Unit IV: Pharmacodynamics:

Dose-Response Relationships

❖ Drug Dose and Clinical Response

To make rational therapeutic decisions, it is necessary to understand the fundamental concepts linking drug doses to concentrations to clinical responses. The concentration-response relationships for drugs may be graded or quantal. A **graded concentration-response curve** can be constructed for responses measured on a continuous scale, eg, heart rate. Graded concentration-response curves relate the intensity of response to the size of the dose and, hence, are useful to characterize the actions of drugs. A **quantal concentration-response curve** can be constructed for drugs that elicit an all-or-none response, eg, presence or absence of convulsions. For most drugs, the doses required to produce a specified quantal effect in a population are log normally distributed, so that the frequency distribution of responses plotted against log dose is a gaussian normal distribution curve. The percentage of the population requiring a particular dose to exhibit the effect can be determined from this curve. When these data are plotted as a cumulative frequency distribution, a sigmoidal dose-response curve is generated.

The **equilibrium dissociation constant of the receptor-drug complex, K_D**, is the ratio of rate constants for the reverse (k_2) and forward (k_1) reaction between the drug and receptor and the drug-receptor complex (see Drug Concentration and Effect). K_D is also the drug concentration at which receptor occupancy is half of maximum. Drugs with a high K_D (low affinity) dissociate rapidly from receptors; conversely, drugs with a low K_D (high affinity)

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dissociate slowly from receptors. These effects impact the rate at which biologic responses end.

Potency describes the relationship between the drug dose and the magnitude of the effect. High potency induces a strong effect with a low drug dose. Potency refers to the concentration (EC_{50}) or dose (ED_{50}) of a drug required to produce 50% of the drug's maximal effect as depicted by a graded dose-response curve. EC_{50} equals K_D when there is a linear relationship between occupancy and response. Often, signal amplification occurs between receptor occupancy and response, which results in the EC_{50} for response being much less (ie, positioned to the left on the x-axis of the log dose-response curve) than K_D for receptor occupancy. Potency depends on both the affinity of a drug for its receptor and the efficiency with which drug-receptor interaction is coupled to response. The dose of drug required to produce an effect is inversely related to potency. In general, low potency is important only if it results in a need to administer the drug in large doses that are impractical. Quantal dose-response curves provide information on the potency of drugs that is different from the information derived from graded dose-response curves. In a quantal dose-response relationship, the ED_{50} is the dose at which 50% of individuals exhibit the specified quantal effect.

The **median inhibitory concentration**, or IC_{50}, is the concentration of an antagonist that reduces a specified response to 50% of the maximal possible effect.

Efficacy is the in vivo potency, or the maximum response achieved from a drug. The interaction (e.g., absorption, metabolism, and excretion) of the drug in the body may alter the relative bioavailability and, thus, change the theoretic effect of the drug. Rapid metabolism of a high-potency drug, for example, may render it of low efficacy whereas rapid absorption, minimal first-pass

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metabolism, and delayed excretion may create higher efficacy despite much lower potency. Efficacy (also referred to as intrinsic activity) of a drug is the ability of the drug to elicit a response when it binds to the receptor.Conformational changes in receptors as a result of drug occupancy initiate biochemical and physiologic events that characterize the drug's response. In some tissues, agonists demonstrating high efficacy can result in a maximal effect, even when only a small fraction of the receptors is occupied (the concept of spare receptors is discussed above).

Generally speaking, the ideal drug will be easy to administer, fully absorbed, not plasma bound, of rapid onset, spontaneously eliminated, chemically stable, highly selective and specific, and of high affinity, potency, and efficacy. It will also have a useful duration of action, a high therapeutic index (no adverse effects), and no interactions. However, there are no examples of synthetic or natural drugs that satisfy all these criteria. Furthermore, there may be circumstances under which these ideal properties are not wanted. For example, high affinity can also cause a prolonged action that may not be desirable, such as in the case of dipyridamole versus adenosine. High potency is also not always desirable—for example, in a drug with poor selectivity. That is, a drug that has a nonselective biodistribution will have a poorer safety profile if it is also highly potent than if it is less potent.

