

APPLIED BIOPHARMACEUTICS & PHARMACOKINETICS

FIFTH EDITION

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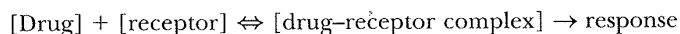
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RELATIONSHIP BETWEEN PHARMACOKINETICS AND PHARMACODYNAMICS

PHARMACODYNAMICS AND PHARMACOKINETICS

Previous chapters in this book have discussed the importance of using pharmacokinetics to develop dosing regimens that will result in plasma concentrations in the therapeutic window and yield the desired therapeutic or pharmacologic response. The interaction of a drug molecule with a receptor causes the initiation of a sequence of molecular events resulting in a pharmacodynamic or pharmacologic response. The term *pharmacodynamics* refers to the relationship between drug concentrations at the site of action (receptor) and pharmacologic response, including the biochemical and physiologic effects that influence the interaction of drug with the receptor. Early pharmacologic research demonstrated that the pharmacodynamic response produced by the drug depends on the chemical structure of the drug molecule. Drug receptors interact only with drugs of specific chemical structure, and the receptors were classified according to the type of pharmacodynamic response induced.

Since most pharmacologic responses are due to noncovalent interaction between the drug and the receptor, the nature of the interaction is generally assumed to be reversible and conforms to the *Law of Mass Action*. One or several drug molecules may interact simultaneously with the receptor to produce a pharmacologic response. Typically, a single drug molecule interacts with a receptor with a single binding site to produce a pharmacologic response, as illustrated below.



where the brackets [] denote molar concentrations. This scheme illustrates the *occupation theory* and the interaction of a drug molecule with a receptor molecule. The following assumptions are made in this model.

1. The drug molecule combines with the receptor molecule as a bimolecular association, and the resulting drug-receptor complex disassociates as a unimolecular entity.
2. The binding of drug with the receptor is fully reversible.
3. The basic model assumes a single type of receptor binding site, with one binding site per receptor molecule. It is also assumed that a receptor with multiple sites may be modeled after this (Taylor and Insel, 1990).

It is assumed that the occupancy of the drug molecule at one receptor site does not change the affinity of more drug molecules to complex at additional receptor sites. However, the model is not suitable for drugs with *allosteric* binding to receptors, in which the binding of one drug molecule to the receptor affects the binding of subsequent drug molecules, as in the case of oxygen molecules binding to iron in hemoglobin. As more receptors are occupied by drug molecules, a greater pharmacodynamic response is obtained until a maximum response is reached.

The receptor occupancy concept was extended to show how drugs elicit a pharmacologic response as an *agonist*, or produce an opposing pharmacologic response as an *antagonist* through drug-receptor interactions. Basically, three types of related responses may occur at the receptor: (1) a drug molecule that interacts with the receptor and elicits a maximal pharmacologic response is referred to as an *agonist*; (2) a drug that elicits a partial (below maximal) response is termed a *partial agonist*; and (3) an agent that elicits no response from the receptor, but inhibits the receptor interaction of a second agent, is termed an *antagonist*. An antagonist may prevent the action of an agonist by competitive (reversible) or noncompetitive (irreversible) inhibition.

Spare, unoccupied receptors are assumed to be present at the site of action, because a maximal pharmacologic response may be obtained when only a small fraction of the receptors are occupied by drug molecules. Equimolar concentrations of different drug molecules that normally bind to the same receptor may give different degrees of pharmacologic response. The term *intrinsic activity* is used to distinguish the relative extent of pharmacologic response between different drug molecules that bind to the same receptor. The *potency* of a drug is the concentration of drug needed to obtain a specific pharmacologic effect, such as the EC_{50} (see E_{\max} model, below).

The receptor occupation theory, however, was not consistent with all kinetic observations. An alternative theory, known as the *rate theory*, essentially states that the pharmacologic response is not dependent on drug-receptor complex concentration but rather depends on the rate of association of the drug and the receptor. Each time a drug molecule "hits" a receptor, a response is produced, similar to a ball bouncing back and forth from the receptor site. The rate theory predicts that an agonist will associate rapidly to form a receptor complex, which dissociates rapidly to produce a response. An antagonist associates rapidly to form a receptor-drug complex and dissociates slowly to maintain the antagonist response.

Both theories are consistent with the observed saturation (*sigmoidal*) drug-dose response relationships, but neither theory is sufficiently advanced to give a detailed description of the "lock-and-key" or the more recent "induced-fit" type of drug interactions with enzymatic receptors. Newer theories of drug action are based on *in-vitro* studies on isolated tissue receptors and on observation of the conformational and binding changes with different drug substrates. These *in-vitro* studies show that other types of interactions between the drug molecule and the receptor are possible. However, the results from the *in-vitro* studies are difficult to extrapolate to *in-vivo* conditions. The pharmacologic response in drug therapy is often a product of physiologic adaptation to a drug response. Many drugs trigger the pharmacologic response through a cascade of enzymatic events highly regulated by the body.

Unlike pharmacokinetic modeling, pharmacodynamic modeling can be more complex because the clinical measure (change in blood pressure or clotting time) is often a surrogate for the drug's actual pharmacologic action. For example, after the drug is systemically absorbed, it is then transported to site of action where the pharmacologic receptor resides. Drug-receptor binding may then cause a secondary response, such as signal transduction, which then produces the desired effect. Clinical measurement of drug response may only occur after many such biologic events, such as transport or signal transduction (an *indirect effect*), so pharmacodynamic modeling must account for biologic processes involved in eliciting drug-induced responses.

The complexity of the molecular events triggering a pharmacologic response is less difficult to describe using a pharmacokinetic approach. Pharmacokinetic models allow very complex processes to be simplified. The process of pharmacokinetic modeling continues until a model is found that describes the real process quantitatively. The understanding of drug response is greatly enhanced when pharmacokinetic modeling techniques are combined with clinical pharmacology, resulting in the development of *pharmacokinetic-pharmacodynamic models*. Pharmacokinetic-pharmacodynamic models use data derived from the plasma drug concentration-versus-time profile and from the time course of the pharmacologic effect to predict the pharmacodynamics of the drug. Pharmacokinetic-pharmacodynamic models have been reported for antipsychotic medications, anticoagulants, neuromuscular blockers, antihypertensives, anesthetics, and many antiarrhythmic drugs (the pharmacologic responses of these drugs are well studied because of easy monitoring).

RELATION OF DOSE TO PHARMACOLOGIC EFFECT

The onset, intensity, and duration of the pharmacologic effect depend on the dose and the pharmacokinetics of the drug. As the dose increases, the drug concentration at the receptor site increases, and the pharmacologic response (effect) increases up to a maximum effect. A plot of the pharmacologic effect to dose on a linear scale generally results in a hyperbolic curve with maximum effect at the plateau (Fig. 19-1). The same data may be compressed and plotted on a log-linear scale and results in a sigmoid curve (Fig. 19-2).

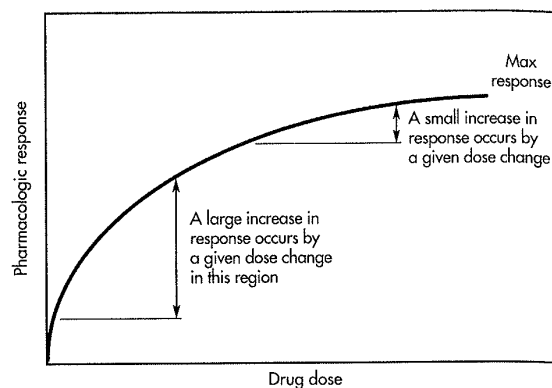


Figure 19-1. Plot of pharmacologic response versus dose on a linear scale.

For many drugs, the graph of log dose–response curve shows a linear relationship at a dose range between 20% and 80% of the maximum response, which typically includes the therapeutic dose range for many drugs. For a drug that follows one-compartment pharmacokinetics, the volume of distribution is constant; therefore, the pharmacologic response is also proportional to the log plasma drug concentration within a therapeutic range, as shown in Figure 19-3.

Mathematically, the relationship in Figure 19-3 may be expressed by the following equation, where m is the slope, e is an extrapolated intercept, and E is the drug effect at drug concentration C :

$$E = m \log C + e \quad (19.1)$$

Solving for $\log C$ yields

$$\log C = \frac{E - e}{m} \quad (19.2)$$

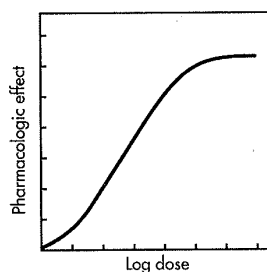


Figure 19-2. Typical log dose versus pharmacologic response curve.

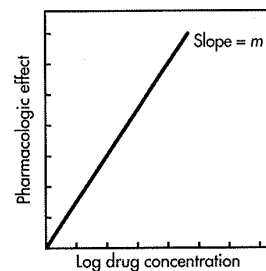


Figure 19-3. Graph of log drug concentration versus pharmacologic effect. Only the linear portion of the curve is shown.

However, after an intravenous dose, the concentration of a drug in the body in a one-compartment open model is described as follows:

$$\log C = \log C_0 - \frac{kt}{2.3} \quad (19.3)$$

By substituting Equation 19.2 into Equation 19.3, we get Equation 19.4, where E_0 = effect at concentration C_0 :

$$\begin{aligned} \frac{E - e}{m} &= \frac{E_0 - e}{m} - \frac{kt}{2.3} \\ E &= E_0 - \frac{kmt}{2.3} \end{aligned} \quad (19.4)$$

The theoretical pharmacologic response at any time after an intravenous dose of a drug may be calculated using Equation 19.4. Equation 19.4 predicts that the pharmacologic effect will decline linearly with time for a drug that follows a one-compartment model, with a linear log dose–pharmacologic response. From this equation, the pharmacologic effect declines with a slope of $km/2.3$. The decrease in pharmacologic effect is affected by both the elimination constant k and the slope m . For a drug with a large m , the pharmacologic response declines rapidly and multiple doses must be given at short intervals to maintain the pharmacologic effect.

The relationship between pharmacokinetics and pharmacologic response can be demonstrated by observing the percent depression of muscular activity after an IV dose of (+)-tubocurarine. The decline of pharmacologic effect is linear as a function of time (Fig. 19-4). For each dose and resulting pharmacologic response, the slope of each curve is the same. Because the values for each slope, which include km (Eq. 19.4), are the same, the sensitivity of the receptors for (+)-tubocurarine is assumed to be the same at each site of action. Note that a plot of the log concentration of drug versus time yields a straight line.

A second example of the pharmacologic effect declining linearly with time was observed with lysergic acid diethylamide, or LSD (Fig. 19-5). After an IV dose of the drug, log concentrations of drug decreased linearly with time except for a brief distribution period. Furthermore, the pharmacologic effect, as measured by the performance score of each subject, also declined linearly with time. Because the

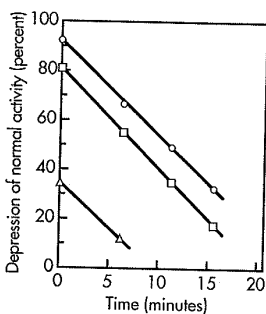


Figure 19-4. Depression of normal muscle activity as a function of time after IV administration of 0.1–0.2 mg (+)-tubocurarine per kilogram to unanesthetized volunteers, presenting mean values of 6 experiments on 5 subjects. Circles represent head lift; squares, hand grip; and triangles, inspiratory flow. (Adapted from Johansen et al, 1964, with permission.)

