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BASIC PHARMACOLOGICAL PRINCIPLES

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Introduction

Unfortunately, drugs do not distribute in living organisms as though injected into balloons filled with fluid. The study of how drugs react in living tissues and organisms is pharmacology. The science of pharmacology includes many different fields. The relationship between the dose of a drug given to an animal and the use of that drug in treating diseases are described by pharmacokinetics, what the body does to a drug and pharmacodynamics, what the drug does in the body (pharmacodynamics), whether it is desirable or undesirable (toxicology).

Pharmacokinetics is the study of absorption, distribution, biotransformation (metabolism) and excretion of drugs. The end result is determined by the physical, chemical and biochemical principles that govern the transfer and distribution of drugs across biological membranes. These factors and the dosage (route, dose and frequency) determine the drug concentration at the site of action and the intensity of a drug’s effects as a function of time. Pharmacodynamics is the study of the mechanisms of action of drugs and their biochemical and physiological effects. Toxicology is the field of pharmacology that deals with the adverse effects of drugs used in therapy and other non-drug chemicals.

A drug’s usefulness as a therapeutic agent is critically dependent on its ability to produce desirable effects and a tolerable level of undesirable effects. Therefore, the selectivity of a drug’s effects is one of its most important characteristics. Drug therapy is based on the correlation of the effects of drugs with the physiological, biochemical, microbiological and/or immunological aspects of the disease in question. Disease may modify the pharmacokinetic properties of drugs by altering absorption into the systemic circulation and drug disposition (distribution, metabolism and elimination).

Sufficient concentrations of a drug must be present at its sites of action to produce its characteristic effects.
Clearly this is a function of the dose given and the concentrations reached in association with the extent and rates of absorption, distribution, biotransformation and excretion.

**Physicochemical factors in the transfer of drugs across biological membranes**

Drugs are transported in the aqueous phase of blood plasma. To have an effect drugs must enter cells or reach cell membrane receptors. All aspects of the absorption, distribution, biotransformation and elimination of drugs involve transfer across cell membranes. Other barriers, including multiple layers of cells (e.g. the intestinal epithelium or epidermis) exist also.

Biological membranes are essentially lipid, thus the rate at which drug molecules cross these barriers is dictated primarily by their lipid solubility. Molecular size and shape and the solubility at the site of absorption, also directly affect the absorption of drugs. The other important factor that determines the ability of a drug to cross these biological barriers is the degree of ionization.

Most drugs are weak acids or bases that are present in solution as both the ionized and unionized forms. Ionized molecules are usually unable to penetrate lipid cell membranes because they are hydrophilic and poorly lipid soluble. Unionized molecules are usually lipid soluble and can diffuse across cell membranes. ‘Like is unionized in like’, meaning that a weak acid will be most unionized in a fluid with an acidic pH and a weak base will be most unionized in a fluid with a basic pH. Under most circumstances, the transmembrane distribution of a weak acid or base is determined by its acidic dissociation constant (pKa) and by the pH gradient across the membrane. The proportions of drug in each state are calculated using the Henderson-Hasselbach equation. For a weak acid:

\[
\text{pH} = \text{pKa} + \log(A-/HA),
\]

where A- is the ionized drug and HA the unionized drug. For a weak base:

\[
\text{pH} = \text{pKa} + \log(B/HB+),
\]

where B is the unionized drug and HB+ is the ionized drug. Thus, when the local pH is equal to the pKa of the drug, the drug will be 50% ionized and 50% unionized (log 1 = 0). There is further information on this area in the suggested reading.

Passive diffusion across the cell membranes dominates the absorption and distribution of most drugs. Drugs enter cells down concentration gradients. This transfer is directly proportional to the magnitude of the concentration gradient across the membrane and to the oil to water partition coefficient of the drug (lipid solubility). Thus, diffusion is fastest when there is a large partition coefficient and large concentration gradient across the membrane. For ionized compounds, the equilibrium concentrations are dependent on the differences in pH across the membrane and the pKa of the drug. For unionized compounds once the equilibrium is reached, the concentration of free drug is the same on both sides of the membrane.

Active, selective mechanisms play an important role in the absorption of some drugs. Energy is used to
move drugs across membranes often against the concentration gradient. There is active transport of some drugs in the kidneys (tubular cells), liver and nervous system. Facilitated diffusion is a carrier-mediated transport process that requires no input of energy, it does not occur against an electrochemical gradient.

