Handbook of Veterinary Pharmacology
To the memory of my parents, Han-Po Hsu and Hua-Eng Yuan Hsu, for their discipline and endless love. They are the ones who taught me: “Never give up, no matter what is going on.”

To my wife, Rou-Jean, for her love and putting up with me all these years with my long working hours.

To my children, Susan, Karen and her husband, Bob, for their love and patience.

To my lovely grandson, Nathan Wei-Ming.

To my brothers, Hong and Tsao, my sisters, Yun and Hui (Michelle) for their love and support since childhood.

To my old friend, Charles Cheng-Chau Wang, for sharing many thoughts and interests for more than forty years.

To my mentors, Dr. Cary W. Cooper, Dr. Gordon L. Coppoc, Dr. Franklin A. Ahrens, and Dr. Donald C. Dyer, who guided me to do research and teaching in pharmacology.

To my teachers, friends, colleagues, and students for their teaching so I can keep improving myself and treat people and animals with care and fairness.
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The Handbook of Veterinary Pharmacology is written in a concise format, which is the extension of the National Veterinary Medical Series Pharmacology Book (Editor: F. A. Ahrens) published in 1996. This book is not intended to provide a lengthy discussion of veterinary drugs; instead, it is designed as a handbook that contains concise descriptions of pharmacological concepts and information for the commonly used veterinary drugs available in the United States. Every effort has been made to keep the information on basic and clinical veterinary pharmacology up-to-date and concise. Whenever possible, each class of drugs is explored under the heading of “general considerations” or “introduction” to convey the basic concept and information, which is followed by a description of the pharmacology of each drug with the headings of (1) chemistry/preparations, (2) pharmacological effects/mechanism of action, (3) therapeutic uses, (4) administration, (5) pharmacokinetics, and (6) adverse effects/contraindications.

The ultimate goal of this book is to provide to both the veterinary students and practitioners the information on pharmacology that is applicable and easily retrievable. A list of suggested reading at the end of each chapter is provided for further reading of the subject. In addition, 10–20 study questions and explanations are presented at the end of each chapter.

There are two appendices at the end of the book; one on the withdrawal times for drugs used in production animals and the other on the drug dosages in various domestic species. The drug dosages in both generic name and selected trade names are listed according to chapter, drug class, route of administration, and species. I hope these two appendices will be useful to veterinary practitioners, particularly when a quick decision is needed on drug therapy.

To complete the task of writing such a book requires strong commitment of many of my colleagues. I am most grateful to the 11 contributors who put a great deal of effort in writing chapters amid their busy schedules and to their acceptance and tolerance of my editing. A special thanks to Mr. Nasser Syed, one of my graduate students, for providing many of the illustrations and helping create the index. I would also like to thank Dr. Dai Tan Vo, another graduate student of mine, for his meticulous efforts in compiling the appendices and some of the tables for this book. I am grateful to Dr. Kim D. Lanholz and Dr. Alison E. Barnhill for reviewing some of the chapters. I am indebted to Dr. Donald C. Dyer for his generosity in allowing us to utilize the information and illustrations in the chapters that he wrote for the National Veterinary Medical Series Pharmacology Book. The secretarial assistance of Ms. Hilary Renaud and Ms. Marilee Eischeid in preparing the manuscripts is greatly appreciated.

It is our hope that the Handbook of Veterinary Pharmacology will become a valuable tool for both veterinary students and practitioners.

Please send me an e-mail (whsu@iastate.edu) if you detect errors and/or have comments/suggestions for improvement of the book in the next edition. Your input will be deeply appreciated.

Walter Haw Hsu
I. INTRODUCTION. Pharmacology is the study of the properties of chemicals used as drugs for therapeutic purposes. It is divided into the study of pharmacokinetics and pharmacodynamics. Veterinary pharmacology focuses on drugs that are used in domestic animals. Pharmacokinetics is the study of drug absorption, distribution, biotransformation (metabolism), and excretion. Pharmacokinetic processes affect the route of administration, doses, dose intervals, and toxicities of drugs given to animals. Pharmacodynamics is the study of cell/tissue responses and selective receptor effects. In this chapter, we introduce standard concepts of pharmacokinetics and pharmacodynamics and comment on the need to be aware of species variation when considering principles of veterinary pharmacology.

