DRUG ABSORPTION, DISTRIBUTION AND ELIMINATION; PHARMACOKINETICS

I. DRUG ADMINISTRATION

Often the goal is to attain a therapeutic drug concentration in plasma from which drug enters the tissue (therapeutic window between toxic concentration and minimal effective concentration).

A. Enteral Routes

1. Sublingual (buccal)

Certain drugs are best given beneath the tongue or retained in the cheek pouch and are absorbed from these regions into the local circulation. These vascular areas are ideal for lipid-soluble drugs that would be metabolized in the gut or liver, since the blood vessels in the mouth bypass the liver (do not undergo first pass liver metabolism), and drain directly into the systemic circulation. This route is usually reserved for nitrates and certain hormones.

2. Oral

By far the most common route. The passage of drug from the gut into the blood is influenced by biologic and physicochemical factors (discussed in detail below), and by the dosage form. For most drugs, two- to five-fold differences in the rate or extent of gastrointestinal absorption can occur, depending on the dosage form. These two characteristics, rate and completeness of absorption, comprise <u>bioavailability</u>. Generally, the bioavailability of oral drugs follows the order: solution > suspension > capsule > tablet > coated tablet.

3. Rectal

The administration of suppositories is usually reserved for situations in which oral administration is difficult. This route is more frequently used in small children. The rectum is devoid of villi, thus absorption is often slow.

B. Parenteral Routes

1. Intravenous injection

Used when a rapid clinical response is necessary, e.g., an acute asthmatic episode. This route allows one to achieve relatively precise drug concentrations in the plasma, since bioavailability is not a concern. Most drugs should be injected over 1-2 minutes in order to prevent the occurrence of very high drug concentrations in the injected vein, possibly causing adverse effects. Some drugs, particularly those with narrow therapeutic indices or short half-lives, are best administered as a slow IV infusion or drip.

2. Intra-arterial injection

Used in certain special situations, notably with anticancer drugs, in an effort to deliver a high concentration of drug to a particular tissue. Typically, the injected artery leads directly to the target organ.

3. Intrathecal injection
   The blood-brain barrier limits the entry of many drugs into cerebrospinal fluid. Under some circumstances, usually life-threatening, antibiotics, antifungals and anticancer drugs are given via lumbar puncture and injection into the subarachnoid space.

4. Intramuscular injection
   Drugs may be injected into the arm (deltoid), thigh (vastus lateralis) or buttocks (gluteus maximus). Because of differences in vascularity, the rates of absorption differ, with arm > thigh > buttocks. Drug absorption may be slow and erratic. The volume of injection, osmolality of the solution, lipid solubility and degree of ionization influence absorption. It should <u>not</u> be assumed that the IM route is as reliable as the IV route.

5. Subcutaneous injection
   Some drugs, notably insulin, are routinely administered SC. Drug absorption is generally slower SC than IM, due to poorer vascularity. Absorption can be facilitated by heat, massage or vasodilators. It can be slowed by coadministration of vasoconstrictors, a practice commonly used to prolong the local action of local anesthetics. As above, arm > thigh.

6. Inhalation
   Volatile anesthetics, as well as many drugs which affect pulmonary function, are administered as aerosols. Other obvious examples include nicotine and tetrahydrocannabinol (THC), which are absorbed following inhalation of tobacco or marijuana smoke. The large alveolar area and blood supply lead to rapid absorption into the blood. Drugs administered via this route are not subject to first-pass liver metabolism.

7. Topical application
   a. Eye
      For desired local effects.
   b. Intravaginal
      For infections or contraceptives.
   c. Intranasal
      For alleviation of local symptoms.
   d. Skin
      Topical drug administration for skin disorders minimizes systemic exposure. However, systemic absorption does occur and varies with the area, site, drug, and state of the skin. Dimethyl sulfoxide (DMSO) enhances the percutaneous absorption of many drugs, but its use is controversial because of concerns about its toxicity.
   e. Drug patches (drug enters systemic circulation by zero order kinetics – a constant amount of drug enters the circulation per unit time).

II. DRUG ABSORPTION

A. Biologic Factors

1. Membrane structure and function

The cell membrane is a semipermeable lipoid sieve containing numerous aqueous channels, as well as a variety of specialized carrier molecules.

a. For most tissues, passive aqueous diffusion through channels occurs only for molecules less than 150-200 MW. A notable exception is the endothelial capillary lining, whose relatively large pores allow molecules of 20-30,000 to pass. However, the capillaries of most of the brain lack these large pores.

b. Passive lipid diffusion is probably the most important absorptive mechanism. Lipid-soluble drugs dissolve in the membrane, and are driven through by a concentration gradient across the membrane.

c. Carrier-mediated facilitated transport occurs for some drugs, particularly those which are analogs of endogenous compounds for which there already exist specific membrane carrier systems. For example, methotrexate, an anticancer drug which is structurally similar to folic acid, is actively transported by the folate membrane transport system.

2. Local blood flow

Local blood flow is a strong determinant of the rate of absorption because it continuously maintains the concentration gradient necessary for passive diffusion to occur. For orally administered drugs, remember that the blood supply draining the gut passes through the liver before reaching the systemic circulation. Since the liver is a major site of drug metabolism, this first-pass effect may reduce the amount of drug reaching the target tissue. In some cases, the first-pass effect results in metabolic activation of an inert pro-drug.

3. Gastric emptying times

Gastric emptying times vary among patients and contribute significantly to intersubject variability in drug absorption.

4. Drug binding

Many drugs will bind strongly to proteins in the blood or to food substances in the gut. Binding to plasma proteins will increase the rate of passive absorption by maintaining the concentration gradient of free drug. For many drugs, the gastrointestinal absorption rate, but not the extent of absorption, is reduced by the presence of food in the gut. Some drugs are not affected by food, while the absorption of a third group of drugs is enhanced by food (bile secretion by liver in response to food in GI tract increases drug absorption). Some drugs are irritating and should be administered with meals to reduce adverse effects.

B. Physicochemical Factors: pH Partition Theory

1. Background review

The simplest definition of an acid is that it is a substance, charged or uncharged, that liberates hydrogen ions (H^+) in solution. A base is a substance that can bind H^+ and remove them from solution. Strong acids, strong bases, as well as strong electrolytes are essentially completely ionized in aqueous solution. Weak acids and weak bases are only partially ionized in aqueous solution and yield a mixture of the undissociated compound and ions.

Thus a weak acid (HA) dissociates reversibly in water to produce hydrogen ion H^+ and A^-.

$$HA \rightleftharpoons H^+ + A^- \qquad (1)$$

Applying the mass law equation, which demands that concentrations are in moles per liter, we obtain the following equation:

$$\frac{[H+]\,[A^-]}{[HA]} = Ka \qquad (2)$$

where Ka is the ionization or dissociation constant of the acid. Since the ion concentrations are in the numerator, the stronger the acid, the higher the value of Ka. Similarly, one could derive Kb for a weak base BOH. Rearranging equation (2) yields the following:

$$[H^+] = \frac{Ka\,[HA]}{[A^-]} \qquad (3)$$

Taking the log of both sides of the equation:

$$\log [H^+] = \log Ka + \log [HA] - \log [A^-] \qquad (4)$$

And multiplying by -1, we obtain:

$$-\log [H^+] = -\log Ka - \log [HA] + \log [A^-] \qquad (5)$$

By definition, $-\log [H^+] = pH$, and $-\log Ka = pKa$. Thus, we obtain the important relationships

$$\text{for acids: } pH = pKa + \log \frac{[A^-]}{[HA]} \qquad (6)$$

$$\text{for bases: } pH = pKa + \log \frac{[B]}{[BH^+]} \qquad (7)$$

From the pKa, one can calculate the proportions of drug in the charged and uncharged forms at any pH:

$$\log \frac{[A^-]}{[HA]} = (pH - pKa) \qquad (8)$$

$$\frac{[A^-]}{[HA]} = 10^{(pH - pKa)} \qquad (9)$$

$$\frac{[B]}{[BH^+]} = 10^{(pH-pKb)} \qquad (10)$$

$$pKb = (1-pKa)$$

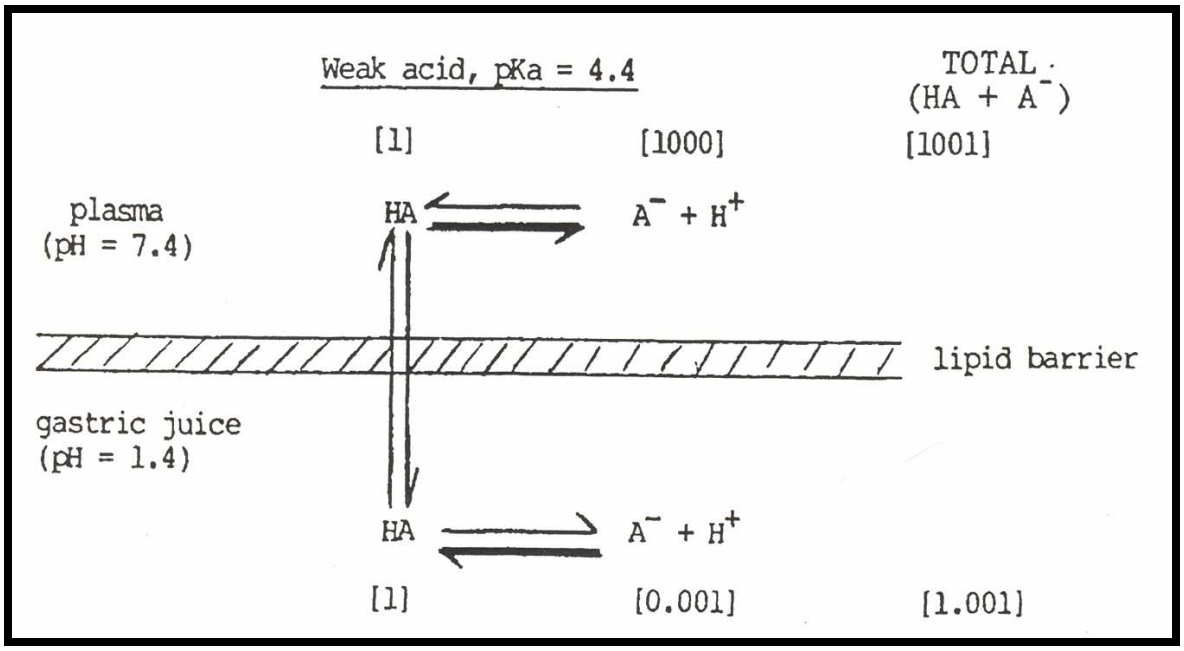
2. Ion trapping
The influence of pH on transfer of drugs across membranes.

What does this background review have to do with pharmacology. Plenty! Most drugs are too large to pass through membrane channels and must diffuse through the lipid portion of the cell membrane. Nonionized drug molecules are readily lipid-soluble, while ionized molecules are lipophobic and are insoluble.

The distribution of a drug across the cell membrane is usually determined by its pKa and the pHs on both sides of a membrane. The difference of pH across a membrane influences the total concentration of drug on either side, since, by diffusion, at equilibrium the concentration of nonionized drug will be the same on either side.

For example, let's consider the influence of pH on the distribution of a drug which is a weak acid (pKa = 4.4) between plasma (pH = 7.4) and gastric juice (pH = 1.4). The mucosa can be considered to be a simple lipid barrier.

Figure 1



At equilibrium, the concentration of the unionized drug [HA] on either side of lipid barrier will be the same. Using equation (9), we can calculate the molar ratios of ionized drug $[A^-]$ to [HA] on each side of the membrane.