**Absorption**

Absorption is the rate and extent at which a drug leaves its site of administration. Many variables affect the transport of drugs across membranes and hence influence the absorption of drugs. Absorption is dependent on drug solubility. Drugs given in aqueous solution are absorbed more rapidly than those given in lipid solutions, because they mix more readily with the aqueous phase at the absorption site. Drugs in solid form must first dissolve and this may be the limiting factor in absorption.

Bioavailability indicates the extent to which a drug enters the systemic circulation. Factors that modify the absorption of a drug can change its bioavailability. A drug that is absorbed from the gastrointestinal tract enters the portal circulation and must first pass through the liver before it reaches the systemic circulation. Drugs that are not absorbed from the gastrointestinal tract, or are metabolized extensively in the liver and/or excreted in bile will be inactivated or diverted before reaching the general circulation. If the metabolic or excretory capacity of the liver for a drug is excessive, the bioavailability of the drug will be substantially decreased (i.e. first pass effect). Reduced bioavailability is not only a function of the anatomical site of absorption but is also affected by many physiological and pathological factors. The choice of the route of drug administration is based on understanding these conditions.

**Drug Administration**

**Intravenous administration**

Problems with absorption can be circumvented using (i.v.) administration of an aqueous solution of a drug. The desired concentration of a drug in blood is obtained with great accuracy and immediacy. The dosage can be titrated to effect, such as in induction of anesthesia, where the drug dose is not predetermined but adjusted to the animal’s response. In addition, irritant solutions can be given in this manner, since blood vessel walls are relatively insensitive to drug forms that are highly irritant when given by other routes. The major liability of intravenous administration is that adverse reactions are more likely to occur since high concentrations of drug are reached rapidly both in plasma and tissues. Repeated intravenous injections require an intact vein or, often, catheter placement.

**Intramuscular administration**

Drugs in aqueous solution are absorbed rapidly following intramuscular (i.m.) injection, although this varies depending on factors such as the blood flow to the injection site. In human beings, absorption from the deltoid or vastus lateralis muscles is faster than from the gluteus maximus. Absorption from this site is even slower in females than in males. This has been attributed to sex differences in the distribution of subcutaneous fat, since fat is a relatively poorly perfused tissue.

**Subcutaneous administration**

Non-irritant drugs can be administered by subcutaneous (s.c.) injection. The rate of absorption may be sufficiently constant and slow to provide a sustained effect.
**Oral administration**

Absorption from the gastrointestinal tract is governed by a number of factors, such as the physical state of the drug, the surface area for absorption, blood flow to the absorption site and the drug concentration at the absorption site. Most drug absorption is by passive diffusion, thus absorption from the gastrointestinal tract is favored when a drug is in its unionized, more lipophilic form. In general, the absorption of weak acids is optimal from the acidic environment of the stomach and the relatively alkaline environment of the small intestine facilitates the absorption of weak bases. This is of course an oversimplification.

**Pulmonary administration**

Drugs may be administered directly into the respiratory tract for activity on, or through, the pulmonary epithelium and mucous membranes. Access to the systemic circulation is relatively enhanced and rapid following administration by this route. The pulmonary surface area is large. A drug solution can be administered as an aerosol that is inhaled. The advantage of this route of administration is the almost instantaneous absorption of drugs into the bloodstream, avoidance of the hepatic first pass effect and local (topical) application of the drug in the case of pulmonary disease.

**Topical Application**

Drugs are applied topically primarily for local effects, however this route can be used to administer drugs for systemic action. Few drugs readily penetrate intact skin. The absorption of drugs that do penetrate the skin is proportional to the surface area over which they are applied and to their lipid solubility. Increased cutaneous blood flow also enhances absorption. Systemic toxicity can become evident when highly lipid-soluble substances (e.g. lipid-soluble insecticides) are absorbed through the skin. Controlled-release patches are now commonly used in human medicine for transcutaneous drug administration.

Other routes of administration

Intraarticular administration, local perfusion and ocular administration are useful in veterinary medicine.

The intraarterial, intrathecal and intraperitoneal routes are used only rarely in veterinary medicine.

