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

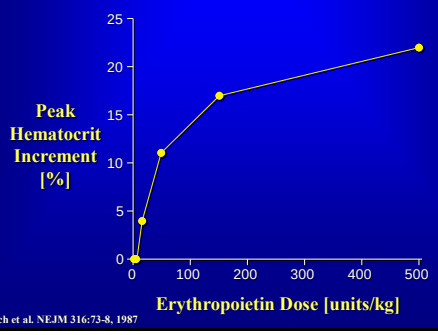
Graded

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

Quantal

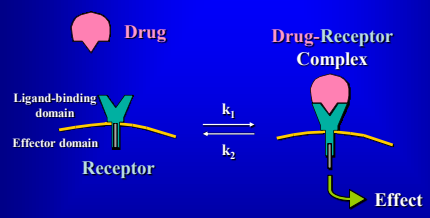
- All-or-none pharmacologic effect
- Population studies
- Relates dose to frequency of effect

Erythropoietin and Anemia



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

Drug-Receptor Interactions



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

$(K_D = k_2/k_1)$

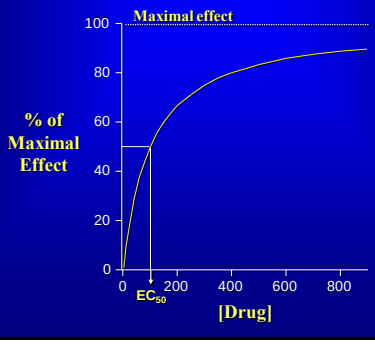
Dose-Effect Relationship

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

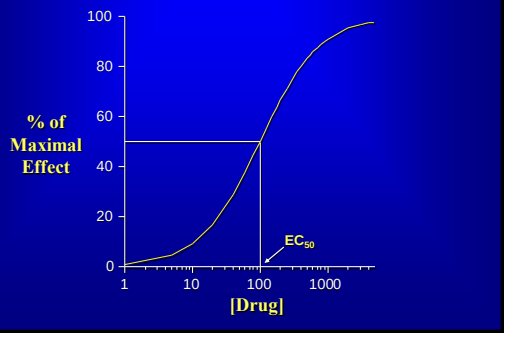
$$\text{Effect} = \text{Maximal effect} \quad \frac{[\text{Drug}]}{K_D + [\text{Drug}]}$$

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

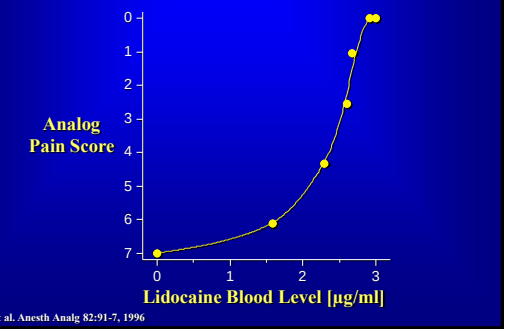
Graded Dose-Effect Curve



Log Dose-Effect Curve

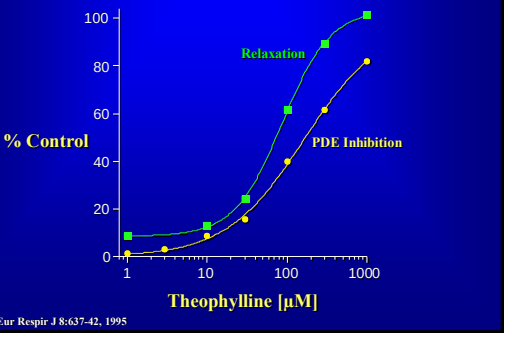


Lidocaine Graded Dose-Effect



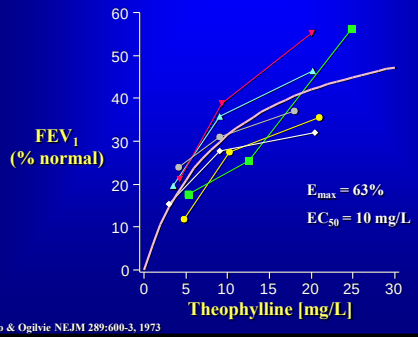
Ferrante et al. Anesth Analg 82:91-7, 1996

