Dose Response and Concentration Response Analysis of Drug Effects

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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

**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

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

\[(K_D = k_2/k_1)\]
Drug-Receptor Interactions

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

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

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

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

Theophylline Dose-Effect

Theophylline Pharmacodynamics

FEV\textsubscript{1} (% normal)

\[ E_{\text{max}} = 63\% \]
\[ EC_{50} = 10 \text{ mg/L} \]

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

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

Cytotoxic Effect

Thioguanine

Mercaptopurine

Thiopurine Metabolic Activation
Oral Mercaptopurine

MP AUC [µM•hr]

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

Receptor-Mediated Effects

- Agonist
- Partial agonist
- Antagonist

% Maximum Effect

[Drug]
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

% of Maximal Effect

[Drug]

Agonist
Agonist + competitive antagonist
Agonist + non-competitive antagonist
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

# of Subjects

Threshold Dose

ED$_{50}$
## 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

Indices:

- ED<sub>99</sub>
- ED<sub>50</sub>
- TD<sub>1</sub>
- TD<sub>50</sub>
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

Percent of patients

Digoxin (single oral dose, µg/kg)
Doxorubicin Cardiotoxicity

Probability of CHF vs Total Doxorubicin Dose [mg/m²]

Lidocaine Quantal Dose-Effect

% Achieving Complete Analgesia

ED$_{50}$ = 400 mg

ED$_{90}$ = 490 mg

Total Lidocaine Dose (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>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

% with Maximal Effect

Desirable Dose Range

Adverse Effects

Dose Range most often used

Log Dose
Relating Dose to Effect *In Vivo*

Dose → Effect site Concentration → Effect

**Pharmacokinetics**
- Age
- Absorption
- Distribution
- Elimination
- Drug interactions

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

Peripheral

\[ \frac{dX_p}{dt} = k_{12} \cdot C \cdot V_c - k_21 \cdot X_p \]

Central

\[ \frac{dC}{dt} = \frac{k_0}{V_c} - (k_{10} + k_{12}) \cdot C + \frac{k_{21} \cdot X_p}{V_c} \]

Effect

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

Effect

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

Non-Steady State

Conc./Amount

Effect [% of E_max]

Time

Central Compartment

Peripheral Compartment

Effect Compartment

Effect

Non-Steady State
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 (%) vs. [Drug]

- $H = 0.1$
- $H = 0.5$
- $H = 1$
- $H = 2$
- $H = 5$

EC$_{50}$
Hysteresis and Proteresis Loops

Intensity of Drug Effect

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

Intensity of Drug Effect

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)