Dose Response and Concentration Response Analysis of Drug Effects

Juan J. L. Lertora, M.D., Ph.D.
NIH Clinical Center
January 27, 2011

DOSE-EFFECT RELATIONSHIP

The intensity and duration of a drug’s effects are a function of the drug dose and drug concentration at the effect site

(The contribution of Frank M. Balis, M.D. is gratefully acknowledged)

Monitoring Dose-Effect

• Level
  – Molecular (e.g., enzyme inhibition)
  – Cellular (in vitro tissue culture, blood cells)
  – Tissue or organ (in vitro or in vivo)
  – Organism
• Endpoint used to measure effect may be different at each level
• Overall effect = sum of multiple drug effects and physiological response to drug effects
Endpoints to Monitor Drug Effect

Farnesyltransferase Inhibitors for Cancer

<table>
<thead>
<tr>
<th>LEVEL</th>
<th>ENDPOINT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular</td>
<td>Farnesyltransferase inhibition</td>
</tr>
<tr>
<td>Cellular</td>
<td>Proliferation rate, apoptosis</td>
</tr>
<tr>
<td>Tumor</td>
<td>Response (change in tumor size)</td>
</tr>
<tr>
<td>Organism</td>
<td>Survival, quality of life</td>
</tr>
</tbody>
</table>

Dose-Effect Endpoints

**Graded**
- Continuous scale (↑dose → ↑effect)
- Measured in a single biologic unit
- Relates dose to intensity of effect

**Quantal**
- All-or-none pharmacologic effect
- Population studies
- Relates dose to frequency of effect

Erythropoietin and Anemia

*Eschbach et al. NEJM 316:73-8, 1987*
Drug-Receptor Interactions

\[
\text{Effect} = \frac{\text{Maximal effect} \cdot [\text{Drug}]}{K_D + [\text{Drug}]}
\]
\[
K_D = \frac{k_2}{k_1}
\]

Dose-Effect Relationship

\[
\text{Effect} = \frac{\text{Maximal effect} \cdot [\text{Drug}]}{K_D + [\text{Drug}]}
\]

\[
\text{Effect} = \text{Maximal effect} \left( \frac{[\text{Drug}]}{K_D + [\text{Drug}]} \right)
\]

\[
\text{Effect} = \text{Maximal effect} \quad \text{if} \ [\text{Drug}] \gg K_D
\]

Graded Dose-Effect Curve

\[
\% \text{ of Maximal Effect} = \frac{[\text{Drug}]}{EC_{50} + [\text{Drug}]}
\]

\[
EC_{50} = \frac{k_2}{k_1}
\]
Log Dose-Effect Curve

[Graph showing the relationship between log dose and percentage of maximal effect.]

Lidocaine Graded Dose-Effect

[Graph showing the relationship between lidocaine blood level and analog pain score.]

Theophylline Dose-Effect

[Graph showing the relationship between theophylline concentration and percentage of control.]

Theophylline Pharmacodynamics

FEV₁ (% normal) vs Theophylline [mg/L]

Eₘₐₓ = 63%
EC₅₀ = 10 mg/L


Metformin Dose-Response

Decrease in FPG from Placebo [mg/dL] vs Decrease in HbA₁c from Placebo [%]


Dose-Effect Parameters

POTENCY: The sensitivity of an organ or tissue to the drug

EFFICACY: The maximum effect
Comparing Dose-Effect Curves

\[ \text{Effect} = \frac{\text{Maximal effect} \times [\text{Drug}]}{K_D + [\text{Drug}]} \]

Thiopurine Cytotoxicity

Thiopurine Metabolic Activation

Graded Dose-Effect Analysis

- Identify the therapeutic dose/concentration
- Define site of drug action (receptor)
- Classify effect produced by drug-receptor interaction (agonist, antagonist)
- Compare the relative potency and efficacy of drugs that produce the same effect
- Assess mechanism of drug interactions