**Distribution**

Once a drug is absorbed, it distributes to many tissues including its sites of action. The pattern of drug distribution reflects the physiological and physicochemical properties of the drug. The initial phase of distribution often reflects cardiac output and regional blood flow. Drug is delivered to the heart, liver, kidney, brain and other well-perfused organs during the first few minutes after absorption. The second much slower phase of drug distribution involves delivery of the drug to skeletal muscle, other viscera, skin and fat. These tissues may require several minutes to several hours before steady-state concentrations are reached.

Distribution can be limited by binding of drugs to plasma proteins, particularly albumin, for acidic drugs and alphal-acid glycoprotein, for basic drugs. Protein bound drug is too large to pass through biological membranes; drug that is extensively protein bound will have limited access to intracellular sites of action (Martinez 1998b). Bound and free drug are in equilibrium on either side of membranes and free (unionized)
drug is in equilibrium across cell membranes. The ability of a bound drug to contribute to these equilibriums is
determined by the ferocity of its adherence to the protein moiety.

Protein bound drugs may be also be metabolized and eliminated more slowly than expected. They may also
accumulate in tissues in greater concentrations than would be expected from their physicochemical properties
because of intracellular binding, partitioning into lipid and ion trapping (pH partitioning). This may provide a
reservoir that prolongs drug action. Protein binding also limits the glomerular filtration of a drug. However, it
does not generally limit renal tubular secretion or biotransformation, since these processes lower the free drug
caloration in plasma, which rapidly causes dissociation of the drug-protein complex and increases the total
unbound fraction.

The degree of protein binding is only clinically significant for those drugs that are more than 90% protein
bound. For these drugs, conditions that decrease plasma protein concentrations, such as liver and kidney disease,
will cause significant increases in the amount of free drug available for pharmacologic actions. Protein binding
may also be involved in drug interactions. If a highly protein bound drug is coadministered with a drug that uses
the same protein binding site, it can displace the first drug from the plasma protein and thus increase the amount
of the first drug available for pharmacologic action. The classical example of this is the interaction between
phenylbutazone and warfarin, where phenylbutazone displaces warfarin from the protein-binding site. Reducing
the amount of protein bound warfarin from 99% to 98% effectively doubles the plasma concentrations of free
warfarin (which has anticoagulant activity) and can lead to bleeding problems.

**Central Nervous System**

Entry of drugs into the cerebrospinal fluid (CSF) and extracellular space of the central nervous system is
relatively restricted. The endothelial cells of the central nervous system have tight junctions and do not have
intercellular pores and pinocytotic vesicles.

**Bone**

Divalent metal ion chelating agents (e.g. tetracyclines) and heavy metals accumulate in bone by adsorption
onto the bone-crystal surface and eventual incorporation into the crystal lattice.

**Placental transfer**

If drugs are transferred across the placental they may be potentially hazardous to the fetus. Drugs primarily
cross the placenta by passive diffusion. Lipid soluble, unionized drugs can enter the fetal bloodstream. The fetal
bloodstream is relatively protected from drugs that are relatively lipid insoluble and/or highly ionized in plasma.
However, the fetus is, at least to some extent, exposed to essentially all drugs administered to its mother.

**Transcellular compartments**

Drugs may accumulate in the transcellular fluids. The major transcellular fluid compartment is in the
gastrointestinal tract. Weak bases can enter the stomach from the circulation and concentrate there. Drugs may
also be secreted in bile either in an active form or as a conjugate that can be hydrolyzed in the intestines. Thus,
the gastrointestinal tract can serve as a drug reservoir. Under normal circumstances, the CSF, aqueous humor
and joint fluids generally do not accumulate significant total quantities of drugs.
Biotransformation

Biotransformation detoxifies and/or removes foreign chemicals from the body and thus promotes survival. The main metabolic enzyme systems are located in the hepatic smooth endoplasmic reticulum. Some enzyme systems are also located in the kidneys, lungs and gastrointestinal epithelium. The first pass effect (presystemic metabolism) can thus be a combination of gastrointestinal and hepatic enzyme systems. Biotransformation can also improve therapeutic activity (e.g. metabolic activation of ceftiofur to desfuroyleftiofur).

