

DRUG DOSE & RESPONSE RELATIONSHIP

SOURCES:

- BERTRAM G. KATZUNG BASIC & CLINICAL PHARMACOLOGY 16TH EDITION
- GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 13TH EDITION.

Motto And Vision



To impart evidence based research oriented medical education

To provide best possible patient care

To inculcate the values of mutual respect and ethical practice of medicine





Dose Response Curve: Learning Objectives

- Dose & Response in patients
- Definition
- Types
- Efficacy
- Potency
- Significance

Dose Response Curve

- Rational Therapeutic decision
- Relationship between dose and response
- Variation in dose and response



Dose Response Curve: Types

Graded Dose response curve

- Sigmoid
- Parabolic
- Quantal Dose Response curve



Dose Response Curve

- Magnitude of the pharmacological effect.....Drug concentration....Dose and pharmacokinetic profile....Dose response relationship....Dose response curve
 - Graded dose response relationship/Curve
 - Quantal Dose response relationship/Curve

- Proportional relationship
- Graded dose response curve
- Dose Vs Magnitude of the response
- Maximal response
- Rectangular Hyperbola.....Sigmoid
- Implications
 - Efficacy
 - Potency





Quantification of activity of drug:

- Threshold
- Slope
- Maximal asymptote



The drug-receptor interaction is characterized by

- 1. Binding of drug to receptor
- 2. Generation of a response in a biological system

High-affinity drug has a low KD and will bind a greater number of a particular receptor at a low concentration than a low-affinity drug

- Efficacy reflects the capacity of a drug to activate a receptor and generate a cellular response
- A drug with high efficacy may be a ______, eliciting, at some concentration a full response.
- A drug with a low intrinsic efficacy will be
- A drug that binds to a receptor and exhibits zero efficacy is ______.

Partial agonist, Antagonist, Full agonist









- Potency....Measure of an amount of drug necessary to produce an effect of a given magnitude
- The dose(ED50) or concentration(EC50) of a drug required to produce 50 % of its maximal efficacy
- Position of curve on dose axis.....Index of potency
- EC 50.....Inverse relation with potency
- Relative Potency





- Efficacy.....Maximal efficacy...Emax
- Magnitude of drug response
- Limit of dose response relationship
- Drug receptor interaction
 - Number of drug receptor complexes
 - Partial agonist











Dose-response curves for drugs with high, medium and low potency acting on the same target

Note that the drug with the highest potency has the lowest efficacy and vice versa









Concentration of drug in plasma (ng/ml)

Figure 3–6. The relation of the therapeutic window of drug concentrations to the therapeutic and adverse effects in the population. The ordinate is linear; the abcissa is logarithmic.



- Quantal effect... All or none/Either or
- Variations in response
- Dose response relationship between dose of drug and population responding
- Quantal response selection....Clinical relevance
- Predetermined level of graded response...Quantal response
- Dose for majority patients
- Implications
 - Parameters
 - Information









Parameters derived

- ED50....Median effective dose
- TD50...Median Toxic dose
- LD50....Median lethal dose
- TI....THERAPEUTIC Index....TD50/ED50 OR LD50/ED50...Measure of safety







A population therapeutic window expresses a range of concentrations at which the likelihood of efficacy is high and the probability of adverse effects is low





- Information obtained
 - Potency
 - ED50 of different drugs
 - Selectivity of drugs
 - ED50 of different Quantal effects
 - Margin of safety
 - Therapeutic Index
 - Variability of responsiveness
 - Frequency distribution of response



- Variability of responsiveness
 - Alteration in Concentration of Drug That Reaches the Receptor
 - Variation in Concentration of an Endogenous Receptor Ligand
 - Alterations in Number or Function of Receptors
 - Changes in Components of Response Distal to the Receptor

Further reading

Ethical issues, Artificial Intelligence Spiral integration

- Lynöe N, Hoeyer K. Quantitative aspects of informed consent: considering the dose response curve when estimating quantity of information. Journal of Medical Ethics. 2005 Dec 1;31(12):736-8.
- Ritz C, Baty F, Streibig JC, Gerhard D. Dose-response analysis using R. PloS one. 2015 Dec 30;10(12):e0146021.
- Streffer C, Bolt H, Follesdal D, Hall P, Hengstler JG, Jacob P, Oughton D, Prieß K, Rehbinder E, Swaton E. Low dose exposures in the environment: dose-effect relations and risk evaluation. Springer Science & Business Media; 2004 May 3.

Ethical issues, Artificial Intelligence Spiral integration

- røstheim M, Eikemo M, Haaker J, Frost JJ, Leknes S. Opioid antagonism in humans: a primer on optimal dose and timing for central mu-opioid receptor blockade.
- Neuropsychopharmacology. 2023 Jan;48(2):299-307Liu C, Xu Y, Liu Q, Zhu H, Wang Y. Application of machine learning based methods in exposure-response analysis. Journal of Pharmacokinetics and Pharmacodynamics. 2022 Aug;49(4):401-10.