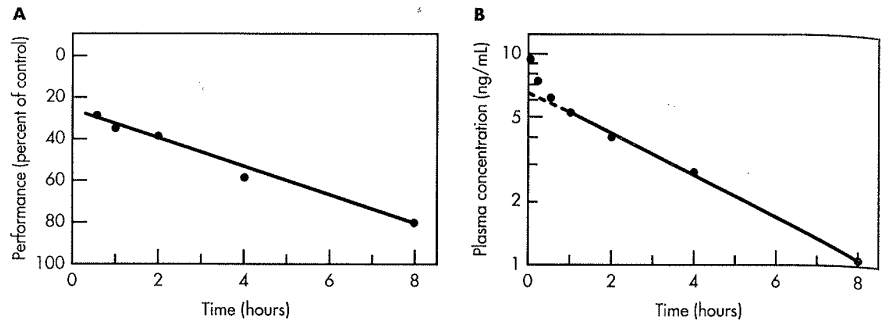


Figure 19-5. Mean plasma concentrations of LSD and performance test scores as a function of time after IV administration of 2 μg LSD per kilogram to 5 normal human subjects. (Adapted from Aghajanian and Bing, 1964, with permission.)

slope is governed in part by the elimination rate constant, the pharmacologic effect declines much more rapidly when the elimination rate constant is increased as a result of increased metabolism or renal excretion. Conversely, a longer pharmacologic response is experienced in patients when the drug has a longer half-life.

RELATIONSHIP BETWEEN DOSE AND DURATION OF ACTIVITY (t_{eff}), SINGLE IV BOLUS INJECTION

The relationship between the duration of the pharmacologic effect and the dose can be inferred from Equation 19.3. After an intravenous dose, assuming a one-compartment model, the time needed for any drug to decline to a concentration C is given by the following equation, assuming the drug takes effect immediately:

$$t = \frac{2.3 (\log C_0 - \log C)}{k} \quad (19.5)$$

Using C_{eff} to represent the minimum effective drug concentration, the duration of drug action can be obtained as follows:

$$t_{\text{eff}} = \frac{2.3 [\log (D_0 / V_D) - \log C_{\text{eff}}]}{k} \quad (19.6)$$

Some practical applications are suggested by this equation. For example, a doubling of the dose will not result in a doubling of the effective duration of pharmacologic action. On the other hand, a doubling of $t_{1/2}$ or a corresponding decrease in k will result in a proportional increase in duration of action. A clinical situation is often encountered in the treatment of infections in which C_{eff} is the bacteriocidal concentration of the drug, and, in order to double the duration of the antibiotic, a considerably greater increase than simply doubling the dose is necessary.



PRACTICE PROBLEM

The minimum effective concentration (MEC) in plasma for a certain antibiotic is $0.1 \mu\text{g/mL}$. The drug follows a one-compartment open model and has an apparent volume of distribution, V_D , of 10 L and a first-order elimination rate constant of 1.0 hr^{-1} .

- What is the t_{eff} for a single 100-mg IV dose of this antibiotic?
- What is the new t_{eff} or t'_{eff} for this drug if the dose were increased 10-fold, to 1000 mg?

Solution

- The t_{eff} for a 100-mg dose is calculated as follows. Because $V_D = 10,000 \text{ mL}$,

$$C_0 = \frac{100 \text{ mg}}{10,000 \text{ mL}} = 10 \mu\text{g/mL}$$

For a one-compartment-model IV dose, $C = C_0 e^{-kt}$. Then

$$0.1 = 10 e^{-(1.0)t_{\text{eff}}}$$

$$t_{\text{eff}} = 4.61 \text{ hr}$$

- The t'_{eff} for a 1000-mg dose is calculated as follows (prime refers to a new dose). Because $V_D = 10,000 \text{ mL}$,

$$C'_0 = \frac{1000 \text{ mg}}{10,000 \text{ mL}} = 100 \mu\text{g/mL}$$

and

$$C'_{\text{eff}} = C'_0 e^{-kt'_{\text{eff}}}$$

$$0.1 = 100 e^{-(1.0)t'_{\text{eff}}}$$

$$t'_{\text{eff}} = 6.91 \text{ hr}$$

The percent increase in t_{eff} is therefore found as

$$\text{Percent increase in } t_{\text{eff}} = \frac{t'_{\text{eff}} - t_{\text{eff}}}{t_{\text{eff}}} \times 100$$

$$\text{Percent increase in } t_{\text{eff}} = \frac{6.91 - 4.61}{4.61} \times 100$$

$$\text{Percent increase in } t_{\text{eff}} = 50\%$$

This example shows that a 10-fold increase in the dose increases the duration of action of a drug (t_{eff}) by only 50%.

EFFECT OF BOTH DOSE AND ELIMINATION HALF-LIFE ON THE DURATION OF ACTIVITY

A single equation can be derived to describe the relationship of dose (D_0) and the elimination half-life ($t_{1/2}$) on the effective time for therapeutic activity (t_{eff}). This expression is derived below.

$$\ln C_{\text{eff}} = \ln C_0 - kt_{\text{eff}}$$

Because $C_0 = D_0/V_D$,

$$\ln C_{\text{eff}} = \ln\left(\frac{D_0}{V_D}\right) - kt_{\text{eff}}$$

$$kt_{\text{eff}} = \ln\left(\frac{D_0}{V_D}\right) - \ln C_{\text{eff}} \quad (19.7)$$

$$t_{\text{eff}} = \frac{1}{k} \ln\left(\frac{D_0/V_D}{C_{\text{eff}}}\right)$$

Substituting $0.693/t_{1/2}$ for k ,

$$t_{\text{eff}} = 1.44t_{1/2} \ln\left(\frac{D_0}{V_D C_{\text{eff}}}\right) \quad (19.8)$$

From Equation 19.8, an increase in $t_{1/2}$ will increase the t_{eff} in direct proportion. However, an increase in the dose, D_0 , does not increase the t_{eff} in direct proportion. The effect of an increase in V_D or C_{eff} can be seen by using generated data. Only the positive solutions for Equation 19.8 are valid, although mathematically a negative t_{eff} can be obtained by increasing C_{eff} or V_D . The effect of changing dose on t_{eff} is shown in Figure 19-6 using data generated with Equation 19.8. A nonlinear increase in t_{eff} is observed as dose increases.

EFFECT OF ELIMINATION HALF-LIFE ON DURATION OF ACTIVITY

Because elimination of drugs is due to the processes of excretion and metabolism, an alteration of any of these elimination processes will effect the $t_{1/2}$ of the drug. In certain disease states, pathophysiologic changes in hepatic or renal function will

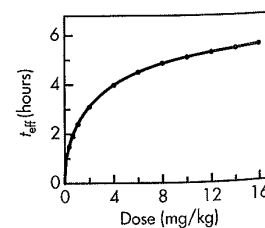


Figure 19-6. Plot of t_{eff} versus dose.

decrease the elimination of a drug, as observed by a prolonged $t_{1/2}$. This prolonged $t_{1/2}$ will lead to retention of the drug in the body, thereby increasing the duration of activity of the drug (t_{eff}) as well as increasing the possibility of drug toxicity.

To improve antibiotic therapy with the penicillin and cephalosporin antibiotics, clinicians have intentionally prolonged the elimination of these drugs by giving a second drug, probenecid, which competitively inhibits renal excretion of the antibiotic. This approach to prolonging the duration of activity of antibiotics that are rapidly excreted through the kidney has been used successfully for a number of years. Similarly, Augmentin is a combination of amoxicillin and clavulanic acid; the latter is an inhibitor of β -lactamase. This β -lactamase is a bacterial enzyme that degrades penicillin-like drugs. The data in Table 19.1 illustrate how a change in the elimination $t_{1/2}$ will affect the t_{eff} for a drug. For all doses, a 100% increase in the $t_{1/2}$ will result in a 100% increase in the t_{eff} . For example, for a drug whose $t_{1/2}$ is 0.75 hour and that is given at a dose of 2 mg/kg, the t_{eff} is 3.24 hours. If the $t_{1/2}$ is increased to 1.5 hours, the t_{eff} is increased to 6.48 hours, an increase of 100%. However, the effect of doubling the dose from 2 to 4 mg/kg (no change in elimination processes) will only increase the t_{eff} to 3.98 hours, an increase of 22.8%. The effect of prolonging the elimination half-life has an extremely important effect on the treatment of infections, particularly in patients with high metabolism, or clearance, of the antibiotic. Therefore, antibiotics must be dosed with full consideration of the effect of alteration of the $t_{1/2}$ on the t_{eff} . Consequently, a simple proportional increase in dose will leave the patient's blood concentration below the effective antibiotic level most of the time during drug therapy. The effect of a prolonged t_{eff} is shown in lines *a* and *c* in Figure 19-7, and the disproportionate increase in t_{eff} as the dose is increased 10-fold is shown in lines *a* and *b*.

TABLE 19.1 Relationship between Elimination Half-Life and Duration of Activity

DOSE (mg/kg)	$t_{1/2} = 0.75$ hr t_{eff} (hr)	$t_{1/2} = 1.5$ hr t_{eff} (hr)
2.0	3.24	6.48
3.0	3.67	7.35
4.0	3.98	7.97
5.0	4.22	8.45
6.0	4.42	8.84
7.0	4.59	9.18
8.0	4.73	9.47
9.0	4.86	9.72
10	4.97	9.95
11	5.08	10.2
12	5.17	10.3
13	5.26	10.5
14	5.34	10.7
15	5.41	10.8
16	5.48	11.0
17	5.55	11.1
18	5.61	11.2
19	5.67	11.3
20	5.72	11.4

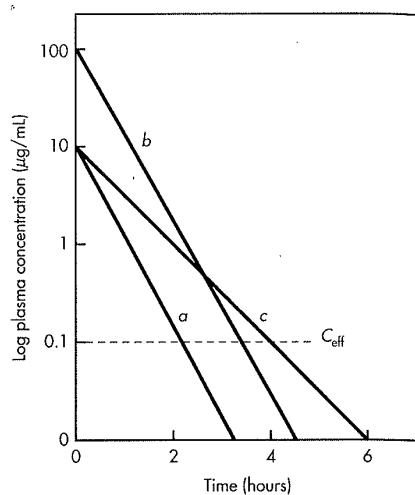


Figure 19-7. Plasma level-time curves describing the relationship of both dose and elimination half-life on duration of drug action. C_{eff} = effective concentration. Curve *a* = single 100-mg IV injection of drug; $k = 1.0 \text{ hr}^{-1}$. Curve *b* = single 1000-mg IV injection; $k = 1.0 \text{ hr}^{-1}$. Curve *c* = single 100-mg IV injection; $k = 0.5 \text{ hr}^{-1}$. V_D is 10 L.



CLINICAL EXAMPLES

Pharmacokinetic/Pharmacodynamic Relationships and Efficacy of Antibiotics

In the previous section, the time above the effective concentration, t_{eff} , was shown to be important in optimizing the therapeutic response of many drugs. This concept has been applied to antibiotic drugs (Drusano, 1988; Craig, 1995; Craig and Andes, 1996; Scaglione, 1997). For example, Craig and Andes (1996) discussed the antibacterial treatment of otitis media. Using the minimum inhibitory antibiotic concentration (MIC) for the microorganism in serum, the percent time for the antibiotic drug concentration to be above the MIC was calculated for several antibacterial classes, including cephalosporins, macrolides, and trimethoprim-sulfamethoxazole (TMP/SMX) combination (Table 19.2). Although the drug concentration in the

TABLE 19.2 Middle Ear Fluid-to-Serum Ratios for Common Antibiotics

ANTIBIOTIC	MIDDLE EAR FLUID (MEF)/SERUM RATIO
Cephalosporins	
Cefaclor	0.18–0.28
Cefuroxime	0.22
Macrolide antibiotic	
Erythromycin	0.49
Sulfa drug	
Sulfisoxazole	0.20

From Craig and Andes (1996).

