Dose-response-time data analysis: A poorly explored topic in PK and PD practice

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My Key Messages

- What is and why dose-response-time $DRT$ data analysis?
- Biophase functions are derived from pharmacological response-time data
- $DRT$ has a tremendous (but poorly explored) potential
- $DRT$ does not replace systemic exposure in safety assessment
Dose-Response-Time Data Analysis

Models help

Data
Acute experiment

Model(s)

Output
Steady-state

- Tail-flick response (s)
- Time (min)
- Dose-Response-Time Data Analysis
- Models help
Dose-Response-Time Data Analysis

Plasma vs. ‘biophase’ kinetics

Victor Smolen & Gerhard Levy
pioneers

Quantitative determination of drug bioavailability and biokinetic behavior from pharmacological data for ophthalmic and oral administration of a mydriatic drug

*J. Pharm. Sci.* 60:354 (1971)
Dose-Response-Time Data Analysis

Examples in pharmacology

- Muscle relaxants (Levy 1964, 1966)
- Chemotherapeutics (Pillai et al 2004)
- Calcimimetic agents (LaLonde et al 2009)
- Anesthetics (Warwick)
- Pediatrics (Todd 2008)
- FFA turnover (Ahlström 2009, Andersson 2015)
- CNS stimulants (van Rossum 1968)
- Antinociceptive (pain) models (G&W 1994-2010)
Dose-Response-Time Data Analysis

Plasma vs. ‘biophase’ kinetics

Traditional approach

Dose $\rightarrow C_p \rightarrow$ response

DRT approach

Dose $\rightarrow$ biophase $\rightarrow$ response

What does the time-course of pharmacological data contain?

1. Baseline
2. Time-delay
3. Peak-shift
4. Saturation
5. Different slopes
6. Biophase avail. F*

Gallery of biophase functions

- **Bolus**
  - $A_b \xrightarrow{K} A_b$

- **Zero order**
  - $A_b \xrightarrow{Inf} A_b \xrightarrow{K} A_b$

- **Multi-compartment**
  - $A_b \xrightarrow{K} A_b$

- **First order**
  - $A_b \xrightarrow{K_a} A_b$

- **Michaelis-Menten input**
  - $A_b \xrightarrow{MM} A_b$

- **Michaelis-Menten elimination**
  - $A_b \xrightarrow{MM} A_b$

Dose-Response-Time Data Analysis

Provocations ‘smoke out’ biophase structure

Different
• doses (intensity and duration of response)
• routes (onset, biophase availability)
• modes of administration (adaptation, synergy)

narrow down what is the ’biophase’ separated from pharmacological target behavior

Tail-flick Response

Laser challenge

1. Baseline
2. Time-delay
3. Peak-shift
4. Saturation
5. Different slopes
6. Transduction
Tail-flick Response

Laser challenge

Fast removal of tail from beam

Delayed removal of tail from beam
Dose-Response-Time Data Analysis Model

\[
\frac{dA_b}{dt} = K_a \cdot F^* \cdot \text{Dose} \cdot e^{-K_a \cdot t} - K \cdot A_b
\]

- Biophase function

\[
\frac{dA_b}{dt} = -K \cdot A_b
\]

- Drug-mechanism function

\[
S(A_b) = 1 + \frac{S_{\text{max}} \cdot A_b^n}{SD_{50}^n + A_b^n}
\]

- Turnover transduction model

\[
\frac{dR_{\text{recept}}}{dt} = \frac{1}{\tau} \left( S(A_b) \cdot E_0 - R_{\text{recept}} \right)
\]

\[
\frac{dR_n}{dt} = \frac{1}{\tau} \left( R_{\text{recept}} - R_n \right)
\]
Dose-Response-Time Data Analysis

Results from fitting model to all data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>0.89</td>
<td>11</td>
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<tr>
<td>K</td>
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</tr>
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<td>$K_A$</td>
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<td>$SD_{50}$</td>
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</tr>
<tr>
<td>$k_{out}$</td>
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<td>8</td>
</tr>
</tbody>
</table>

$D = R_0 \cdot S_{max}$
Dose-Response-Time Data Analysis

What did we gain beyond the AUC-approach?

- Nonlinear dynamics
- Biophase availability
- Flip/flop biophase kinetics
- Model for future designs

Dose-Response-Time Data Analysis

Typical situations when DRT helps

- Local administrations
- Poor or lacking systemic (plasma) information
- Identification of active metabolites
- Experimental design
- Bioequivalence testing
- Drug scheduling
- Combination therapies
Conclusions - **Utility**

- No need for linear or 1-cmpt kinetics, linear dynamics, instantaneous equilibrium or baseline subtraction
- Characterize DRT profile with $F$, $ED_{50}/ID_{50}$ and $k_{out}$
- Discriminate between drug ($ED_{50}$) and system ($k_{in}$, $k_{out}$)
- Local drug delivery, no systemic exposure, unconventional dynamics and/or kinetics
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