DOSE-EFFECT RELATIONSHIP

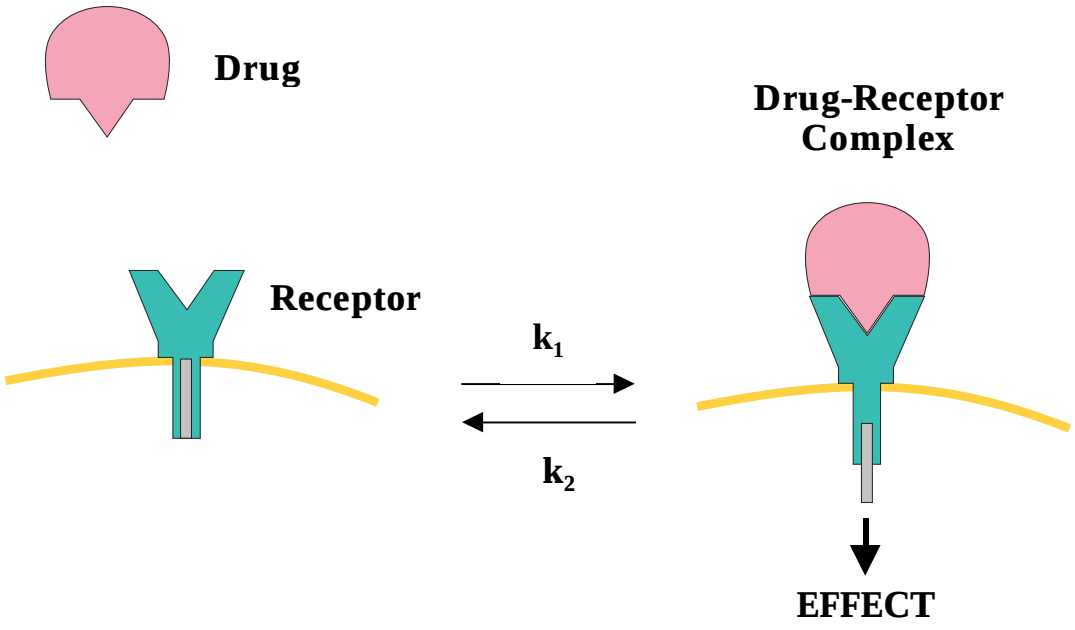
A fundamental principle of pharmacology is that the intensity of effect produced by a drug is a function of the quantity of drug administered (or the concentration of the drug at the target site).

The relationship between dose and drug effect can be expressed mathematically by two methods, which are called **graded** and **quantal**.

- **Graded** - The graded dose-effect is measured in a single biologic unit (a cell, a tissue or organ, or an entire organism). The effect is measured on a continuous scale and the *intensity* of effect is proportional to the dose.
- **Quantal** - A quantal effect is an all-or-none effect such as alive or dead, asleep or awake, pain-free or in pain. Quantal dose-effect studies are performed in populations of subjects and they relate dose to the *frequency* of the all-or-none effect, such as the % of animals that are killed.

GRADED DOSE-EFFECT RELATIONSHIP

The effects of most drugs result from their interaction with macromolecules, which are called *receptors*. A receptor can be any cellular macromolecule to which a drug binds to initiate its effect. Proteins form the most important class of drug receptors



Cellular proteins that are receptors for endogenous regulatory ligands (hormones, growth factors, neurotransmitters) are the most important drug receptors. These proteins have a ligand binding domain where the drug interacts and an effector domain that propagates the message, leading to an effect. Other receptors include enzymes (e.g., acetylcholinesterase), transport proteins (e.g., Na+,K+-ATPase), structural proteins (e.g., tubulin), and nucleic acids.

