The challenge of PKPD modelling for inhaled delivery

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• Benefits of PKPD reasoning to Discovery/Development

• Hurdles for PKPD model development introduced by the inhaled dose route – Primarily lack of relevant exposure data in target tissue.

• Measurements of lung and epithelial lining fluid (ELF) in pre-clinical PK – utility?

• Overview of possible techniques for measuring lung and ELF exposure in the clinic

• Predicting lung PK in man based on modelling approaches

• Conclusions/Summary
What is quantitative PKPD?

Relationship between dose, concentration and response, with special emphasis on the onset, intensity and duration of response and the mechanism(s) of action.

Dose → Concentration → Response

- Distribution
- Binding
- Turnover
- Transduction

- Includes both efficacy and safety endpoints
- An integrative approach (e.g. *in vitro/in vivo*)
- **Quantitative**
Advantages for Discovery & Development

- Rational setting of CDTP criteria
- Provide building blocks for experimental design
- Ability to optimize study design (dose scheduling, sampling...)
- Make simulation of study outcomes possible (efficiency, 3Rs...)
- PKPD as a BM validation tool – Means to connect pharmacology
- Accurate assessment of *in-vivo* potency
- Pick the right compound to take into development (best concentration/response time profile in man (*vs.* safety)
- Reduced attrition rate in development
Scope of the Presentation

- Focus of the presentation is on the unique challenges introduced by inhaled administration – rather than disease specific challenges round ethical issues, biomarkers, endpoints, disease models etc....
Classification of Biomarkers*

Lung conc technically difficult to measure
Difficult to infer from plasma concentration (low dose level, multi-phasic absorption, ‘downstream’ of lung)

Humans

Type 0 Genotype Phenotype → Type 1 Drug conc → Type 2 Target Occupancy → Type 3 Target Function → Type 4 Physiologic al response → Type 5 Pathophysiologic al process → Type 6 Clinical response

Animals

Type 0 Genotype Phenotype → Type 1 Drug conc → Type 2 Target Occupancy → Type 3 Target Function → Type 4 Physiologic al response → Type 5 Pathophysiologic al process → Type 6 Clinical response

Whole lung homogenates?
BAL? – how to assess ‘free levels’

*Adapted from Danhof et al. Pharmaceutical Research, 2005, 1432-1437
Literature review

- Scientific literature in this area is surprisingly sparse

- Searches combining ‘PK/PD’ with ‘inhalation’ does produce numerous references – but most relate to systemic effects driven by systemic exposure rather than local efficacy driven by local exposure within the lung

- Numerous papers on pharmacokinetics and pharmacodynamics for ICS (Hochhaus, Derendorf) – but the PK and PD properties are not generally linked in a quantitative sense

- Considerable data on drug concentrations in epithelial lining fluid – mainly relating to anti-infective agents delivered orally (checking ELF conc exceeds susceptibility breakpoints)

- Why has this area not been developed further?
  - Tractability?
  - Inhaled therapeutics represent a comparatively small sector?
  - Few first-in-class drugs – easy to rely on simple potency ratios for precedent mechanisms?
Key Aspects of Lung Physiology

- Large surface area, thin alveolar/capillary membrane (average thickness <0.5 µm), small aqueous volume at absorptive surface (9 ml), highly perfused – Properties result in generally rapid absorption of small molecules from the lung.

- Differences in physiology exist between the airways (trachea, bronchi & bronchioles) & the alveolar region.

- Alveolar region has a much greater surface area (airways only ~ 2-3 m²).

- Expect ‘free’ drug concentration to vary throughout the lung following inhalation.

Common Strategies for drug retention in the lung

- Low permeability
- Slow dissociation from target receptor
- Slow dissolution rate
- High Tissue affinity
- Fatty acid esterification
- Formulation approaches – encapsulation in liposomes, microspheres etc.