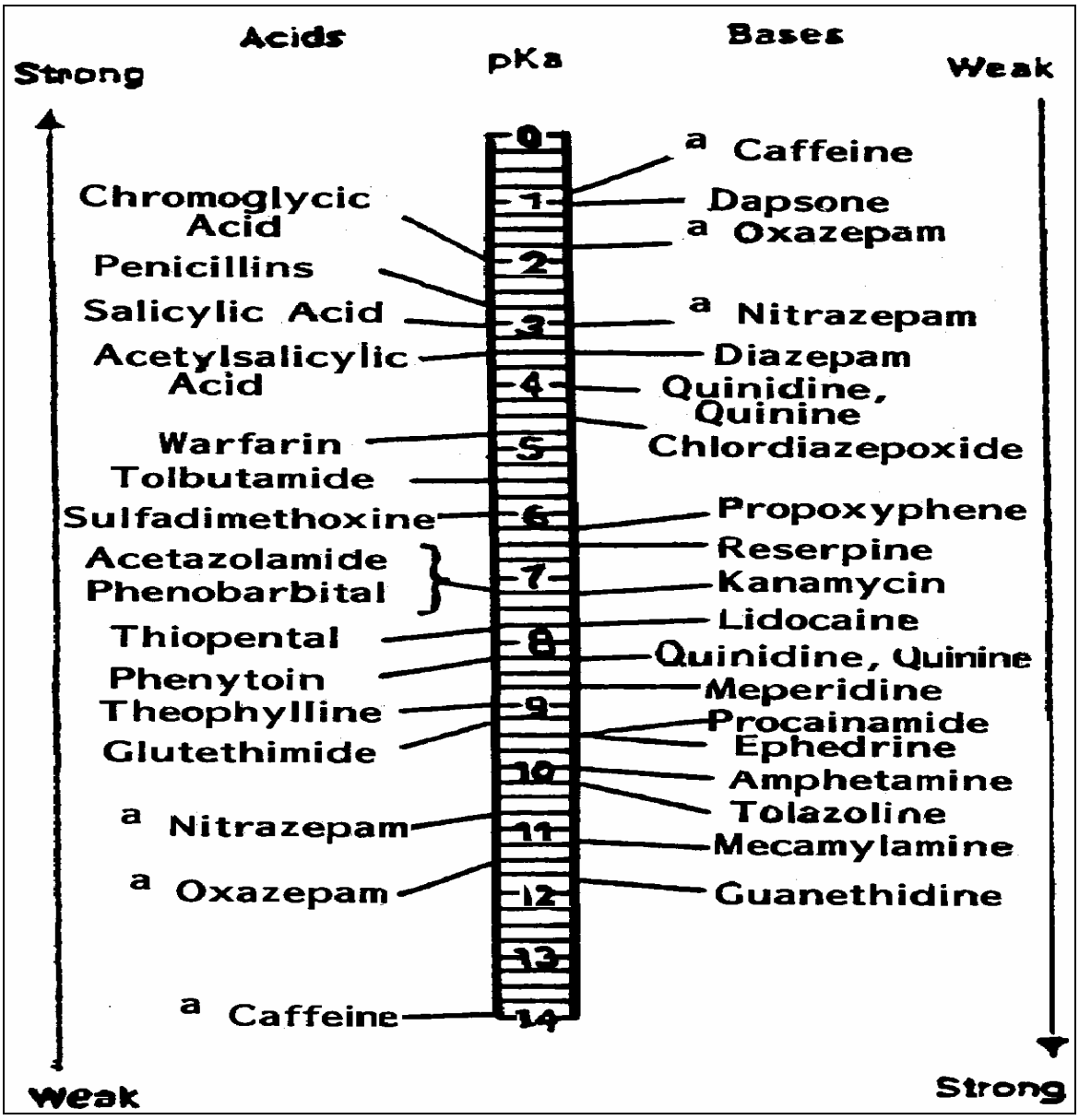
in plasma:

$$\frac{[A^-]}{[HA]} = 10^{(7.4 - 4.4)} = 10^3 = 1000$$

in gastric juice:

$$\frac{[A^-]}{[HA]} = 10^{(1.4 - 4.4)} = 10^{-3} = .001$$

Figure 2



The pKa values of certain acidic and basic drugs. Those drugs denoted with an * are amphoteric. (From Rowland, M., and Tozer, T.N.)

III. DRUG DISTRIBUTION

Once in the blood, drugs are simultaneously distributed throughout the body and eliminated. Typically, distribution is much more rapid than elimination, is accomplished via the circulation, and is influenced by regional blood flow.

A. Compartments

1. Central Compartment
   The central compartment includes the well-perfused organs and tissues (heart, blood, liver, brain and kidney) with which drug equilibrates rapidly.

2. Peripheral Compartment(s)
   The peripheral compartment(s) include(s) those organs (e.g., adipose and skeletal muscle) which are less well-perfused, and with which drug therefore equilibrates more slowly. Redistribution from one compartment to another often alters the duration of effect at the target tissue. For example, thiopental, a highly lipid-soluble drug, induces anesthesia within seconds because of rapid equilibration between blood and brain. Despite the fact that the drug is slowly metabolized, however, the duration of anesthesia is short because of drug redistribution into adipose tissue, which can act as a storage site, or drug reservoir.

3. Special Compartments
   Several special compartments deserve mention. Entry of drug into the cerebrospinal fluid (CSF) and central nervous system (CNS) is restricted by the structure of the capillaries and pericapillary glial cells (the choroid plexus is an exception). The blood-brain barrier limits the success of antibiotics, anticancer drugs and other agents used to treat CNS diseases. Drugs also have relatively poor access to pericardial fluid, bronchial secretions and fluid in the middle ear, thus making the treatment of infections in these regions difficult.

B. Protein Binding

Many drugs bind to plasma proteins. Weak acids and neutral drugs bind particularly to albumin, while basic drugs tend to bind to alpha-1-acid glycoprotein (orosomucoid). Some drugs even bind to red cell surface proteins.

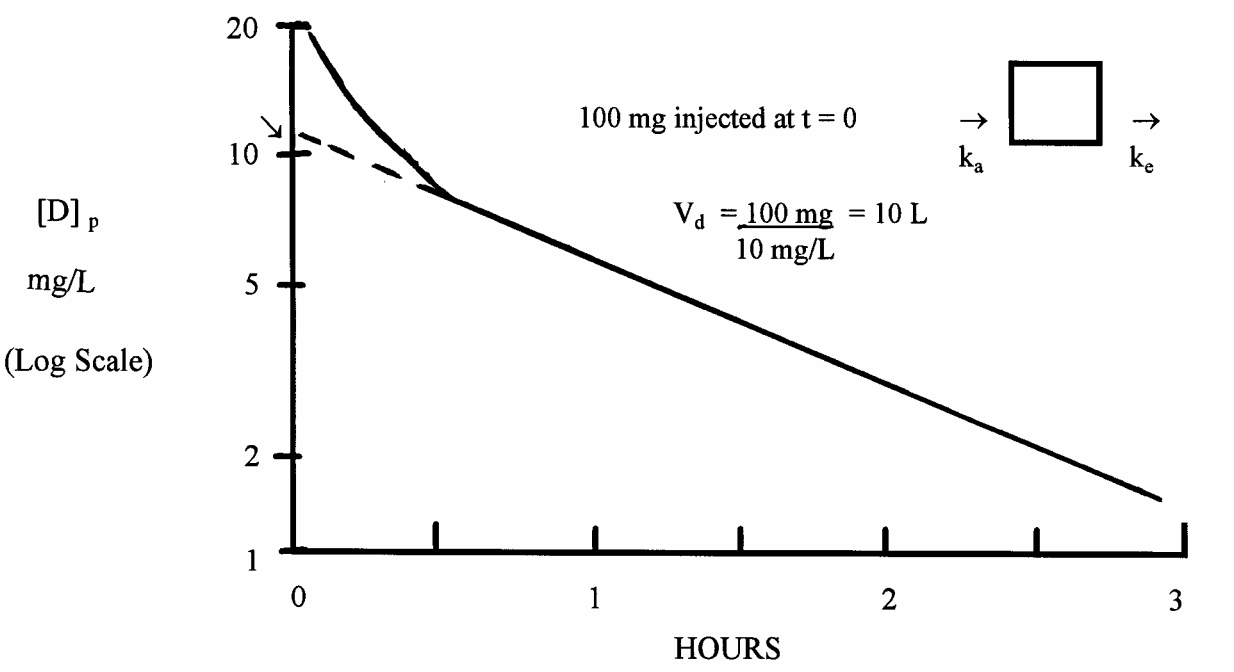
1. Effects on drug distribution
   Only that fraction of the plasma drug concentration which is freely circulating (i.e., unbound) can penetrate cell membranes. Protein binding thus decreases the net transfer of drug across membranes. Drug binding to plasma proteins is generally weak and rapidly reversible, however, so that protein-bound drug can be considered to be in a temporary storage compartment. The protein concentration of extravascular fluids (e.g., CSF, lymph, synovial fluid) is very low. Thus, at equilibrium (when the concentrations of free drug are equal), the total drug concentration in plasma is usually higher than that in extravascular fluid. The extent of protein binding must be considered in interpreting "blood levels" of drugs.

2. Effects on drug elimination
The effects of plasma protein binding on drug elimination are complex. For drugs excreted only by renal glomerular filtration, protein binding decreases the rate of elimination since only the free drug is filtered. For example, the rates of renal excretion of several tetracyclines are inversely related to their extent of plasma protein binding. Conversely, however, if drug is eliminated by hepatic metabolism or renal tubular secretion, plasma protein binding may promote drug elimination by increasing the rate that that drug is presented for elimination.

3. Tissue binding
Binding to tissue proteins may cause local concentration of drug. For example, if a drug is bound more extensively at intracellular than at extracellular sites, the intracellular and extracellular concentrations of free drug may be equal or nearly so, but the total intracellular drug concentration may be much greater than the total extracellular concentration.

C. Apparent volume of distribution (AVD or Vd).
The volume of distribution, or more properly the apparent volume of distribution, is calculated from measurements of the total concentration of drug in the blood compartment after a single IV injection. Suppose that we injected someone IV with 100 mg of a drug, and measured the blood concentration of the drug repeatedly during the next several hours. We then plot the blood concentrations (on a log scale) against time, and obtain the following graph:

Figure 3



If the drug is assumed to follow two-compartment kinetics, the initial curvilinear portion of the data reflects the drug distribution phase, with drug moving from the blood into tissues. The linear portion of the curve reflects drug elimination. By extrapolation of the linear portion, we can find the blood concentration at time 0, had mixing between both compartments been instantaneous; it is 10 mg/ml. We can also calculate V_d, which is defined as:

$$V_d = \frac{\text{amount of drug injected}}{\text{blood concentration at time 0}} = \frac{100\ mg}{10\ mg/L} = 10L$$

V_d does not represent a real volume, but rather indicates the size of the pool of body fluids that would be required if the drug were distributed equally throughout the body. Drug concentrations in body compartments will vary according to the physicochemical properties of the drug. Thus, V_d is a characteristic property of the drug rather than the patient, although disease states may influence V_d. If binding to plasma proteins is marked, most of the drug will be maintained within the intravascular compartment and V_d will be small. If there is extravascular binding, or storage in fat or other tissues, V_d will be large. For example, digoxin, a hydrophobic drug which distributes into fat and muscle, has a V_d of 640 liters (in a 70 kg man), approximately nine times the total volume of the man! The usefulness of the V_d concept will become more apparent when we discuss pharmacokinetics and perform calculations of blood levels of drugs.

In general, acidic drugs bind to plasma proteins and have small V_ds, while basic drugs tend to bind more extensively to extravascular sites and have larger V_ds. V_d may be influenced by disease states. For example, patients with chronic liver disease have lower serum albumin concentrations. Plasma protein binding will be reduced, leading to lower plasma drug concentrations and higher V_ds.

IV. DRUG BIOTRANSFORMATION

The body is exposed to a wide variety of foreign compounds, called xenobiotics. Exposure to some such compounds is unintentional (e.g., environmental or food substances), while others are deliberately used as drugs. The following discussion of drug biotransformation is applicable to all xenobiotics, and to some endogenous compounds (e.g., steroids) as well.

The kidneys are capable of eliminating drugs which are low in molecular weight, or which are polar and fully ionized at physiologic pH. Most drugs do not fit these criteria, but rather are fairly large, unionized or partially ionized, lipophilic molecules. The general goal of drug metabolism is to transform such compounds into more polar (i.e., more readily excretable) water soluble products. For example, were it not for biotransformation to more water-soluble products, thiopental, a short-acting, lipophilic anesthetic, would have a half-life of more than 100 years! Imagine, without biotransformation reactions, anesthesiologists might grow old waiting for patients to wake up.

Most products of drug metabolism are less active than the parent compound. In some cases, however, metabolites may be responsible for toxic, mutagenic, teratogenic or carcinogenic effects. For example, overdoses of acetaminophen owe their hepatotoxicity to a minor metabolite which reacts with liver proteins. In some cases, with metabolism of so-called prodrugs, metabolites are actually the active therapeutic compounds. The best example of a prodrug is cyclophosphamide, an inert compound which is metabolized by the liver into a highly active anticancer drug.

A. Sites of drug metabolism

1. At the organ level

The liver is the primary organ of drug metabolism. The gastrointestinal tract is the most important extrahepatic site. Some orally administered drugs (e.g., isoproterenol) are conjugated extensively in the intestinal epithelium, resulting in decreased bioavailability. The lung, kidney, intestine, skin and placenta can also carry out drug metabolizing reactions. Because of its enormous perfusion rate and its anatomic location with regard to the circulatory system, the lungs may exert a first-pass effect for drugs administered IV.

