD}_{74} > 2.5$ for Indacaterol & MABA’s

**Glucocorticoids**
- Neutral and low soluble, slow dissolving
- Solubility $< 1 \mu\text{M}$ for MF, FP & FF
- Solubility $> 40 \mu\text{M}$ for Bud

**Beta agonist: single basic MABA’s: dibasic**

![Graph showing lung retention profiles for bronchodilators and glucocorticoids over time.](https://via.placeholder.com/150)
Lung retention drivers: tissue binding, lysosomal trapping vs slow dissolution

Pharmokinetic lung profiles after pulmonary delivery

**Bronchodilators**
Basic and highly soluble

- LogD$_{74}$ < -1.5 Salbutamol & Terbutaline
- LogD$_{74}$ > 2.5 Indacaterol & MABA's

**Glucocorticoids**
Neutral and low soluble, slow dissolving

- Solubility < 1 µM MF, FP & FF
- Solubility > 40 µM Bud

Beta agonist: single basic
MABA's: dibasic

*Graph showing lung retention profiles for different drugs.*
Pulmonary Drug Disposition of Low Solubles


Models describing:
Regional drug deposition
Drug dissolution
Mucociliary clearance (MCC)
Flux to/from the systemic circulation
Receptor binding

Several simultaneous processes
Parallel absorption (lung, gut and nose)

Figure from: Bäckman et al., Clin Pharmacol Ther., vol. 95(5), pp. 509-520, June 2014
Linking PK – Target Occupancy via PBPK model

PBPK model includes e.g.
- Drug deposition in nose, peripheral lung and central lung
- Receptor binding in all tissue compartments
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Models describing:
- Regional drug deposition
- Drug dissolution
- Mucociliary clearance
- Flux to/from the systemic circulation
- Receptor binding

PBPK model – physiologically-based pharmacokinetic model
PBPK Predictions Inhaled Fluticasone Propionate

Predicting lung & systemic total concentrations after inhaled

Lung deposited dose: 11.3 nmol/kg; $C_{\text{lung}} =$ total lung concentration of drug; $C_{\text{spleen}} =$ total spleen concentration of drug; $C_p =$ total plasma concentration of drug
PBPK Predictions Inhaled Fluticasone Propionate

Predicted and measured receptor occupancy (RO)

Models simulations indicate that lung-selectivity cannot be obtained in the peripheral lung (perfused by entire cardiac output)

$$RO_{\text{spleen}} = RO_{\text{peripheral}}$$
PBPK Predictions Inhaled Fluticasone Propionate Propionate
Targeting central lung over peripheral/system

Simulated occupancy:
---Whole lung occupancy

Lung occupancy measurements
-Reflect whole lung occupancy, not (yet) possible to experimentally distinguish between central and peripheral lung occupancy

\( RO_c = \text{receptor occupancy central lung} \)
PBPK Simulations Receptor Occupancy

Lung selectivity / targeting how can it be obtained?

What properties are beneficial for inhaled drugs?

Lung-selectivity is defined as $RO_{lung} > RO_{systemic}$
PBPK Simulations Receptor Occupancy

*Lung selectivity / targeting how can it be obtained?*

*What properties are beneficial for inhaled drugs?*

Lung-selectivity unattainable in well-perfused regions (peripheral lung)

Lung-selectivity is defined as \( RO_{\text{lung}} > RO_{\text{systemic}} \)
PBPK Simulations Receptor Occupancy

*Lung selectivity / targeting how can it be obtained?*

What properties are beneficial for inhaled drugs?

Lung-selectivity unattainable in well-perfused regions (peripheral lung)

The occupancy in the central lung \((RO_{lung,C})\) used for evaluation of lung-selectivity.

Lung-selectivity is defined as

\[
RO_{lung,C} > RO_{systemic}
\]
PBPK Simulations Receptor Occupancy

Does solubility (dissolution) affect lung-selectivity?

Impact of solubility on lung-selectivity

Lung-selectivity achieved during dissolution phase
PBPK Simulations Receptor Occupancy

*Does solubility (dissolution) affect lung-selectivity?*

**Impact of solubility on lung-selectivity**

- **High solubility** (50 µM)
- **Low solubility** (2.5 µM)

**Lung-selectivity achieved during dissolution phase**
PBPK Simulations Receptor Occupancy

Does dissociation rate ($K_{off}$) affect lung-selectivity?

A transient concentration gradient created during dissolution of a highly soluble compound can give rise to a prolonged lung-selectivity given a slow $K_{off}$. 

Fast off-rate ($t_{1/2,Koff} = 0.3$ h)

--- $RO_{lung, central}$

--- $RO_{spleen}$
PBPK Simulations Receptor Occupancy

Does dissociation rate ($K_{off}$) affect lung-selectivity?

A transient concentration gradient created during dissolution of a highly soluble compound can give rise to a prolonged lung-selectivity given a slow $K_{off}$.
Does particle size distribution affect lung-selectivity?

As bigger particles give rise to a longer dissolution phase, lung-selectivity is dependent on particle size distribution.
PBPK Simulations Receptor Occupancy

Does particle size distribution affect lung-selectivity?

