Dose Response and Concentration Response Analysis of Drug Effects

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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

(The contribution of Frank M. Balis, M.D. is gratefully acknowledged)

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

LEVEL	ENDPOINT
Molecular	Farnesyltransferase inhibition
Cellular	Proliferation rate, apoptosis
Tumor	Response (change in tumor size)
Organism	Survival, quality of life

Dose-Effect Endpoints

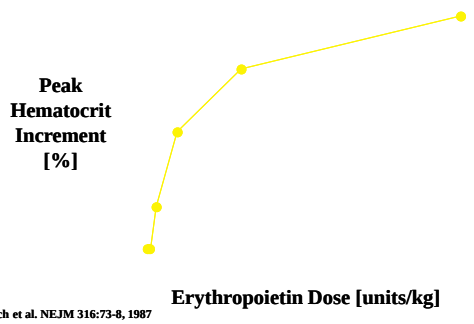
Graded

- Continuous scale (↑dose → ↑effect)
- Measured in a single biologic unit
- Relates dose to intensity of effect

Quantal

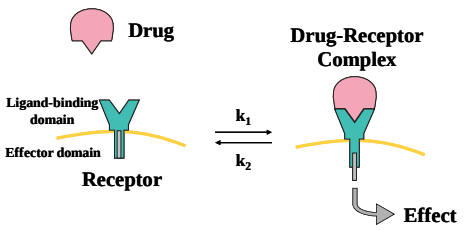
- All-or-none pharmacologic effect
- Population studies
- Relates dose to frequency of effect

Erythropoietin and Anemia



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

Drug-Receptor Interactions



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

$(K_D = k_2/k_1)$

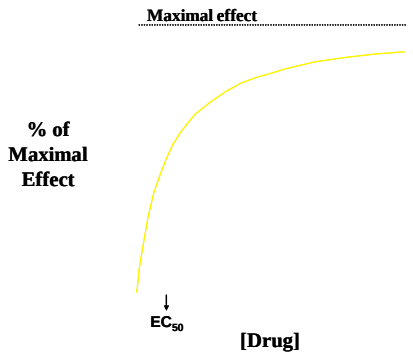
Dose-Effect Relationship

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

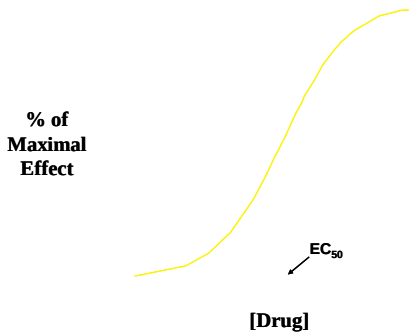
$$\text{Effect} = \text{Maximal effect} \frac{[\text{Drug}]}{K_D + [\text{Drug}]}$$

$$\text{Effect} = \text{Maximal effect} \quad \text{if } [\text{Drug}] >> K_D$$

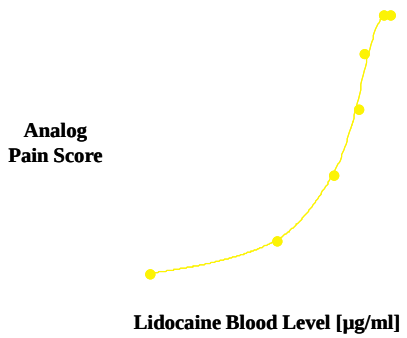
Graded Dose-Effect Curve



Log Dose-Effect Curve

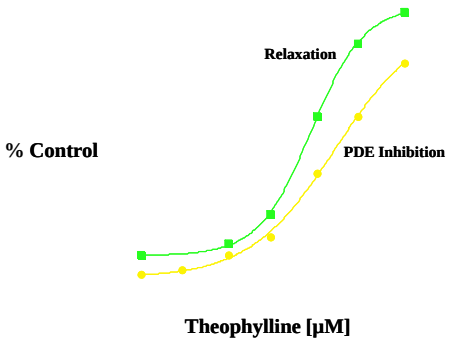


Lidocaine Graded Dose-Effect



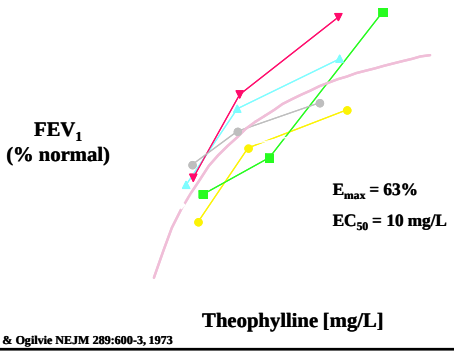
Ferrante et al. Anesth Analg 82:91-7, 1996