With the exception of ‘low permeability’ – all strategies rely on retaining the drug in some type of ‘depot’ within the lung tissue or lining fluid

Topical selectivity produced by first pass loading of ‘depots’
Lung homogenates

- Whole lung is removed and homogenised
- Allows measurement of total drug anywhere within the tissue
- The use of multiple animals allows full lung PK profile to be obtained
- ‘Free’ fraction in dilute homogenate can be assessed by dialysis or ultrafiltration techniques – and an assessment made of ‘free fraction’ in ‘non-diluted lung homogenate’ by correcting for dilution

\[ f_{u_L} = \frac{f_{u_H} \cdot V_{\text{lung}}}{V_{\text{dil}} + V_{\text{lung}} - f_{u_H} \cdot V_{\text{dil}}} \]

Mechanical disruption of the tissue, processing time & dilution are all likely to result in liberation of compound from ‘depots’ (undissolved particles, compound trapped in lysosomes etc) – leading to a potentially erroneous estimate of true free concentration within the intact lung.
Pre-clinical lung concentration measurements

**BAL**

- Volume(s) of saline introduced and then removed from the lungs – to sample ELF

- Urea often used as an endogenous marker to measure volume of ELF sampled (conc urea in ELF assumed = conc urea in plasma)

- ‘Dwell time’ of fluid can give rise to errors –
  - Diffusion of urea from tissue/blood into fluid can lead to overestimation of ELF volume sampled
  - Transfer of drug from tissue into fluid may occur leading to overestimation of ELF concentration

- Albumin conc in ELF is low (~3% that of plasma)* – but binding in ELF will still be significant for drugs with high ppb

- ELF contains a large number of cells (primarily AM; 4-10% volume) – lysis of cells during BAL processing can artificially elevate apparent free concentration in ELF

*Kiem & Schentag, Antimicrobial agents & chemotherapy, 2008, 24-36*
PKPD analyses based on lung concentration data?

- Obtaining an accurate measure of ‘free’ concentration is difficult
- During terminal phase the ratio of total/free drug is likely to be constant
- Possible to apply standard PKPD analyses (effect-compartment; turnover models etc.) to generate *in-vivo* estimates of potency in pre-clinical models
- A strategy for human prediction *might* be to assume that ratio of *in-vivo/*in-vitro potency is constant cross-species (depending on nature of depot)

By correcting for differences in non-specific binding (determined in lung homogenate) it can be possible to establish a reasonably consistent *in-vivo/*in-vitro potency ratio within a chemical series – allowing efficacy in animal models to be predicted from lung PK and *in-vitro* potency.
Measuring lung exposure in the clinic

• Lung biopsy – viability of technique depends on disease being treated, representative of overall exposure in the lung? Single timepoint.

• Microdialysis – *in vivo* technique for accurately (and continuously) measuring the free drug concentrations in interstitial space fluid in the lung*. Highly invasive.

• Imaging techniques
  - Two-dimensional gamma scintigraphy (relies on $^{99m}$Tc, $T_{1/2} = 6$hr, usually in formulation)
  - SPECT (single photon emission computed tomography) – allows 3D reconstruction of lungs
  - PET (Positron emission tomography) – direct incorporation of $^{11}$C or $^{18}$F into drug molecule. (short $T_{1/2} = 22$ min, 110 min).

  • Mainly used to determine lung deposition following inhalation (bioequivalence, dose response studies, identifying areas of deposition etc.)

*example: Tomaselli et al, Antimicrobial Agents & Chemotherapy, 2004, 2228-2232
Measuring ELF exposure in the clinic

Extensive publications in this area – mainly around assessing anti-biotic concentrations in ELF for patients with pneumonia

- **Bronchoalveolar lavage (BAL)** - bronchoscope, 3 x50 ml saline, usually 1 timepoint

- **‘Mini-BAL’** - non-bronchoscopic, lower volume saline, multiple samples possible

**Bronchoscopic Microsampling**
- Consists of 2.5 mm outer diameter polyethylene sheath with an inner 1.9 mm polyester fibre rod that absorbs fluid
- Inserted under local anaesthesia and the probe placed against targeted bronchial wall for 10s
- Multiple samples possible
Modelling lung concentrations

- Lung concentration profiles in man (following inhalation) may be predicted using similar approaches/assumptions used to predict systemic pharmacokinetics
- Difficult to validate!
- Key to success is building a sufficiently mechanistic model to
  - Accurately describe pre-clinical lung data
  - Be able to translate to man
- Model must incorporate relevant kinetics of any ‘depot’ (dissolution rate, receptor off-rate...)
- Assumptions need to made concerning cross-species differences in absorption rate & tissue binding...
1\textsuperscript{st} order lung absorption – constant cross species?