The chemical peculiarities of drug molecules that allow for their rapid passage across cellular membranes during absorption and distribution also delay elimination. The enzymatic biotransformation of drugs into more polar, less lipid-soluble (more water-soluble) metabolites promotes elimination. Conjugation of drugs further increases their water solubility and hence elimination. Horses tend to conjugate drugs to glucuronide (Dirikolu et al 2000, Harkins et al 2000).

Elimination

Drugs are eliminated from the body either unchanged or after biotransformation (metabolites). The excretory organs tend to eliminate polar, less lipid soluble compounds more efficiently than compounds with high lipid solubility.

The kidney is the most important organ for elimination of drugs and metabolites. Some substances are excreted via the gastrointestinal tract, for the most part drugs that were unabsorbed or metabolites excreted in the bile and not reabsorbed. Pulmonary excretion is important mainly for the elimination of anesthetic gases. The efficacy of some drugs may be partially dependent on excretion in the pulmonary secretions. Drugs are also excreted into milk, skin, sweat, saliva and tears but these routes are usually of minor importance. In lactating mares, excretion of drugs in milk may be significant to affect suckling foals. Elimination by the latter routes is via unionized lipid soluble moiety diffusion through the gland epithelial cells and is pH dependent.

Urinary excretion

Elimination of drugs and metabolites by the kidneys is by three mechanisms: glomerular filtration, active tubular secretion and passive tubular reabsorption. The amount of drug filtered through the glomeruli is dependent on the degree of plasma protein binding and the glomerular filtration rate. Organic anions and cations are added to the glomerular filtrate by active tubular secretion in the proximal tubule. Most organic acids (e.g. penicillin) and glucuronide metabolites are transported by the same system that is used for excretion of natural metabolites, such as uric acid. Organic bases are transported by a separate system that is designed to excrete bases such as choline and histamine. Both of these systems are relatively nonselective and may be bidirectional with some drugs being both eliminated and reabsorbed. However, the main direction of transport is into the renal tubules for excretion. Clearly the rate of passage into the renal tubules is dependent on the pKa of the drug and its metabolites and on urine pH. As an example, increasing urine pH can produce a dramatic increase in excretion of acidic compounds such as salicylate.

Gastrointestinal excretion

Many metabolites produced by hepatic metabolism are eliminated into the intestinal tract via the bile. These metabolites may be excreted in feces, but are often reabsorbed. Organic anions (i.e. glucuronides) and cations
are actively transported into bile by carrier systems that are similar to those in the renal tubules. Similarly charged ions can compete for transport by these systems because both are nonselective. Steroidal and related substances are transported by a third carrier mechanism. Glucuronide conjugated metabolites undergo extensive enterohepatic recirculation, a cycle of absorption from the gastrointestinal tract, metabolism in the liver and excretion in bile and this cycle delays elimination when the final step in elimination from the body is via the kidneys.

**Excretion in milk**

Suckling foals may potentially receive high doses of drug via milk. Normal milk is more acidic than plasma. Weak bases are highly unionized in plasma and the unionized drug fraction crosses readily into the mammary gland and then becomes ‘ion trapped’ in the more acidic milk. Weak acids are highly ionized in plasma and therefore do not penetrate the mammary glands very well. These factors are used in the systemic treatment of mastitis but should be borne in mind when treating lactating mares with any therapeutic agent.

**Pharmacokinetics**

Clinical pharmacokinetics assumes that there is a relationship between the serum concentration versus time profile and the response to a drug. Drug concentration versus time data can be described using compartmental (model-dependent) or non-compartmental (model-independent) pharmacokinetics. The majority of publications use compartmental pharmacokinetics, where the models used to describe the drug concentration versus time data assume that drug in the central compartment (blood and rapidly equilibrating tissues) is distributed to one or more peripheral or tissue compartments and that drug is eliminated only from the central compartment. A graph of the plasma drug concentration (on a logarithmic scale) versus time (on a linear scale) following intravenous administration can be divided into a series of linear segments and can be described using mono-, bi- or triexponential equations, which reflect the number of compartments in the model. One-, two- and three-compartment models have been used to describe drug disposition in the horse. Some authors use the non-compartmental approach, which is based on statistical moment theory.

The three most important indices in pharmacokinetics are clearance (related to the rate of elimination), apparent volume of distribution (the volume into which a drug distributes in the body) and bioavailability (the fraction of a drug absorbed into the systemic circulation).