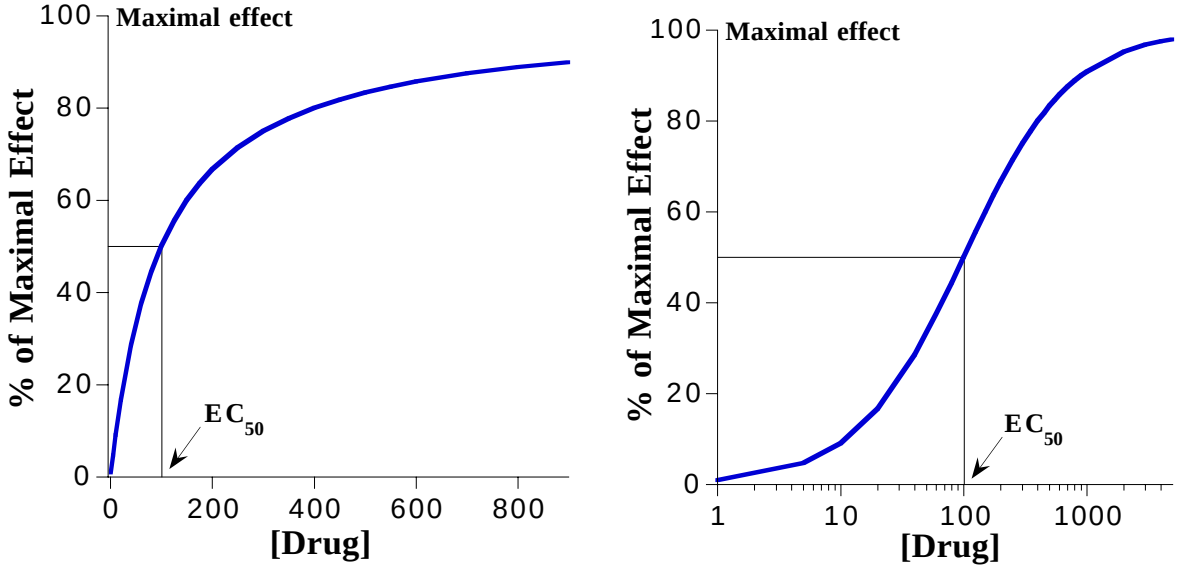
The effect of a drug is proportional to the fraction of receptors occupied by drug and the *maximal effect* results when all receptors are occupied. The dose-effect relationship can be explained based on the laws governing chemical equilibrium or

mass action, assuming that response to drug is directly proportional to the % of total receptor occupied by the drug and the amount of drug bound to receptor is negligible (i.e., the concentration of free drug remains constant). In the interaction scheme, k_1 and k_2 are the proportionality constants for the formation and dissociation of the drug-receptor complex (the interaction is reversible).

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

At equilibrium, the reaction can also be expressed by this equation which takes the same form as the Michaelis-Menten equation, where *Maximal effect* is the intensity of the effect that occurs when all receptors are occupied, *[Drug]* is the concentration of free drug and K_D is the dissociation rate constant for the complex. K_D is equal to k_2 / k_1, the ratio of the proportionality constants. The expression, $\frac{[Drug]}{K_D + [Drug]}$ represents the fraction of receptors occupied and when the *[Drug]* >> K_D, then this expression becomes 1 (all receptors are occupied with drug) and the *Effect = Maximal effect*.