Theophylline Dose-Effect



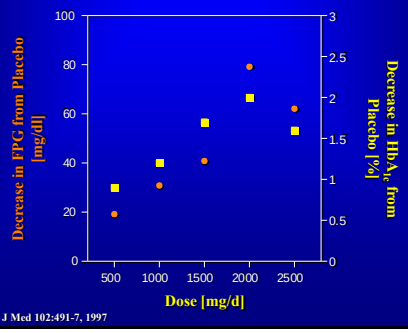
Rabe et al. Eur Respir J 8:637-42, 1995

Theophylline Pharmacodynamics



Mitenko & Ogilvie NEJM 289:600-3, 1973

Metformin Dose-Response



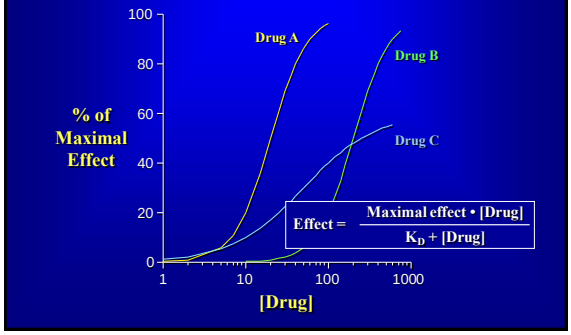
Garber et al. Am J Med 102:491-7, 1997

Dose-Effect Parameters

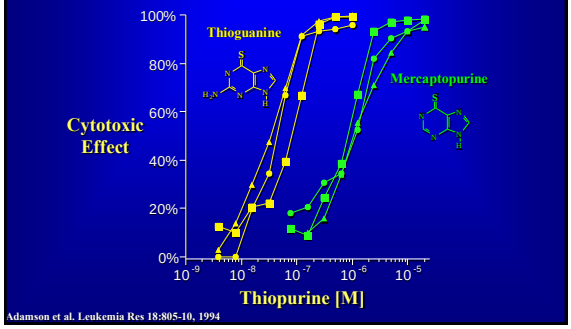
POTENCY: The sensitivity of an organ or tissue to the drug