Quantal Dose-Effect Distribution

Cumulative Dose-Effect Curve
Cumulative Dose-Effect Study

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>No. of Subjects</th>
<th>No. Responding</th>
<th>% Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>7</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>10</td>
<td>8</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>9</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>10</td>
<td>10</td>
<td>100</td>
</tr>
</tbody>
</table>

Therapeutic and Toxic Effects

Therapeutic Indices

Therapeutic Ratio = \( \frac{TD_{10}}{ED_{50}} = 2.5 \)

Certain Safety Factor = \( \frac{TD_{1}}{ED_{99}} = 1.3 \)

Standard Safety Margin = \( \frac{TD_{1} - ED_{99}}{ED_{99}} \times 100 = 31\% \).
**Digoxin Therapeutic Index**

- **Ventricular slowing**
- **Vomiting**

- **Digoxin (single oral dose, µg/kg)**

- **Percent of patients**

**Doxorubicin Cardiotoxicity**

- **Probability of CHF**

- **Total Doxorubicin Dose [mg/m²]**


**Lidocaine Quantal Dose-Effect**

- **% Achieving Complete Analgesia**

- **ED₅₀ = 490 mg**

- **ED₉₀ = 490 mg**

Antihypertensive Dose-Effect

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Range [mg]</th>
<th>Lowest Effective Dose [mg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>160-5000</td>
<td>80</td>
</tr>
<tr>
<td>Atenolol</td>
<td>100-2000</td>
<td>25</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>50-400</td>
<td>12.5</td>
</tr>
<tr>
<td>Captopril</td>
<td>75-1000</td>
<td>37.5</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>500-6000</td>
<td>750</td>
</tr>
</tbody>
</table>

Antihypertensive Drugs

% with Maximal Effect vs. Log Dose

Relating Dose to Effect In Vivo

Dose — Effect site Concentration — Effect

Pharmacokinetics — Pharmacodynamics

Age
Absorption
Distribution
Elimination
Drug interactions

Tissue/organ sensitivity (receptor status)
Effect Compartment (PK/PD Model)

\[
\begin{align*}
\frac{dC}{dt} &= k_0 V_c - (k_{10} + k_{12}) \times C + k_{21} \times X_p V_c \\
\frac{dX_p}{dt} &= k_{12} \times C \times V_c - k_{21} \times X_p \\
\frac{dC_e}{dt} &= k_{1e} \times C \times V_c - k_{0e} \times C_e
\end{align*}
\]

Concentration and Effect vs. Time

Pharmacodynamic Models

- Fixed effect model
  \[\text{Effect} = E_0 + S \times \text{Drug}\]
- Linear model
  \[\text{Effect} = I + S \times \log(\text{Drug})\]
- Log-linear model
  \[\text{Effect} = \frac{E_{\text{max}} \times \text{Drug}^n}{E_{\text{max}}^n + \text{Drug}^n}\]
- \(E_{\text{max}}\) model
  \[\text{Effect} = \frac{E_{\text{max}} \times \text{Drug}^n}{E_{\text{max}}^n + \text{Drug}^n}\]
- Sigmoid \(E_{\text{max}}\) model
### Sigmoid $E_{\text{max}}$ PD Model

- **Effect (%)** vs **[Drug]**
- Curves for different $H$ values: $H = 5$, $H = 2$, $H = 1$, $H = 0.5$, $H = 0.1$
- Key: $EC_{50}$

### Hysteresis and Proteresis Loops

- **Intensity of Drug Effect** vs **Plasma Drug Concentration**
- Hysteresis Loop: Counterclockwise
  - Equilibration delay in plasma and effect site conc.
  - Formation of active metabolite
  - Receptor up-regulation
- Proteresis Loop: Clockwise
  - Tolerance
  - Receptor tachyphylaxis

### Role of Dose-Effect Studies

- **Drug development**
  - Site of action
  - Selection of dose and schedule
  - Potency, efficacy and safety
  - Drug interactions
- **Patient management**
  - Therapeutic drug monitoring
  - Risk-benefit (therapeutic indices)