II. DRUG ABSORPTION AND DISPOSITION

A. General principles. An overview of the principles involved in a drug's journey in the body beginning from its administration to the pharmacologic response.

How do drugs reach their site of action? It is apparent from Figure 1-1 that a drug usually crosses several biological membranes from its locus of administration to reach its site of action and thereby produce the drug response. The manner by which drugs cross membranes are fundamental processes, which govern their absorption, distribution, and excretion from the animal.

1. Passive diffusion. Cell membranes have a bimolecular lipoprotein layer, which may act as a barrier to drug transfer across the membrane. Cell membranes also contain pores. Thus, drugs cross membranes based on their ability to dissolve in the lipid portion of the membrane and on their molecular size, which regulates their filtration through the pores.

a. Weak acids and weak bases. The majority of drugs are either weak acids or weak bases. The degree to which these drugs are fat soluble (nonionized, the form which is able to cross membranes) is regulated by their \( pK_a \) and the pH of the medium containing the drug. \( pK_a = pH \) at which 50% of the drug is ionized and 50% is nonionized.

b. To calculate the percent ionized of a drug or to determine the concentration of a drug across a biological membrane using the Henderson-Hasselbalch equation one needs to know whether a drug is an acid or a base.

If the drug is a weak acid use:

\[
pK_a = pH + \log \frac{\text{Concentration of nonionized acid}}{\text{Concentration of ionized acid}}
\]

If the drug is a weak base use:

\[
pK_a = pH + \log \frac{\text{Concentration of ionized base}}{\text{Concentration of nonionized base}}
\]

c. In monogastric animals with a low stomach pH, weak acids such as aspirin (\( pK_a = 3.5 \)) tend to be better absorbed from the stomach than weak bases because of the acidic conditions. In ruminants, the pH varies with feeds and the pH is often not low.
d. Weak bases are poorly absorbed from the stomach since they exist mostly in the ionized state (low lipid solubility) because of the acidic conditions. Weak bases are better absorbed from the small intestine due to the higher environmental pH.

2. Filtration
   a. Some low molecular weight chemicals, water, urea, and so forth, cross membranes better than predicted on the basis of their lipid solubility, suggesting that membranes possess pores/channels.
   b. The glomerular filtration process in the kidney provides evidence for large pores, which permit the passage of large molecular weight substances but small enough to retain albumin (mw ∼60,000).

3. Facilitated diffusion
   a. No cellular energy is required and it does not operate against a concentration gradient.
   b. Transfer of drug across the membrane involves attachment to a carrier (a macromolecular molecule).
   c. Examples: Reabsorption of glucose by the kidney and absorption from the intestine of vitamin B₁₂ with intrinsic factor.
   d. This is not a major mechanism for drug transport.

4. Active transport
   a. Requires cellular energy and operates against a concentration gradient.
   b. Chemical structure is important in attaching to the carrier molecule.
   c. Examples: Penicillins, cephalosporins, furosemide, thiazide diuretics, glucuronide conjugates, and sulfate conjugates are examples of acidic drugs that are actively secreted by the proximal renal tubule. Amiloride, procainamide, quaternary ammonium compounds, and cimetidine are examples of basic drugs that are actively secreted by the proximal renal tubule cells. Intestinal absorption of 5-fluorouracil, an anticancer drug, which is transported by the same system used to transport uracil.
5. **Pinocytosis.** This is a minor method for drug absorption, but it may be important in the absorption process for some polypeptides, bacterial toxins, antigens, and food proteins by the gut.

**B. Routes of administration.** All routes of administration except intravascular (see Figure 1-1) involve an absorption process in which the drug must cross one or more membranes before getting into the blood.