**Clearance**

Clearance (CL) can be used to design an appropriate dosage regimen for long-term drug administration. The total systemic clearance (CL\(_T\)) is the sum of clearance by all mechanisms (e.g. renal (CL\(_R\)), hepatic (CL\(_H\))). CL is the volume of plasma that is completely depleted of drug to account for the rate of elimination. It is usually constant for a drug within the desired clinical concentrations but does not indicate how much drug is being removed.

\[ CL = \frac{kel}{C_p}, \]

where kel is the rate of elimination and C\(_p\) is the concentration in plasma
Excretion systems have a high ceiling and so are rarely saturated under clinical circumstances. The elimination rate is essentially a linear function of the drug concentration in plasma; elimination follows first-order kinetics. This means that there is a constant fraction of drug eliminated per unit time. This is why doubling the dose e.g. of intravenous penicillin, does not reduce the need for frequent dosing. If elimination mechanisms become saturated, the kinetics follow a zero-order pattern and a constant quantity of drug is eliminated per unit of time. In this situation, CL varies with time.

**Half-life (t½)**

The elimination or terminal half-life (t½) is the time needed for the drug concentration in plasma to decrease by 50%. For most drugs the half-life remains constant for the duration of the drug dose in the body. The elimination half-life can be calculated following intravenous drug administration whereas terminal half-life is calculated following drug administration via other routes (non-intravenous).

\[
t_{\frac{1}{2}} = \frac{0.693}{k_{el}},
\]

where 0.693 is the natural logarithm of 2. Terminal half-life is calculated using \( l_n \), the terminal slope of the concentration versus time profile for the nth compartment, in place of \( k_{el} \).

Clinically the half-life determines the interdosing interval, how long a pharmacologic or toxic effect will persist and drug withdrawal times in food producing animals and performance horses (Martinez 1998a). The plasma concentration of drug remaining at any given time (Cpt) can be calculated:

\[
(C_{p0}) e^{-\left(\frac{0.693}{t_{\frac{1}{2}}}\right) t},
\]

where \( C_{p0} \) equals the plasma concentration of drug at time zero and \( t \) is the time from \( C_{p0} \) to Cpt. Table 2 shows the relationship between half-life and the amount of drug in the body. With each half-life, the amount of drug remaining reduces by 50%. Note it takes 10 half-lives to eliminate 99.9% of a drug from the body. Also recognize that doubling the dose of a drug (so that the table would start at 200%) does not double the withdrawal time, but merely adds one additional half-life to reach the same concentration end-point (Baggot 1992). Steady-state concentrations are reached after three to five half-lives have elapsed.

**Mean residence time (MRT)**

MRT is the equivalent of half-life that is calculated when pharmacokinetic parameters are calculated using non-compartmental methods. Some pharmacokinetic studies report MRT instead of half-life. MRT is actually the time taken for the plasma drug concentration to decrease by 63.2% and should thus be somewhat greater than half-life.

**Volumes of Distribution**

Volumes of distribution are used as an indication of a drugs ability to escape the vascular compartment. These are mathematical terms that describe the apparent volume in the body into which a drug is dissolved with units in milliliters or liters per kilogram (mL/kg or L/kg) (Riviere 1999). The apparent distribution volumes vary depending on the physical characteristics of drug molecules, including ionization (pKa), lipid solubility, molecular size and protein binding, that determine their ability to cross membranes (Martinez 1998b).
To understand the concept of Vd, think of the body as a beaker filled with fluid (Fig. 1), where the fluid represents the plasma and the other extracellular fluid (ECF). If the drug does not readily cross lipid membranes, it will be confined mainly to the ECF. If this drug is administered intravenously, it will distribute rapidly in the ECF, as represented by the stars in the beaker on the left. A sample taken from this beaker will have a high drug concentration. The higher the measured concentration in relation to the original dose, the lower the numerical value of Vd. Some drugs readily cross lipid membranes and distribute into tissues. This is represented by the beaker on the right, where the stars at the bottom of the beaker represent drug molecules that have been taken up by tissues. A sample taken from the fluid in this beaker will have a low drug concentration in proportion to the original dose and will have a high numerical value for Vd.

