Dose-Effect and Concentration-Effect Analysis of Drug Action

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Dose-Effect Relationship

- Recommended reading:
  ES Lowe and JJL Lertora:
  Dose-effect and concentration-effect analysis

(*) Includes contributions of FM Balis in earlier editions.

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

(*) Also “dose-response relationship”
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

Peak Hematocrit Increment [%]

Erythropoietin Dose [units/kg]

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

Drug-Receptor Interactions

Effect = \frac{\text{Maximal effect} \times [\text{Drug}]}{K_D + [\text{Drug}]} \\
\frac{k_i}{k_2}

Dose-Effect Relationship

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

Graded Dose-Effect Curve

Log Dose-Effect Curve

Lidocaine Graded Dose-Effect

Theophylline Dose-Effect

Theophylline Pharmacodynamics

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

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

Thiopurine Cytotoxicity

Thiopurine Metabolic Activation

Oral Mercaptopurine

Receptor-Mediated Effects
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

- ED₅₀
- Threshold Dose vs # of Subjects
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 = \( \frac{TD_{50}}{ED_{50}} = 2.5 \)

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**

![Graph showing the relationship between digoxin dose and side effects.](image)

**Doxorubicin Cardiotoxicity**

![Graph showing the probability of CHF versus total doxorubicin dose.](image)
Lidocaine Quantal Dose-Effect

- ED$_{50}$ = 400 mg
- ED$_{90}$ = 400 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>Drug</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>


Antihypertensive Drugs

- Desired Dose Range
- Dose Range most often used

Adverse Effects

% with Maximal Effect

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)

\[
\frac{dC_e}{dt} = k_1 e \cdot C \cdot V_c - k_0 e \cdot C_e \cdot V_e
\]

Concentration and Effect vs. Time

**Non-Steady State**

[Graph showing concentration and effect vs. time]
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
  \[ \text{Effect} = \text{EC}_{50} + \text{[Drug]} \]
- \( E_{\max} \) model
  \[ \text{Effect} = \frac{E_{\max} \cdot \text{[Drug]}^n}{\text{EC}_{50} + \text{[Drug]}^n} \]
- Sigmoid \( E_{\max} \) model

Sigmoid \( E_{\max} \) PD Model

Hysteresis and Proteresis Loops

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