1. **Alimentary routes**
   a. **Oral (per os, PO)**
      (1) **Advantages**
         (a) Usually safest, convenient, economical, but some animals are difficult to administer this way.
         (b) May require the drug to be mixed in the food to facilitate administration.
         (c) Food may stimulate bile secretion, which will help dissolve lipophilic drugs to increase absorption.
      (2) **Disadvantages**
         (a) Acidic environment of stomach and digestive enzymes may destroy the drug.
         (b) In ruminants the bacterial enzymes may inactivate the drug.
         (c) Some drugs may irritate the GI mucosa.
         (d) The presence of food may adversely alter absorption.
         (e) Some drugs are extensively metabolized by the GI mucosa and the liver before they reach the systemic circulation (e.g., propranolol) and this is referred to as the **first-pass effect**.
         (f) Antimicrobials may alter the digestive process in ruminants and other herbivores.
   b. **Rectal**
      (1) **Advantages**
         (a) Can be used in the unconscious animal and in those vomiting.
         (b) Absorption is slower compared to the intramuscular route.
         (c) There are some drugs like diazepam and phenytoin that have an erratic oral absorption and are better given rectally.
         (d) In dogs, influence of the first-pass effect is reduced because the rectal veins bypass the portal circulation and go to the caudal vena cava.

2. **Parenteral routes (circumvents the GI tract)**
   a. **Examples**
      (1) **Intravenous (IV)**
      (2) **Intramuscular (IM)**
      (3) **Subcutaneous (SC)**
      (4) **Intraperitoneal (IP)**
      (5) **Spinal and subdural.** Used for regional anesthesia.
   b. **Advantages**
      (1) Rapid onset (IV > IM > SC), may be useful in an unconscious or vomiting patient, absorption is more uniform and predictable.
      (2) Absorption from IM and SC injection sites is mostly determined by the amount of blood flow to that site. The absorption of local anesthetics is often purposely slowed by coadministration with epinephrine, which decreases the blood flow to the injection site.
   c. **Disadvantages**
      (1) Asepsis is necessary.
      (2) Cause pain.
      (3) May penetrate a blood vessel during IM injection.
      (4) The speed of onset is so rapid as with IV administration that cardiovascular responses may occur to drugs, which normally have minimal effects on this system.
      (5) In food animals, discoloration of the meat or abscess formation may occur to IM injection and these may be expected to devalue the carcass.
3. Other routes
   a. Dermal or topical
      (1) Degree of absorption is dependent on the drug's lipid solubility.
      (2) Abraded or damaged skin may be expected to absorb more drug than intact skin.
      (3) Animals with thin skin, like cats, may absorb drugs like corticosteroids readily if they are applied topically than animals with thicker skin.
      (4) It is convenient and allows nonskilled operators to administer the drugs by pour-on methods. For example, topical application of anthelmintics that are lipophilic, like levamisole and macrocyclic lactones, is frequently performed in this manner.
   b. Inhalation
      (1) It is used for volatile or gas anesthetics. Example: isoflurane.
      (2) Response is rapid because of the large surface area of the lungs and large blood flow to the lungs.
      (3) It is reversible if the anesthetic is turned off and the animal ventilated.

C. Drug distribution
   1. Distribution refers to the reversible transfer of drug from one site in the body to another site.
   2. In much of the body, the junctions between the capillary endothelial cells are not tight thereby permitting free (unbound to plasma proteins) drug to rapidly reach equilibrium on both sides of the vessel wall.
   3. Distribution of drugs into the central nervous system (CNS) and cerebrospinal fluid (CSF) is restricted due to the blood–brain barrier (BBB).
      a. There are three processes that contribute to keeping drug concentration in the CNS low:
         (1) In much of the CNS (except: area postrema, pineal body, posterior lobe of hypothalamus), the capillary endothelial junctions are tight and glial cells surround the precapillaries. This reduces the filtration process and requires that drugs diffuse across cell membranes to leave the vascular compartment and thereby enter the extracellular fluid or CSF. This ability to cross cell membranes is dependent upon the drug’s lipid solubility.
         (2) Cerebrospinal fluid production within the ventricles circulates through the ventricles and over the surface of the brain and spinal cord to flow directly into the venous drainage system of the brain. This process continues to dilute out the drug’s concentration in the CSF.
         (3) Active transport mechanisms are found for organic acids and bases in the choroid plexus, which transports drug from the CSF into the blood. P-glycoprotein is one transporter protein that is present in the endothelial cells of the choroid plexus (blood–brain barrier) that contributes to drug entry into and exit from the brain.
         Examples: The macrocyclic lactones, ivermectin, and selamectin but less so with moxidectin, are excluded from the brain via P-glycoprotein. In some breeds of dog, particularly the Collies, P-glycoprotein is defective and ivermectin accumulates in the CNS, leading to toxicity.
         Penicillin (a weak acid) concentrations in the CNS are kept low due to an active organic ion transporter system.
   4. Plasma protein binding of drug can affect drug distribution since only the free (unbound) drug is able to freely cross cell membranes (see Figure 1-1, II A).

