Dose Response and Concentration Response Analysis of Drug Effects

Juan J. L. Lertora. M.D., Ph.D.
NIH Clinical Center
January 14, 2016
DOSE-EFFECT RELATIONSHIP

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

<table>
<thead>
<tr>
<th>Graded</th>
<th>Quantal</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Continuous scale (dose → effect)</td>
<td>• All-or-none pharmacologic effect</td>
</tr>
<tr>
<td>• Measured in a single biologic unit</td>
<td>• Population studies</td>
</tr>
<tr>
<td>• Relates dose to intensity of effect</td>
<td>• Relates dose to frequency of effect</td>
</tr>
</tbody>
</table>
Erythropoietin and Anemia

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

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

(K_D = k_2/k_1)
Drug-Receptor Interactions

• Receptor-Effector system
  (signal-transduction pathway)
  G-protein coupled receptors
  Receptor-enzymes
  Ion channels
  Nuclear receptors
Dose-Effect Relationship

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

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

\[
\text{Effect} = \text{Maximal effect} \quad \text{if} \ [\text{Drug}] >> K_D
\]
Graded Dose-Effect Curve

% of Maximal Effect

Maximal effect

EC\textsubscript{50}

[Drug]

100
90
80
70
60
50
40
30
20
10
0

0 200 400 600 800
Log Dose-Effect Curve

% of Maximal Effect

[Drug]

EC$_{50}$
Lidocaine Graded Dose-Effect

Theophylline Dose-Effect

% Control

Theophylline [µM]

Theophylline Pharmacodynamics

FEV₁ (% normal)

Eₘₐₓ = 63%
EC₅₀ = 10 mg/L

Mitenko & Ogilvie NEJM 289:600-3, 1973
Metformin Dose-Response

Dose-Effect Parameters

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

**EFFICACY:** The maximum effect
Comparing Dose-Effect Curves

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

% of Maximal Effect

[Drug]
Thiopurine Cytotoxicity

Cytotoxic Effect

Thioguanine

Mercaptopurine

Thiopurine Metabolic Activation
Oral Mercaptopurine

\[ AUC = \frac{\text{Dose} \times F}{\text{Clearance}} \]

MP AUC [\( \mu \text{M} \cdot \text{hr} \)]

MP Dose (mg/m\(^2\))

Receptor-Mediated Effects

<table>
<thead>
<tr>
<th>[Drug]</th>
<th>% Maximum Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>100</td>
<td>60</td>
</tr>
<tr>
<td>1000</td>
<td>40</td>
</tr>
<tr>
<td>10000</td>
<td>20</td>
</tr>
<tr>
<td>100000</td>
<td>0</td>
</tr>
</tbody>
</table>

- **Agonist**
- **Partial agonist**
- **Antagonist**
Receptor-Mediated Effects

- Agonist
- Partial agonist
- Antagonist
- Inverse agonist

Receptors can exist in at least two conformations: active and inactive.

An inverse agonist drives the equilibrium toward the inactive conformation.
Drug Interactions

- Agonist
- Agonist + competitive antagonist
- Agonist + non-competitive antagonist

% of Maximal Effect vs [Drug]
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

Threshold Dose

# of Subjects

ED$_{50}$
Cumulative Dose-Effect Curve

Cumulative % of Subjects

Dose

1 3 5 7 9 11 13 15
### 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
- Toxic

Indices:
- $ED_{99}$
- $TD_1$
- $TD_{50}$

Dose

% Responding
Therapeutic Indices

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

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

Lidocaine Quantal Dose-Effect

% Achieving Complete Analgesia

ED\textsubscript{50} = 400 mg
ED\textsubscript{90} = 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></td>
<td>Early Studies</td>
<td>Present Dose</td>
</tr>
<tr>
<td>Propranolol</td>
<td>160-5000</td>
<td>160-320</td>
</tr>
<tr>
<td>Atenolol</td>
<td>100-2000</td>
<td>50-100</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>50-400</td>
<td>25-50</td>
</tr>
<tr>
<td>Captopril</td>
<td>75-1000</td>
<td>50-150</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>500-6000</td>
<td>500-3000</td>
</tr>
</tbody>
</table>

*Johnston Pharmacol Ther 55:53-93, 1992*
Antihypertensive Drugs

Log Dose

% with Maximal Effect

Desirable Dose Range

Adverse Effects

Dose Range most often used
Relating Dose to Effect \textit{In Vivo}

Dose \rightarrow \text{Effect site concentration} \rightarrow \text{Effect}

\textbf{Pharmacokinetics:}
- Age
- Absorption
- Distribution
- Elimination
- Drug interactions

\textbf{Pharmacodynamics:}
- Tissue/organ sensitivity (receptor status)
Effect Compartment (PK/PD Model)

\[ \frac{dX_p}{dt} = k_{12} \cdot C \cdot V_c - k_{21} \cdot X_p \]

\[ \frac{dC}{dt} = \frac{k_o}{V_c} - (k_{10} + k_{12}) \cdot C + \frac{k_{21} \cdot X_p}{V_c} \]

\[ \frac{dC_e}{dt} = \frac{k_{1e} \cdot C \cdot V_c}{V_e} - k_{e0} \cdot C_e \]

\[ E(t) = \frac{E_{max} \cdot C_e^{H}}{EC_{50}^{H} + C_e^{H}} \]
Concentration and Effect vs. Time

Non-Steady State

Conc./Amount

Time

Effect [% of $E_{\text{max}}$]
Pharmacodynamic Models

- Fixed effect model
  \[ \text{Effect} = E_0 + S \cdot [\text{Drug}] \]
- Linear model
  \[ \text{Effect} = I + S \cdot \log([\text{Drug}]) \]
- Log-linear model
- \( E_{\text{max}} \) model
  \[ \text{Effect} = \frac{E_{\text{max}} \cdot [\text{Drug}]^H}{EC_{50}^H + [\text{Drug}]^H} \]
- Sigmoid \( E_{\text{max}} \) model
Sigmoid $E_{\text{max}}$ PD Model

Effect (%)

Effect (%)

[Drug]
Hysteresis and Proteresis Loops

**Hysteresis Loop (Counterclockwise)**
- Equilibration delay in plasma and effect site conc.
- Formation of active metabolite
- Receptor up-regulation

**Proteresis Loop (Clockwise)**
- Tolerance
- Receptor tachyphylaxis

**Plasma Drug Concentration**
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)