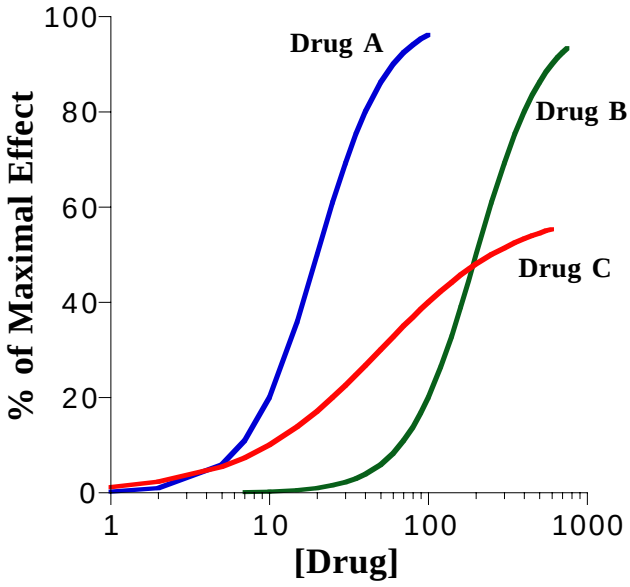
This mathematical relationship between dose and effect based on the drug-receptor interaction can be graphically displayed and the dose-effect curve is shown below. In the graph on the left, the free drug concentration along the X-axis is a linear scale and the shape of the curve is a rectangular hyperbola, in which drug effect asymptotically approaches the maximal effect as the free drug concentration increases. It has become more customary to use semilog dose-effect curves to evaluate the quantitative aspects of the action of a single drug or to compare the actions of several drugs, such as in the plot on the right. When the dose is transformed to a log scale, the dose response curve is sigmoidal. This method of presentation allows for a better assessment of the effects of low doses and for a wide range of doses on the same plot.



The EC_{50} is the drug concentration at which the drug is half-maximally effective. For the semi-log plot, the EC_{50} is the midpoint or inflection point of the curve. When the relationship between receptor occupancy and response is linear, $K_D = EC_{50}$. If there is amplification between receptor occupancy and effect, such as if the receptor has catalytic activity when the receptor ligand is bound, then the EC_{50} lies to the left of the K_D.

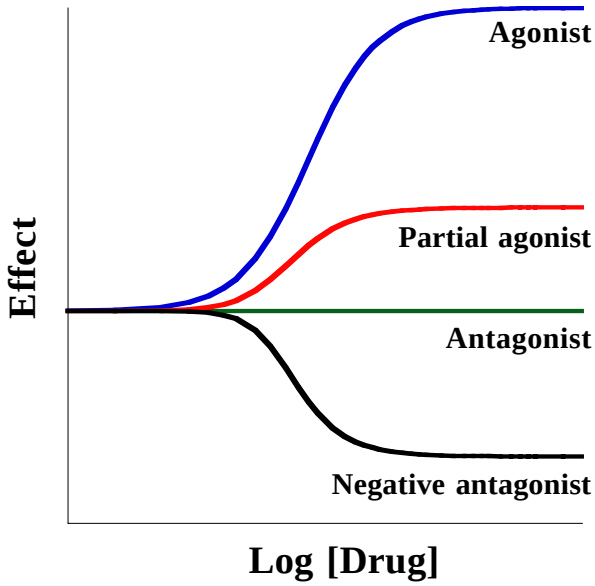
Drugs that produce the same effect vary in terms of **potency** and **efficacy**, and these parameters can be assessed from the dose-response curves of the agents. *Potency* is a measure of the sensitivity of a target organ or tissue to the effect of the drug. It is relative term that relates the amount of one drug required to produce a desired effect compared with another agent. On a dose response curve the more potent agents are to the left (have a lower EC_{50}). *Efficacy* is related to the maximal effect of a drug.

In this graph, Drug A is more potent than Drug B, and Drugs A & B are more efficacious than Drug C. Comparing the dose-effect curves of drugs that produce the same pharmacologic effect can also provide information about the site of action of the drugs. Drugs A and B have dose-effect curves with identical shapes and the same maximal level of response (i.e., the curves are parallel). This suggests that these two drugs act through the same receptor. Conversely, if two drugs that produce the same effect have non-parallel dose-effect curves, such as Drug A and Drug C, they probably have different sites of action.