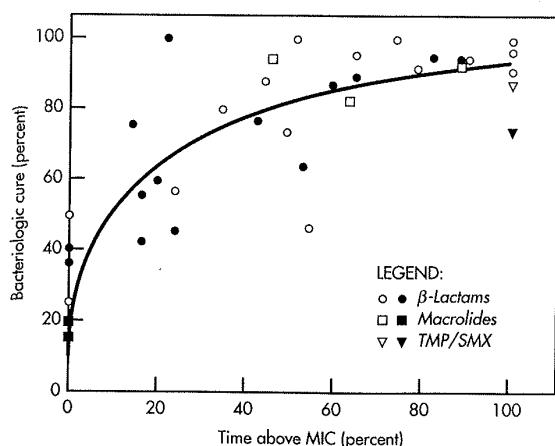


Figure 19-8. Relationship between the percent time above MIC_{90} of the dosing interval during therapy and percent of bacteriologic cure in otitis media caused by *S. pneumoniae* (open symbols) and β -lactamase-positive and -negative *H. influenzae* (closed symbols). (Circles, closed and open = β -lactams; squares, closed and open = macrolides; triangles, closed and open = TMP/SMX.) (From Craig and Andres, 1996, with permission.)

middle ear fluid (MEF) is important, once the ratio (MEF/serum) is known, the serum drug level may be used to project MEF drug levels. The percent time above MIC of the dosing interval during therapy correlated well to the percent of bacteriologic cure (Figure 19-8). An almost 100% cure was attained by maintaining the drug concentration above the MIC for 60–70% of the dosing interval; an 80–85% cure was achieved with 40–50% of the dosing interval above MIC. When the percent of time above MIC falls below a critical value, bacteria will regrow, thereby prolonging the time for eradication of the infection. The pharmacokinetic model was further supported by experiments from a mouse infection model in which an infection in the thigh due to *Pseudomonas aeruginosa* was treated with ticarcillin and tobramycin.

In another study, Craig (1995) compared the AUC/MIC, the time above MIC, and drug peak concentration over MIC and found that the best fit was obtained when colony-forming units (CFUs) were plotted versus time above MIC for cefotaxime in a mouse infection model (Fig. 19-9).

Both Drusano (1988) and Craig (1995) reviewed the relationship of pharmacokinetics and pharmacodynamics in the therapeutic efficacy of antibiotics. For some antibiotics, such as the aminoglycosides and fluoroquinolones, both the drug concentration and the dosing interval have an influence on the antibacterial effect. For some antibiotics, such as the β -lactams, vancomycin, and the macrolides, the duration of exposure (time-dependent killing) or the time the drug levels are maintained above the MIC (t_{eff}) is most important for efficacy. For many antibiotics (eg, fluoroquinolones), there is a defined period of bacterial growth suppression after short exposures to the antibiotic. This phenomenon is known as the *postantibiotic effect* (PAE). Other influences on antibiotic activity include the presence of active metabolite(s), plasma drug protein binding, and the penetration of the antibiotic into the tissues. In addition, the MIC for the antibiotic depends on the infectious microorganism and the resistance of the microorganism to the antibiotic. In the case of ciprofloxacin, a quinolone, the percent of cure of infection at various doses was better related to AUC, which is the product of area under the curve and the

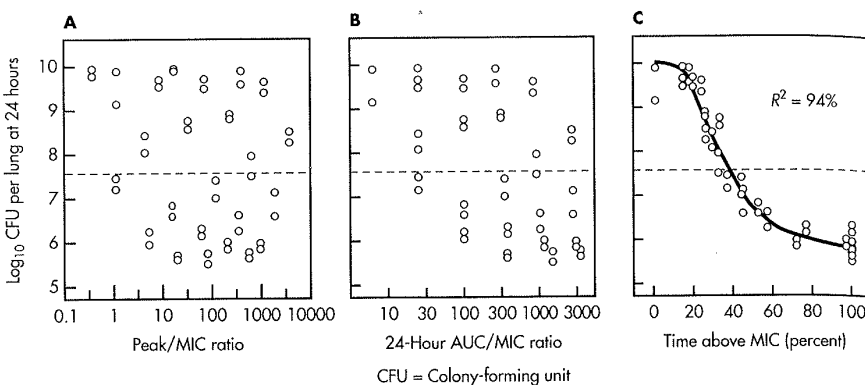


Figure 19-9. Relationship among three pharmacodynamic parameters and the number of *Klebsiella pneumoniae* in the lungs of neutrotropic mice after 24-hour therapy with cefotaxime. Each point represents one mouse.

(From Craig WA, 1995, with permission.)

reciprocal of minimum inhibition concentration, MIC (Forrest et al, 1993). Interestingly, quinolones inhibit bacterial DNA gyrase, quite different from the β -lactam antibiotics, which involve damage to bacterial cell walls.

Relationship between Systemic Exposure and Response—Anticancer Drugs

Plasma drug concentrations for drugs that have highly variable drug clearance in patients fluctuate widely even after intravenous infusion (Rodman and Evans, 1991). For highly variable drugs, there is no apparent relationship between the therapeutic response and the drug dose. For example, the anticancer drug teniposide at three different doses give highly variable steady-state drug concentrations and therapeutic response (Fig. 19-10). In some patients, single-point drug concentrations were variable and even higher with lower doses. Careful pharmacokinetic-pharmacodynamic analysis showed that a graded response curve may be obtained when responses are plotted versus systemic exposure as

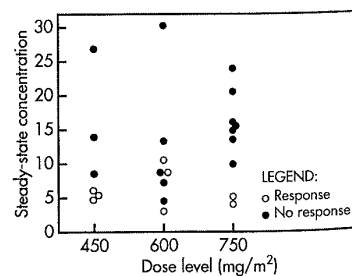


Figure 19-10. Steady-state concentration and response after three levels of teniposide administered by intravenous infusion.

(From Rodman and Evans, 1991, with permission.)

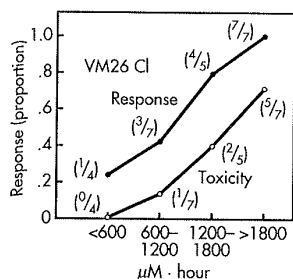


Figure 19-11. Relationship between systemic exposure for teniposide and toxicity and efficacy, shown as proportions of patients.

(From Rodman and Evans, 1991, with permission.)

measured by “concentration \times time” (Fig. 19-11). This is one example showing that anticancer response may be better correlated to total area under the drug concentration curve (AUC), even when no apparent dose–response relationship is observed. Undoubtedly, the cytotoxic effect of the drug involves killing cancer cells with multiple-resistance thresholds that require different time exposures to the drug. The objective of applying pharmacokinetic–pharmacodynamic principles is to achieve therapeutic efficacy without triggering drug toxicity. This relationship is illustrated by the sigmoid curves for response and toxicity (Fig. 19-11), both of which lie close to each other and intensify as concentration increases.

RATE OF DRUG ABSORPTION AND PHARMACODYNAMIC RESPONSE

The rate of drug absorption influences the rate in which the drug gets to the receptor and the subsequent pharmacologic effect. For drugs that exert an acute pharmacologic effect, usually a direct-acting drug agonist, extremely rapid drug absorption may have an intense and possibly detrimental effect. For example, niacin (nicotinic acid) is a vitamin given in large doses to decrease elevated plasma cholesterol and triglycerides. Rapid systemic absorption of niacin when given in an immediate-release tablet will cause vasodilation, leading to flushing and postural hypertension. Extended-release niacin products are preferred because the more slowly absorbed niacin allows the baroreceptors to adjust to the vasodilation and hypotensive effects of the drug. Phenylpropanolamine was commonly used as a nasal decongestant in cough and cold products or as an anorectant in weight-loss products. Phenylpropanolamine acts as a pressor, increasing the blood pressure much more intensely when given as an immediate-release product compared to an extended-release product.

Equilibration Pharmacodynamic Half-Life

For some drugs, the half-time for drug equilibration has been estimated by observing the onset of response. A list of drug half-times reported by Lalonde (1992) is shown in Table 19.3. The factors that affect this parameter include perfusion of

TABLE 19.3 Equilibration Half-Times Determined Using the Effect Compartment Method

DRUG	EQUILIBRATION $t_{1/2}$ (min)	PHARMACOLOGIC RESPONSE
<i>d</i> -Tubocurarine	4	Muscle paralysis
Disopyramide	2	QT prolongation
Quinidine	8	QT prolongation
Digoxin	214	LVET shortening
Terbutaline	7.5	FEV ₁
Terbutaline	11.5	Hypokalemia
Theophylline	11	FEV ₁
Verapamil	2	PR prolongation
Nizatidine	83	Gastric pH
Thiopental	1.2	Spectral edge
Fentanyl	6.4	Spectral edge
Alfentanil	1.1	Spectral edge
Ergotamine	595	Vasoconstriction
Vecuronium	4	Muscle paralysis
<i>N</i> -Acetylprocainamide	6.4	QT prolongation

From Lalonde (1992), with permission.

the effect compartment, blood–tissue partitioning, drug diffusion from capillaries to the effect compartment, protein binding, and elimination of the drug from the effect compartment.

Substance Abuse Potential

The rate of drug absorption has been associated with the potential for substance abuse. Drugs taken by the oral route have the lowest abuse potential. For example, cocoa leaves containing cocaine alkaloid have been chewed by South American Indians for centuries (Johanson and Fischman, 1989). Cocaine abuse has become a problem as a result of the availability of cocaine alkaloid (“crack” cocaine) and because of the use of other routes of drug administration (intravenous, intranasal, or smoking) that allow a very rapid rate of drug absorption and onset of action (Cone, 1995). Studies on diazepam (deWit et al, 1993) and nicotine (Henningfield and Keenan, 1993) have shown that the rate of drug delivery correlates with the abuse liability of such drugs. Thus, the rate of drug absorption influences the abuse potential of these drugs, and the route of drug administration that provides faster absorption and more rapid onset leads to greater abuse.

DRUG TOLERANCE AND PHYSICAL DEPENDENCY

The study of drug tolerance and physical dependency is of particular interest in understanding the actions of abused drug substances, such as opiates and cocaine. Drug *tolerance* is a quantitative change in the sensitivity of the drug and is demonstrated by a decrease in pharmacodynamic effect after repeated exposure to the same drug. The degree of tolerance may vary greatly (Cox, 1990). Drug tolerance has been well described for organic nitrates, opioids, and other drugs. For example,

the nitrates relax vascular smooth muscle and have been used for both acute angina (eg, nitroglycerin sublingual spray or transmucosal tablet) or angina prophylaxis (eg, nitroglycerin transdermal, oral controlled-release isosorbide dinitrate). Well-controlled clinical studies have shown that tolerance to the vascular and antianginal effects of nitrates may develop. For nitrate therapy, the use of a low nitrate or nitrate-free periods has been advocated as part of the therapeutic approach. The magnitude of drug tolerance is a function of both the dosage and the frequency of drug administration. *Cross tolerance* can occur for similar drugs that act on the same receptors. Tolerance does not develop uniformly to all the pharmacologic or toxic actions of the drug. For example, patients who show tolerance to the depressant activity of high doses of opiates will still exhibit "pinpoint" pupils and constipation.

The mechanism of drug tolerance may be due to (1) disposition or pharmacokinetic tolerance or (2) pharmacodynamic tolerance. *Pharmacokinetic tolerance* is often due to enzyme induction (discussed in earlier chapters), in which the hepatic drug clearance increases with repeated drug exposure. *Pharmacodynamic tolerance* is due to a cellular or receptor alteration in which the drug response is less than what is predicted in the patient given subsequent drug doses. Measurement of serum drug concentrations may differentiate between pharmacokinetic tolerance and pharmacodynamic tolerance. Acute tolerance, or *tachyphylaxis*, which is the rapid development of tolerance, may occur due to a change in the sensitivity of the receptor or depletion of a cofactor after only a single or a few doses of the drug. Drugs that work indirectly by releasing norepinephrine may show tachyphylaxis. Drug tolerance should be differentiated from genetic factors which account for normal variability in the drug response.

Physical dependency is demonstrated by the appearance of withdrawal symptoms after cessation of the drug. Workers exposed to volatile organic nitrates in the workplace may initially develop headaches and dizziness followed by tolerance with continuous exposure. However, after leaving the workplace for a few days, the workers may demonstrate nitrate withdrawal symptoms. Factors that may affect drug dependency may include the dose or amount of drug used (intensity of drug effect), the duration of drug use (months, years, and peak use) and the total dose (amount of drug \times duration). The appearance of withdrawal symptoms may be abruptly precipitated in opiate-dependent subjects by the administration of naloxone (Narcan), an opioid antagonist that has no agonist properties.