Theophylline Dose-Effect



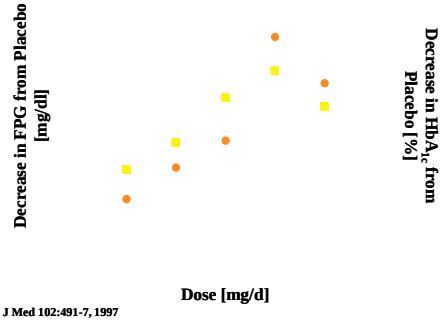
Rabe et al. Eur Respir J 8:637-42, 1995

Theophylline Pharmacodynamics



Mitenko & Ogilvie NEJM 289:600-3, 1973

Metformin Dose-Response



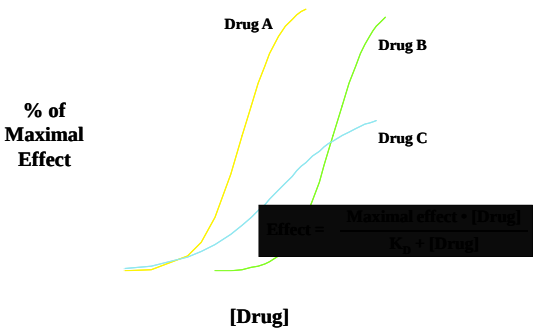
Garber et al. Am J Med 102:491-7, 1997

Dose-Effect Parameters

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

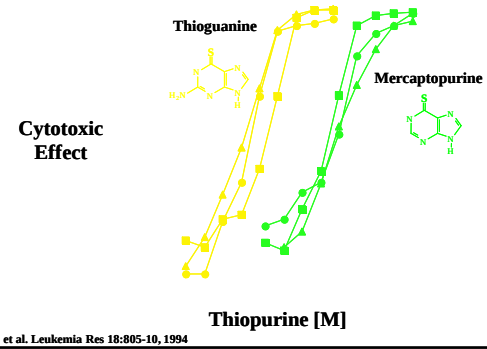
EFFICACY: The maximum effect

Comparing Dose-Effect Curves



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

Thiopurine Cytotoxicity



Adamson et al. Leukemia Res 18:805-10, 1994

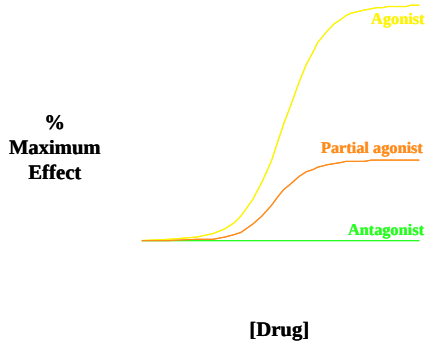
Thiopurine Metabolic Activation

Oral Mercaptopurine

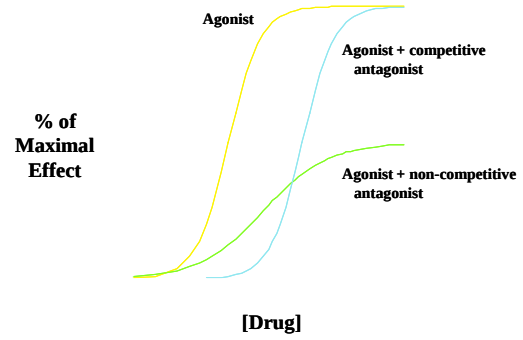
$$AUC = \frac{Dose \cdot F}{Clearance}$$