EFFICACY: The maximum effect

Comparing Dose-Effect Curves

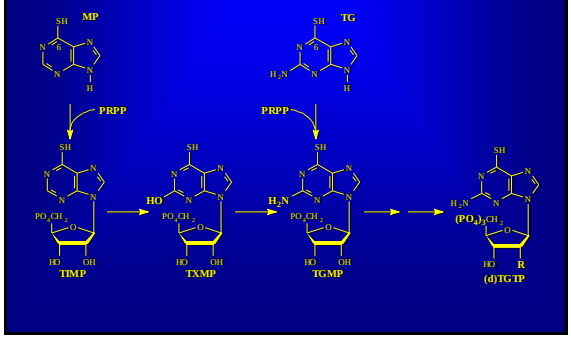


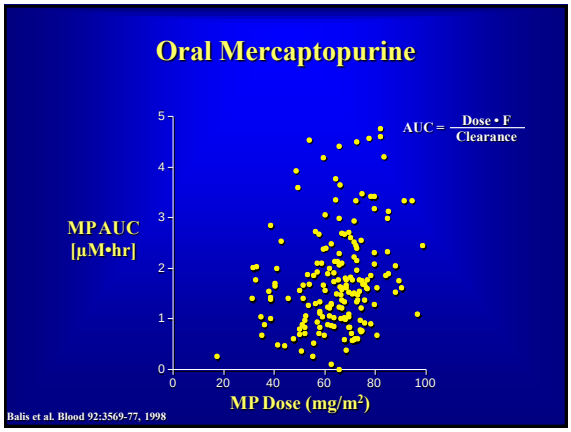
Thiopurine Cytotoxicity

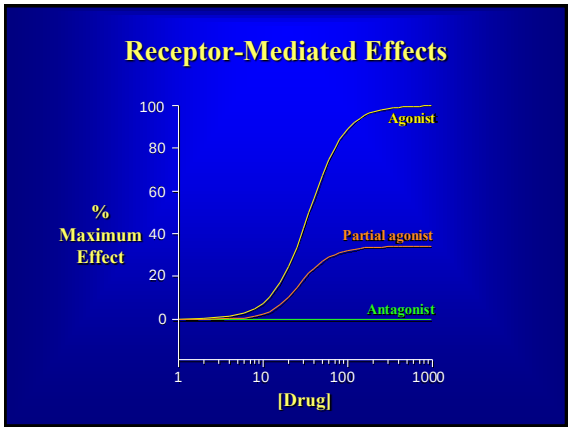


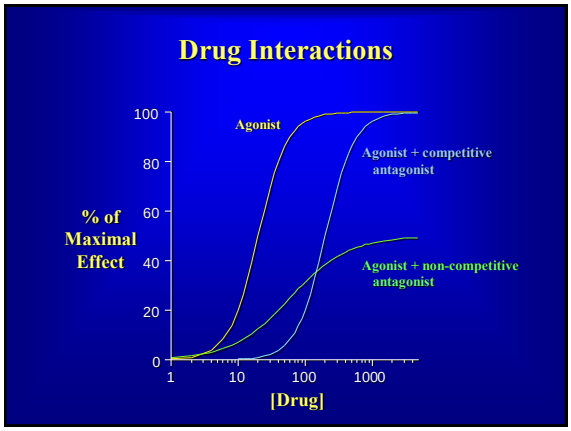
Adamson et al. Leukemia Res 18:805-10, 1994

Thiopurine Metabolic Activation




Oral Mercaptopurine
AUC = Dose • F / Clearance
MP AUC [µM•hr]
MP Dose (mg/m²)
0
1
2
3
4
5
0
20
40
60
80
100
Balis et al. Blood 92:3569-77, 1998

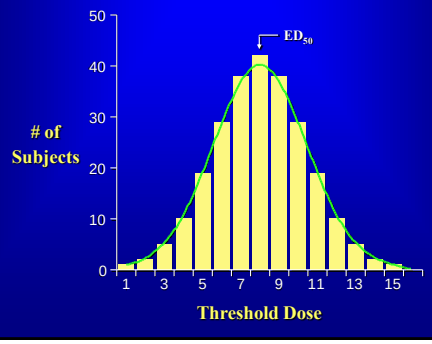

Receptor-Mediated Effects
% Maximum Effect
[Drug]
Agonist
Partial agonist
Antagonist
0
20
40
60
80
100
1
10
100
1000


Drug Interactions
% of Maximal Effect
[Drug]
Agonist
Agonist + competitive antagonist
Agonist + non-competitive antagonist
0
20
40
60
80
100
1
10
100
1000

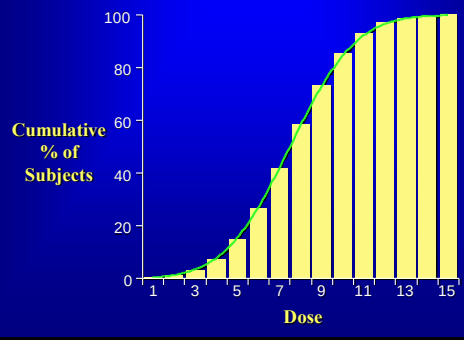
Graded Dose-Effect Analysis

- 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



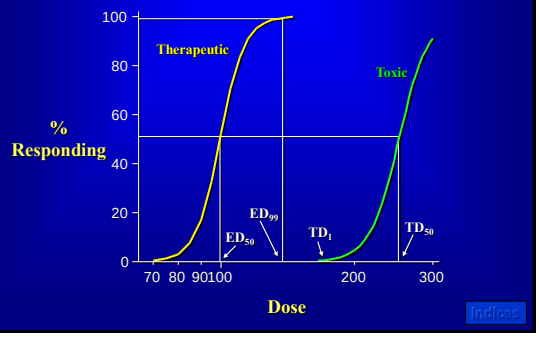
Cumulative Dose-Effect Curve



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



Indices

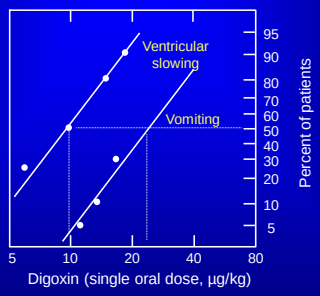
Therapeutic Indices

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

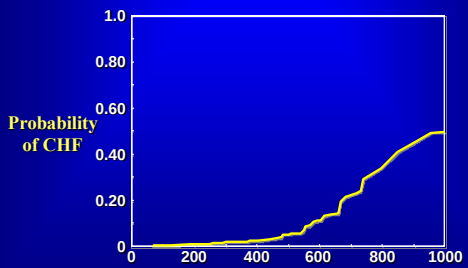
$$\text{Certain Safety Factor} = \frac{TD_{1}}{ED_{99}} = 1.3$$

