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

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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
## 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

Chart showing peak hematocrit increment (%) over Erythropoietin Dose [units/kg]

Example of Dose-Effect curve.

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

Graphic illustration of drug-receptor complex with ligand-binding and effector domains.

\[
\text{Effect} = \frac{\text{Maximal effect} \times [\text{Drug}]}{(K_D - [\text{Drug}])}
\]

\[(K_D = k_2/k_1)\]
Dose-Effect Relationship

Effect = Maximal effect \times [\text{Drug}] \over (K_D + [\text{Drug}])

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

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

Chart showing % of Maximal Effect over Drug concentration.

Graphic illustration of EC$_{50}$. 
Log Dose-Effect Curve

Chart showing % of maximal effect over log drug concentration.

Graphic illustration of EC$_{50}$.
Lidocaine Graded Dose-Effect

Chart showing analog pain score over Lidocaine blood level [μg/ml]

Theophylline Dose-Effect

Chart showing % control over Theophylline [µM] for bronchial smooth muscle relaxation and PDE inhibition.

Metformin Dose-Response

Chart showing decrease in FPG from placebo [mg/dl] and decrease in HbA from placebo (%) over 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

Chart showing % of maximal effect over [Drug] for Drugs A, B, and C. Illustration of different potency and efficacy.

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

Chart showing % cytotoxic effect over Thiopurine [M] (thioguanine and mercaptopurine).

Receptor-Mediated Effects

Chart showing % maximum effect over [Drug] for agonist, partial agonist and antagonist
Drug Interactions

Chart showing % of maximal effect over [Drug] for agonist, agonist + competitive antagonist, and 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

Frequency histogram of subjects responding to threshold dose in a population.
Cumulative Dose-Effect Curve

Cumulative % of subjects responding over 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

Chart showing % responding over dose for therapeutic and toxic effects.

Graphic illustration of ED_{50}, ED_{99}, TD_{1} and TD_{50}.
Doxorubicin Cardiotoxicity

Chart showing probability of CHF over total doxorubicin dose \([\text{mg/m}^2]\)

Lidocaine Quantal Dose-Effect

Chart showing % achieving complete analgesia over total lidocaine dose (mg)

$ED_{50} = 400 \text{ mg}, \; ED_{90} = 490 \text{ mg}$

# 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

Chart showing % with maximal effect over log dose showing desirable dose range, dose range most often used, and adverse effects.
Dose Intensity in Breast Cancer

Chart showing response rate (%) over relative dose intensity

Hryniuk & Bush J Clin Oncol 2:1281, 1984
Doxorubicin Dose in Osteosarcoma

Chart showing % with >90% necrosis over dose intensity (mg/m²/wk)

Smith et al. JNCI 83:1460, 1993
# Relating Dose to Effect *In Vivo*

<table>
<thead>
<tr>
<th>Effect Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
</tr>
<tr>
<td>Concentration</td>
</tr>
</tbody>
</table>

↑ Pharmacokinetics  ↑ Pharmacodynamics

- Age
- Absorption
- Distribution
- Elimination
- Drug interactions

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

Graphic illustration of a 2-compartment PK model with an effect compartment (PK/PD).
Concentration and Effect vs. Time

Chart showing Non-steady state - Conc./Amount over time in central, peripheral, and effect compartments.
**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)
## 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>
Thiopurine Metabolic Activation

Chemical structures
Therapeutic Indices

Therapeutic Ratio = $\frac{TD_{50}}{ED_{50}} = 2.5$

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

Standard Safety Margin = $\frac{TD_{1} - ED_{99}}{ED_{99}} \times 100 = 31\%$
## Relative Dose Intensity

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drugs</th>
<th>Dose Rate ( \text{mg/m}^2/\text{wk} )</th>
<th>R.D.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cyclo</td>
<td>350</td>
<td>1</td>
</tr>
<tr>
<td>CAF-1</td>
<td>Doxo</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>FU</td>
<td>250</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Cyclo</td>
<td>125</td>
<td>0.36</td>
</tr>
<tr>
<td>CAF-2</td>
<td>Doxo</td>
<td>12.5</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>FU</td>
<td>125</td>
<td>0.50</td>
</tr>
</tbody>
</table>
**Oral Mercaptopurine**

Chart indicating MP AUC [µM x hr] over MP Dose (mg/M²). \( \text{AUC} = \frac{\text{Dose} \times F}{\text{Clearance}} \)

Pharmacodynamic Models

Fixed effect model

Linear model

Log-linear model

$E_{\text{max}}$ model

Sigmoid $E_{\text{max}}$ model

\[
\text{Effect} = E_0 + S \times [\text{Drug}]
\]

\[
\text{Effect} = I + S \times \log([\text{Drug}])
\]

\[
\text{Effect} = \frac{E_{\text{max}} \times [\text{Drug}]^H}{E_{C50}^H + [\text{Drug}]^H}
\]
Sigmoid $E_{\text{max}}$ PD Model

Two graphs, both indicating effect (%) over drug. The graph on the left indicates $H = 5$, $H = 2$, $H = 1$, $H = 0.5$ and $H = 0.1$ with $EC_{50}$ equal for all. The graph on the right indicates $EC_{50}$ on log scale.
Theophylline Pharmacodynamics

Graph indicating FEV$_1$ (% normal) over Theophylline [mg/L] with $E_{\text{MAX}} = 63\%$ and $EC_{50} = 10$ mg/L

Mitenko & Ogilvie NEJM 289:600-3, 1973
Carboplatin PK/PD

Two graphs. One shows the % decrease platelet over Carboplatin AUC [μg x hr/ml] and the other Carboplatin CI_{TB} [ml/min] over Creatinine clearance [ml/min].
Carboplatin Adaptive Dosing

ADULTS

\[
D[mg/m^2] = 0.091 \times \text{CL}_{cr}[\text{ml/min/m}^2] \times \left(\frac{\text{rePlt} - \text{trgtPlt}}{\text{prePlt}} \times 100 - \text{prior Rx}\right) + 86
\]

\[
D[\text{mg}] = \text{trgtAUC}[\text{mg \times min/ ml}] \times (\text{GRF}[\text{ml/min}] + 25)
\]

CHILDREN

\[
D[mg/m^2] = \text{trgtAUC}[\text{mg \times min/ ml}] \times (0.93 \times \text{GRF}[\text{ml/min/m}^2] + 15)
\]

\[
D[\text{mg}] = \text{trgtAUC}[\text{mg \times min/ ml}] \times \text{GFR}[\text{ml/min}] + (0.36 \times \text{BW}[\text{kg}])
\]