Balis et al. Blood 92:3569-77, 1998

Receptor-Mediated Effects



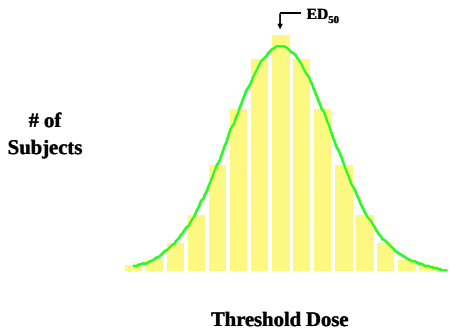
Drug Interactions



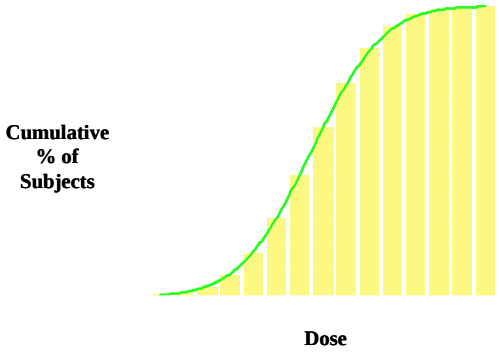
Graded Dose-Effect Analysis

- 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



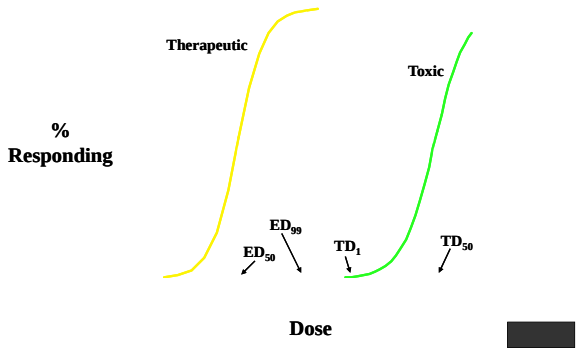
Cumulative Dose-Effect Curve



Cumulative Dose-Effect Study

Dose Level	No. of Subjects	No. Responding	% Response
1	10	0	0
2	10	1	10
3	10	3	30
4	10	5	50
5	10	7	70
6	10	8	80
7	10	9	90
8	10	10	100

Therapeutic and Toxic Effects



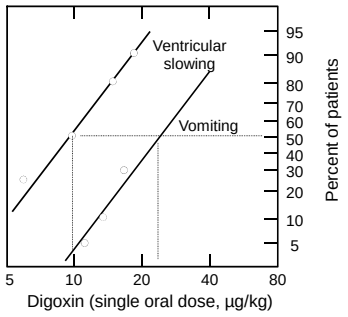
Therapeutic Indices

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

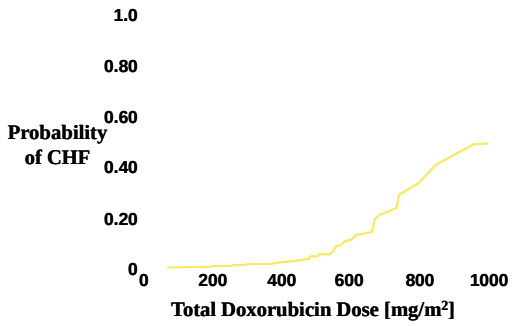
$$\text{Certain Safety Factor} = \frac{TD_{1}}{ED_{99}} = 1.3$$

$$\text{Standard Safety Margin} = \frac{TD_{1} - ED_{99}}{ED_{99}} \times 100 = 31\%$$

Digoxin Therapeutic Index

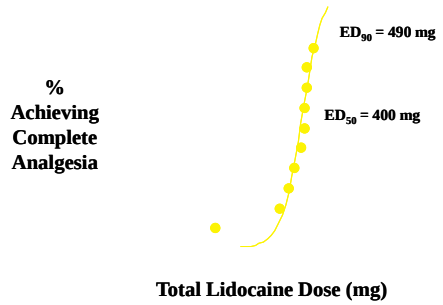


Doxorubicin Cardiotoxicity



von Hoff et al. Ann Intern Med 91:710-7, 1979

Lidocaine Quantal Dose-Effect



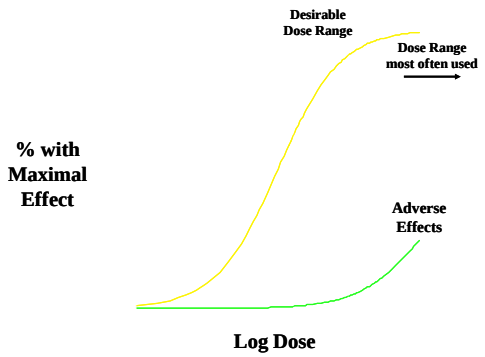
Ferrante et al. Anesth Analg 82:91-7, 1996