Specificity is the measure of a receptor's ability to respond to a single ligand. Low specificity generally results in physiologic responses not targeted or intended by the drug; side effects are a good example. Indeed, it is not uncommon for a drug to be developed with a theoretic action, but poor specificity for that action undermines efficacy while a side effect emerges as the new targeted role. A classic example is sildenafil (Viagra; Pfizer), which was developed to treat hypertension and angina. The drug was not particularly

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effective for that purpose, but an observed side effect became the new targeted role of the drug. Examples of specific drugs include atropine (a muscarinic receptor antagonist), salbutamol (a β_2-adrenoceptor agonist), and cimetidine (an H_2-receptor antagonist). By contrast, nonspecific drugs result in drug effects through several mechanisms of action. For example, phenothiazine causes blockade of D_2-dopamine receptors, α-adrenergic receptors, and muscarinic receptors.

Selectivity defines the ability of the receptor to distinguish between drugs and has the same implications as specificity; indeed, the terms are often used interchangeably. Selectivity refers to the structural specificity of drug binding to receptors. For example, cyclooxygenase-2 (COX-2) preferential NSAIDs demonstrate partial specificity for COX-2, the inducible enzyme formed at sites of inflammation. By comparison, COX-2 selective NSAIDs are without significant effect on COX-1, the constitutive enzyme that performs a range of physiologic functions. For certain drugs, selectivity is species dependent. For example, *S*(+)-carprofen is COX-2 selective in dogs and cats, nonselective of COX-1 and COX-2 in horses, and COX-2 preferential in calves. Adenosine is nonselective (4 adenosine receptors with different actions) and as a result has the unwanted effect of potential bronchospasm (A_1 receptor), whereas regadenoson is selective for the A_{2A} receptor (vasodilation and bronchodilation).

Affinity defines the strength of attraction between the drug and its receptor (ie, the K_D). The chemical forces in drug-receptor interactions include electrostatic forces, van der Waal forces, and the forces associated with hydrogen bonds and hydrophobic bonds. Variation in the strength of these forces, and therefore the thermal energy in the system, determines the degree of association and dissociation of the drug and the receptor. Covalent binding of drug to receptor (exemplified by fluoroquinolones acting on bacteria) leads to formation of an

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irreversible link. A high affinity is generally associated with a lower dose requirement (compared with low affinity for the same receptor).

The **therapeutic index** of a drug is the ratio of the dose that results in an undesired effect to the dose that results in a desired effect. The therapeutic index of a drug is usually defined as the ratio of LD_{50} to ED_{50} (median lethal and median effective doses, respectively, in 50% of individuals), which indicates how selective the drug is in eliciting its desired effect. Values of LD_{50} and ED_{50} for this purpose are derived from quantal dose-response curves generated in animal studies.

The information obtained from dose- and concentration-response curves is critically important when choosing between drugs and when determining the dose to administer. A drug is chosen largely on the basis of its clinical effectiveness for a particular therapeutic indication. In this context, the drug concentration at the receptor (determined by the pharmacokinetic properties of the drug) and the efficacy of the drug-receptor complex are the primary determinants of a drug's clinical effectiveness. The administered dose of a drug, by comparison, depends to a greater extent on potency than on maximal efficacy.

The maximal efficacy of the drug-receptor complex to result in a graded effect is E_{max} or I_{max} on a graded dose-response curve. E_{max} or I_{max} is derived from a quantitative dose-response relationship for a single animal and varies among individuals. The extrapolation of this value of E_{max} to a clinical case is only an estimate, but it facilitates a comparison of the maximal efficacy of drugs that result in a specified effect by identical receptors. A drug's potency (ie, EC_{50}, ED_{50}, or IC_{50}) obtained from either graded or quantal dose-response curves is used to determine the dose that should be administered. The slope of the graded dose-response curve (n in the Hill equation, above) provides

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information concerning the dose range over which a drug elicits its effect. Other information concerning the selectivity of drug action and the therapeutic index is also obtained from the graded dose-response curve. When quantal effects are being considered, information concerning pharmacologic potency, selectivity of drug action, the margin of safety, and the potential variability of responsiveness among individuals is obtained from quantal dose-response curves.

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