HYPERSENSITIVITY AND ADVERSE RESPONSE

Many drug responses, such as hypersensitivity and allergic responses, are not fully explained by pharmacodynamics and pharmacokinetics. Allergic responses generally are not dose related, although some penicillin-sensitive patients may respond to threshold skin concentrations, but, otherwise, no dose-response relationship has been established. Skin eruption is a common symptom of drug allergy. Allergic reactions can occur at extremely low drug concentrations. Some urticaria episodes in patients have been traced to penicillin contamination in food or to penicillin contamination during dispensing or manufacturing of other drugs. Allergic reactions are important data that must be recorded in the patient's profile along with other

adverse reactions. Penicillin allergic reaction in the population is often detected by skin test with benzylpenicilloyl polylysine (PPL). The incidence of penicillin allergic reaction occurs in about 1–10% of patients. The majority of these reactions are minor cutaneous reactions such as urticaria, angioedema, and pruritus. Serious allergic reactions, such as anaphylaxis, are rare, with an incidence of 0.021–0.106% for penicillins (Lin, 1992). For cephalosporins, the incidence of anaphylactic reaction is less than 0.02%. Anaphylactic reaction for cefaclor was reported to be 0.001% in a postmarketing survey. There are emerging trends showing that there may be a difference between the original and the new generations of cephalosporins (Reisman and Reisman, 1995). Cross sensitivity to similar chemical classes of drugs can occur.

Allergic reactions may be immediate or delayed and have been related to IgE mechanisms. In β -lactam (penicillin) drug allergy, immediate reactions occur in about 30 to 60 minutes, but delayed reaction, or accelerated reaction, may occur from 1 to 72 hours after administration. Anaphylactic reaction may occur in both groups. Although some early evidence of cross hypersensitivity between penicillin and cephalosporin was observed, the incidence in patients sensitive to penicillin show only a twofold increase in sensitivity to cephalosporin compared with that of the general population. The report rationalized that it is safe to administer cephalosporin to penicillin-sensitive patients and that the penicillin skin test is not useful in identifying patients who are allergic to cephalosporin, because of the low incidence of cross reactivity (Reisman and Reisman, 1995). In practice, the clinician should evaluate the risk of drug allergy against the choice of alternative medication. Some earlier reports showed that cross sensitivity between penicillin and cephalosporin was due to the presence of trace penicillin present in cephalosporin products.

DRUG DISTRIBUTION AND PHARMACOLOGIC RESPONSE

After systemic absorption, the drug is carried throughout the body by the general circulation. Most of the drug dose will reach unintended target tissues, in which the drug may be passively stored, produce an adverse effect, or be eliminated. A fraction of the dose will reach the target site and establish an equilibrium. The receptor site is unknown most of the time, but, kinetically, it is known as the *effect compartment*. The time course of drug delivery to the effect compartment will determine whether the onset of pharmacologic response is immediate or delayed. The delivery of drug to the effect compartment is affected by the rate of blood flow, diffusion, and partition properties of the drug and the receptor molecules.

At the receptor site, the onset, duration, and intensity of the pharmacologic response are controlled by receptor concentration and the concentration of the drug and/or its active metabolites. The ultimate pharmacologic response (*effect*) may depend largely on the stereospecific nature of the interaction of the drug with the receptor and the rates of association and dissociation of the drug–receptor complex. Depending on their location and topography, not all receptor molecules are occupied by drug molecules when a maximum pharmacologic response

is produced. Other variables, such as age, sex, genetics, nutrition, and tolerance, may also modify the pharmacologic response, making it difficult to relate the pharmacologic response to plasma drug concentration. To control data fluctuation and simplify pharmacodynamic fitting, the pharmacologic response is often expressed as a percent of response above a baseline or percent of maximum response. By combining pharmacokinetics and pharmacodynamics, some drugs with relatively complex pharmacologic responses have been described by pharmacodynamic models that account for their onset, intensity, and duration of action.

After the pharmacodynamics of a drug are characterized, the time course of pharmacologic response may be predicted after drug administration. Also, from these data, it is possible to determine from the pharmacokinetic parameters whether an observed change in pharmacologic response is due to pharmacodynamic factors, such as tachyphylaxis or tolerance, or to pharmacokinetic factors, such as a change in drug absorption, elimination, or distribution.

Drug-Receptor Theory Relating Pharmacologic Effect and Dose

The relationship between pharmacologic effect and dose was advanced by Wagner (1968), who derived a kinetic expression that relates drug concentration to pharmacologic effect. This theoretical development transformed the semiempirical dose-effect relationship (the hyperbolic or log sigmoid profile) into a theoretical equation that relates pharmacologic effect to pharmacokinetics (ie, a pharmacokinetics/pharmacodynamic, PK/PD model). Because the equation was developed for a drug receptor with either single or multiple drug binding, many drugs with a sigmoid concentration effect profile may be described by this model. The slope of the profile also provides some insight into the drug-receptor interaction.

The basic equation mimics somewhat the kinetic equation for protein drug binding (Chapter 10). One or more drug molecules may interact with a receptor to form a complex that in turn elicits a pharmacodynamic response, as illustrated in Figure 19-12. The rate of change in the number of drug-receptor complexes is expressed as db/dt . From Figure 19-12, a differential equation is obtained as shown:

$$\frac{db}{dt} = k_1 c^s (a - b) - b k_2 \tag{19.9}$$

where $k_1 c^s (a - b)$ = rate of receptor complex formation and $b k_2$ = rate of dissociation of the receptor complex.

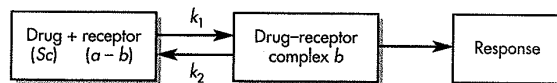


Figure 19-12. Model of the drug-receptor theory: a = total number of drug receptors, c = concentration of drug, S = number of moles of drug that combine with one receptor (constant for each drug), and b = number of drug-receptor complexes.

At steady state, $db/dt = 0$ and Equation 19.9 reduces to

$$k_1 c^s a - k_1 c^s b - b k_2 = 0$$

$$\frac{b}{a} = \frac{k_1 c^s}{k_1 c^s + k_2} = \frac{1}{1 + (k_2/k_1 c^s)} \quad (19.10)$$

For many drugs, the pharmacologic response (R) is proportional to the number of receptors occupied:

$$R \propto \frac{b}{a} \quad (19.11)$$

The pharmacologic response (R) is related to the maximum pharmacologic response (R_{\max}), concentration of drug, and rate of change in the number of drug receptor complexes occupied:

$$R = \frac{R_{\max}}{1 + (k_2/k_1 c^s)} \quad (19.12)$$

A graph of Equation 19.12 constructed from the percent pharmacologic response, $(R/R_{\max}) \times 100$, versus the concentration of drug gives the response-concentration curve (Fig. 19-13). This type of theoretical development explains that the pharmacologic response-dose curve is not completely linear over the entire dosage range, as is frequently observed.

The total pharmacologic response elicited by a drug is difficult to quantitate in terms of the intensity and the duration of the drug response. The *integrated pharmacologic response* is a measure of the total pharmacologic response and is expressed mathematically as the product of these two factors (ie, duration and intensity of drug action) summed up over a period of time. Using Equation 19.12, an integrated pharmacologic response is generated if the drug plasma concentration-time curve can be adequately described by a pharmacokinetic model.

Table 19.4 is based on a hypothetical drug that follows a one-compartment open model. The drug is given intravenously in divided doses. With this drug, the total integrated response increases considerably when the total dose is given in a greater number of divided doses. By giving the drug in a single dose, two doses, four doses, and eight doses, an integrated response was obtained that ranged from 100% to 138.9%, using the single-dose response as a 100% reference. It should be noted that when the bolus dose is broken into a smaller number of doses, the largest percent increase in the integrated response occurs when the bolus dose is divided into two doses. Further division will cause less of an increase, proportionally. The

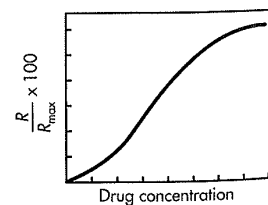


Figure 19-13. Graph of drug concentration versus pharmacologic response.

TABLE 19.4 Hypothetical Drug Given Intravenously in Single and Divided Doses^a

DOSE NUMBER	SINGLE DOSE	DOSE GIVEN INITIALLY AND AT 12th hr	DOSE GIVEN AT 0, 6, 12, 18 hr	DOSE GIVEN AT 0, 3, 6, 9, 12, 15, 18, 21 hr
1	422	272	139.4	62.53
2		276	148.2	71.46
3			148.5	74.41
4			149.0	75.61
5				76.27
6				76.44
7				76.71
8				76.81
Total response	422	548	585.1	590.2
Percent response	100	130	138.7	138.9

^aThe drug follows a one-compartment open model. Each value represents a unit of integrated pharmacologic response.

Adapted with permission from Wagner (1968).

actual percent increase in integrated response depends on the $t_{1/2}$ of the drug as well as the dosing interval.

The values in Table 19.4 were generated from theory. However, these data illustrate that the pharmacologic response depends on the dosing schedule. A large total dose given in divided doses may produce a pharmacologic response quite different from that obtained by administering the drug in a single dose.

Correlation of pharmacologic response to pharmacokinetics is not always possible with all drugs. Sometimes intermediate steps are involved in the mechanism of drug action that are more complex than is assumed in the model. For example, warfarin (an anticoagulant) produces a delayed response, and there is no direct correlation of the anticoagulant activity to the plasma drug concentration. The plasma warfarin level is correlated with the inhibition of the prothrombin complex production rate. However, many correlations between pharmacologic effect and plasma drug concentration are performed by proposing models that may be discarded after more data are collected. The process of pharmacokinetic modeling can greatly enhance our understanding of the way drugs act in a quantitative manner.

PHARMACODYNAMIC MODELS

No unified general pharmacodynamic model based on detailed drug-receptor theory that relates pharmacologic response to pharmacokinetics is available. Most of the drug-receptor-based models are descriptive and lack quantitative details. Successful modeling of pharmacologic response has been achieved with semiempirically based assumptions and usually with some oversimplification of the real process. Many of the classic pharmacodynamic models were developed without detailed knowledge of the drug-receptor interaction. The successful modeling of the degree of muscle paralysis of *d*-tubocurarine to plasma concentrations is an

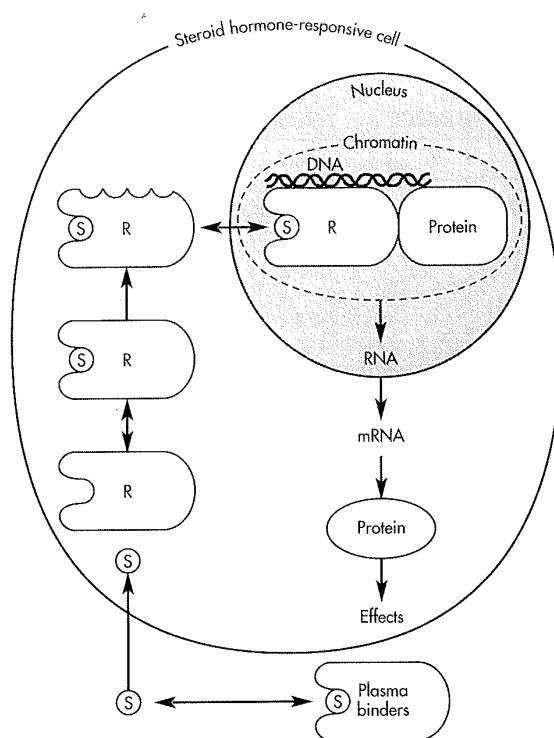


Figure 19-14. Receptor-mediated (R) mechanism of action of corticosteroid (S) hormones.
(From Baxter and Funder, 1979, with permission. Cited by Boudinot et al, 1986.)

interesting example in which the exact mechanism of the drug-receptor interaction was not considered. One of the few pharmacodynamic models that takes into account the interaction between the receptor and the drug molecule leading to a pharmacologic effect was described by Boudinot et al (1986) using the drug prednisolone as an example. Prednisolone is a corticosteroid that binds to cytosolic receptors within the cell (Fig. 19-14). The bound steroid receptor complex is activated and translocated into the nucleus of the cell. Within the cell, the drug-receptor complex associates with specific DNA sequences and modulates the transcription of RNA, which ultimately initiates protein synthesis (Boudinot et al, 1986). Tyrosine aminotransferase (TAT) is an enzyme protein that is increased (induced) by the action of prednisolone. In the liver cell, the prednisolone concentration, drug-receptor concentration, and TAT enzyme were measured with respect to time.

