Dose-Effect and Concentration-Effect Analysis of Drug Action

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Dose-Effect Relationship

• Recommended reading:

ES Lowe and JYL 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 $\rightarrow$ 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} \cdot [\text{Drug}]}{K_D + [\text{Drug}]}

(K_D = \frac{k_2}{k_1})

Ligand-binding domain

Effector domain

Drug-Receptor Complex

Effect
Dose-Effect Relationship

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

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

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

% of Maximal Effect

Maximal effect

EC\(_{50}\)

[Drug]
Log Dose-Effect Curve

% of Maximal Effect

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

Theophylline Dose-Effect

% Control

Relaxation

PDE Inhibition

Theophylline [µM]

Theophylline Pharmacodynamics

FEV₁ (% normal)

$E_{max} = 63\%$

$EC_{50} = 10 \text{ mg/L}$

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

Decrease in FPG from Placebo [mg/dl]

Decrease in HbA1c from Placebo [%]

Dose [mg/d]

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

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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

- Agonist
- Partial agonist
- Antagonist

% Maximum Effect vs [Drug]
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

Number of Subjects

Threshold Dose

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

Cumulative % of Subjects

Dose
# 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

Dose

% Responding

Therapeutic

Toxic

ED<sub>50</sub>  ED<sub>99</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

Percent of patients

Digoxin (single oral dose, µg/kg)

Ventricular slowing
Vomiting
**Doxorubicin Cardiotoxicity**

Probability of CHF

Lidocaine Quantal Dose-Effect

## 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

% with Maximal Effect

Desirable Dose Range

Dose Range most often used

Adverse Effects

Log Dose
Relating Dose to Effect *In Vivo*

Dose $\rightarrow$ Effect site Concentration $\rightarrow$ Effect

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

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

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

\[
\frac{dC}{dt} = \frac{k_0}{V_c} - (k_{10} + k_{i2}) \cdot C + \frac{k_{21} \cdot X_p}{V_c}
\]

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

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

Non-Steady State

Conc./Amount

Effect [% of E\textsubscript{max}]

Time

Central Compartment
Peripheral Compartment
Effect
Effect Compartment
Pharmacodynamic Models

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

Effect (%) vs [Drug]

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

$EC_{50}$

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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
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)