$$\text{drug + protein (free) } \rightleftharpoons \text{Drug – protein (bound)}$$

Acidic drugs are bound primary to albumin and basic drugs are bound primarily to $\alpha_1$-acid glycoprotein. Steroid hormones and thyroid hormones are bound by specific globulins, respectively, with high affinity.
   a. Drug–protein binding reaction is reversible and obeys the laws of mass action.
b. Binding does not prevent a drug from reaching its site of action but retards/slow the rate at which it reaches a concentration sufficient to produce a pharmacologic effect.

c. Drug–protein binding limits glomerular filtration as an elimination process since bound drugs cannot be filtered. Example: sulfa drugs with a high degree of binding to protein are eliminated more slowly in urine than those sulfa drugs with a lower binding affinity for plasma proteins.

d. Binding to albumin does not totally prevent the elimination of drugs that are actively secreted by the kidney or metabolized by the liver, rather it slows the rates of metabolism and/or secretion. Binding lowers the free drug concentration but there is still release from the drug–protein complex for the metabolism or secretion.

e. Drug interactions may occur when two drugs are used that bind at the same site on the plasma proteins. Competition for the same site will increase the percent of drug in the free form, thereby increasing the pharmacologic/toxicological response by the displaced drug.

5. **Drug redistribution** can terminate the drug response.

   a. The biologic response to a drug is usually terminated by metabolism/biotransformation and excretion.

   b. Redistribution of a drug from its site of action to other tissues will lower its concentration at its site of action, thereby terminating the drug response.

   c. Drugs exhibiting the redistribution phenomenon are highly lipid soluble. Thiopental is the classic example in dogs where redistribution from the brain to less vascular area of the body, including the muscle and fat, allows recovery. In sheep and goats, however, liver biotransformation takes place at such a high rate so that in these species it is metabolism, not redistribution that dominates the duration of anesthesia. Propofol is very lipophilic and is rapidly redistributed following IV injection so that in goats and dogs anesthesia is ultrashort. Interestingly, the redistribution process varies between breeds of dogs due to the different leanness of the different breed. Very lean breeds like Greyhounds with less fat for the lipophilic anesthetics to redistribute to, take longer to recover.

6. Drug distribution from dam to fetus.

   a. Drug transfer across the placenta occurs primarily by simple diffusion.

   b. **Drugs** cross the placenta best if they are lipid soluble (nonionized weak base or acid).

   c. The fetus is exposed to some extent even to drugs with low lipid solubility when given to the dam.

   d. **General rule**: Drugs with an effect on the maternal CNS have the physical–chemical characteristics to freely cross the placenta and affect the fetus. Examples: anesthetics, analgesics, sedatives, tranquilizers, and so forth.

D. **Drug metabolism/biotransformation** is the term used to describe the chemical alteration of drugs (xenobiotics) as well as normally found substances in the body.

1. **Principles**

   a. Following filtration at the renal glomerulus most lipophilic drugs are reabsorbed from the filtrate.

   b. Biotransformation of drugs to more water-soluble (polar) chemicals reduces their ability to be reabsorbed once filtered by the kidney. This enhances their excretion and reduces their volume of distribution.

   c. The liver is the most important organ for biotransformation but the lung, kidney, and GI epithelium also play a role.

   d. Drug biotransformation frequently reduces the biological activity of the drug/chemical/toxicant.

   e. Drug metabolism/biotransformation is not synonymous with drug inactivation as the parent chemical may be transformed to a chemical with greater or significant biologic activity.
Example:

- Acetylsalicylic acid → salicylate
- Inactive (aspirin) → active anti-inflammatory
- Febantel → fenbendazole/oxfendazole
- Inactive → active anthelmintic
- Primidone → phenobarbital
- Inactive → active anticonvulsant
- Codeine → morphine
- Active analgesic → more active analgesic