The pharmacodynamic model accounted for the delayed response of prednisolone, a characteristic of corticosteroid response. In this model, prednisolone is first bound to plasma protein, and free drug must leave the plasma compartment and enter the cell to form a drug-receptor complex; creation of this complex then triggers the pharmacologic events leading to an increase in intracellular TAT concentration. A decrease in free receptor or an increase in bound receptor complexes after drug administration was observed. Plasma prednisolone concentrations were

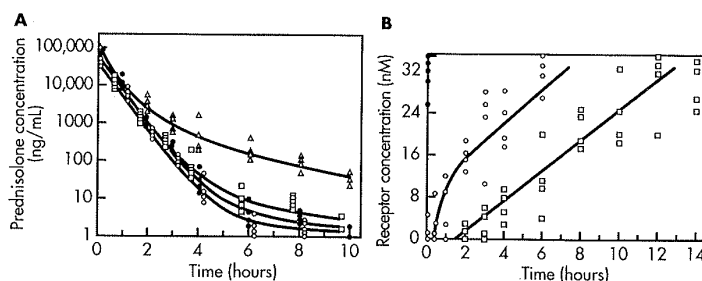


Figure 19-15. **A.** Prednisolone levels in plasma (\square) and liver (Δ) fall exponentially after 50 mg/kg of drug IV during the first 10 hours, as described by a pharmacokinetic model. **B.** Free cytosolic glucocorticoid receptor (CGR) concentration fell from control level (\bullet) after 5- (\circ) and 50-mg/kg (\square) IV doses of prednisolone. Free CGR fell as prednisolone interacted with receptor to form receptor complex. The free CGR returned to baseline level after about 10 hours.

(From Boudinot et al, 1986, with permission.)

described by a triexponential equation, and a time lag was built into the model to account for the delay between TAT increase and the drug-receptor-DNA complex formation (Figs. 19-15 and 19-16). A review on PK/PD modelling has been published by Meibohm and Derendorf, 1997.

Maximum Effect (E_{\max}) Model

The *maximum effect model* (E_{\max}) is an empirical model that relates pharmacologic response to drug concentrations. This model incorporates the observation known as the *law of diminishing return*, which shows that an increase in drug concentration near the maximum pharmacologic response produces a disproportionately smaller increase in the pharmacologic response (Fig. 19-17). The E_{\max} model describes drug action in terms of maximum effect (E_{\max}) and EC_{50} , the drug concentration that produces 50% maximum pharmacologic effect.

$$E = \frac{E_{\max} C}{EC_{50} + C} \quad (19.13)$$

where C is the plasma drug concentration and E is the pharmacologic effect.

Equation 19.13 is a saturable process resembling Michaelis-Menton enzyme kinetics. As the plasma drug concentration C increases, the pharmacologic effect

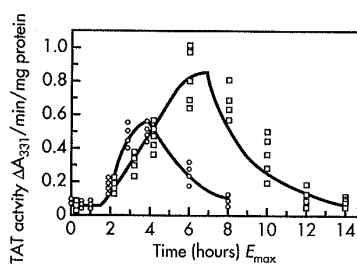


Figure 19-16. Tyrosine aminotransferase (TAT) activity in liver was described by a pharmacodynamic model (solid line) after 5 (\circ) and 50 mg/kg (\square) IV prednisolone. The pharmacodynamic model accounts for the delay of TAT activity.

(From Boudinot et al, 1986, with permission.)

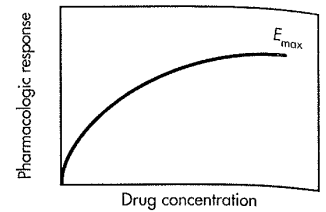


Figure 19-17. Plot of pharmacologic response versus plasma drug concentration in a hyperbolic model.

E approaches E_{\max} asymptotically. A double-reciprocal plot of Equation 19.13 may be used to linearize the relationship, similar to a Lineweaver–Burke equation.

E_{\max} is the maximum pharmacologic effect that may be obtained by the drug. EC_{50} is the drug concentration that produces one-half (50%) of the maximum pharmacologic response. In this model, both E_{\max} and EC_{50} can be measured. For example, the bronchodilator activity of theophylline may be monitored by measuring FEV_1 (forced expiratory volume) at various plasma drug concentrations (Fig. 19-18). For theophylline, a small gradual increase in FEV_1 is obtained as the plasma drug concentrations are increased higher than 10 mg/L. Only a 17% increase in FEV_1 is observed when the plasma theophylline concentration is doubled from 10 to 20 mg/L. The EC_{50} for theophylline is 10 mg/L. The E_{\max} is equivalent to 63% of normal FEV_1 . A further increase in the plasma theophylline concentration will not yield an improvement in the FEV_1 beyond E_{\max} . Either drug saturation of the receptors or other limiting factors prevent further improvement in the pharmacologic response.

The E_{\max} model describes two key features of the pharmacologic response: (1) the model mimics the hyperbolic shape of the pharmacologic response–drug concentration response curve, and (2) a maximum pharmacologic response (E_{\max}) may be induced by a certain drug concentration, beyond which no further increase

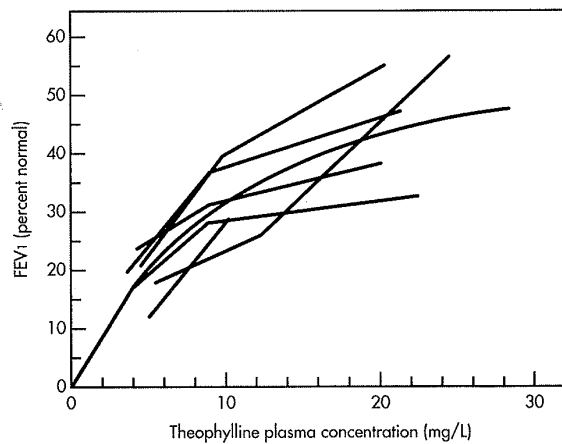


Figure 19-18. Use of E_{\max} model to describe the effects of theophylline on change in normalized forced expiratory volume (FEV_1); $E_{\max} = 63\%$, $EC_{50} = 10$ mg/L. (From Mitenko and Ogilvie, 1973, and Holford and Sheiner, 1981, with permission.)

in pharmacologic response is obtained (Fig. 19-17). The drug concentration that produces a 50% maximum pharmacologic response (EC_{50}) is useful as a guide for achieving drug concentration that lies within the therapeutic range.

In many cases, the measured pharmacologic effect has some value when drug is absent (eg, blood pressure, heart rate, respiration rate). E_0 is the measured pharmacologic effect (baseline activity) at zero drug concentration in the body. The measurement for E_0 may be variable due to intra- and intersubject differences. Using E_0 as a baseline constant-effect term, Equation 19.13 may be modified as follows:

$$E = E_0 + \frac{E_{\max}C}{EC_{50} + C} \quad (19.14)$$

Sigmoid E_{\max} Model

The *sigmoid E_{\max} model* describes the pharmacologic response–drug concentration curve for many drugs that appear to be S-shaped (ie, sigmoidal) rather than hyperbolic as described by the simpler E_{\max} model. The model was first used by Hill (1910) to describe the association of oxygen with hemoglobin, in which the association with one oxygen molecule influences the association of the hemoglobin with the next oxygen molecule. The equation for the sigmoid E_{\max} model is an extension of the E_{\max} model:

$$E = \frac{E_{\max}C^n}{EC_{50} + C^n} \quad (19.15)$$

where n is an exponent describing the number of drug molecules that combine with each receptor molecule. When n is equal to unity ($n = 1$), the sigmoidal E_{\max} model reduces to the E_{\max} model. A value of $n > 1$ influences the slope of the curve and the model fit.

The sigmoidal E_{\max} model has been used to describe the effect of tocainamide on the suppression of ventricular extrasystoles (Winkle et al, 1976). As shown in Figure 19-19, the very steep slope of the tocainamide concentration–response curve

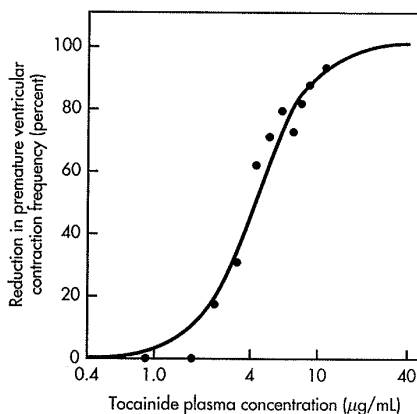


Figure 19-19. Steep concentration response curve for tocainide requiring use of the sigmoid E_{\max} model. (From Winkle et al, 1976, with permission.)

required that $n = 20$ in order to fit the model. Although this model was developed empirically, the mathematical equation describing the model is similar to the one elaborated by Wagner (1968) and discussed earlier in this chapter.

In the sigmoid E_{\max} model, the slope is influenced by the number of drug molecules bound to the receptor. Moreover, a very large n value may indicate *allosteric* or *cooperative effects* in the interaction of the drug molecules with the receptor.

Pharmacokinetic Pharmacodynamic Models with an Effect Compartment

Many pharmacokinetic models describe the time course for drug and metabolite concentrations in the body. Using either the sigmoid E_{\max} or one of the other pharmacodynamic models described earlier, the pharmacologic response may be obtained at various time periods. This simple approach has worked for some neuromuscular blockers and anesthetic agents, whose activities are related to plasma drug concentrations.

For some drugs, the time course for the pharmacologic response may not directly parallel the time course of the plasma drug concentration. The maximum pharmacologic response produced by the drug may be observed before or after the plasma drug concentration has peaked. Moreover, other drugs may produce a delayed pharmacologic response unrelated to the plasma drug concentration.

A pharmacokinetic/pharmacodynamic model with an effect compartment is used to describe the pharmacokinetics of the drug in the plasma and the time course of a pharmacologic effect of a drug in the site of action. To account for the pharmacodynamics of an indirect or delayed drug response, a hypothetical *effect compartment* has been postulated (Fig. 19-20). This effect compartment is not part of the pharmacokinetic model but is a hypothetical pharmacodynamic compartment that links to the plasma compartment containing drug. Drug transfers from the plasma compartment to the effect compartment, but no significant amount of drug moves from the effect compartment to the plasma compartment. Only free drug will diffuse into the effect compartment, and the transfer rate constants are usually first order. The pharmacologic response is determined from the rate constant, k_{e0} , and the drug concentration in the effect compartment (Fig. 19-20).

The amount of drug in the hypothetical effect compartment after a bolus IV dose may be obtained by writing a differential describing the rate of change in drug amounts in each compartment:

$$\frac{dD_e}{dt} = k_{1e}D_1 - k_{e0}D_e \quad (19.16)$$

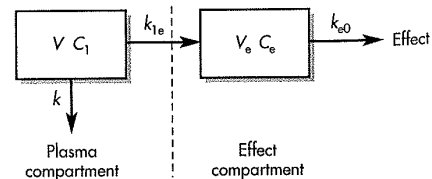


Figure 19-20. Pharmacokinetic-pharmacodynamic model with an effect compartment.

where D_e is the amount of drug in the effect compartment, D_1 is the amount of drug in the central compartment, k_{1e} is the transfer rate constant for drug movement from the central compartment into the effect compartment, and k_{e0} is the transfer rate constant out of the effect compartment.