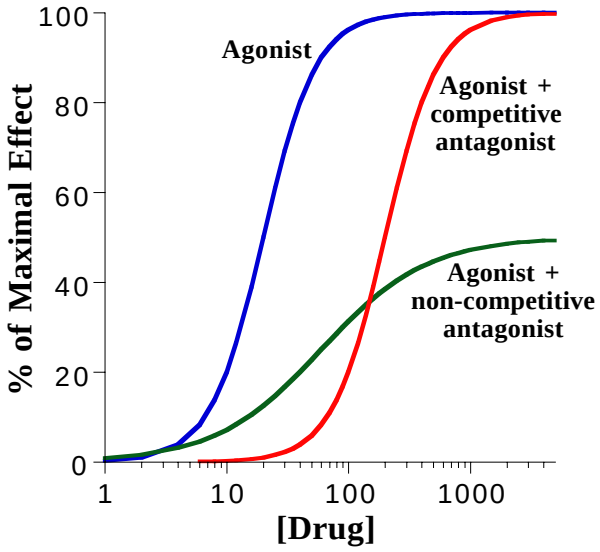
If we return to the issue of potency and keeping in mind the equation that describes the relationship between drug effect and dose, the only way that unequal doses of two drugs can produce the same effect is if their dissociation constants (K_D) differ. So the dissociation constant is a measure of the **affinity** of the drug for its receptor, just like the Michaelis-Menten constant (K_m) is a measure of the affinity of a substrate for its enzyme.

The interaction of a drug with a receptor can produce a range of different types of effects. The types of interactions that can occur are shown graphically below. Drugs that bind to a receptor and mimic the effect of the endogenous ligand are called *agonists*. If a drug produces less than a full effect even at doses that saturate the receptor, it is a *partial agonist*. Partial agonist are less efficacious. An *antagonist* is a drug that binds to a receptor but does not produce an effect. Antagonists produce a pharmacologic effect by inhibiting the effect of an agonist. Less commonly drugs that bind to a receptor can produce a negative effect and these agents are called *negative antagonists* or *inverse agonists.*



Drug receptor interactions can be complex and the dose-effect curve can take on a shape other than the classical sigmoidal curve. The pharmacologic effect can the sum the interaction of a drug with multiple receptors. There are also drugs that produce a pharmacologic effect that is not mediated through a receptor, such as antacids.

The plot below shows the dose-effect curves for an agonist alone, the agonist combined with a competitive antagonist and combined with a noncompetitive antagonist. A competitive antagonist combines reversibly with the same binding site as the agonist or active drug and can be displaced from the binding site by an excess of the agonist. The maximal effect of the agonist can still be achieved if sufficient agonist is used. A competitive inhibitor lowers the *potency* of the agonist but does not alter its *efficacy*.



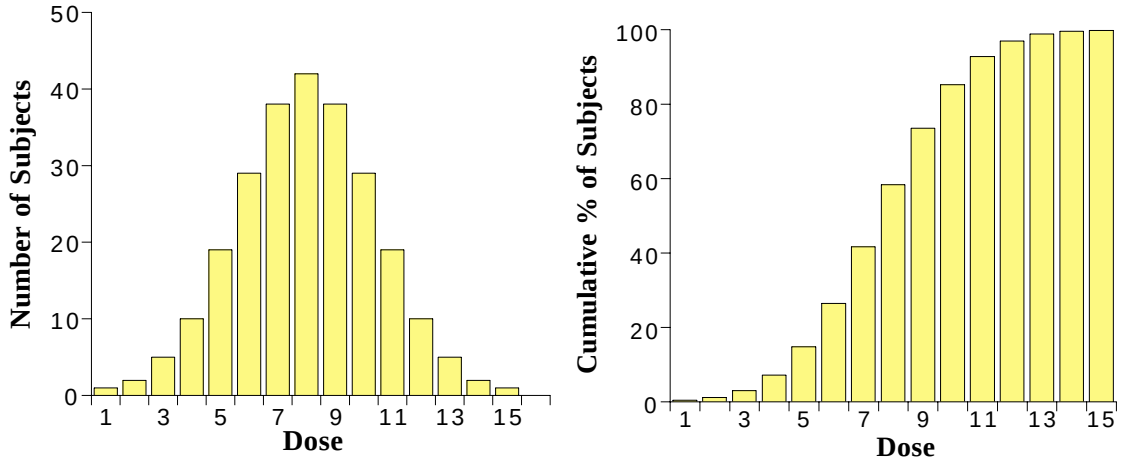
A non-competitive antagonist binds irreversible to the receptor binding site or interacts with other components of the system to decrease or eliminate the effect of the drug binding to the receptor. A non-competitive receptor prevents the agonist, at any concentration, from producing a maximal effect. Typically the dose-effect curve with this type of antagonist reveals reduced apparent *efficacy*, but the *potency* is not altered. Using the dose-effect curve to study drug interactions can obviously be helpful in elucidating the mechanism of the drug interaction.