Human compartmental PK models (obtained by fitting to IV PK data) when combined with 1\textsuperscript{st} order lung absorption rate constants observed in rat and/or dog IT studies generally resulted in relatively accurate ‘predicted’ plasma profiles following inhaled dosing.

**Terbutaline; Inhalation in man**

- Plasma conc. (ng/ml)
- Time (hours)
- Measured plasma; Inhaled dose
- Human IV model; rat IT Ka
- Human IV model; dog inhalation Ka

**Rofleponide; inhalation in man**

- Plasma conc. (ng/ml)
- Time (hours)
- ‘Resting’ plasma
- ‘Exercised’ plasma
- Modelled (human iv micro+dog Ka)
- Modelled (human iv micro+2*dog Ka)
Predicting dog PK from rat PK model

Rare opportunity to generate dog lung concentration data. IT instillation (cassette dosing) of 4 inhaled drugs and 1 AZ project example

Provided data to test PK model translation strategies – can dog lung IT PK profile be predicted by cross-species translation of rat model?

IT PK profiles in dog lung were accurately predicted - built confidence in corresponding predictions in man
Notes about human inhalation PK modelling

- Inhaled lung dose is treated either as
  - bolus to the lung (where dose is administered over a short interval)
  - zero-order infusion to the lung (in the case of longer inhalation periods)
- Lung deposited drug was assumed to be 100% bioavailable
- Oral bioavailability values were obtained from published oral dosing studies. Oral $K_a$ values were calculated to fit published oral dosing data
- For compounds with significant (known) oral bioavailability the fraction of the inhaled dose deposited in the lung ($F_{\text{lung}}$) was calculated from the observed systemic exposure using the equation -

\[
F_{\text{lung}} = \frac{\text{systemically available dose-Dose}_{\text{INH}} \times F}{\text{Dose}_{\text{INH}} \times (1-F)}
\]
Predicted human PK profiles: Formoterol & Terbutaline

**Formoterol (54 µg inhaled; 27 µg infusion)**
- Based on rat

**Terbutaline (1 mg inhaled 209 µg infusion)**
- Based on dog

- Inhaled Lung (predicted)
- IV Plasma (predicted)
- Inhaled Plasma (predicted)
- IV Plasma (measured)
- Inhaled Plasma (measured)
Predicted human PK profiles: Ipratropium & Tiotropium

Ipratropium (2 mg inhaled 2 mg infusion)

Tiotropium (18 µg inhaled; 4.8 µg infusion)

Inclusion of receptor binding/off-rate in the model improves predicted shape of inhaled PK profile
Example: PKPD from predicted human lung PK

• PK Model created to predict human lung PK profile [translated from lung PK model in rats & integrating in-vitro muscarinic binding kinetics]

• Prediction of muscarinic receptor occupancy profile in lung following inhaled dosing

• Diurnal variation of FEV1 modelled (as a sinusoidal fluctuation in cholinergic tone)

• Tiotropium $K_i$ (competitive inhibition) assumed to be equal to $K_d$ for muscarinic receptor binding

• Antagonist occupancy profile & diurnal variation in baseline combined to give accurate description of observed FEV₁ profile following inhaled dosing of Tiotropium in COPD patients

Conclusions

• Quantitative PKPD of topical efficacy following inhaled drug delivery is a challenging scientific area clearly in need of further development

• Primary obstacle is lack of relevant exposure data in target tissue – plasma is ‘downstream’ of the lungs preventing standard PKPD analyses based on systemic exposure

• Total lung and ELF concentrations can be assessed in preclinical models - and can be used as the bases for valuable PKPD analyses

• Assessment of lung and ELF levels in the clinic is possible – are these techniques being fully utilised?

• Integration of PhysChem, in-vitro & pre-clinical PK data into an appropriate mechanistic PK framework allows prediction of human lung levels – which can form the bases of dose-exposure-response analyses following inhaled dosing