Integrating Equation 19.16 yields the amount of drug in the effect compartment D_e :

$$D_e = \frac{D_0 k_{1e}}{(k_{e0} - k)} (e^{-kt} - e^{-k_{e0}t}) \quad (19.17)$$

Dividing Equation 19.17 by V_e , the volume of the effect compartment, yields the concentration C_e of the effect compartment:

$$C_e = \frac{D_0 k_{1e}}{V_e (k_{e0} - k)} (e^{-kt} - e^{-k_{e0}t}) \quad (19.18)$$

where D_0 is the dose, V_e is the volume of the effect compartment, and k is the elimination rate constant from the central compartment. Equation 19.18 is not very useful because the parameters V_e and k_{1e} are both unknown and cannot be obtained from plasma drug concentration data. Several assumptions were made to simplify this equation.

The pharmacodynamic model assumes that even though an effect compartment is present in addition to the plasma compartment, this hypothetical effect compartment takes up only a negligible amount of the drug dose, so that plasma drug level still follows a one-compartment equation. After an IV bolus dose, the rate of drug entering and leaving the effect compartment is controlled by the incoming rate constant k_{1e} and the elimination rate constant k_{e0} . (There is no diffusion of drug from the effect compartment into the plasma compartment.) At steady state, both the input and output rates from the effect compartment are equal,

$$k_{1e} D_1 = D_e k_{e0} \quad (19.19)$$

Rearranging,

$$D_1 = \frac{k_{e0} D_e}{k_{1e}} \quad (19.20)$$

Dividing by V_D yields the steady-state plasma drug concentration C_1 :

$$C_1 = \frac{k_{e0} D_e}{k_{1e} V_D} \quad (19.21)$$

$$D_e = \frac{D_0 k_{1e}}{(k_{e0} - k)} (e^{-kt} - e^{-k_{e0}t}) \quad (19.22)$$

Substituting for D_e into Equation 19.21 yields

$$C_1 = \frac{k_{e0} D_0 k_{1e}}{k_{1e} V_D (k_{e0} - k)} (e^{-kt} - e^{-k_{e0}t}) \quad (19.23)$$

Cancelling the common term k_{1e} ,

$$C_1 = \frac{k_{e0}D_0}{V_D(k_{e0} - k)}(e^{-kt} - e^{-k_{e0}t}) \quad (19.24)$$

At steady state, C_1 is unaffected by k_{1e} and is controlled only by the elimination constant k and k_{e0} . C_1 is called C_{pss} , or steady-state drug concentration, and has been used successfully to relate the pharmacodynamics of many drugs, including some with delayed equilibration between the plasma and the effect compartment. Thus, k and k_{e0} jointly determine the pharmacodynamic profile of a drug. In fitting the pharmacokinetic–pharmacodynamic model, the IV bolus equation is fitted to the plasma drug concentration–time data to obtain k and V_D , while C_{pss} , or C_1 from Equation 19.24, is used to substitute into the concentration in Equation 19.15 to fit the pharmacologic response.

Many drug examples have been described by this type of pharmacokinetic–pharmacodynamic model. The key feature of this model is its dynamic flexibility and adaptability to pharmacokinetic models that account for drug distribution and pharmacologic response. The aggregate effects of drug elimination, binding, partitioning, and distribution in the body are accommodated by the model. The basic assumptions are practical and pragmatic, although some critics of the model (Colburn, 1987) believe the hypothetical effect compartment may oversimplify more complex drug–receptor events. On the positive side, the model represents elegantly an *in-vivo* pharmacologic event relating to the plasma drug concentrations that a clinician can monitor and adjust.

Until more information is known about the effect compartment, a pharmacokinetic–pharmacodynamic model is proposed to describe these kinetic processes combining some of the variables. A good fit of the data to the model is useful but does not necessarily describe the actual pharmacodynamic process. The process of model development evolves until a better model replaces an inadequate one. Several examples of drugs incorporating the effect compartment concept cited in the next section support the versatility of this model. The model accommodates some difficult drug response–concentration profiles, such as the puzzling hysteresis profile of some drug responses (eg, responses to cocaine and ajmaline).

Pharmacodynamic Models Using an Effect Compartment

The antiarrhythmic drug ajmaline slows the heart rate by delaying the depolarization of the heart muscle in the atrium and the ventricle. The pharmacologic effect of the drug is observed in the ECG by measuring the prolongation of the PQ and QRS interval after an IV infusion of ajmaline. A two-compartment model with binding described the pharmacokinetics of the drug and a pharmacodynamic model with an effect compartment was linked to the central compartment in which free drug may diffuse into the effect compartment. The effect compartment was necessary because the plasma ajmaline concentration did not correlate well with changes in recorded ECG events. When the effect-compartment drug concentration was used instead, drug activity was well described by the model (Figs. 19-21 and 19-22).

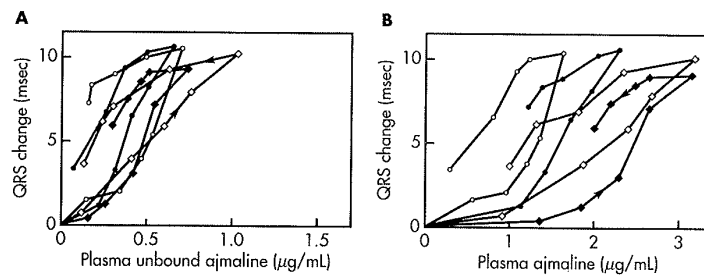


Figure 19-21. Plot of ajmaline concentration versus change in QRS interval for four dogs: (◆) 1, (◇) 2, (●) 3, (○) 4. **A.** Unbound plasma ajmaline versus response. **B.** Plasma ajmaline versus response. (From Yasuhara et al, 1987, with permission.)

Hysteresis of Pharmacologic Response

Many pharmacologic responses are complex and do not show a direct relationship between pharmacologic effect and plasma drug concentration. Some drugs have a plasma drug concentration–pharmacologic response that resembles a *hysteresis loop* (Fig. 19-23). For these drugs, an identical plasma concentration can result in significantly different pharmacologic responses, depending on whether the plasma drug concentration is on the ascending or descending phase of the loop. The time-dependent nature of a pharmacologic response may be due to tolerance, induced metabolite deactivation, reduced response, or translocation of receptors at the site of action. This type of time-dependent pharmacologic response is characterized by a clockwise profile when pharmacologic response is plotted versus plasma drug concentrations over time (Fig. 19-23).

For example, fentanyl (a lipid-soluble, opioid anesthetic) and alfentanil (a closely related drug) display *clockwise* hysteresis, apparently due to rapid lipid partition. β -Adrenoreceptors, such as isoproterenol, apparently have no direct relationship between response and plasma drug concentration and show hysteresis features. The diminished pharmacologic response was speculated to be a result of cellular response and physiologic adaptation to intense stimulation of the drug. A decrease in the number of receptors as well as translocation of receptors was proposed as the explanation for the observation. The euphoria produced by cocaine also displayed a clockwise profile when responses were plotted versus plasma cocaine concentration (Fig. 19-24).

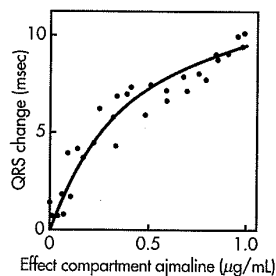


Figure 19-22. Plot of change in QRS interval versus ajmaline concentration in the effect compartment in dog 2. The lines were generated based on the effect compartment model.

(From Yasuhara et al, 1987, with permission.)

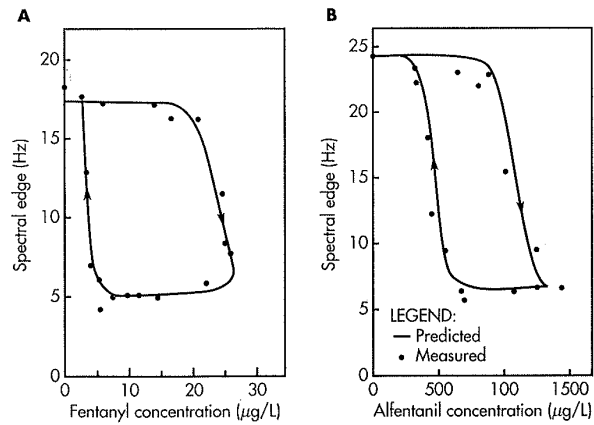


Figure 19-23. Response of the EEG spectral edge to changing fentanyl **(A)** and alfentanil **(B)** serum concentrations. Plots are data from single patients after rapid drug infusion. Time is indicated by arrows. The clockwise hysteresis indicates a significant time lag between blood and effect site. (From Scott and Stanski, 1985, with permission.)

A second type of pharmacologic response shows a *counterclockwise* hysteresis profile (Fig. 19-25). The pharmacologic response increases with time as the pharmacologic response is plotted versus plasma drug concentrations. An example of a counterclockwise hysteresis loop is the antiarrhythmic drug ajmaline. When the QRS interval changes in dogs were plotted versus plasma ajmaline concentration in each dog, an interesting counterclockwise hysteresis loop was seen (Fig. 19-21). Yasuhara and co-workers (1987) developed a pharmacodynamic model to analyze the molecular events between drug concentration and change in ECG parameters such as QRS. A relationship was established between pharmacologic response and drug concentration in the effect-compartment drug level (Fig. 19-22). The hysteresis profile (Fig. 19-21) is the result of the drug being highly bound to the plasma protein (α_1 -acid glycoprotein), and of a slow initial diffusion of drug into the effect compartment.

Counterclockwise hysteresis curves may also result when the measured pharmacodynamic response is not the primary effect of the drug, ie, there is an *indirect*

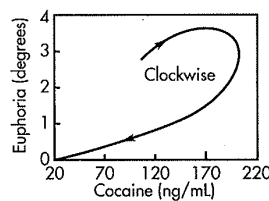


Figure 19-24. Clockwise hysteresis loop typical of tolerance is seen after intranasal administration of cocaine when related to degree of euphoria experienced in volunteers. (From van Dyke et al, 1978.)

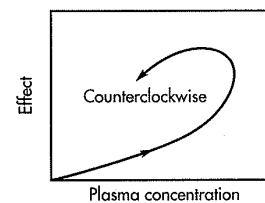


Figure 19-25. Counterclockwise hysteresis loop indicating equilibration delay between plasma concentration and the effect site producing the effect. (From Holford and Sheiner, 1981.)

effect. For example, warfarin inhibits hepatic synthesis of clotting factors II, VII, IX, and X, but prothrombin time is measured as a surrogate for warfarin activity and clotting factor concentration.

To predict the time course of drug response using a pharmacodynamic model, a mathematical expression is developed to describe the drug concentration–time profile of the drug at the receptor site. This equation is then used to relate drug concentrations to the time course and intensity of the pharmacologic response. Most pharmacodynamic models assume that pharmacologic action is due to a drug–receptor interaction, and the magnitude of the response is related quantitatively to the drug concentration in the receptor compartment. In the simplest case, the drug receptor lies in the plasma compartment and pharmacologic response is established through a one-compartment model with drug response proportional to log drug concentration (Eq. 19.1). A more complicated model involving a receptor compartment that lies outside the central compartment was proposed by Sheiner and associates (1979). This model locates the receptor in an effect compartment in which a drug equilibrates from the central compartment by a first-order rate constant k_{1e} . There is no back diffusion of drug away from the effect compartment, thereby simplifying the complexity of the equations. This model was applied successfully to monitor the pharmacologic effects of the drug trimazosin (Meredith et al, 1983).

The pharmacokinetics of trimazosin are described as a two-compartment open model with conversion to a metabolite by a first-order rate constant k_{1m} . The pharmacokinetics of the metabolite are described by a one compartment model with a first-order elimination constant k_{m0} . The drug effect may be described by two pharmacodynamic models, either model A or B. Model A assumes that the drug effect in the effect compartment is produced by the drug only. Model B assumes that both the drug and a metabolite produce drug effect (Fig. 19-26).