QUANTAL DOSE-EFFECT RELATIONSHIP

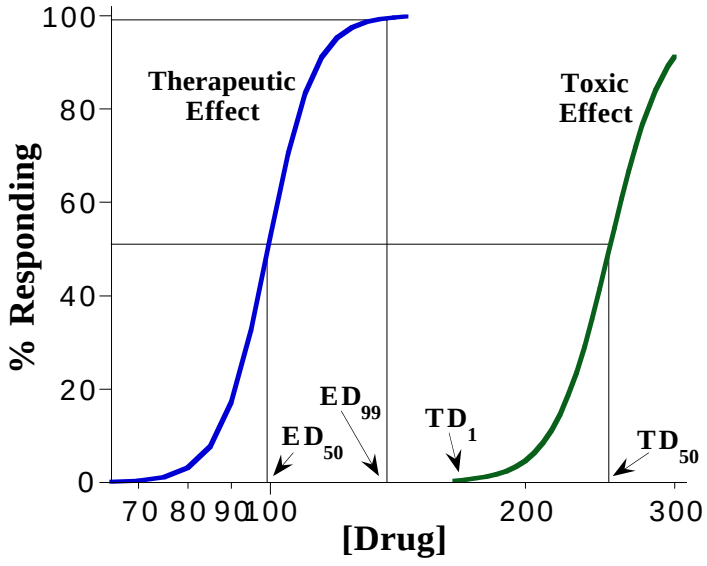
When a drug effect is an all-or-none effect, the relationship between dose and response is assessed in a population study and dose is related to the minimum or threshold dose that produces the effect in each subject of the population.

This graph of dose vs. the number of subjects responding at that dose is a frequency distribution plot. Within a population there is usually a wide range of doses were required to produce the effect. The maximum frequency at which the effect occurs is in the middle portion of the dose range. The frequency distribution takes on the

shape of a bell-shaped curve, which is also known as a **normal frequency distribution** (graph on left, below).



A more convenient way to express a *quantal* dose-effect curve is to plot the dose vs. the cumulative percentage of subjects experiencing the effect. The normal distribution is transformed into a familiar S-shaped or sigmoidal curve (graph on right, above). Although this curve resembles the graded dose-effect curve, remember that the graded curve expresses the relationship between intensity of effect with a change in the dose, whereas the quantal curve is a measure of the variation in the threshold dose required to produce a defined all-or-none effect in a group of subjects. The median effective dose (ED_{50}) of the quantal dose-effect curve is the dose at which 50% of the population responds.



Defining the threshold dose in each subject is usually not practical; therefore, population dose-effect studies are typically designed to treat groups of subjects at different dose levels. The fraction of subjects responding at each dose level would then be those subjects for which the dose is at or above their threshold dose. This essentially represents a cumulative response at each dose level.

There is no single dose-effect curve that can adequately characterize the full spectrum of activity of a drug. All drugs produce at least 2 effects (the desired therapeutic effect and side effect[s]) and therefore drugs have at least two quantal dose-response curves - one for the therapeutic effect and one or more for the toxic effect. The safety of a drug depends on the degree of separation

between the doses producing a therapeutic effect and the doses that produce side effects.

Therapeutic indices, which are a measure of a drugs relative safety, can be estimated from the dose-effect curves.