2. Enzymatic reactions in biotransformation usually occur in two phases (Figure 1-2):
   a. **Phase I** biotransformation enzymes are found in the smooth endoplasmic reticulum of the hepatic cells (also referred to as the microsomal enzymes since they are found in the microsomal fraction following high-speed centrifugation).
   1. **Oxidation** is carried out by a family of isozymes termed cytochrome P450s.
   2. The enzyme system is also called a **mixed function oxidase** since one atom of oxygen is incorporated in the drug molecule and the other atom of oxygen combines with hydrogen to form water. Nicotinamide adenine dinucleotide phosphate (NADPH) provides the reducing equivalents. Examples of microsomal oxidation:
      - **Side chain and aromatic hydroxylation**: pentobarbital, phenytoin, phenylbutazone, propranolol
      - **O-dealkylation**: morphine, codeine, diazepam
      - **N-oxidation**: acetaminophen, nicotine, phenylbutazone, pentobarbital
      - **S-oxidation**: phenothiazines (acepromazine, chlorpromazine), cimetidine
      - **Deamination or N-dealkylation**: lidocaine
      - **Desulfuration**: thiopental
   3. **Nonmicrosomal oxidation**
      A few chemicals are oxidized by cytosol or mitochondrial enzymes.
      - **Alcohol dehydrogenase** and **aldehyde dehydrogenase**. Example: ethanol, acetaldehyde, ethylene glycol
      - **Monoamine oxidase**. Example: epinephrine, norepinephrine, dopamine, serotonin
      - **Xanthine oxidase**. Example: theophylline
   4. **Oxidative metabolism**. There are considerable differences among the species in the activity of the oxidative enzymes. Generally, the difference has been attributed to differences between the kinetic parameters (Michaelis constants and Max velocity) of the species enzymes. Oxidation is higher in horses than cattle, which in turn are higher than dogs. Oxidation is lowest in cats among domestic animals. The level of oxidative enzymes is lower in very young animals. The duration of pentobarbital anesthesia in horses is much shorter than in dogs. Young calves are much more sensitive to pentobarbital and lindane than adult cattle.
TABLE 1-1. Drug Conjugation Reactions

<table>
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<th>Conjugation Reaction</th>
<th>Drug Conjugated</th>
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</table>
| Glucuronidation       | Aspirin, morphine, sulfadimethoxine, digitoxin, steroids, thyo-
|                      | roxine, phenobarbital, phenytoin, chloramphenicol, phenylbu-
|                      | tazone                                               |
| Acetylation           | Sulfonamides, clonazepam, procainamide               |
| Glutathione formation | Ethacrynic acid                                      |
| Glycine formation     | Salicylic acid, nicotinic acid                       |
| Sulfate formation     | Catecholamines, acetaminophen                        |
| Methylation           | Catecholamines, histamine                            |

(5) Reduction biotransformation reactions are less frequent than oxidation-type reactions. Enzymes are located in both microsomal and nonmicrosomal fractions. Examples: chloramphenicol and naloxone.

(6) Hydrolysis reactions occur with either ester (esterases) or amide linked chemicals (amidases).
(a) Esterases occur primarily in nonmicrosomal systems and are found in the plasma, liver, and other tissues. Examples of drugs hydrolyzed: acetylcholine, succinylcholine, and procaine.
(b) Amidases are nonmicrosomal enzymes found primarily in the liver. Examples of drugs hydrolyzed: acetazolamide, lidocaine, procainamide, sulfacetamide, and sulfadimethoxine.

b. Phase II biotransformation (conjugation) may occur to a phase I metabolite or to a parent drug/chemical. This involves the coupling of an endogenous chemical (glucuronic acid, acetate, glutathione, glycine, sulfate, or methyl group to the drug). Enzyme systems are present in the microsomes, cytosol, and in the mitochondria.
(1) Products of phase II biotransformation have greater water solubility and are more readily excreted via the kidney.
(2) Examples of drugs undergoing phase II biotransformation (Table 1-1).
(3) Species variation in phase II metabolism. There are considerable species defects in certain conjugation reactions:
(a) In the cat, glucuronide synthesis where the target is −OH, −COOH, −NH₂, =NH, −SH is only present at a low rate. Thus, cats often have longer plasma t₁/₂ for many drugs than other species.
(b) In the dog acetylation of aromatic-NH₂ groups is absent and this affects the metabolism of sulfonamides and other drugs.
(c) In the pig sulfate conjugation of aromatic-OH, aromatic-NH₂ groups are only present at a low extent.