2. At the cellular level

Most enzymes involved in drug metabolism are located within the lipophilic membranes of the smooth endoplasmic reticulum (SER). When the SER is isolated in the laboratory by tissue homogenation and centrifugation, the SER membranes re-form into vesicles called microsomes. Since most of the enzymes carry out oxidation reactions, this SER complex is referred to as the microsomal mixed function oxidase (MFO) system.

3. At the biochemical level

Phase I reactions refer to those which convert a drug to a more polar compound by introducing or unmasking polar functional groups such as -OH, $-NH_2$, or -SH. Some Phase I products are still not eliminated rapidly, and hence undergo Phase II reactions involving conjugation of the newly established polar group with endogenous compounds such as glucuronic acid, sulfuric acid, acetic acid, or amino acids (typically glycine). Glucuronide formation is the most common phase II reaction. Sometimes,

the parent drug may undergo phase II conjugation directly. In some cases, a drug may undergo a series of consecutive reactions resulting in the formation of dozens of metabolites.

Most phase I MFO biotransformation reactions are oxidative in nature and require a reducing agent (NADPH), molecular oxygen, and a complex of microsomal enzymes; the terminal oxidizing enzyme is called cytochrome P_{450}, a hemoprotein so named because its carbon monoxide derivative absorbs light at 450 nm. We now know that cytochrome P_{450} is actually a family of enzymes which differ primarily with regard to their substrate specificities. Advances in molecular biology have led to the identification of more than 70 distinct P_{450} genes in various species.

The nomenclature of the P_{450} reductase gene products has become complex. Based upon their amino acid homologies, the P_{450} reductases have been grouped into families such that a cytochrome P_{450} from one family exhibits < 40% amino acid sequence identity to a cytochrome P_{450} in another gene family. Several of the gene families are further divided into subfamilies, denoted by letters A, B, C, etc. Eight major mammalian gene families have been defined (see Table 1).

Table 1: **Major Cytochrome P450 Gene Families**

P_{450} Gene Family/Subfamily	**Characteristic Substrates**	**Characteristic Inducers**	**Characteristic Inhibitor**
CYP 1A2	Acetominophen Estradiol Caffeine	Tobacco Char-Grilled Meats Insulin	Cimetidine Amiodarone Ticlopidine
CYP 2C19	Diazepam, Omeprazole Progesterone	Prednisone Rifampin	Cimetidine Ketoconazole Omeprazole
CYP 2C9	Tamoxifen Ibuprofen Fluoxetine	Rifampin Secobarbital	Fluvastatin Lovastatin Isoniazid
CYP 2D6	Debrisoquine Ondansetron Amphetamine	Dexamethasone? Rifampin?	Cimetidine Fluoxetine Methadone
CYP 2E1	Ethanol Benzene Halothane	Ethanol Isoniazid	Disulfiram Water Cress
CYP 3A4, 5, 7	Cyclosporin Clarithromycin Hydrocortisone Vincristine Many, many others	Barbiturates Glucocorticoids Carbamazepine St. John's Wort	Cimetidine Clarithromycin Ketoconazole Grapefruit Juice Many others

B. Enzyme Induction

An interesting and important feature of the cytochrome P_{450} mixed function oxidase system is the ability of some xenobiotics to induce the synthesis of new enzyme. Microsomal enzyme induction is a complex and poorly understood process associated with an increase in liver weight, proliferation of the SER, and synthesis of P_{450} enzymes. For example, phenobarbital induces the P_{450}IIB subfamily, while polycyclic aromatic hydrocarbons (e.g., found in cigarette smoke or charcoal broiled foods) induce the P_{450}IA subfamily; these and other inducers are listed in Table 1, above. Obviously, the dose and frequency of drug administration required to achieve therapeutic drug concentrations in blood may vary enormously from person to person, depending upon the degree of exposure to microsomal inducers.

For example, consider patients who routinely ingest barbiturates or tranquilizers (P_{450} inducers) who must, for medical reasons, be treated with warfarin or dicumarol (oral anticoagulants). Because of a faster rate of drug metabolism, the dose of warfarin will need to be high. If the patient should for some reason discontinue the barbiturates, the blood level of warfarin will rise, perhaps leading to a bleeding disorder.

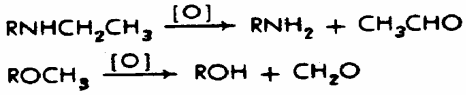
C. Enzyme Inhibition

Relatively few xenobiotics are known to inhibit microsomal enzymes. Some drugs are used therapeutically because they inhibit specific enzyme systems (e.g., monoamine oxidase inhibitors for depression, xanthine oxidase inhibitors for gout, etc.). Sometimes such drugs are not totally specific and inhibit other enzyme systems to some extent. However, cimetidine, a widely used anti-ulcer drug, is an important, potent inhibitor of microsomal drug metabolism which retards the metabolism of many other drugs, including warfarin and similar anticoagulants, theophylline and caffeine, phenobarbital, phenytoin, carbamazepine, propranolol, diazepam, and chlordiazepoxide. Other inhibitors are erythromycin and ketonazole. You will encounter these drugs later in the course. Grapefruit juice also inhibits cytochrome P_{450}.

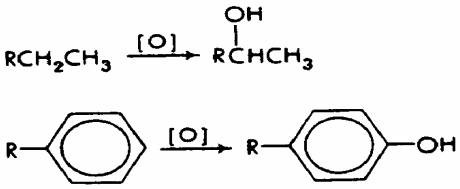
Table 2: Drug Biotransformation Reactions (Goodman & Gilman, 7th edition, pp. 16-17)

I. *Oxidative Reactions* (Microsomal)

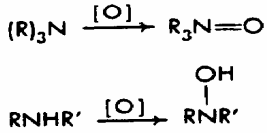
(1) N- and O-Dealkylation



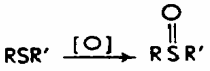
(2) Side Chain (Aliphatic) and Aromatic Hydroxylation



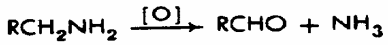
(3) N-Oxidation and N-Hydroxylation



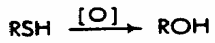
(4) Sulfoxide Formation



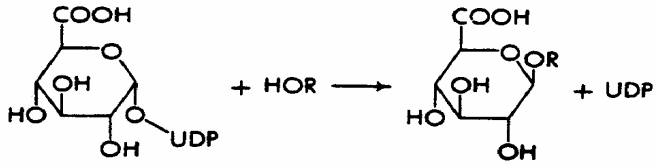
(5) Deamination of Amines



(6) Desulfuration



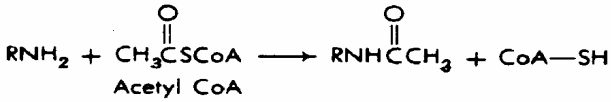
II. *Glucuronide Synthesis* (Microsomal)



UDP–Glucuronic Acid

III. *Other Conjugation Reactions*

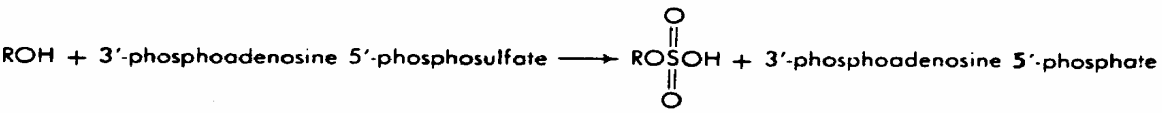
(1) Acetylation



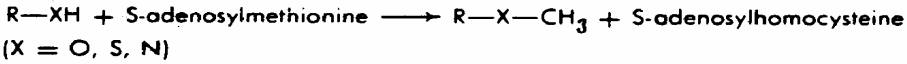
Acetyl CoA

(2) Conjugation with Glycine

(3) Conjugation with Sulfate

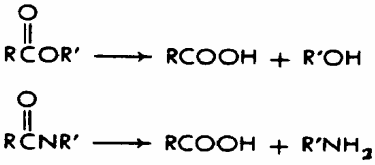


(4) O-, S-, and N-Methylation



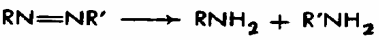
(X = O, S, N)

IV. *Hydrolysis of Esters and Amides*



V. *Reduction*

(1) Azo Reduction



(2) Nitro Reduction

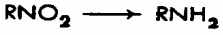
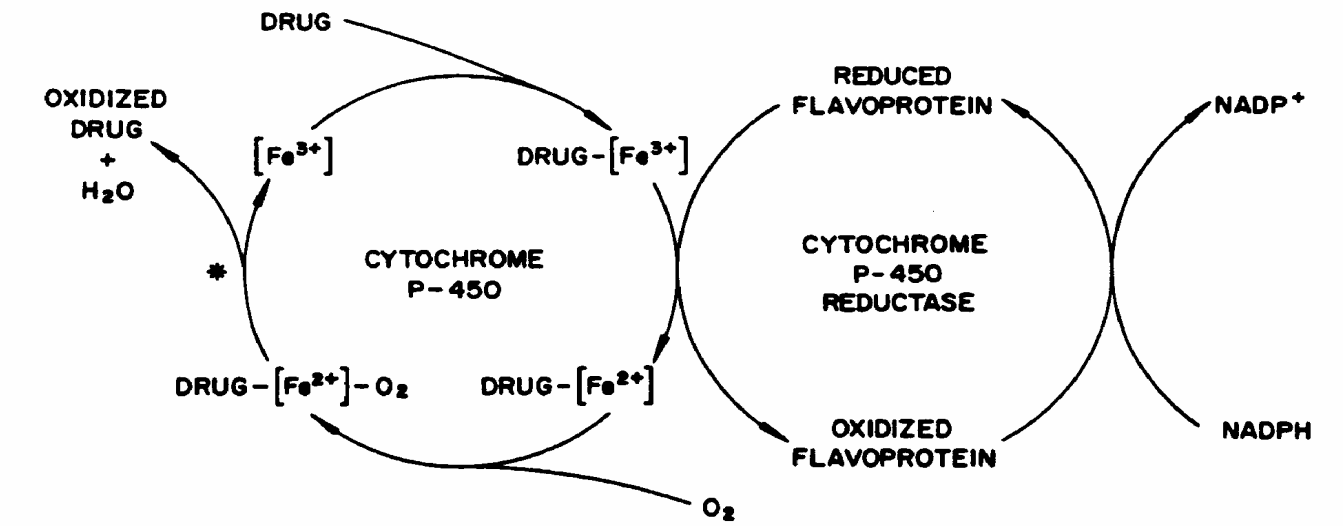


Figure 4



*** Denotes contribution of a second electron and two hydrogen ions from NADH–flavoprotein–cytochrome b_5 or from NADPH–flavoprotein.**

Major components of the hepatic microsomal drug-metabolizing enzyme system.

(Goodman & Gilman, 8th edition, p. 16.)

V. DRUG ELIMINATION

The kidney is the most important organ for the excretion of drugs and/or their metabolites. Some compounds are also excreted via bile, sweat, saliva, exhaled air, or milk, the latter a possible source of unwanted exposure in nursing infants. Drug excretion may involve one or more of the following processes.

A. Renal Glomerular Filtration

Glomeruli permit the passage of most drug molecules, but restrict the passage of protein-bound drugs. Changes in glomerular filtration rate affect the rate of elimination of drugs which are primarily eliminated by filtration (e.g., digoxin, kanamycin).

B. Renal Tubular Secretion

The kidney can actively transport some drugs (e.g., dicloxacillin) against a concentration gradient, even if the drugs are protein-bound. (Actually, only free drug is transported, but the protein-drug complex rapidly dissociates.) A drug called probenecid competitively inhibits the tubular secretion of the penicillins, and may be used clinically to prolong the duration of effect of the penicillins.

C. Renal Tubular Reabsorption

Many drugs are passively reabsorbed in the distal renal tubules. Reabsorption is influenced by the same physicochemical factors that influence gastrointestinal absorption: nonionized, lipid-soluble drugs are extensively reabsorbed into

plasma, while ionized and polar molecules will remain in the renal filtrate and be excreted via urine. Thus, as in the gut, urine pH plays an important role, as does urine volume. Urine pH may vary widely from 4.5 to 8.0, may be influenced by diet, exercise, or disease, and tends to be lower during the day than at night. It is sometimes clinically useful, particularly in drug overdose cases, to alter the pH of the urine (of the patient). For drugs which are weak acids, urine alkalinization favors the ionized form and promotes excretion. Alternatively, acidification promotes the renal clearance of weak bases.

