Dose Response and Concentration Response Analysis of Drug Effects

Juan J.L. Lertora, M.D., Ph.D.
NIH Clinical Center
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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

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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

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

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

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

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

Thiopurine Metabolic Activation

Chemical structures

Oral Mercaptopurine

Chart indicating MP AUC [μM x hr] over MP Dose (mg/M_2). AUC = Dose x F

Clearance

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

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}.

Therapeutic Indices

Therapeutic Ratio = $\frac{TD50}{ED_{50}} = 2.5$

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

Digoxin (single oral dose, µg/kg) showing ventricular slowing for 90% of patients and vomiting for 55% of patients

Doxorubicin Cardiotoxicity

Chart showing probability of CHF over total doxorubicin dose [mg/m2]

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 1	**00-2000**	**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.

Relating Dose to Effect *In Vivo*

	Effect Site	
Dose	Concentration → EFFECT	
↑		↑
Pharmacokinetics		Pharmacodynamics
Age		**Tissue/organ sensitivity**
Absorption		**(receptor status)**
Distribution		
Elimination		
Drug interactions		

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.

Pharmacodynamic Models

Fixed effect model

Linear model **Effect = E_0 + S x [Drug]**

Log-linear model **Effect = I + S xLog([Drug])**

E_{max} model

Sigmoid E_{max} model $$\text{Effect} = \frac{E_{MAX} \times [\text{Drug}]^H}{ECH_{50} + [\text{Drug}]^H}$$

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.

Hysteresis and Proteresis Loops

Intensity of drug effect over plasma drug concentration

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)