Several new drugs are being tested for their effects on $\beta_2$-adrenergic receptors. The investigator plots an S-shaped curve of the activity of adenylate cyclase vs. drug dose in response to drug A. When the response of drug D is similarly plotted, D is found to have a lower median effective dose ($ED_{50}$) and a lower maximal response than A. In the presence of drug A plus drug B, the curve has the same shape but is now shifted to the right. In the presence of drug A plus drug C, the curve is not shifted, but the maximal response is lower.

**Which drug, A or D, has a higher efficacy?**

Efficacy refers to the maximal response a drug elicits. Thus, drug A has a higher efficacy, since it produces a higher maximal response (Figure 4-11).

**Which drug is more potent?**

Drug D is more potent (Figure 4-11). Potency is the amount of drug required for a specified response. Typically, potency is measured by the $ED_{50}$ or the dose that gives 50% of the maximal response. The lower the $ED_{50}$, the more potent the drug.

**What type of antagonist is drug B?**

Drug B is a competitive antagonist—that is, it binds to the same site on the receptor as does drug A (Figure 4-12A). It does not affect the maximal response the agonist can elicit, but it does increase the $ED_{50}$ requiring more agonist to achieve the same response, thus decreasing potency.

**What type of antagonist is drug C?**

Drug C is a noncompetitive antagonist (Figure 4-12B). These drugs act by binding irreversibly to a site on the receptor distinct from the site of agonist binding. Noncompetitive antagonists do not affect the $ED_{50}$ but do affect the maximal response (decrease efficacy) that the agonist can elicit.

**How can the effect of drug B be overcome?**

Since competitive antagonists bind at the same site as the agonist, their action can be overcome by increasing agonist dose. If enough agonist is present, the same efficacy can be reached that the agonist had in the absence of an antagonist.
The kinetics of a new pharmaceutical agent is being tested in an animal model. A dose of 50 mg of the substance is injected intravenously into a rat. The concentration of the substance in the animal's blood is measured every 30 minutes thereafter for the next 10 hours. The concentration of the drug plotted against time produces the graph shown in Figure 4-13.

**Is this substance being metabolized by first-order or zero-order kinetics?**
The shape of the graph shows that the drug is being eliminated by first-order kinetics (see Figure 4-14A), meaning that a constant fraction of the substance is eliminated per unit of time. As a result, the rate of elimination is proportional to the concentration of the drug. By contrast, zero-order kinetics (see Figure 4-14B) results in a constant amount of the substance being cleared per unit of time; the elimination rate is constant regardless of the plasma concentration ($C_p$), and the plot of $C_p$ vs. time is a straight line.

![Graphs showing first-order and zero-order kinetics](image)

**Which drugs follow zero-order kinetics?**
Nearly all medications follow first-order kinetics. Three notable exceptions are aspirin, phenytoin, and alcohol.

**Why does the volume of distribution affect the half-life of a drug?**
Volume of distribution ($V_d$) is the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired blood concentration of a drug. A useful equation is the following:

$$V_d = \text{Clearance} - \frac{t_{1/2}}{0.7}$$

As indicated by the equation above, $t_{1/2}$ is directly proportional to $V_d$. This is because the larger the $V_d$, the smaller the amount of drug present in the plasma compartment and therefore the smaller the amount of drug circulated through the kidneys and liver for metabolism and excretion.
What is the half-life of this substance, and how does the half-life change if a dosage of 100 mg is administered?

Half-life ($t_{1/2}$) is the time necessary to decrease the $C_{p}$ of the drug by 50%. As shown in Figure 4-13, at 5 hours the $C_{p}$ of the drug is half of the initial concentration, and thus $t_{1/2}$ is 5 hours. Half-life does not depend on the size of the dose being eliminated.

How would the therapeutic index of this drug be determined, and why is this important?

Therapeutic index is the ratio of a drug's toxic dose to the therapeutic dose. Safe drugs will have a high therapeutic index, indicating a large difference between the dose used to treat patients and the dose resulting in toxicity. Drugs with a low index, such as digoxin, have to be carefully monitored by checking serum levels of the drug.

$$\text{Therapeutic ratio} = \frac{LD_{50}}{ED_{50}}$$

$LD_{50}$ = lethal dose of drug for 50% of population.

$ED_{50}$ = effective dose of drug for 50% of population. Case 13
A 17-year-old high school student is brought to the emergency department after feeling a tearing sensation in his knee when he was tackled playing football. After the initial consult, it is determined that the boy will need surgery to reattach a torn ligament. During anesthesia, a neuromuscular blocking drug (NMBD) is given.

**In what clinical settings are NMBDs used?**
The NMBDs are used for muscle paralysis during surgery or mechanical ventilation.

**What are some examples of NMBD drugs?**
Examples of these agents include succinylcholine, tubocurarine, and most drugs that end in “-curium” (eg, atracurium) or “-curonium” (eg, rocuronium).

**For what type of receptors is this class of drug selective?**
Neuromuscular agents are specific for the motor nicotinic acetylcholine receptors present at the neuromuscular junction.

**What are the two types of neuromuscular blocking drugs?**
There are depolarizing and nondepolarizing (of which succinylcholine is the only one commonly used) blocking agents.

**What is the mechanism of action of depolarizing blocking agents?**
Depolarizing agents such as succinylcholine act in two phases. Phase I consists of active depolarization of sodium channels, which can be potentiated by cholinesterase inhibitors. Phase II keeps sodium channels stuck in their depolarized state. Phase II can be reversed with cholinesterase inhibitors.

**What is the mechanism of action of nondepolarizing blocking agents?**
These drugs are mostly close relatives of tubocurarine. They act by competing with acetylcholine for nicotinic motor receptors. These drugs can be reversed using cholinesterase inhibitors.

**What is an important potential risk of using succinylcholine?**
The combination of inhalational anesthetics and succinylcholine may result in malignant hyperthermia (sympathetic hyperactivity, muscular rigidity, acidosis) due to the prevention of calcium release from the sarcoplasmic reticulum of skeletal muscle. This condition can be treated with dantrolene.