(4) Enterohepatic recirculation
(a) Drugs biotransformed via the formation of a glucuronic acid metabolite may be eliminated via the bile.
(b) Glucuronide metabolites can be hydrolyzed by intestinal or bacterial β-glucuronidases, thereby releasing free drug, which can then be reabsorbed. This process can greatly increase a drug’s residence in the body. This is recognized for etorphine in horses and may give rise to relapse despite initial reversal with the antagonist diprenorphine.

(5) Biotransformation by GI microflora. In addition to the liver, metabolism of drugs can also take place in the rumen and GI tract by the microflora where hydrolytic activity and reductive activity may occur. Gut-active sulfonamides (phthalylsulfathiazole) require hydrolysis for the release of sulfathiazole for antimicrobial action. Cardiac glycosides are hydrolyzed in the rumen and become inactive, the chloramphenicol −NO₂ group is reduced and the drug is inactivated.
E. **Drug excretion** refers to the processes by which a drug/drug metabolite is eliminated from the body. The **kidney** is the primary organ for drug excretion.

1. **Renal excretion.** Primary mechanisms.
   a. **Glomerular filtration.** All drugs (D, Figure 1-3) not bound to plasma proteins are filtered.
   b. **Active tubular secretion.** In the **proximal** portion of the renal tubule active transport mechanisms exist for both **acidic** and **basic drugs**. Examples of drugs actively secreted into the tubule lumen are presented above. **Competiton** among the acidic drugs or basic drugs can be expected to occur for the secretion process (Table 1-2).
   c. **Passive tubular reabsorption.** The lipid nature of the cellular membrane lining the tubule dictates that only **lipophilic drugs will be reabsorbed**.
      - (1) Since most drugs are weak acids or bases the degree of ionized (water soluble, non-reabsorbable) or nonionized (lipid soluble, reabsorbable) form of the drug will vary with the pKₐ of the drug and the pH of the lumen urine.
      - (2) Urinary pH of carnivore animals is acidic (pH 5.5–7.0).
      - (3) Urinary pH range of herbivore animals is 7.0–8.0.
      - (4) Food will influence the urinary pH for both carnivores and herbivores.
      - (5) **Excretion** can be enhanced for drugs eliminated primarily by the kidney through altering the pH of the urine. For practical purposes this is limited to weak acidic or weak basic drugs with a pKₐ of 5–8.
      - (6) Quaternary drugs (R₄N⁺) are polar at all urine pH and can be expected to be eliminated rapidly, since they cannot be reabsorbed.

2. **Other routes of excretion**
   a. **Biliary secretion.** Both the parent drug and glucuronide form of the drug may be eliminated via the bile.
      - (1) **Glucuronide-drug** conjugates eliminated via the bile may be hydrolyzed by β-glucuronidases from gut bacteria. The free drug then may be reabsorbed giving rise to “enterohepatic recycling.”
      - (2) Transport processes exist in the liver for actively transporting acidic, basic, and neutral drugs into the bile. Since these drugs may eventually be reabsorbed from the gut lumen, biliary elimination processes tend to be less important than are renal excretion processes.

### TABLE 1-2. Examples of Drugs Actively Secreted

<table>
<thead>
<tr>
<th>Acid Drugs</th>
<th>Basic Drugs</th>
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<td>Penicillin</td>
<td>Histamine</td>
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<td>Ampicillin</td>
<td>Amiloride</td>
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<tr>
<td>Cephalosporins</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Thiazine duretics</td>
<td>Procainamide</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Neostigmine</td>
</tr>
<tr>
<td>Probenecid</td>
<td>Trimethoprim</td>
</tr>
<tr>
<td>Salicylate</td>
<td>Atropine</td>
</tr>
<tr>
<td>Ethacrynic acid</td>
<td></td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td></td>
</tr>
</tbody>
</table>
(3) **Role of P-glycoprotein in drug excretion.** P-glycoprotein is a transmembrane efflux pump that has a role in the “first-pass clearance” of some oral drugs. P-glycoprotein is also found in the biliary and renal tubular epithelia and thus plays a role in the “secretion” of some but not all drugs into the gut and renal tubules. As stated earlier, this protein is also found in the BBB and its effect there is to “expel” the drug from the CNS. Substrates of P-glycoprotein include azole antifungal agents, corticosteroids, cyclosporine, digoxin, diltiazem, doxorubicin, opioids, macrolide antibiotics, quinidine, and vincristine/vinblastine.