The three most important volume terms used in compartmental analysis are the volume of the central compartment (Vc), the volume of distribution based on elimination (Vd, Vdβ or Vdarea) and the volume of distribution at steady-state (Vdss). The numerical values of these terms differ slightly, but they all give an indication of a drug’s ability to cross membranes. Although similar in magnitude Vd is usually greater than Vdss, because the latter describes the volume that the drug occupies after equilibration has taken place, which is usually greater than Vc. Vdss and hence CL and dose rate, can also be calculated using non-compartmental methods.

The volume of the central compartment (Vc) is the proportionality constant that relates the drug dose to the amount of drug measured in a blood/plasma sample (Cp).

For a one-compartment model, the distribution phase occurs rapidly compared with elimination:

$$Vc = \frac{\text{Dose}}{Cp_0}$$

In this model, the drug concentration in the blood or plasma is proportional to both the concentration in other tissues (e.g. muscle) and to the total amount of drug in the body. When the equilibration of a drug between the central and peripheral compartments occurs less rapidly, relative to elimination, then the disposition kinetics of the drug can be described by assuming that there are two (or sometimes more) distribution compartments. The apparent volume of distribution varies with time after drug administration in these models, due to the time required for equilibration between the compartments. Thus, for a two compartment model, Vc is dose/(A + B), where A and B are the Y intercepts (plasma concentrations at time 0) associated with the distribution and elimination phases respectively.

$$Vd = \frac{\text{Dose}}{\beta \cdot \text{AUC}}$$

where beta is the slope of the terminal phase and AUC is the area under the plasma concentration versus time curve from time 0 to infinity. The apparent volume of distribution at steady-state (Vdss) is quoted in most reference texts. Vdss is when the rate of drug entry from the bloodstream into the tissues is equal to its exit rate from the tissues back into the circulation. It is directly proportional to the tissue binding affinity and the fraction of drug remaining unbound in the blood.

Adult animals are considered to be approximately 60% water; the total body water has a volume of 0.6 L/kg. The ECF compartment is approximately 30% of body weight and has a volume of 0.3 L/kg. Neonates are
considered to have total body water closer to 80% and the additional 20% is found primarily in the ECF compartment. Geriatric animals tend to have reduced total body water primarily due to a reduction in ECF volume.

Compounds may be distributed and confined to the vascular space, or may be distributed into intracellular and extracellular compartments. In the latter case, Vdss approximates the volume associated with total body water. Weakly lipid soluble compounds (e.g. cephalosporins, aminoglycosides, penicillins) generally penetrate poorly into cells. Their natural distribution space tends to be extracellular and Vdss approximates extracellular fluid volume, about 30% of an animal’s body weight (Baggot 1990). The Vd for gentamicin approximates 0.254 L/kg (Pedersoli et al 1980), which implies an ECF distribution, while the Vd for metronidazole is 0.69 L/kg (Specht et al 1992). Highly lipophilic compounds are associated with large Vdss (e.g. propranolol, Vdss = 3.9 L/kg). Thus, a drug with Vd of 0.3 L/kg will be distributed primarily into the ECF, while a drug with a Vd of 3.4 L/kg will be distributed beyond the body water compartments and will achieve high concentrations in tissues, yet relatively low concentrations in plasma. Some of these drugs (e.g. macrolides, fluoroquinolones) are sequestered in within cells or have extensive tissue binding, reflected by estimates of Vdss that exceed the volume of total body water (Atkinson et al 1996). If the Vd is greater than 1 L/kg, the drug concentration will be greater in tissues than in plasma (Evans 1992). While a large Vdss suggests excellent extravascular distribution, it does not guarantee adequate active drug concentrations at the sites of action.

Drug doses are usually determined in normal, healthy adult animals. Vd is constant for any drug and only changes if there are with physiological or pathological changes that alter drug distribution. Any condition that changes ECF volume will dramatically affect the plasma concentrations of drugs with low Vdss. Drugs with high Vd normally distribute throughout the fluid and tissue compartments and so are not significantly affected by changes in body water status. ECF volume contraction and dehydration occur in conditions such as shock, colic and enteritis. Parasitism, heart failure and vasculitis can all cause edema and an increase in the ECF volume. Local changes in acid-base status can alter the ionization of drugs and affect their movement across membrane barriers. Conditions that alter the amount or affinity of plasma proteins will change the Vd of highly protein bound drugs.