D. Biliary Excretion

Comparatively little is known about hepatic drug elimination. Many drugs and metabolites are passed into the small intestine via bile and may undergo enterohepatic cycling. Recent studies have attempted to interrupt enterohepatic cycling of drugs, pesticides and heavy metals through the oral administration of non-absorbable, nonspecific adsorbents such as charcoal or cholestyramine. The results, generally a decrease in drug half-life, have been surprising in that they suggest that many more drugs undergo enterohepatic cycling than previously suspected.

VI. PHARMACOKINETICS

Pharmacokinetics is concerned with the variation in drug concentration with time as a result of absorption, distribution and elimination.

A. The time course of drug action depends on:

1. Drug dose, route of administration, rate and extent of absorption, distribution rate (particularly to site of action) and rate of elimination.

2. The minimum effective concentration and concentration-effect relationship.

Consideration of the time course of drug action is important since usually it is necessary to maintain a certain concentration of drug at its site of action for a finite period of time.

Figure 5

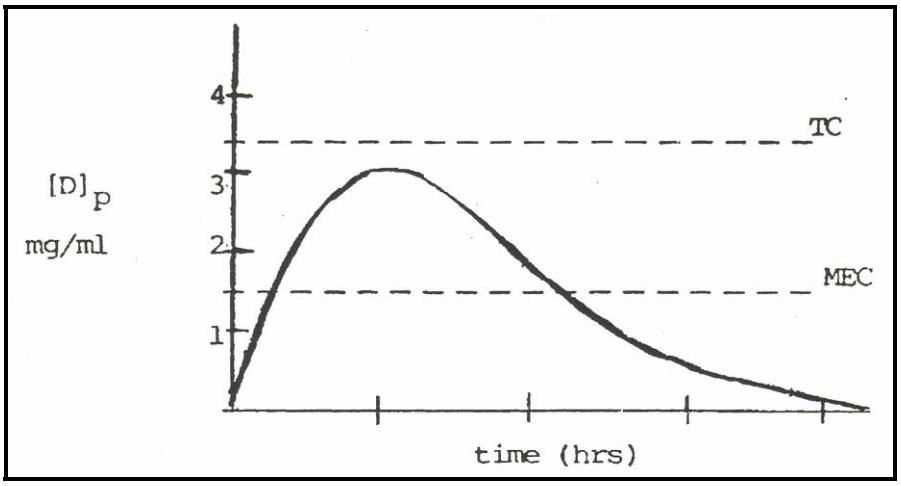
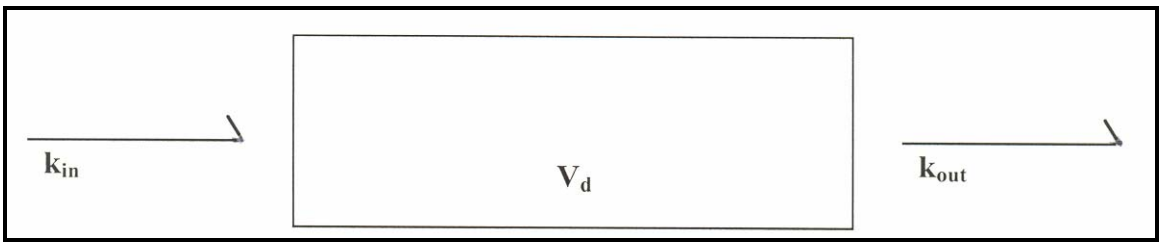


Figure 5 shows the change in plasma drug concentration [D]p with time after administration of a single oral dose. The interrupted horizontal lines show the minimum effective concentration (MEC) and toxic concentration (TC). A therapeutic effect can be expected only when plasma level is above the MEC and below the TC.

Since effect usually is proportional to plasma (or tissue) concentration, the objective of therapy is to attain and maintain the needed plasma concentration for the period needed, whether this is days or years. To do this, one need understand something about pharmacokinetics.

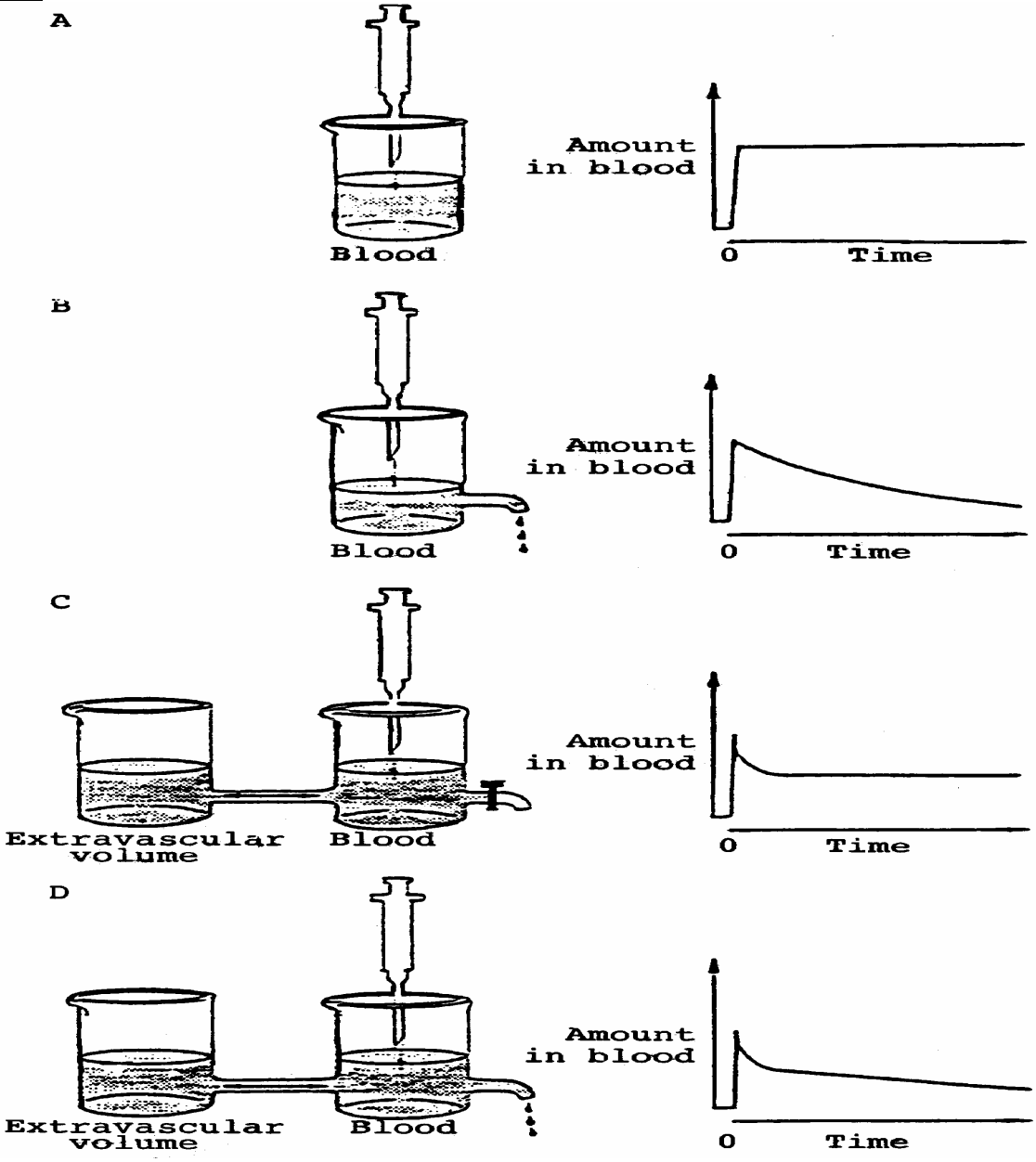
Most of the pharmacokinetic concepts we will deal with describe the behavior of a simple one-compartment model in which drug equilibrates so rapidly in the entire volume that the dominant factors are the rates of absorption (input) and elimination (output).

Figure 6



In this model k_{in} describes the rate of input and k_{out} the rate of output. When these rates are equal, the amount and concentration in the compartment are constant.

Figure 7



Models of drug distribution and elimination.

The effect of adding drug to the blood by rapid intravenous injection is represented by expelling a known amount of the agent into a beaker. The time course of the amount of drug in the beaker is shown in the graphs at the right. In the first example (A), there is no movement of drug out of the beaker, so the graph shows only a steep rise to maximum followed by a plateau. In the second example (B), a route of elimination is presented and the graph shows a slow decay after a sharp rise to a maximum. Because the level of material in the beaker falls, the "pressure" driving the elimination process also falls, and the slope of the curve decreases, approaching the steady state asymptotically. This is an exponential decay curve. In the third model (C), drug placed in the first compartment (blood) equilibrates rapidly with the second compartment (extravascular volume) and the amount of drug in "blood" declines logarithmically to a new steady state. The fourth model (D), illustrates a more realistic combination of elimination mechanism and extravascular equilibration. The resulting graph shows an early distribution phase followed by the slower elimination phase. These curves can be linearized by plotting the logarithm of the amount of drug against time.

B. First order and zero order processes

The rate of absorption or elimination can be expressed either in terms of a half-time ($t_{1/2}$, the time required for 50% to be absorbed or eliminated, or a rate constant (k), the fraction absorbed or eliminated per unit time. For absorption we usually use the symbols k_a and $t_{1/2a}$, and for elimination k_e and $t_{1/2e}$.

If either value is known, the other can be calculated from the relationships:

$$k = 0.693/t_{1/2} \qquad t_{1/2} = 0.693/k$$

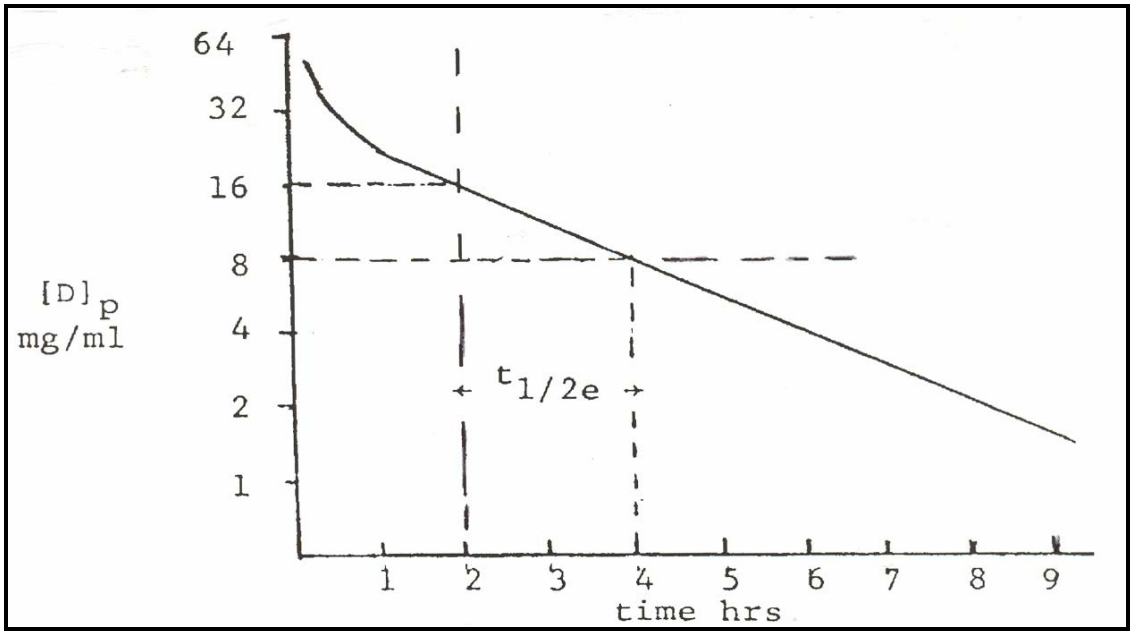
For most sites of administration drug absorption follows first order kinetics and for most routes of elimination the process also is first order or exponential.

1. First order kinetics

A first order process is one by which a constant fraction of the drug present will be absorbed or eliminated in a unit of time.

For a drug eliminated by a first order process, a plot of plasma concentration after the last dose as a function of time will give a straight line on semilog paper. First order elimination is depicted graphically in Figure 8, below.