As bigger particles give rise to a longer dissolution phase, lung-selectivity is dependent on particle size distribution
A mechanistic model for inhaled drug delivery has been developed - can predict regional drug concentrations and receptor occupancy

The model provides a framework for

1) Rational drug design
   - can be used to evaluate what properties that are beneficial for inhaled drugs

2) Facilitated translation from animal to man
   - changing from rodent to human system-specific (i.e. physiological) parameters provides a method for a facilitated translation from animal to man

Further validation underway with more regional lung effect measures (RNA based)
First stepping stone towards more systems pharmacology description inhaled drugs
Modeling Pulmonary PK Soluble Bronchodilators

A semi-physiological compartmental model

- Rat plasma & lung profiles after intra-tracheal (i.t.) and i.v.
- For class of soluble bronchodilators bases/quarternary amines

Modelled by semi-physiological compartmental model

The semi-physiological compartment model best describes the data; “first pass loading of the lung”

Deep compartment could indicate lysosomal trapping (not likely to be target binding)
Modeling Lung and System PK Bronchodilators

Results of modeling the obtained profiles in rat

- Salmeterol
- Formoterol
- Terbutaline
- Salbutamol
- Ipratropium
- Glycopyrronium
- Indacaterol
- Tiotropium
- AZD4818
- AZD2115
- GSK961081
- AZD3199

Single bases (β2 agonists)

Quaternary Amines (muscarinic antagonists)

Lung after intra-tracheal

Plasma after intra-tracheal

Lung after i.v.

Plasma after i.v.
Modeling Lung and System PK Bronchodilators

Results of modeling the obtained profiles in rat lung after intra-tracheal plasma after intra-tracheal lung after i.v. plasma after i.v.

AZD4818

Di-basic (Dual pharmacological active MABAs: β2 agonists and muscarinic antagonist)

Overall good model fits, low %CV on model parameters

Low parameter sensitivity

Salmeterol

Tiotropium

Formoterol

Terbutaline

Salbutamol

Ipratropium

Glycopyrronium

Indacaterol

AZD4818

AZD2115

GSK961081

AZD3199

Lung after intra-tracheal

Plasma after intra-tracheal

Lung after i.v.

Plasma after i.v.
Simulation Lung and System PK in Dog

Results of simulations i.t. profiles in dog

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cross species estimate (Dog/Human)</th>
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<tbody>
<tr>
<td>$k_{12}$</td>
<td>Rat model value</td>
</tr>
<tr>
<td>$CL_{023}$</td>
<td>Rat model value x ($V_{lung}$ dog or human/$V_{lung}$ rat)</td>
</tr>
<tr>
<td>$k_{54}$</td>
<td>Rat model value set equal to $k_{12}$</td>
</tr>
<tr>
<td>$CL_{045}$</td>
<td>Allometrically scaled rat value</td>
</tr>
<tr>
<td>$CL_{012}$</td>
<td>Rat model value x ($V_{lung}$ dog or human/$V_{lung}$ rat)</td>
</tr>
<tr>
<td>$CL_{014}$</td>
<td>Allometrically scaled rat value</td>
</tr>
<tr>
<td>$CL$</td>
<td>Measured Dog or Human CL</td>
</tr>
<tr>
<td>$V_S$</td>
<td>Rat model value</td>
</tr>
<tr>
<td>$V_L$</td>
<td>Physiological lung volume of dog or human (8.5 or 14 mL/Kg BW)</td>
</tr>
<tr>
<td>$f_uV_s$</td>
<td>Rat model value</td>
</tr>
<tr>
<td>$f_u1$</td>
<td>Measured from equilibrium dialyses of plasma</td>
</tr>
<tr>
<td>$f_u2$</td>
<td>Measured from equilibrium dialyses of lung homogenate</td>
</tr>
</tbody>
</table>

Dog IT PK lung data was used to successfully ‘validate’ the proposed mechanism of cross-species PK extrapolation in relation to predicted lung levels.
Simulated human plasma profiles with the scaled model were generally very similar to the observed data, except for Tiotropium.
Correlation Simulated Lung Concentration & Effect

Predicted potency-normalized trough lung concentration correlate with trough FEV$_1$ in COPD patients

Potency-normalization was achieved through division of total lung concentrations by the pharmacological total lung IC$_{50}$ values obtained from the in vivo guinea pig model with histamine/methacholine induced bronchoconstriction
Bronchodilator PKPD Modeling in Human

Predicted potency-normalized trough lung concentration correlate with trough FEV$_1$ in COPD patients per pharmacological class

- $\beta_2$-agonists
- Muscarinic antagonists
- MABAs
Bronchodilator PKPD Modeling in Human

The model captures the accumulation in effect observed following multiple dosing for some of the drugs. The drugs with minor predicted accumulation show only modest increase in FEV$_1$ as opposed to e.g. Batefenterol with a large accumulation and large increase in FEV$_1$. 
Preliminary Findings/Conclusions

- A semi-physiological modeling approach was developed for inhaled soluble drugs.
- The approach was shown to allow translation across animal species to man.
- The observed correlation between predicted lung concentration and clinical lung function efficacy data suggests the approach has the potential to guide the development of novel inhaled soluble drugs and support the estimation of human inhaled therapeutic dose and dose regimen.

The model has been used to provide support around dose selection for in house project in clinical testing phase (data to be awaited…)