The following equation describes the pharmacokinetics and pharmacodynamics of the drug:

$$C_p = Ae^{-at} - Be^{-bt} \quad (19.25)$$

where C_p is the concentration of the drug in the central compartment.

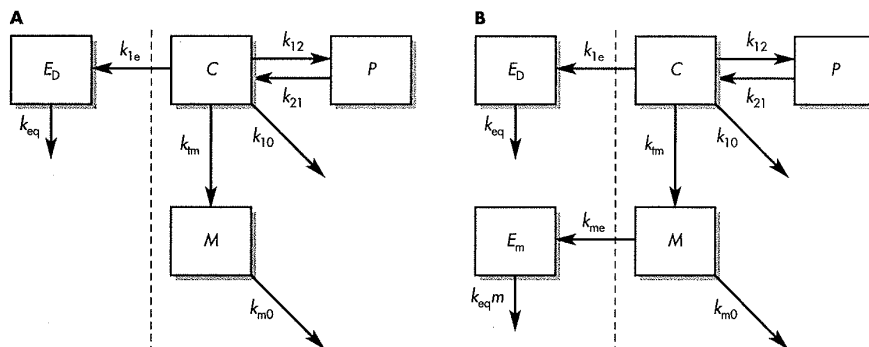


Figure 19-26. Two proposed pharmacodynamic models for describing the hypotensive effect of trimazosin. **A** assumes an effect compartment (left of dashed line) for the drug. **B** assumes an effect compartment for the drug as well as the metabolite.

(From Meredith et al, 1983, with permission.)

$$C_m = \frac{V_1 k_{1m}}{V_m} \left[\frac{A}{(k_{m0} - a)} (e^{-at} - e^{-k_{m0}t}) + \frac{B}{(k_{m0} - b)} (e^{-bt} - e^{-k_{m0}t}) \right] \quad (19.26)$$

where C_m is the concentration of the metabolite in the body, V_m is the volume of distribution of the metabolite, V_1 is the volume of the central compartment of the body, k_{1m} is the first-order constant for converting drug to metabolite, k_{m0} is the elimination rate constant of the metabolite, A and B are two-compartment model coefficients for the drug (see Chapter 4), and k_{10} is the elimination rate constant of the drug.

The drug concentration in the effect compartment is calculated by assuming that at equilibrium the concentration of the drug in the effect compartment and the central compartment are equal,

$$k_{1c} V_1 = k_{eq} V_e \quad (19.27)$$

where V_e is volume of the effect compartment and k_{eq} is the elimination rate constant of the drug from the effect compartment. Therefore, the drug concentration in the effect compartment $C(e, d)$ is calculated as

$$C(e, d) = \frac{AK_{eq}}{(k_{eq} - a)} (e^{-at} - e^{-k_{eq}t}) + \frac{Bk_{eq}}{(k_{eq} - b)} (e^{-bt} - e^{-k_{eq}t}) \quad (19.28)$$

The effect due to drug is assumed to be linear,

$$E = M_d C(e, d) + i \quad (19.29)$$

where M_d is the *sensitivity slope* to the drug (ie, the effect per unit of drug concentration in the effect compartment). The parameters M_d , i , and k_{eq} are determined by least-squares fitting of the data. For the metabolite, the concentration of metabolite in the effect compartment is $C(e, m)$.

$$C(e, m) = \frac{AV_1 k_{1m} k_{eq} m}{V_m} \quad (19.30)$$

$$\times \left[\frac{e^{-at}}{(a - k_{m0})(a - k_{eq}m)} + \frac{e^{-k_{m0}t}}{(a - k_{m0})(k_{eq}m - k_{m0})} \right.$$

$$- \frac{e^{-k_{eq}mt}}{(a - k_{eq}m)(k_{eq}m - k_{m0})}$$

$$+ \frac{BV_1 k_{1m} k_{eq} m}{V_m} \frac{e^{-bt}}{(b - k_{m0})(b - k_{eq}m)}$$

$$\left. + \frac{e^{-k_{m0}t}}{(b - k_{m0})(k_{eq}m - k_{m0})} - \frac{e^{-k_{eq}mt}}{(b - k_{eq}m)(k_{eq}m - k_{m0})} \right]$$

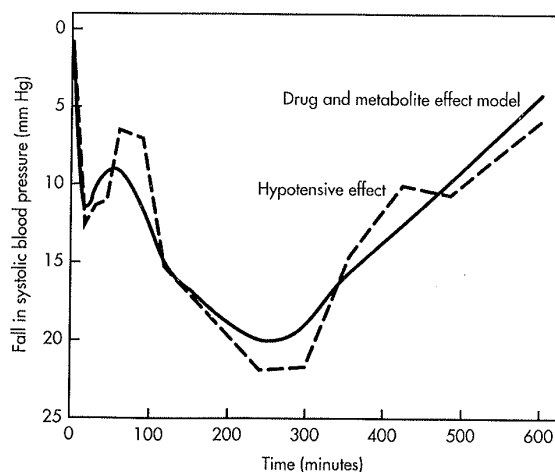


Figure 19-27. Diagram showing the agreement between recorded hypotensive effect (solid line) and hypotensive effect as projected by model B (broken line). (From Meredith et al, 1983, with permission.)

The concentration of the metabolite in the effect compartment is in turn related to drug effect as for the parent drug. The total effect produced is

$$E = M_d C(e, d) + M_m C(e, m) + i \quad (19.31)$$

The five parameters M_d , M_m , i , k_{eq} , k_{eqm} may be estimated from Equation 19.31 by fitting the data to an appropriate model. Figure 19-27 shows the observed decline in systolic blood pressure compared with the theoretical decline in blood pressure predicted by the model. An excellent fit of the data was obtained by assuming that both drug and metabolite are active. This example illustrates that, for a dose of a drug, the drug concentration in the effect compartment and others may be described by a mathematical model. These equations were further developed to describe the time course of a pharmacologic event. In this case, Meredith and associates (1983) demonstrated that both the drug and the metabolite formed in the body may affect the time course of the pharmacologic action of the drug in the body.

Simulation of *In-Vitro* Pharmacodynamic Effect Involving Hysteresis

An *in-vitro* model simulation of the sum of pharmacologic effect contributed by a drug and its active metabolite may explain the observation of the hysteresis response curve *in vivo*. Gupta et al (1993) discussed the factors that affect the shape of the response curve. In the simplest case, pharmacokinetic equations are developed to calculate C_p , the drug concentration, and C_m , the metabolite concentration. To estimate the pharmacologic effect due to both the drug and active metabolite, the potency of the drug is defined as P , the potency of the metabolite is P_m , and

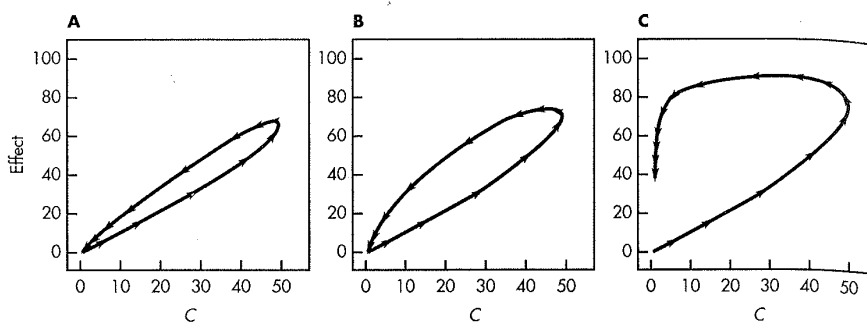


Figure 19-28. Simulated *in-vitro* pharmacodynamic response versus concentration (C) contributed by a drug and a metabolite. Potency of parent drug and metabolite are equal, but **(A)** k_{m0} = large, **(B)** k_{m0} = medium, and **(C)** k_{m0} = small.
(From Gupta et al, 1993, with permission.)

the sum of the pharmacologic effect is as shown below. (In their first simulation, Gupta et al assumed that the effect is linearly related to drug and metabolite concentrations.)

$$E = PC_p + P_m C_m \quad (19.32)$$

The shape of hysteresis simulated is very dependent on P_m and k_{m0} , the rate constant of metabolite elimination. If k_{m0} is given a high, medium, or low value, the effect on the shape of the hysteresis loop is changed dramatically, as shown in Figure 19-28. A temporal effect causes a counterclockwise loop. In the case of a metabolite that acts as an antagonist, the hysteresis loop is clockwise. The more elaborate features of an E_{max} model were simulated by Gupta et al (1993) in their paper.



CLINICAL EXAMPLE

Lorazepam Pharmacodynamics—Example of an In-Vivo Hysteresis Loop

Many drugs that act on the central nervous systems (CNS) have a lag time before the tissues and the plasma are equilibrated with drug. The pharmacokinetics of lorazepam after oral absorption were fitted to a two-compartment model with lag time. Lorazepam was studied because the drug accounts for all the activity, such that the counterclockwise response profile may be attributed to equilibration rather than to metabolism (Gupta et al, 1990).

The description of the plasma drug concentrations, C_p , is obtained by conventional pharmacokinetic equations, whereas the pharmacodynamic effect, E , is

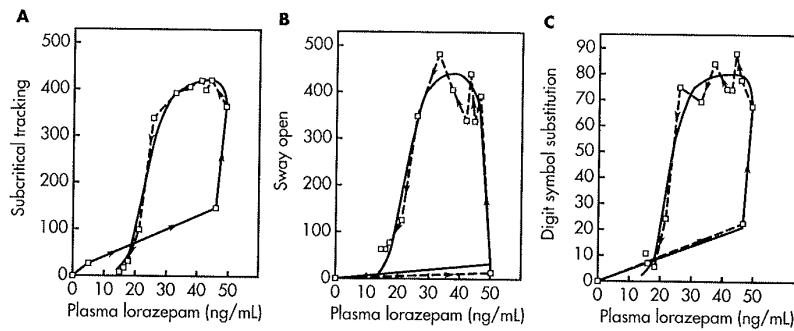


Figure 19-29. Plot of responses of lorazepam versus plasma drug concentration showing counterclockwise hysteresis.

(From Gupta et al, 1990, with permission.)

described by a sigmoid E_{\max} model similar to Equation 19.15, except that the baseline effect is also included. Gupta et al (1990) monitored three pharmacodynamic effects due to lorazepam. The monitored pharmacodynamic effects were mental impairment processes evaluated by the cognitive and psychomotor performance of the subjects, including (A) subcritical tracking, (B) sway open (a measurement of gross body movements), and (C) digital symbol substitution. When the time course of each effect was plotted versus plasma drug concentration, a counterclockwise loop was observed (Fig. 19-29). When the same pharmacodynamic responses were plotted versus lorazepam concentration in the effect compartment accounting for the equilibration lag, a classical sigmoid relation was observed (Fig. 19-30). The observations showed that the temporal response of many drugs may be the result of pharmacodynamic and distributional factors interacting with each other. Thus, a model with an effect compartment can more fully help to understand the time course of the drug response.

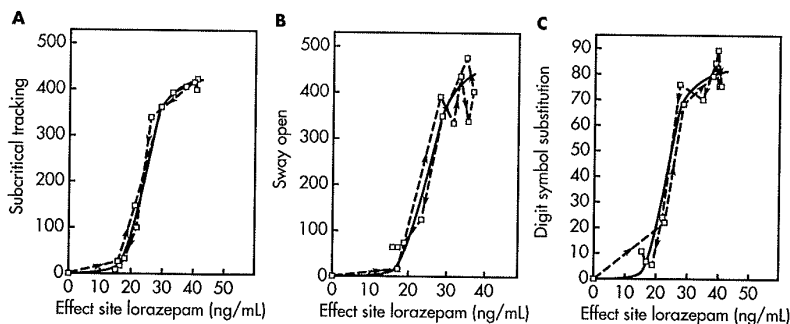


Figure 19-30. Plot of responses to lorazepam versus effect compartment concentration showing sigmoid relationship between effect and concentration without hysteresis.

(From Gupta et al, 1990, with permission.)