Figure 8



When the volume of distribution (V_d = total body store/plasma concentration) is known, the CLEARANCE of a drug can be found from:

$$\text{Clearance} = V_d \cdot k_e$$

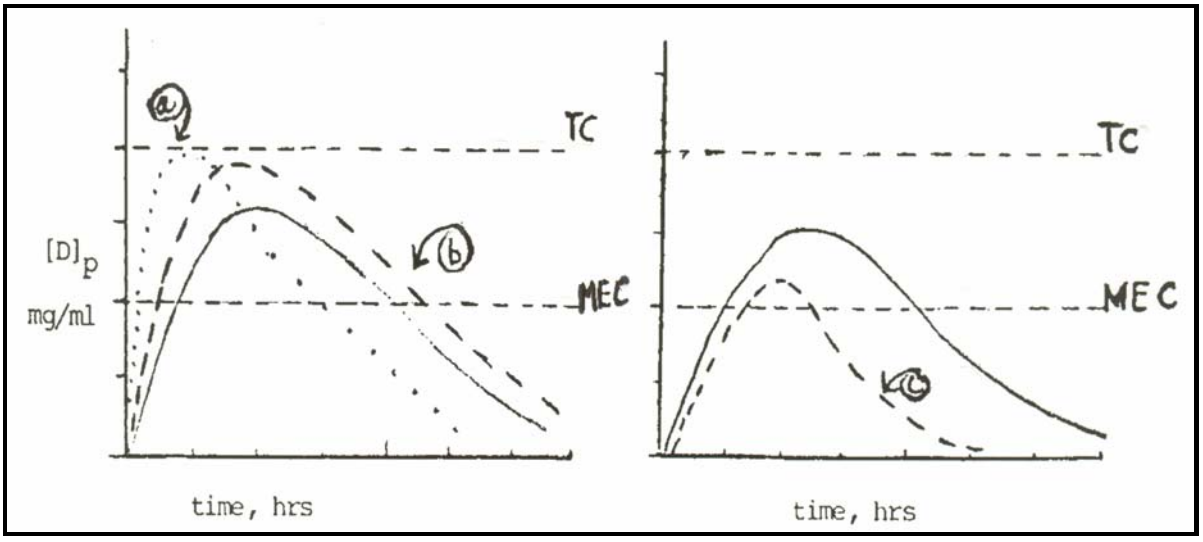
2. Zero order kinetics
   Zero order kinetics describe processes in which a constant amount of drug is absorbed or eliminated per unit time. A constant rate intravenous infusion is one example of a zero order process.

For most drugs, absorption and elimination follow first order kinetics because the drug concentration is not sufficient to saturate the mechanism for absorption or elimination. If the process saturates, then zero order kinetics apply. For some drugs, elimination kinetics are dose-dependent (or more correctly, concentration-dependent). As the plasma level increases, the value of $t_{1/2e}$ increases; the plasma concentration increases disproportionately with increases in dose, and finally, elimination rate becomes independent of plasma concentration.

C. The time course of change in plasma concentration
When a drug is administered in a single dose, and when absorption and elimination are first order processes, it is reasonable to have some idea of the effects of three variables ($t_{1/2a}$, dose and $t_{1/2e}$) on the time-course of change in plasma concentration, as shown in Figure 9.

1. More rapid absorption will increase the peak plasma concentration, decrease the latency (time required to attain drug effect) and decrease the duration of effect.
2. An increase in dose will also decrease latency and increase peak plasma concentration and increase duration of effect.
3. More rapid elimination will decrease peak plasma concentration and duration of effect.

Figure 9



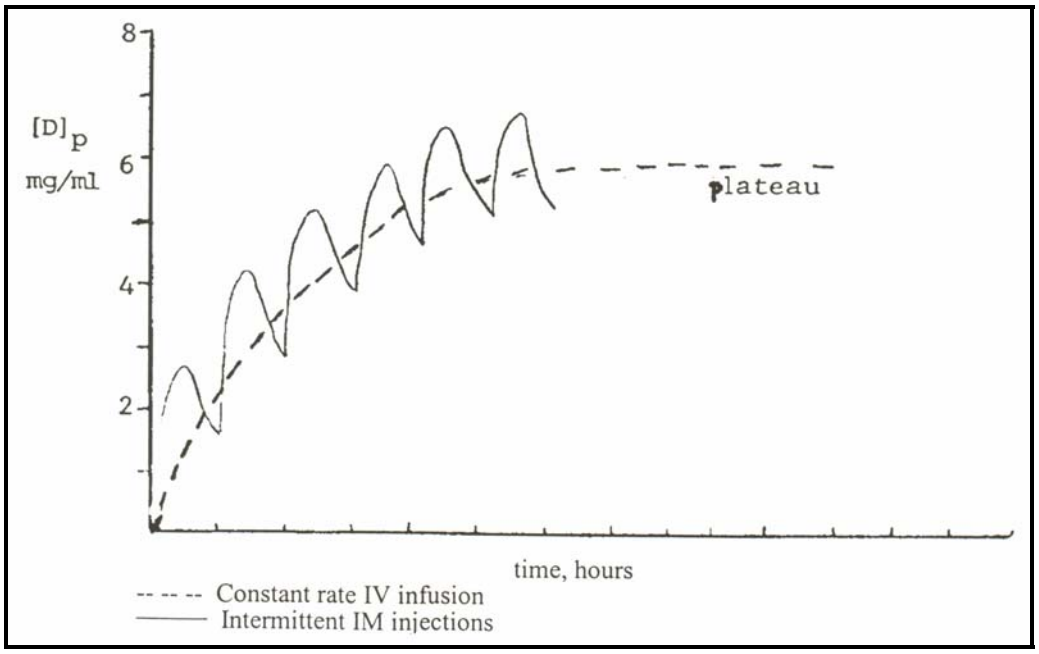
D. The Plateau Effect

When repeated doses of a drug are given at sufficiently short intervals, and elimination is a first order process, the plasma concentration (and total body store) will increase to a steady value or plateau. The same thing will happen if a drug is administered as a constant rate intravenous infusion (zero order in) and eliminated by a first order process. The latter case may be simpler to consider first.

During constant IV infusion, the total body store increases exponentially to a steady value. The half-time for the change in plasma concentration is equal to $t_{1/2e}$. This means that 50% of the final concentration is attained in one $t_{1/2e}$, 75% in two and 87.5% in three. 90% of the final value is attained in $3.3t_{1/2e}$; this is a useful fact to remember.

With intermittent dosing, unless the dose interval is quite long compared to $t_{1/2e}$, accumulation and the increase in plasma concentration will follow a similar time-course, but there will be fluctuations in plasma level between doses. The shorter the dose interval and the smaller the dose, the smaller will be the fluctuations.

Figure 10



E. Some Sometimes Useful Points

The approximate total body storage (TBS) of drug is equal to 1.44 times the amount administered per $t_{1/2e}$. If one can estimate the TBS, and the V_d is known, one can calculate the average plasma concentration. If one knows the desired "plasma level" and V_d, one can estimate the dose needed to attain that value.

For drugs that are rapidly absorbed, a short $t_{1/2e}$ may cause the plasma concentration to fall below MEC between doses unless the dose is large. If the dose is large, the peak plasma concentration may exceed the TC. Avoidance of toxicity and maintenance of a steady effect are easier with drugs for which $t_{1/2e}$ is relatively long.

Sometimes it is desirable to attain the drug effect quite rapidly; to do this it may be necessary to give a loading dose. A loading dose is larger than the usual maintenance dose. An approximate relationship between loading dose (D_1), maintenance dose (D) and dose interval (T) is given by:

$$D_1 = 1.4\ t_{1/2e}\ (D/T)$$

(The loading dose often is given in fractions at intervals shorter than the usual dose interval.)

F. Factors Which Modify Dose and Dose Interval

1. Altered absorption.
2. Altered elimination
3. Altered volume of distribution.

The presence of food in the GI tract and altered GI motility and absorptive properties can influence the rate and extent of absorption. For parenteral administration, changes in local perfusion can have the same effect.

Drug elimination can be strongly influenced by disease. Altered hepatic perfusion (as in shock or heart failure) and altered renal function cause frequent problems. The change in renal clearance of drug can be estimated from the endogenous creatinine clearance (or, less accurately, from serum creatinine or BUN).

G. Pharmacokinetic Parameters

1. Apparent volume of distribution (V_d or AVD)

Let D = amount of drug administered IV
Let C = plasma drug concentration at time 0, had mixing between compartments been instantaneous

Then, $V_d = D/C$

2. Half-time of elimination ($t_{1/2e}$)
The time it takes to eliminate half of the circulating drug. (See Figure 8.)

3. Elimination rate (E_r) and elimination rate constant (k_e)

These parameters describe, in mathematical terms, the elimination of a drug by all processes (i.e., renal + hepatic + all other).

a. Zero order elimination
Implies that a fixed number of drug molecules are eliminated per unit time. Ethanol is a good example. In this case, $E_r = k_e$.

b. First order elimination
Implies that a constant fraction of the drug molecules are eliminated per unit time. This is the case for most drugs. In this case, k_e is simply defined as the slope of decline in plasma drug concentration, i.e.,

$$k_e = \text{delta } y/\text{delta } x = \frac{\ln (2)}{t_{1/2e}} = \frac{0.693}{t_{1/2e}}$$

Once again, look at Figure 8 in the syllabus and this relationship should be apparent.
In this case, $E_r = dD/dt = -k_e/D$.

4. Clearance (Cl)
Clearance refers to the volume of plasma cleared of drug (by all processes) per unit time, i.e.,

$$\mathbf{Cl = k_e \times V_d}$$

5. Absorption rate constant (k_a)
Just as elimination can occur in zero order or first order fashion, so too can absorption from the gut or an injection site occur by zero order or first order kinetics. Typically, absorption follows first order kinetics.

The exceptions are generally limited to depot or slow release preparations (e.g., slow release insulin injections), in which case zero order kinetics apply. For IV drug administration, zero order kinetics also apply, since a given number of drug molecules are infused per unit time.

6. Bioavailability (F)
The rate and extent to which an active drug ingredient is absorbed and becomes available at the site of drug action. By definition, for intravenous drugs, F = 1. Oral bioavailability can be determined by comparing the area under the curve (AUC) (of the plot of plasma drug concentration vs. time) after an oral dose to that for an intravenous dose, i.e.,

$$F = AUC_{oral}/AUC_{IV}$$

7. Relative Bioavailability
The extent to which an oral drug product (e.g., a generic drug product) is absorbed in comparison to the trade name, or currently marketed drug product. This is usually determined by comparing the area under the curve (AUC) (of the plot of plasma drug concentration vs. time) of the new product to that of the trade name product, i.e.,

$$\text{Relative F} = AUC_{generic}/AUC_{trade\ name}$$

For many drugs, however, regulatory decisions concerning generic drugs are based upon the ability of the generic product to achieve the same b_{max} (peak blood concentration) and t_{max} (time at which b_{max} occurs).

H. Kinetics following a single drug dose

1. Intravenous
The curve is triphasic, with a rapid peak, decline (the distribution phase) and a slow elimination phase from which k_e can be calculated.

2. Subcutaneous or intramuscular
The drug takes a finite time to reach the circulation. The levels of drug in blood continue to rise until the number of drug molecules being eliminated per unit time exceeds that being absorbed per unit time. In general, the entire dose will reach the circulation, i.e., bioavailability (F) = 1.

3. Oral
The pattern is similar to that of SC or IM, but usually b_{max} is lower, and t_{max} occurs later.

I. Steady State Kinetics
The administration of a drug at intervals shorter than about 4 elimination half-times will result in accumulation of the drug in the body. The accumulation will continue until the amount of drug absorbed per unit time equals the amount of drug eliminated per unit time, at which time a plateau, or steady state concentration (C_{SS}) will be reached.

1. Constant IV infusions
For constant IV infusions, zero order absorption, and first order elimination apply. At equilibrium, input = output.

$$\text{i.e., } k_a = Cl \times C_{SS} = V_d \times k_e \times C_{SS}$$

$$\text{thus, } \mathbf{C_{SS} = ka/(V_d \times k_e)}$$

The important principle here is that C_{SS} is regulated only by K_a and k_e. Therefore, to double C_{SS}, simply double the drug infusion rate (which is usually in units of mg/hr).

Note: There are important exceptions where doubling the dose does not result in a doubling of C_{ss}. In these cases, "dose-dependent kinetics" apply; in this course, we will not cover the mathematics of dose-dependent kinetics. Most dose-dependent situations occur because one or more of the processes involved in drug absorption, distribution, metabolism, or excretion show saturability, a condition in which the rate of a given process increases or decreases with the drug concentration. For example, the active tubular secretion of penicillin is saturable; thus, as the dose is increased, k_e will decrease. As another example, the first pass hepatic metabolism of propranolol is saturable; thus, as the oral dose is increased, the effective k_a will increase.