- The *therapeutic ratio* ($\frac{TD_{50}}{ED_{50}}$) is a ratio of the TD_{50} (dose at which 50% of subjects experience a toxicity) to the ED_{50}. (the dose at which 50% of patients respond). The therapeutic ratio for drug shown in the graph above is about 2.5, which means that about 2.5 times as much drug is required to cause toxicity in half of the subjects as is needed to produce a therapeutic effect in the same proportion of subjects. However this ratio of toxic to therapeutic dose may not hold across the entire dose range if the dose-effect curves are not parallel.
- The aim of drug therapy is to achieve the desired therapeutic effect in all patients without the producing toxicity in any. A ratio that uses the lowest toxic and highest therapeutic doses is more realistic and consistent with this aim. The *certain safety factor* (CSF) is the ratio of $\frac{TD_1}{ED_{99}}$. A CSF > 1 indicates that the dose effective in 99% of the population is less than that which would be toxic in 1%. If the CSF < 1, there is overlap between the maximally effective and minimally toxic doses. Unlike the therapeutic ratio this measure is independent of the shapes of the quantal dose-effect curves for the therapeutic and toxic effects.
- The *standard safety margin* ($\frac{TD_1 - ED_{99}}{ED_{99}} \times 100$) uses the same extremes (TD_1 and ED_{99}) and derives the percentage by which the ED_{99} has to be increased before the TD_1 is reached.

BETWEEN DOSE AND EFFECT

The quantal dose-effect analyses demonstrate the inherent variability in the effect achieved with a fixed dose in a group of patients, or conversely the wide range of doses required in a population of patients to achieve the same effect. This variability is introduced by the processes responsible for delivering the drug to the target site (*pharmacokinetics*) and the organ or tissue sensitivity to the drug (*pharmacodynamics*).

Advances in the field of pharmacokinetics, including the development of sensitive and specific methods for quantifying drug concentrations in biological samples, have expanded our understanding of the time course of drug concentrations in plasma/serum and the processes (absorption, distribution, metabolism and excretion) that influence that amount of drug that reaches target organs or tissues. Compartmental models have been developed that accurately predict the disposition of drug in plasma/serum and simulate the concentration or amount of drug delivered to non-physiological tissue compartments. However, the time course of drug concentrations in the body cannot in itself predict the time course or

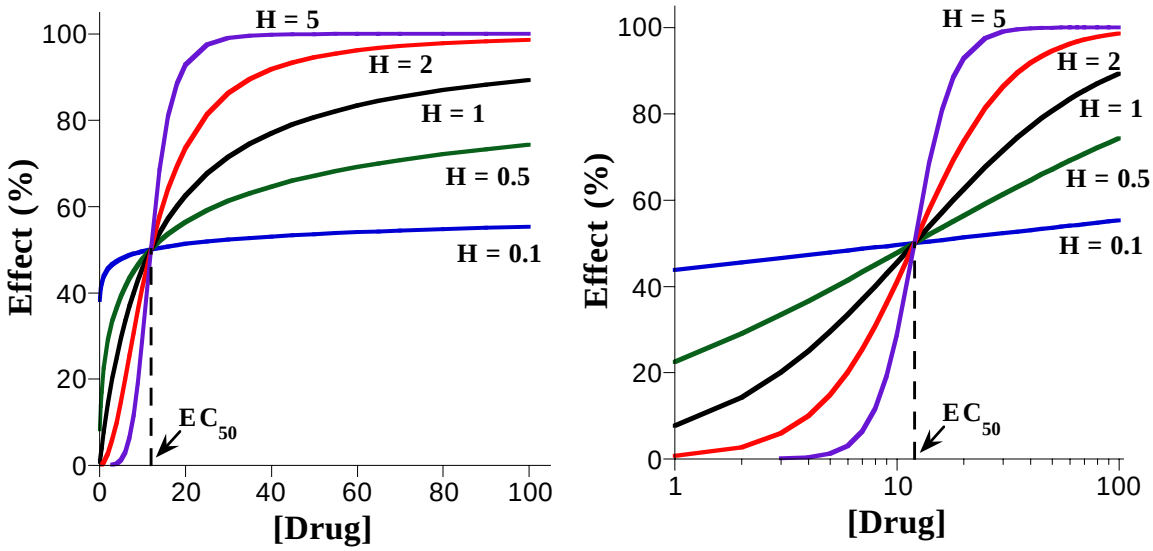
magnitude of drug effect. The linking of pharmacokinetics and pharmacodynamics allows for the prediction of the dose-concentration relationship and the concentration-effect relationship.