Antihypertensive Dose-Effect

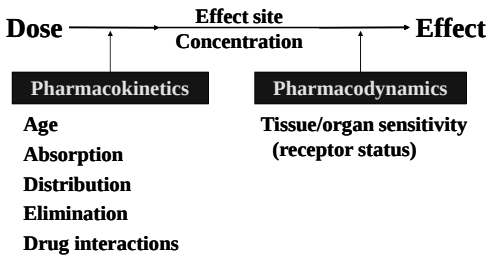
Drug	Dose Range [mg]		Lowest Effective Dose [mg]
	Early Studies	Present Dose	
Propranolol	160-5000	160-320	80
Atenolol	100-2000	50-100	25
Hydrochlorthiazide	50-400	25-50	12.5
Captopril	75-1000	50-150	37.5
Methyldopa	500-6000	500-3000	750

Johnston Pharmacol Ther 55:53-93, 1992

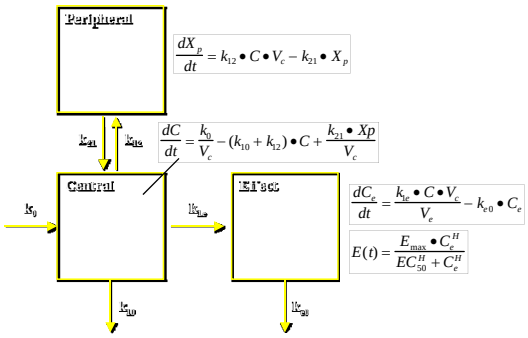
Antihypertensive Drugs



Relating Dose to Effect *In Vivo*



Effect Compartment (PK/PD Model)



$$\frac{dX_p}{dt} = k_{12} \bullet C \bullet V_c - k_{21} \bullet X_p$$

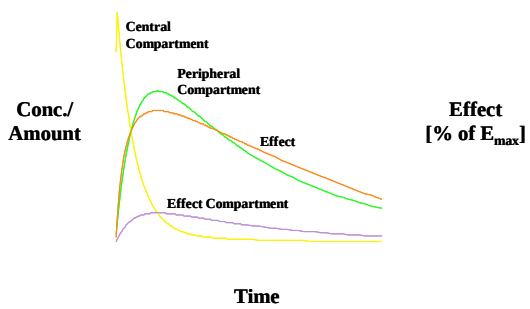
$$\frac{dC}{dt} = \frac{k_0}{V_c} - (k_{10} + k_{12}) \bullet C + \frac{k_{21} \bullet Xp}{V_c}$$

$$\frac{dC_e}{dt} = \frac{k_{1e} \bullet C \bullet V_c}{V_e} - k_{e0} \bullet C_e$$

$$E(t) = \frac{E_{max} \bullet C_e^H}{EC_{50}^H + C_e^H}$$

Concentration and Effect vs. Time

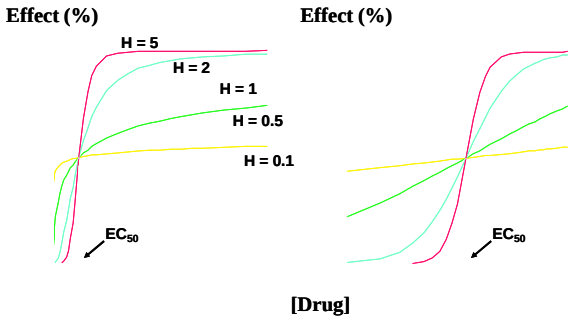
Non-Steady State



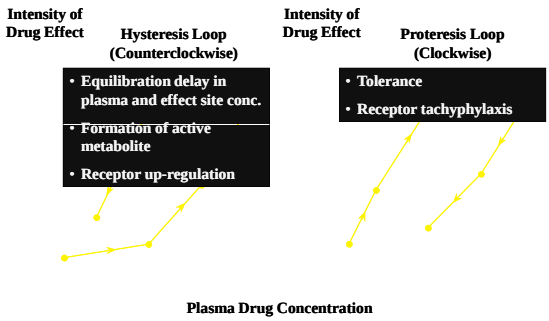
Pharmacodynamic Models

- **Fixed effect model**
- **Linear model** — $Effect = E_0 + S \bullet [Drug]$
- **Log-linear model** — $Effect = I + S \bullet Log([Drug])$
- **E_{max} model**
- **Sigmoid E_{max} model** — $Effect = \frac{E_{max} \bullet [Drug]^H}{EC_{50}^H + [Drug]^H}$

Sigmoid E_{max} PD Model



Hysteresis and Proteresis Loops



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)