2. Repeated oral doses

In this case, k_a is influenced by the bioavailability (F) of the drug, the interval between drug doses, and the dose itself. Thus,

$k_a = F \times Dm/T$,

where Dm = maintenance dose (e.g., in mg)
T = dose interval (e.g., in hours)
F = bioavailability (the fraction absorbed)

Note that the units of k_a are mg/hr, just as in the case of the IV situation described above.

At steady state, input = output, i.e.,

$k_a = F \times Dm/T = C_{ss} \times V_d \times k_e$

Rearranging this equation, we obtain:

$$\mathbf{C_{ss} = D_m\, F/(V_d \times k_e \times T) = (1.44 \times D_m \times F \times t_{1/2e}) /(T \times V_d)}$$

(Note: 1.44 is simply the reciprocal of .693, i.e. 1/0.693)

This last equation is one which you must know in order to calculate maintenance doses and dose intervals. Once you have decided what the target C_{ss} should be, this equation will permit you to calculate dose and dose interval. Note, however, that there is no unique dose (D_m) and dose interval (T), since these are two variables in the same equation. Thus, it is possible that different combination of D_m and T could be used to achieve the same C_{ss}.

3. Initial oral loading dose

When a prompt drug response is needed, e.g., with the use of theophylline to treat an acute asthma episode, it is often useful to initiate treatment with a single "loading dose" which is larger than the typical maintenance dose of the drug. The loading dose allows one to achieve plasma drug concentrations above the minimum effective concentration (MEC) quickly.

The loading dose may be calculated from the equation:

$$\mathbf{D_1 = (V_d \times C_{ss})/F}$$

where D_1 = loading dose and F = bioavailability.

Note that when the loading dose is administered parenterally (intravenous), F can be considered to be equal to 1.

This equation implies that D_1 equals the amount of drug in the body at the desired therapeutic plasma level.

4. Second loading dose

In practice, one often administers an initial loading dose, allows some time to pass, and then obtains a measurement of the plasma drug concentration. Sometimes (hopefully) the measured value will fall in the desired range, in which case no additional loading dose is required and one can proceed with "maintenance" therapy. Other times, however, the measured serum drug concentration will be found to be too low, in which case a second loading dose may need to be administered. How does one calculate this second, smaller loading dose?

The only parameter which needs to be altered in the original loading dose equation is C_{ss}, from which one must subtract the actual measured value. In other words:

$$\mathbf{D_2 = \frac{(Vd)\ (C_{ss} - C_{act})}{F}}$$

where D_2 = the second loading dose
C_{ss} = the desired steady state concentration
F = bioavailability
C_{act} = the actual measured serum drug concentration

Thus, D_2 equals the dose of drug required to alter the serum drug concentration from the observed value to the desired value.

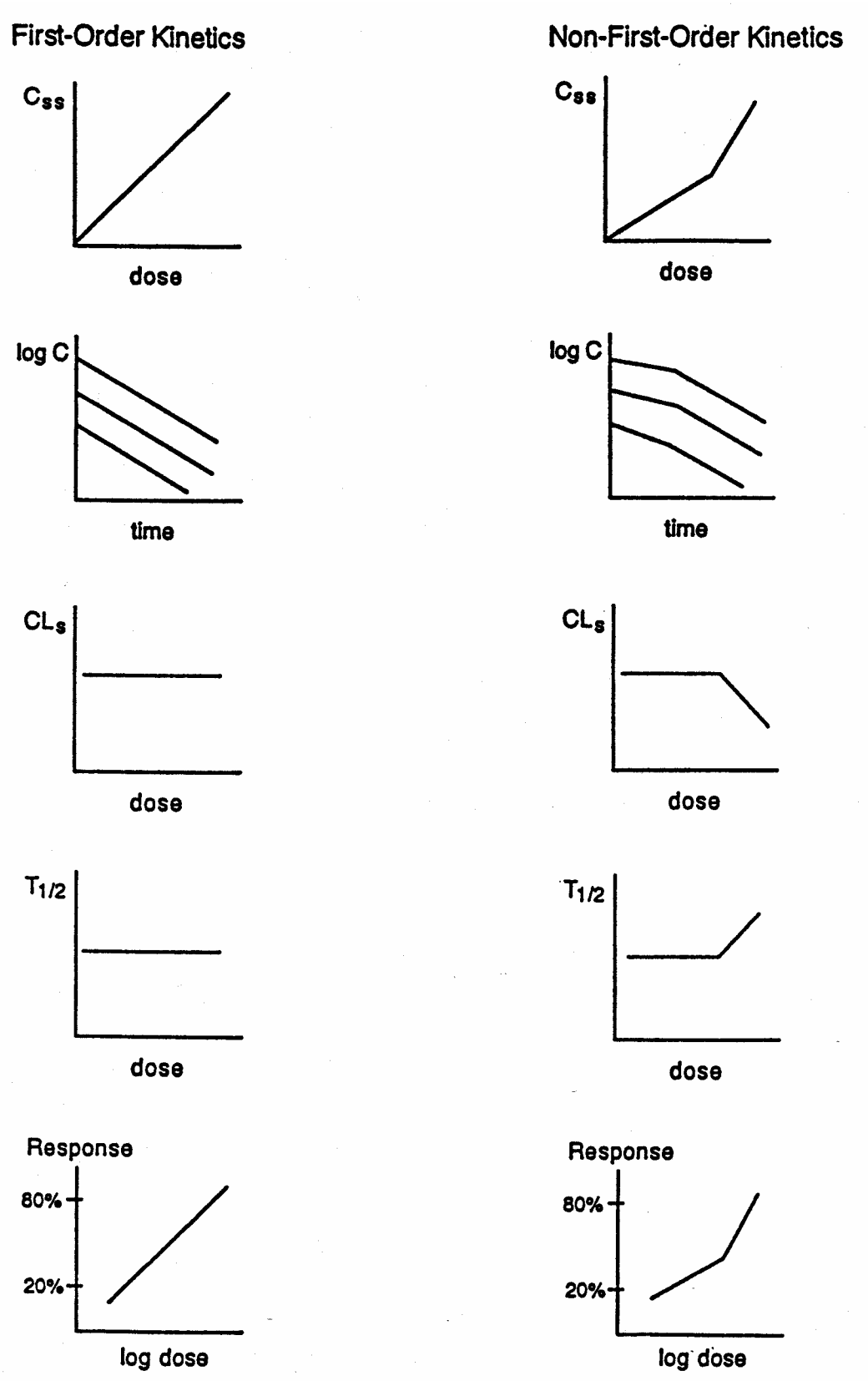
Table 3 Pharmacokinetic and Pharmacodynamic Parameters for Selected Drugs*

Drug	Oral Avail. (percent)	Urinary Excret. (percent)	Bound In Plasma (percent)	Clearance (mL/min/70kg)	Volume of Distrib. (L/70 kg)	Half-Life (hours)	Effective+ Concentrations	Toxic+ Concentrations
Acetaminophen	63±5	3±1	0-15	350±100	67±8	2.0+0.4	10-20 lg/mL	>350 lg/mL
Amikacin		98	4	77±14	15±6	2.3±0.4		
Amoxicillin	93±10	52±15	18	370±90	29±13	1.0±0.1		
Ampicillin	25-70	90±8	18	270±50	20±5	1.3±02		
Aspirin	68±3	1.4±1.2	49	650±80	11±2	0.25±0.3	See Salicylic Acid	
Carbamazepine	>70	<1	82±5	89±37	98±26	15±5	6.5±3.0 lg/mL	>10 lg/mL
Cephalexin	90±9	96	14±3	300+80	18+2	0.90+0.18		
Cephalothin		52	71±3	470±120	18±8	0.57+0.32		
Chloramphenicol	75-90	5±1	53±5	250±120	64	2.7±08		
Chlordiazepoxide	100	<1	96.5±1.8	26±4	21±2	9.9±2.5	>0.7 lg/mL	
Cimetidine	62±6	77±6	19	840±210	150±70	2.1±1.1	>1.0 lg/mL	
Clonidine	75±4	62±11		210±84	150±30	8.5±2.0	0.5-1.5 ng/mL	
Diazepam	100	<1	98±7	27±4	77±20	20-90	>600 ng/mL	
Digitoxin	>90	33±15	90±2	3.2±1.6	36±13	6.9±2.7 days	>10 ng/mL	>35 ng/mL
Digoxin	60-70	72±9	25±5	130±67	640±200	42±19	>0.8 ng/mL	>2 ng/mL
Disopyramide	83±11	55±6	30-70	90±50	55±18	7.8±1.6	3±1 lg/mL	>8 lg/mL
Erythromycin	18-45	10-15	72±3	420±170	50±14	1.1-3.5		
Ethambutol	77±8	79±3	20-30	600±60	110±4	3.1±0.4		>10 lg/mL
Furosemide	40-60	66±7	98.8±0.2	140±30	7.7±1.4	1.5±0.1		
Gentamicin		>90	<10	90±25	18±6	2-3		
Hydralazine	20-60	11-14	87	420-1100	110±21	1.8-3.0	1 lg/mL	
Imipramine	47±21	0-2	89-94	1400±1700	1050±420	13±3	>225 ng/mL	>1 lg/mL
Indomethacin	98	15+8	90	110+14	65+37	2.6+11.2	0.5-3 lg/mL	>6 lg/mL
Lidocaine	35±11	2±1	51±8	640±170	77±28	1.8±0.4	1.2-6 lg/mL	>6 lg/mL
Lithium	100	95±15	0	25±8	55±24	22±8	.7-1.5 meq/L	72 meq/L
Meperidine	52±3	4-22	58±9	1200±350	290±90	3.2±0.8		
Methotrexate	65	94	45±14	105	28	8.4		0.9 lg/mL
Morphine	20-30	6-10	35±2	1100±40	220±50	3.0±1.2	65 ng/mL	
Nortriptyline	51±5	2±1	94.5±0.6	500±130	1300±300	31±13	50-139 ng/mL	>500 ng/mL
Phenobarbital	>80	24±5	51	6.5±3	62±23	4.4±1.0 days	10-25 lg/mL	>30 lg/mL
Phenytoin	98±7	2	89±23	Dose-dependent	45±3	Dose-dependent	>10 lg/mL	>20 lg/mL
Prazosin	57±10	<1	93±2	210±20	42±9	2.9±0.8		
Procainamide	83±16	67±8	16±5	350-840	130±20	3.0±0.6	3-5 lg/mL	>20 lg/mL
Propranolol	36±10	<1	93±1	840±210	270±40	3.9±0.4	20 ng/mL	
Quinidine	70±17	18±5	89±1	330±130	190±80	6.2±1.8	2-5 lg/mL	>8 lg/mL
Salicylic acid	100	Dose-dependent	Dose-dependent	Dose-dependent	12±2	Dose-dependent	150-300 lg/mL	
Sulfamethoxazole	100	30±1	62±5	22±3	15±1.4	8.6±0.3		
Sulfisoxazole	100	53±9	88-92	23±3.5	10.5±1.4	5.9±0.9		
Tetracycline	77	48	65±3	130	91	9.9±1.5		
Theophylline	96±8	8	56±4	48±21	35±11	8.1±2.4	10-20 lg/mL	>20 lg/mL
Tobramycin		90	<10	77	18±6	2.2±0.1		
Tolbutamide	93±10	0	93±1	21±3	11±2	5.9±1.4	80-240 lg/mL	
Trimethoprim	100	53±2	70±5	150+40	130±15	11±1.4		
Tubocurarine		43±8	40±2	160±50	21±8	2.0±1.1	0.6±0.2 lg/mL	
Valproic acid	100	<5	93±4	8.4±2.8	9.1±2.8	16±3	55-100 lg/mL	>150 lg/mL
Verapamil	19±12	<3	90±2	830±350	280±60	4.8±2.4	100 ng/mL	
Warfarin	100	0	99	3.2±1.7	7.7±0.7	37±15	2.2+0.4 lg/mL	

*The values in this table represent the parameters determined when the drug is administered to healthy normal volunteers or to patients who are generally free from disease except for the condition for which the drug is being prescribed. The values presented here are adapted and updated from Benet LZ, Sheiner LB: Design and optimization of dosage regimens: Pharmacokinetic data. Pages 1675-1737 in: Goodman and Gilman's The Pharmacological Basis of Therapeutics 6th ed. Gilman AG, Goodman LS, Gilman A (editors). Macmillan, 1980. This source may be consulted for the effects of disease states on the pertinent pharmacokinetic parameters.

+No pharmacodynamic values are given for antibiotics since these vary depending upon the infecting organism.

