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

Frank M. Balis, M.D.

January 22, 2009

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

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

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

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

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]

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

Theophylline Dose-Effect

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

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

Metformin Dose-Response

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

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

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).

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

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

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

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 [mg/m^2]

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

Lidocaine Quantal Dose-Effect

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

ED_{50} = 400 mg, ED_{90}= 490 mg

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

Antihypertensive Dose-Effect

	Dose Range [mg]		Lowest Effective Dose [mg]
Drug	**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

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

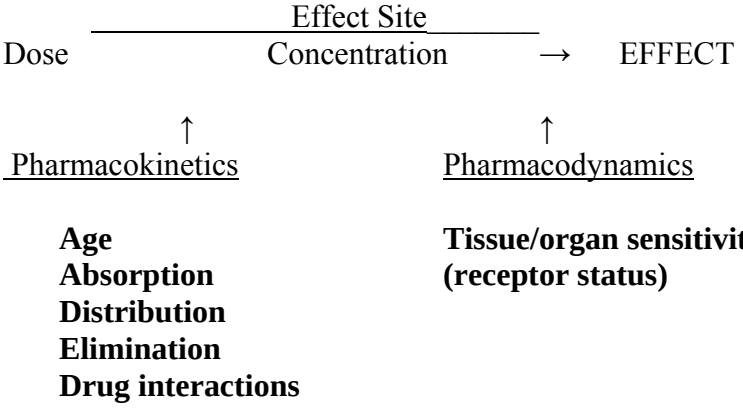
Hryniuk & Bush J Clin Oncol 2:1281, 1984

Doxorubicin Dose in Osteosarcoma

Chart showing % with >90% necrosis over dose intensity ($mg/m^2/wk$)

Smith et al. JNCI 83:1460, 1993

Relating Dose to Effect *In Vivo*



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)	Proteresis Loop (Clockwise)
Equilibration delay in plasma and effect site conc.	Tolerance
Formation of active metabolite.	Receptor tachyphylaxis
Receptor up-regulation	

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

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

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 = $\frac{TD_{1} - ED_{99}}{ED_{99}}$ X 100 = 31%

Relative Dose Intensity

Regimen	Drugs	Dose Rate mg/m^2/wk	R.D.I. Drugs	R.D.I. Regimen
	Cyclo	350	1	
CAF-1	Doxo	15	1	1
	FU	250	1	
	Cyclo	125	0.36	
CAF-2	Doxo	12.5	0.83	0.56
	FU	125	0.50	

Oral Mercaptopurine

Chart indicating MP AUC [μM x hr] over MP Dose (mg/M^2). AUC = $\frac{\text{Dose x F}}{\text{Clearance}}$

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

Pharmacodynamic Models

Fixed effect model

Linear model

Log-linear model

E_{max} model

Sigmoid E_{max} model

Effect = E_0 + S x [Drug]

Effect = I + S xLog([Drug])

$$\text{Effect} = \frac{E_{max} x [Drug]^H}{EC_{50}^H + [Drug]^H}$$

Sigmoid E_{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_{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

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

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

CHILDREN

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

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