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

Digoxin Therapeutic Index

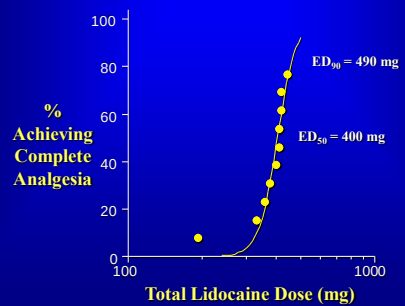


Doxorubicin Cardiotoxicity



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

Lidocaine Quantal Dose-Effect



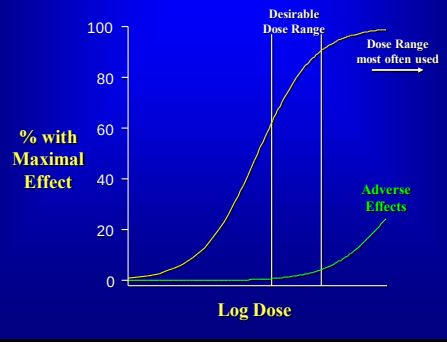
Ferrante et al. Anesth Analg 82:91-7, 1996

Antihypertensive Dose-Effect

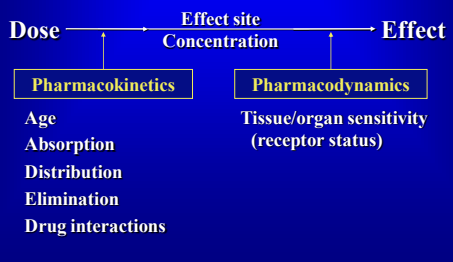
Drug	Dose Range [mg]		Lowest Effective Dose [mg]
	Early Studies	Present Dose	
Propranolol	160-5000	160-320	80
Atenolol	100-2000	50-100	25
Hydrochlorthiazide	50-400	25-50	12.5
Captopril	75-1000	50-150	37.5
Methyldopa	500-6000	500-3000	750

Johnston Pharmacol Ther 55:53-93, 1992

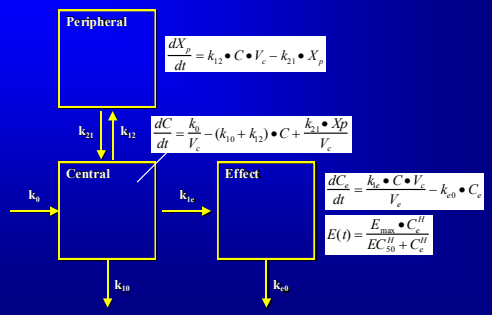
Antihypertensive Drugs



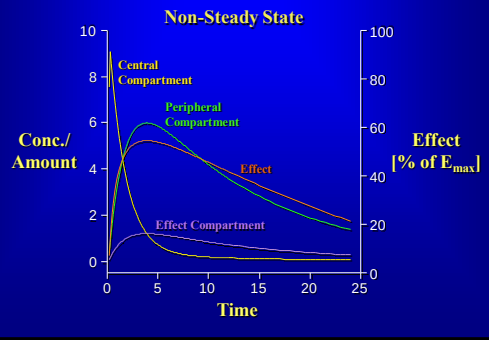
Relating Dose to Effect *In Vivo*



Effect Compartment (PK/PD Model)



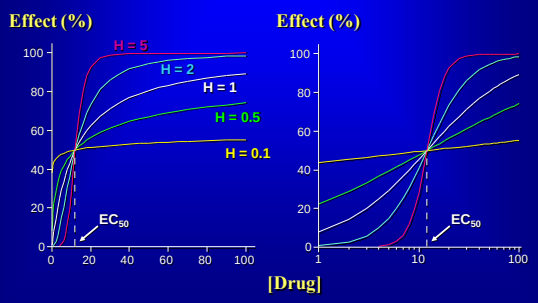
Concentration and Effect vs. Time



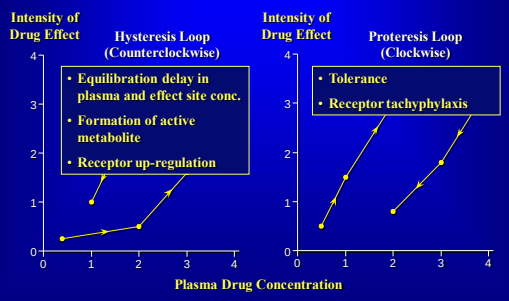
Pharmacodynamic Models

- 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)