Comparison of First-Order and Non-First-Order Kinetics



Elimination Rate Constant (K) and Elimination Half Live ($t_{1/2}$)

Assumption: - First-order kinetics
- IV bolus injection

rate of loss $\propto$ concentration in body (C).

$-dC/dt \propto C$

$-dC/dt = K \cdot C$ or $dC/dt = K \cdot C$

By integration, $C = C^0 \cdot e^{-Kt}$

Using natural log, $\ln C = \ln C^0 - Kt$

or, $\log C = \log C^0 - \frac{Kt}{2.303}$

Relation between K (β, $\lambda\eta$) and $t_{1/2}$

$t_{1/2} = \frac{0.693}{K}$ (unit: hr, min)

Why:

From: $\log C = \log C^0 - \frac{Kt}{2.303}$

we have: $\frac{Kt}{2.303} = \log C^0 - \log C$; $t = \frac{2.303}{K} \log \frac{C^0}{C}$

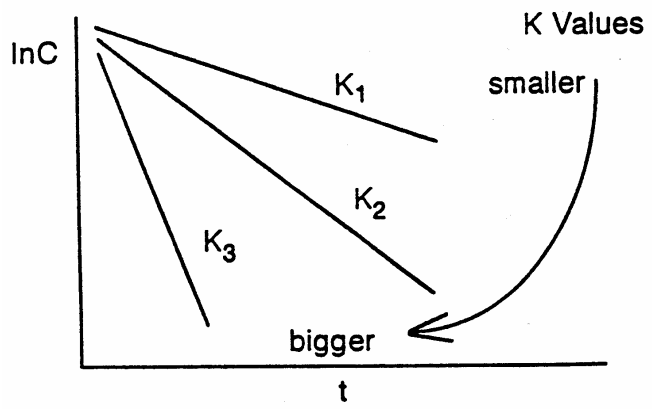
since: $t_{1/2}$ is the time when $C = 1/2C^0$

thus, $t_{1/2} = \frac{2.303}{K} \log \frac{C^0}{1/2C^0} = \frac{2.303}{K} \log 2 = \frac{2.303 \times 0.301}{K} = 0.693/K$

No matter what kind of model we deal with, this relation between the terminal-phase elimination $t_{1/2}$ and the terminal-phase rate of elimination is always true

More about K:

K: elimination rate constant (hr^1, min^{-1})



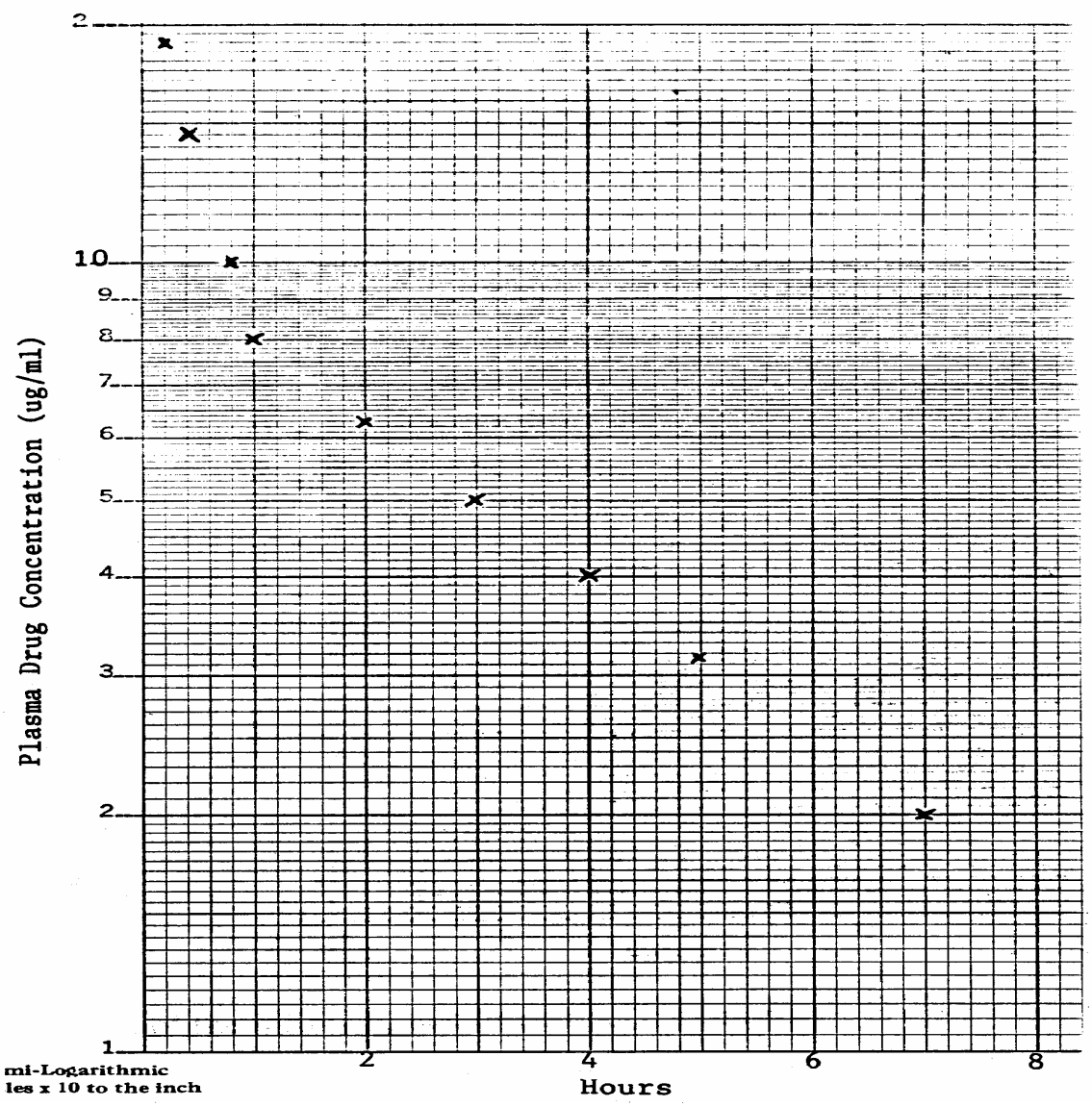
Values: $K_3 > K_2 > K_1$

The bigger the values of K, the faster the elimination of the drug.

Practice Problems with solutions

1. Calculation of V_d and k_e
Following the administration of 1 gram of a drug to a normal 70 kg volunteer, serial plasma drug measurements yielded the data shown below.

Figure 11



Which of the following statements is (are) correct?

a. The apparent volume of distribution is about 100 L.
b. The apparent volume of distribution is about 10 L.
c. The rate constant of elimination is about 0.231/hr.
d. The rate constant of elimination is about 0.832/hr.

Solution: $V_d = 1000 \text{ mg}/(10 \text{ mg/L}) = 100 \text{ L}$
$k_e = 0.693/t_{1/2}e = 0.693/3 \text{ hrs} = 0.231/\text{hr}$

2. Clearance
Morphine has an apparent volume of distribution of 220 L/70 kg and a half-life of elimination of 3 hours. In a 70 kg man, what is its approximate rate of clearance?

a. 1300 ml/min
b. 850 ml/min
c. 50 ml/min
d. 35 ml/min

Solution: $Cl = V_d \times k_e$

$V_d = 220L$; $k_e = 0.693/180$ minutes = .00385/min

$Cl = 220L \times .00385/min = 0.847$ L/min = 847 ml/min

3. C_{ss} with a constant IV infusion
A patient is receiving a constant IV infusion of a drug at a rate of 30 mg/hour. The elimination half-life of the drug is 4 hours and the volume of distribution is 50L. Which of the following is(are) correct?

a. After 4 hours, the approximate plasma drug concentration is 1.73 μg/ml.
b. After 8 hours, the approximate plasma drug concentration is 2.60 μg/ml.
c. After 24 hours, the approximate plasma drug concentration is 3.46 μg/ml.
d. After 48 hours, the approximate plasma drug concentration is 30 μg/ml.

Answer : a, b and c are correct.

Solution: $C_{ss} = k_a/(V_d \times k_e)$

$k_e = 0.693/4$ hours = 0.173/hour

$C_{ss} = (30$ mg/hr) / (50 L x 0.173/hr)

= 3.46 mg/L = 3.46 μg/ml

After 4 hours, i.e., one half-life of elimination, we will have achieved 50% of the steady-state concentration. Thus, at 4 hours, the plasma drug concentration will be 3.46 μg/ml x 0.5, or 1.73 μg/ml; answer a is correct. After 8 hours, i.e., two half-lives of elimination, we will have achieved 75% of the steady-state concentration. Thus, at 8 hours, the plasma drug concentration will be 3.46 μg/ml x 0.75. or 2.60 μg/ml; answer b is correct. After 24 hours, i.e., after more than 4 half-lives of elimination (4 half-lives being the "rule of thumb" for achievement of the steady-state), we will have achieved the steady-state concentration of 3.46 μg/ml; answer c is correct. Answer d is wrong because it is not possible to reach a concentration higher than C_{ss}.

4. C_{ss} with an oral dosing

A drug has the following properties: V_d = 25 L/70 kg
k_e = 0.231/hr
bioavailability = 0.8

If a 70 kg patient took 50 mg of the drug every 8 hours for ten days, what would be the patient's approximate plasma drug concentration?

a. 0.86 μg/ml
b. 24 μg/ml
c. 10 ng/ml
d. 0.23 μg/ml
e. None of the above

Solution: $C_{ss} = (1.44 \times D_m \times F \times t_{1/2}e)/(T \times V_d)$

$t_{1/2}\, e = 0.693/k_e = 0.693/0.231\ hr^{-1} = 3$ hours

$C_{ss} = (1.44 \times 50\ mg \times .8 \times 3\ hrs)/(8\ hrs \times 25\ L)$

$= 172.8\ mg/200\ L = 0.86\ mg/L = 0.86\ \mu g/ml$

5. Loading Dose

A patient comes into the emergency room with a severe infection and requires immediate therapy with an antibiotic. The patient weighs 70 kg. The volume of distribution of the antibiotic is 100 L/70 kg, its bioavailability is 0.5, and the desired steady state concentration is 10 μg/ml. What would be an appropriate oral loading dose?

a. 1 gram
b. 2 grams
c. 200 mg
d. 800 mg
e. None of the above

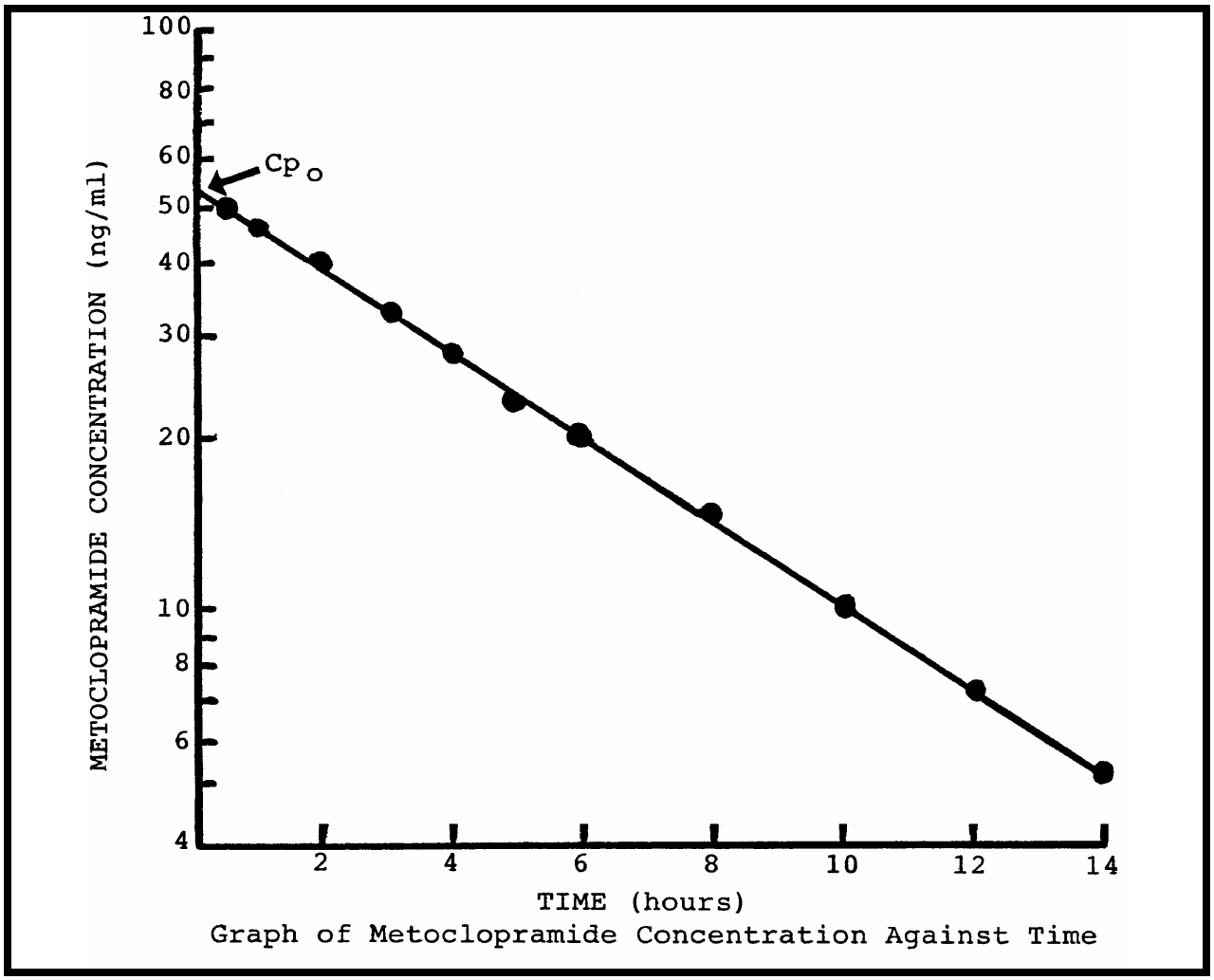
Solution: $D_1 = (V_d \times C_{ss})/F = (100{,}000\ ml \times 10\ \mu g/ml)/0.5$