Unlike, pharmacokinetic models, mathematical PD models are time-independent and describe the equilibrium relationship between drug concentration and effect. Examples of the types of pharmacodynamic models that have been employed include:

- **E_{max} and Sigmoid E_{max} model**. This mathematical model has the same format as the equation describing the drug-receptor interactions which are responsible for producing the drug effect, and is called the Hill equation:

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

where E_{max} is the maximal effect, EC_{50} is the drug concentration producing 50% of E_{max}, and the exponential constant, H (Hill constant), controls the slope of the sigmoid-shaped curve, as shown in the plots below. The E_{max} model is a Sigmoid E_{max} model with a slope factor, H = 1 ($Effect = \frac{E_{\max} \bullet C}{EC_{50} + C}$).



This model presents a hyperbolic relationship between concentration and effect, such that as the concentration rises above the EC_{50}, there is diminishing increment in effect.

- **Linear and Log-Linear model.** Over a narrow range of drug concentrations the relationship between concentration and effect may appear to be linear ($Effect = E_0 + S \bullet [Drug]$), where S if the slope of the line and E_0 is the baseline effect with no drug present. The linear model is intuitively popular, but rarely applies. The log-linear model ($Effect = S \bullet \log(C) + I$, where I is the intercept) is applicable between 20% and 80% of the maximal effect, where the relationship between the effect and logarithm of the concentration is linear (see plot on right, above). Neither the linear or log-linear models predicts for a maximal effect.

The ultimate goal of understanding the dose-effect relationship is to derive optimum dosing regimens, and this can be achieved by linking pharmacokinetics and pharmacodynamics to derive the *effect-time relationship.* For example, integrating the simplest models, a one compartment model with bolus dosing and an E_{max} model to describe drug effect yields the following equations and plot:

One-compartment Model:

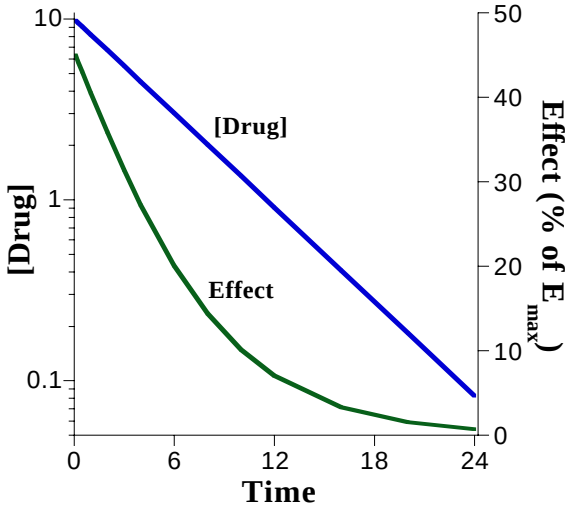
$$Conc. = \frac{Dose}{V_d} \bullet e^{-k_e t}$$

where Conc. is the drug concentration at time t, V_d is the volume of the single compartment (10 L) and k_e is the elimination rate constant (0.2 hr).

PK-PD Model:

$$Effect = \frac{E_{\max} \bullet Dose \bullet e^{-k_e t}}{EC_{50} \bullet V_d + Dose \bullet e^{-k_e t}}$$

where E_{max} is 100% and EC_{50} is 12. The concentration-time and effect-time plots are shown at the right on a double-Y graph.



More rational and individualized dosing regimens which incorporate adaptive dosing and therapeutic drug monitoring have evolved from integrating our knowledge of pharmacokinetics and pharmacodynamics.

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