**Bioavailability**

Bioavailability (F) is a measure of the extent of absorption. It is an indication of the amount of drug that is absorbed from the administration site. Drugs administered intravenously essentially have a bioavailability of 100%. Drugs administered orally will have variable bioavailability. The rate of absorption is clearly important, for if the rate is very slow, the drug may not reach active concentrations before it is eliminated and if very rapid, unsafe plasma concentrations may be reached.

AUC is a frequency distribution of the number of molecules within the body versus time. When measured out to infinity (\(\infty\)), the area under the serum concentration time-profile curve (AUC0\(-\infty\)) represents the total drug exposure. Its value is unaffected by the rate of absorption (assuming linear kinetics) but is affected by dose, CL and bioavailability. Bioavailability is calculated by comparing the total amount of drug in the body (area under the plasma concentration versus time curve, AUC) following administration by a non-intravenous route with that obtained following intravenous administration (100%), corrected for dose.

\[
F = \frac{\text{AUCnon-i.v.} \times \text{Dosei.v.}}{\text{AUCi.v.} \times \text{Dose non-i.v.}}
\]
Other clinically relevant concepts

The loading dose

A loading dose is an initial dose of drug that is administered at a dose rate higher than that normally used. A loading dose is used when the time needed to reach steady-state concentrations (i.e. about three to five half-lives) is long relative to the need for treatment. It rapidly increases plasma concentrations so that steady-state concentrations are approached more rapidly.

Maximum plasma concentration ($C_{\text{max}}$)

The $C_{\text{max}}$ reflects the extent of drug bioavailability. The Cmax can be used in relation to minimum inhibitory concentration (MIC) to predict the efficacy of concentration-dependent antimicrobial agents (e.g. fluoroquinolones, aminoglycosides). Both the maximum (peak) and minimum (trough) plasma concentrations are used during therapeutic drug monitoring to maximize efficacy and minimize the occurrence of undesirable effects.

References

Suggested reading


Table 1.1. Common routes of drug administration and their characteristics

<table>
<thead>
<tr>
<th>Route</th>
<th>Absorption</th>
<th>Use</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>None (directly into the circulation). Potentially immediate effects.</td>
<td>Emergency use or large volumes. Absorption is bypassed.</td>
<td>Increased risk of adverse effects; inject solutions slowly. Not suitable for most lipid solutions or insoluble substances.</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Rapid if an aqueous solution. Less rapid if depot formulations.</td>
<td>Some less soluble suspensions and implantation of solid pellets or depot forms.</td>
<td>Not suitable for large volumes. Irritant substances cause pain and/or necrosis.</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>Rapid if an aqueous solution. Less rapid if depot forms.</td>
<td>Moderate volumes; lipid vehicles; irritant drugs.</td>
<td>Inadvertent intravenous injection; pain or necrosis at injection site</td>
</tr>
<tr>
<td>Oral</td>
<td>Rate and extent are highly variable and dependent on many factors.</td>
<td>Maximize compliance (convenient); economical; usually safe.</td>
<td>Absorption (bioavailability) may be erratic and incomplete.</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Rapid; local application for pulmonary disease.</td>
<td>Usually for the treatment of pulmonary disease.</td>
<td>Irritant substances must be avoided; rapid absorption may induce high plasma concentrations and adverse effects.</td>
</tr>
</tbody>
</table>

Table 1.2. Relationship of elimination half-life ($t\frac{1}{2}$) to amount of drug in the body

<table>
<thead>
<tr>
<th>Number of half-lives</th>
<th>Fraction of drug remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>1</td>
<td>50%</td>
</tr>
<tr>
<td>2</td>
<td>25%</td>
</tr>
<tr>
<td>3</td>
<td>12.5%</td>
</tr>
<tr>
<td>4</td>
<td>6.25%</td>
</tr>
<tr>
<td>5</td>
<td>3.125%</td>
</tr>
<tr>
<td>6</td>
<td>1.56%</td>
</tr>
<tr>
<td>7</td>
<td>0.78%</td>
</tr>
<tr>
<td>8</td>
<td>0.39%</td>
</tr>
<tr>
<td>9</td>
<td>0.195%</td>
</tr>
<tr>
<td>10</td>
<td>0.0975%</td>
</tr>
</tbody>
</table>