$= 1{,}000{,}000\ \mu g/0.5 = 1g/0.5 = 2.0\ g$

Additional Practice Problems, with solutions appended:

1. The following plasma metoclopramide concentrations were found in a female patient given a 5 mg IV bolus dose

Figure 12



Graph of Metoclopramide Concentration Against Time

1.1 What was the order of decay?

1.2 What was the half-life of elimination of metoclopramide in this patient?

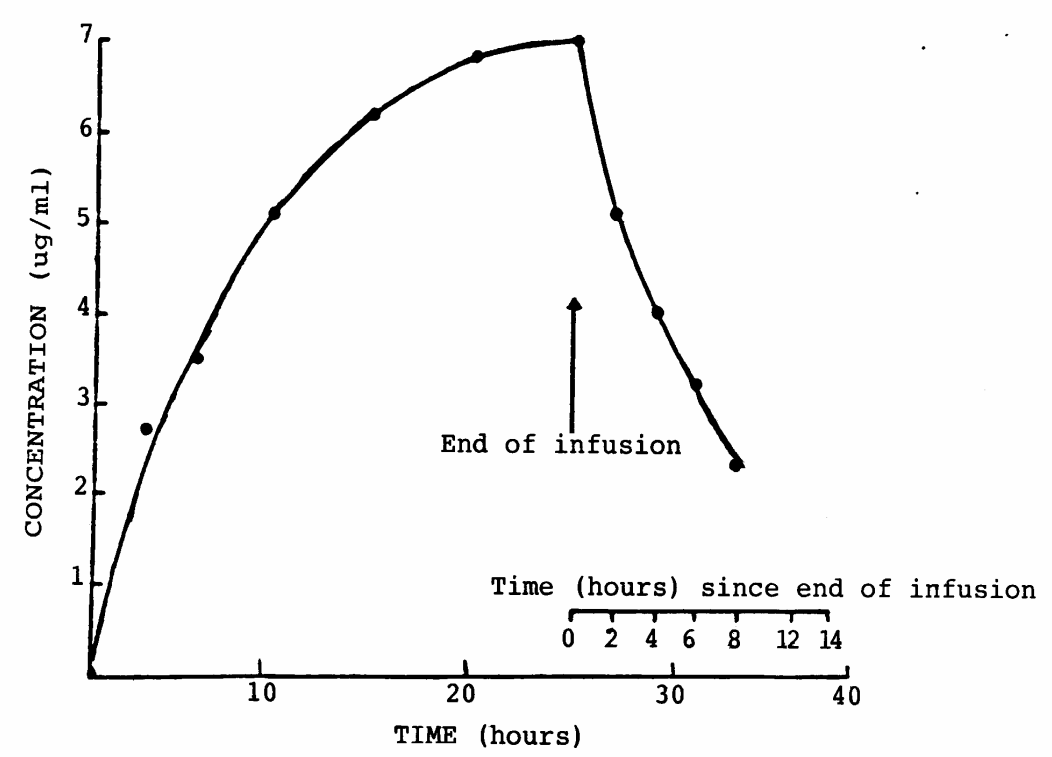
1.3 What was the rate constant of elimination?

1.4 What was the apparent volume of distribution of metoclopramide in this patient?

1.5 In another patient, the half-life was 3.1 hours and V_d was 87.6L. Calculate the total clearance rate in that patient.

2. Procainamide was infused IV into a 60 kg patient for 25 hours at a rate of 2 mg/minute. The following plasma drug levels were recorded during an after the infusion:

Figure 13



Graph of procainamide concentration against time

2.1 What was the approximate half-life of elimination of the drug in plasma once the infusion was stopped?

2.2 What was the apparent volume of distribution of procainamide in this patient?

3. An orally active drug has the following properties:

bioavailability = 0.80

V_d = 40L/70 kg

half-time of elimination = 12 hours

half-time of absorption = 1 hour

minimum effective concentration (MEC) = 10 μg/ml

toxic concentration of 25 μg/ml

Which of the following dose schedules would be effective and non-toxic in a 70 kg patient?

a. 100 mg three times a day
b. 250 mg three times a day
c. 600 mg four times a day
d. 300 mg four times a day

4. During a third year rotation, you are presented a 70 kg female patient who has just received a renal transplant. The patient is receiving oral cyclosporine, an immunosuppressive drug which should prevent rejection of her newly transplanted kidney. For this patient, the drug dose and drug regimen are critical. If the steady-state concentration (C_{ss}) of cyclosporine is less than 100 ng/ml, the patient will likely reject the transplant; if C_{ss} is more than 200 ng/ml. she may suffer serious toxic effects on, ironically, the kidney.

Although the attending physician has prescribed a dose of 1 gm, to be taken every 24 hours, the tired resident is worried that this dose may be in error. Since you are the one who has taken pharmacology most recently, you are asked to calculate C_{ss} for this dose regimen. The bioavailability of the drug is 0.5, the apparent volume of distribution is 1.2 L/kg, and the half-life of elimination is 6 hours.

You calculate C_{ss} and report that:

a. C_{ss} is 150 ng/ml; the dose appears appropriate.
b. C_{ss} is 214 ng/ml; the dose is slightly high.
c. C_{ss} is 75 ng/ml; good grief, she'll reject her new kidney.
d. C_{ss} is 2140 ng/ml; good grief, we're poisoning her new kidney.

5. The same tired resident asks your help with another patient, a 100 kg man with osteomyelitis who is receiving IV antibiotic therapy. The man has been receiving a constant IV infusion at a rate of 10 mg/hr for the past 48 hours. The minimal effective drug concentration is 1.0 μg/ml, while the toxic concentration is 4.0 μg/ml. The apparent volume of distribution (V_d) is 0.5 L/kg, and the half-life of the drug is 12 hours. A blood sample obtained last night, 24 hours after the initiation of the infusion, has been found to have a drug concentration of 2.6 μg/ml. In this case, you calculate that the infusion rate of 10 mg/hr is delivering a dose which is:

   a. too low
   b. appropriate
   c. slightly high
   d. probably lethal

6. A seven year old girl weighing 31 kg appears in the emergency room suffering from asthma. The decision is made to initiate treatment with the drug theophylline. The desired steady-state concentration is 15 μg/ml. The apparent volume of distribution (V_d) for theophylline is 0.5 L/kg, and its oral bioavailability is 0.60. Which of the following would be the most appropriate intravenous loading dose?

   a. 380 mg
   b. 232 mg
   c. 2.32 gm
   d. 3.80 gm

Solution to Problems:

1:

1.1 A straight line on semi-log paper indicates first order kinetics.

1.2 The half-life from the graph is approximately 4 hours. The exact answer might vary as a function of one's artistic skill, but should fall between 3.8 and 4.6 hours.

1.3 $k_e = 0.693/t_{1/2}e = 0.693/4 \text{ hours} = 0.17/\text{hour}$

1.4 V_d = Dose/concentration at $t_0 = \frac{5\text{mg}}{54 \text{ ng/ml}} = 92.5 \text{ L}$

1.5 $Cl = V_d \times k_e = 87.6\text{L} \times (0.693/3.1 \text{ hours}) = 19.6 \text{ L/hour}$

2:

2.1 The half-life of elimination can be determined from the graph, utilizing points obtained after the infusion was stopped. For example, at 4 hours post-infusion the concentration was 4 μg/ml, while at 9 hours post-infusion the concentration was 2 μg/ml. Thus, $t_{1/2e}$ is 5 hours.

2.2 With a half-life of about 5 hours, the steady state concentration (C_{ss}) had been approached by 22 hours, at which time the infusion was stopped, i.e., more than 4 half-lives of elimination had transpired. Thus, from the graph, one can assume that the concentration at the time infusion was stopped, i.e.,7.0 μg/ml, was equal to C_{ss}. Using the IV steady-state equation, the rest is "easy":

$C_{ss} = k_a/(V_d \times k_e)$, or

$V_d \times k_e \times C_{ss} = k_a$, or

$V_d = k_a/(k_e \times C_{ss})$; $k_e = 0.693/5 \text{ hours} = .14 \text{ hour}$

$k_a = 2 \text{ mg/min} = 120 \text{ mg/hour}$

$= 120{,}000 \text{ μg/hour}$

$$V_d = \frac{120{,}000 \text{ μg/hour}}{.14/\text{hour} \times 7 \text{ μg/ml}} = \frac{120{,}000}{0.98 \text{ ml}} = 122.4 \text{ L}$$

3: b and d are correct

Solution:

a. $C_{ss} = (1.44 \times D_m \times F \times t_{1/2}e)/(T \times Vd)$
$= (1.44 \times 100 \text{ mg} \times 0.80 \times 12 \text{ hrs})/(8 \text{ hrs} \times 40 \text{ L})$
$= 4.32 \ \mu g/ml$
(This is less than the MEC and therefore not effective.)

b. C_{ss} = 10.80 μg/ml, which is more than the MEC but less than the toxic concentration.

c. C_{ss} = 34.6 μg/ml, which is toxic

d. C_{ss} = 17.28 μg/ml, which is also more than the MEC but less than the toxic concentration.

4:

$$\frac{C_{ss} = 1.44 \times Dm \times F \times t1/2e}{T \times V_d} = \frac{1.44 \times 1000mg \times .5 \times 6 \text{ hrs}}{24 \text{ hrs} \times 84L}$$

$$= \frac{4320 \text{ mg}}{2016 \text{ L}} = 2.14 \text{ mg/L} = 2.14 \ \mu g/ml = 2140 \text{ ng/ml}$$

5:

$k_e = 0.693/12 \text{ hrs} = .058/\text{hour}$
$C_{ss} = k_a/(V_d \times k_e) = (10 \text{ mg/hr})/(50L \times .058/\text{hr})$
$= 3.45 \text{ mg/L} = 3.45 \ \mu g/ml$

Note: After 12 hours (i.e., two half-lives, the concentration would be expected to be 3.45 μg/ml x 0.75, or 2.58 μg/ml.

6:

$DL = C_{ss} \times V_d$
$V_d = 0.5L/kg \times 31 \text{ kg} = 15.5L$
$DL = 15.0 \text{ mg/L} \times 15.5L$
$= 232.5 \text{ mg}$

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1. Gibaldi, M. Biopharmaceutics and Clinical Pharmacokinetics. 3rd Edition. Lea & Febiger, Philadelphia, 1984.

2. Goldstein, A., Aronow, L. and Kalman, S.M. Principles of Drug Action: The Basis of Pharmacology. Chapters 2 and 3. John Wiley & Sons, New York 1974.

3. Sipes, IG, Gandolfi, AJ: Biotransformation of Toxicants. IN, Toxicology, The Basic Science of Poisons, Fourth Edition, MO Amdur, J Doull, CD Klaassen, eds., Pergamon Press, New York, 1991, pp. 88-126.

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DRUGS REQUIRED FOR EXAMS

(Within the context of the lectures and syllabus.)

Drug absorption, distribution and elimination

dimethyl sulfoxide (DMSO)
cimetidine
phenobarbital
probenecid
penicillin