FREQUENTLY ASKED QUESTIONS

1. Explain why doubling the dose of a drug does not double the pharmacodynamic effect of the drug.
2. What is meant by a hysteresis loop? Why do some drugs follow a clockwise hysteresis loop and other drugs follow a counterclockwise hysteresis loop?
3. What is meant by an effect compartment? How does the effect compartment differ from pharmacokinetic compartments, such as the central compartment and the tissue compartment?



LEARNING QUESTIONS

1. On the basis of the graph in Figure 19-31, answer "true" or "false" to statements (a)–(e) and state the reason for each answer.
 - a. The plasma drug concentration is more related to the pharmacodynamic effect of the drug compared to the dose of the drug.
 - b. The pharmacologic response is directly proportional to the log plasma drug concentration.
 - c. The volume of distribution is not changed by uremia.
 - d. The drug is exclusively eliminated by hepatic biotransformation.
 - e. The receptor sensitivity is unchanged in the uremic patient.
2. What do clavulanate, sulbactam, and tazobactam have in common? Why are they used together with antibiotics?
3. Explain why subsequent equal doses of a drug do not produce the same pharmacodynamic effect as the first dose of a drug.
 - a. Provide an explanation based on pharmacokinetic considerations.
 - b. Provide an explanation based on pharmacodynamic considerations.

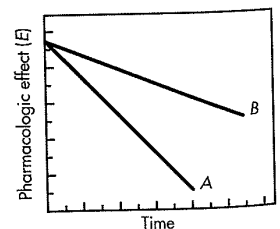


Figure 19-31. Graph of pharmacologic response E as a function of time for the same drug in patients with normal (**A**) and uremic (**B**) kidney function, respectively.

4. How are the parameters AUC and t_{eff} used in pharmacodynamic models?
5. What class of drug tends to have a lag time between the plasma and the effect compartment?
6. Name an example of a pharmacodynamic response that does not follow a drug dose-response profile?
7. When an antibiotic concentration falls below the MIC, there is a short time period in which bacteria fail to regrow because of postantibiotic effect (PAE). This time period is referred to as PAT. What is PAT?
8. What is AUIC with regard to an antibiotic?

REFERENCES

- Aghajanian OK, Bing OHL: Persistence of lysergic acid diethylamide in the plasma of human subjects. *Clin Pharmacol Ther* 5:611-614, 1964
- Baxter JD, Funder JW: Hormone receptors. *N Engl J Med* 301:1149-1161, 1979
- Boudinot FD, D'Ambrosio R, Jusko WJ: Receptor-mediated pharmacodynamics of prednisolone in the rat. *J Pharmacokinet Biopharm* 14:469-493, 1986
- Colburn WA: Perspectives in pharmacokinetics: Pharmacokinetic/pharmacodynamic modeling: What is it? *J Pharmacokinet Biopharm* 15:545-553, 1987
- Cone EJ: Pharmacokinetics and pharmacodynamics of cocaine. *J Anal Toxicol* 19:459-478, 1995
- Cox, BM: Drug tolerance and physical dependence. In WB Pratt, P Taylor (eds): *Principles of Drug Action. The Basis of Pharmacology*. New York, Churchill Livingstone, 1990, chap 10
- Craig, WA: Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad-spectrum cephalosporins. *Diag Microbiol Infect Dis* 22:89-96, 1995
- Craig WA, Andes D: Pharmacokinetics and pharmacodynamics of antibiotics in otitis media. *J Pediatr Infect Dis* 15:255-259, 1996
- deWit H, Dudish S, Ambre J: Subjective behavioral effects of diazepam depend upon its rate of onset. *Psychopharmacology* 112:324-330, 1993
- Drusano GL: Minireview: Role of pharmacokinetics in the outcome of infections. *Antimicrob Agents Chemother* 32(3):289-297, 1988
- Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ: Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. *Antimicrob Agents Chemother* 37(5):1073-1081, 1993
- Gupta SK, Ellinwood EH, Nikaido AM, Heatherly DG: Simultaneous modeling of the pharmacokinetic and pharmacodynamic properties of benzodiazepines I: Lorazepam. *J Pharmacokinet Biopharm* 18:89-102, 1990
- Gupta SK, Hwang SS, Benet LZ, Gumbleton M: Interpretation and utilization of effect and concentration data collected in an *in vivo* pharmacokinetic and *in vitro* pharmacodynamic study. *Pharm Res* 10:889-894, 1993
- Henningfield JE, Keenan RM: Nicotine delivery kinetics and abuse liability. *J Consult Clin Pharmacol* 61:743-750, 1993
- Hill AV: The possible effects of the aggregation of the molecules of haemoglobin on its dissociation curves. *J Physiol* 40:4-7, 1910
- Holford NHG, Sheiner LB: Understanding the dose-effect relationship. Clinical application of pharmacokinetic-pharmacodynamic models. *Clin Pharmacokinet* 6:429-453, 1981
- Holford NHG, Sheiner LB: Kinetics of pharmacologic response. *Pharm Ther* 16:143-166, 1982
- Johanson C-E, Fischman MW: The pharmacology of cocaine related to its abuse. *Pharmacol Rev* 41:3-52, 1989
- Johansen SH, Jorgensen M, Molbech S: Effect of tubocurarine on respiratory and nonrespiratory muscle power in man. *J Appl Physiol* 19:990-991, 1964

- Lalonde RL: Pharmacodynamics. In Evans WE et al. (eds): *Applied Pharmacokinetics*, 3rd ed. Vancouver, WA, Applied Therapeutics, 1992, chap 4
- Lin RY: A perspective on penicillin allergy. *Arch Intern Med* 152:930-937, 1992
- Meredith PA, Kelman AW, Eliott HL, Reid JL: Pharmacokinetic and pharmacodynamic modeling of trimazosin and its major metabolite. *J Pharmacokinet Biopharm* 11:323-334, 1983
- Meibohm B, Derendorf H: Basic concepts of pharmacokinetic/pharmacodynamic (PK/PD) modelling. *Int J Clin Pharmacol* 35(10):401-413, 1997
- Mitenko PA, Ogilvie RI: Rational intravenous doses of theophylline. *N Engl J Med* 289:600-603, 1973
- Reisman AS, Reisman RE: Risk of administering cephalosporin antibiotics to patients with histories of penicillin allergy. *Ann Allergy Asthma Immunol* 74:167-170, 1995
- Rodman JH, Evans WE: Targeted systemic exposure for pediatric cancer therapy. In D'Argenio (ed): *Advanced Methods of Pharmacokinetic and Pharmacodynamic Systems Analysis*. New York, Plenum Press, 1991, pp 177-183
- Scaglione F: Predicting the clinical efficacy of antibiotics: Toward definitive criteria. *Pediatr Infect Dis J* 3:S56-S59, 1997
- Scott JC, Stanski DR: Decreased fentanyl/alfentanil dose requirement with increasing age: A pharmacodynamic basis. *Anesthesiology* 63:A374, 1985
- Sheiner LB, Stanski DR, Vozeh S, et al: Simultaneous modeling of pharmacokinetics and pharmacodynamics: Application to *d*-tubocurarine. *Clin Pharmacol Ther* 25:358-370, 1979
- Taylor P, Insel PA: Molecular basis of pharmacologic selectivity. In Pratt WB, Taylor P (eds): *Principles of Drug Action. The Basis of Pharmacology*, 3rd ed. New York, Churchill Livingstone, 1990
- van Dyke C, Jatlow P, Ungerer J, et al: Oral cocaine: Plasma concentration and central effects. *Science* 200:211-213, 1978
- Wagner JC: Kinetics of pharmacologic response: 1. Proposed relationship between response and drug concentration in the intact animal and man. *J Theor Biol* 20:173-201, 1968
- Winkle RA, Meffin PJ, Fitzgerald JW, Harrison DC: Clinical efficacy and pharmacokinetics of a new orally effective antiarrhythmic tocinamide. *Circulation* 54:884-889, 1976
- Yasuhara M, Hashimoto Y, Okumura K, et al: Kinetics of ajmaline disposition and pharmacologic response in beagle dogs. *J Pharmacokinet Biopharm* 15:39-56, 1987

BIBLIOGRAPHY

- Derendorf H, Meibohm B: Modeling of pharmacokinetic/pharmacodynamic (PK/PD) relationships: Concepts and perspectives. *Pharm Res* 6:176-185, 1999
- Drusano GL: Human pharmacodynamics of beta-lactams, aminoglycosides and their combination. *Scand J Infect Dis* 74(suppl):235-248, 1991
- Drusano GL, Craig WA: Relevance of pharmacokinetics and pharmacodynamics in the selection of antibiotics for respiratory tract infections. *J Chemother* 9(suppl 3):38-44, 1997
- Galeazzi RL, Benet LZ, Sheiner LB: Relationship between the pharmacokinetics and pharmacodynamics of procainamide. *Clin Pharmacol Ther* 20:278-289, 1976
- Gibaldi M, Levy G, Weintraub H: Drug distribution and pharmacologic effects. *Clin Pharmacol Ther* 12:734, 1971
- Gunderson BW, Ross GH, Ibrahim KH, Rotschafer JC: What do we really know about antibiotic pharmacodynamics? *Pharmacotherapy* 21(11s):302s-318s, 2001
- Harron DWG: Digoxin pharmacokinetic modeling—10 years later. *Int J Pharm* 53:181-188, 1989
- Hochhaus G, Barrett JS, Derendorf H: Evolution of pharmacokinetics and pharmacokinetic/dynamic correlations during the 20th century. *J Clin Pharmacol* 40(9):908-917, 2000
- Holford NHG: Clinical pharmacokinetics and pharmacodynamics of warfarin. Understanding the dose-effect relationship. *Clin Pharmacokinet* 11:583-604, 1986
- Jusko WJ: Pharmacodynamics of chemotherapeutic effects: Dose-time-response relationship for phase-nonspecific agents. *J Pharm Sci* 60:892, 1971
- Levy G: Kinetics of pharmacologic effects. *Clin Pharmacol Ther* 1:362, 1966
- Meffin PJ, Winkle RA, Blaschke RF, et al: Response optimization of drug dosage: Antiarrhythmic studies with tocinamide. *Clin Pharmacol Ther* 22:42-57, 1977

- Meibohm B, Derendorf H: Pharmacokinetic/pharmacodynamic studies in drug product development. *J Pharm Sci* **91**:18-31, 2002
- Mueller M, de la Pena A, Derendorf H: Issues in pharmacokinetics and pharmacodynamics of anti-infective agents: Kill curves versus MIC. *Antimicrob Agents Chemother* **48**(2):369-377, 2004
- Packer M, Carver JR, Rodeheffer RJ, et al: Effect of oral milrinone on mortality in severe chronic heart failure. *N Engl J Med* **21**:1468, 1991
- Schwinghammer TL, Kroboth PD: Basic concepts in pharmacodynamic modeling. *J Clin Pharmacol* **28**:388-394, 1988
- Seeman P, Lee T, Chau-Wong M, Wong K: Antipsychotic drug doses and neuroleptic/dopamine receptors. *Nature* **261**:717-719, 1976
- Sheiner LB: Commentary to pharmacokinetic/pharmacodynamic modeling: What it is! *J Pharmacokinet Biopharm* **15**:553-555, 1987
- Suresh A, Reisman RE: Risk of administering cephalosporin antibiotics to patients with histories of penicillin allergy. *Ann Allergy Asthma Immunol* **74**:167-170, 1995
- Swerdlow BN, Holley FO: Intravenous anaesthetic agents. Pharmacokinetic/pharmacodynamic relationships. *Clin Pharmacokinet* **12**:79-110, 1987
- Verrijck R, Vleeming W, Hans H, et al: Plasma elimination of milrinone in rats in relation to its hemodynamic effects. *J Pharm Sci* **79**:236-239, 1990
- Whiting B, Holford NHG, Sheiner LB: Quantitative analysis of the disopyramide concentration-effect relationship. *Br J Clin Pharmacol* **9**:67-75, 1980