b. **Milk.** While this is not a major route for drug excretion for the dam, it is important since the drugs given to the dam appear in the milk and produce residues requiring a withdrawal period if the milk is to be used for human consumption. Antimicrobial drugs given to the dam appear in concentrations sufficient to treat mastitis. Milk is acidic relative to plasma. Therefore, weak organic bases will diffuse from the plasma into the milk where they will become more ionized, thereby preventing passage back to the plasma. This is an example of **ion trapping.** Drugs which are basic (tylosin, erythromycin, and lincomycin) can be expected to be found in milk in higher concentrations than in the plasma.

c. **Saliva.** This is not a major route for excretion but is important in herbivores receiving parenteral antimicrobial drugs. Drugs enter the saliva by passive diffusion from the blood. Copious salivation by cattle and sheep and the swallowing of antimicrobial-drug-laden saliva may upset the digestive process in the rumen.

d. **Expired air.** This route of elimination is primarily important for volatile drugs such as gas anesthetic drugs.

e. **Minor routes of excretion: tears and sweat.**

F. **Pharmacokinetics** is the mathematical description of drug concentrations in the body. Frequently in pharmacokinetics, the distribution of drugs is depicted as being in a compartment, that is, a one-compartment model or in a two- or three-compartment model. Since many drugs used in veterinary medicine can be described by a two-compartment open model this will be the only model described but the reader should refer to standard textbooks for information on other pharmacokinetic models.

1. **Two-compartment model** (Figure 1-4)
   
a. Mathematically, the log-concentration–time graph can be depicted as composed of two straight lines.
   (1) The line representing the distribution phase has an intercept “A” and a slope $-\alpha$.
   (2) The line representing the elimination phase has an intercept “B” and a slope $-\beta$; $\beta$ is used to calculate the elimination half-life, see below.

b. The theoretical plasma concentration at time zero ($C_p^0$) is: $C_p^0 = A + B$. Units are usually $\mu$g/mL or $\mu$g/L.

c. The apparent volume of distribution ($V_d$) is a proportionality constant relating the plasma drug concentration to the total amount of drug in the body.

$$V_d = \frac{\text{Dose}}{\left( \frac{A}{\alpha} + \frac{B}{\beta} \right) \beta}.$$

The apparent volume of distribution gives a measure of how well distributed the drug is within the body. A high volume of distribution like 1 L/kg for a drug implies that the drug is widely distributed throughout the body water.

d. **Half-life** ($t_{1/2}$) of a drug is the time needed for the drug concentration to be reduced by half. This value is determined during the elimination phase of the drug.

$$t_{1/2} = \frac{\ln 2}{\beta} = \frac{0.693}{\beta}.$$
FIGURE 1-4. (a) The plasma-concentration–time graph following IV injection of a drug exhibiting two-compartment pharmacokinetics. The distribution phase is represented by the line with intercept A and slope $-\alpha$. The elimination phase is represented by the line with intercept B and slope $-\beta$. (b) A model of a two-compartment open model. The central compartment represents rapid equilibration and represents fluids such as the blood, interstitial fluid, and highly perfused organs (e.g., the lungs). The peripheral compartment reaches equilibrium more slowly and represents organs such as bone and fat. $K_{12}$ and $k_{21}$ = the rate constants of distribution between the central and peripheral compartments. (From Figure 1-3, NVMS Pharmacology.)

(1) $t_{1/2}$ is usually limited by the processes of biotransformation and renal excretion; sometimes it is governed by slow release from tissue sites like bone or fat.

(2) Indicates the time required to attain 50% of the steady state or to lose 50% of the steady state concentration.

(3) Has limited value as an indicator of drug residues or distribution.

e. Total body clearance ($Cl_B$) is the volume of blood that is effectively cleared of a drug in a specified period of time.

\[
Cl_B = \beta \cdot V_d = \frac{0.693 \cdot V_d}{t_{1/2}}
\]

Clearance expresses the rate of drug removal from the body that is independent of $t_{1/2}$. Disease and infection may alter drug distribution and clearance, but not necessarily the $t_{1/2}$ value. Therefore, the volume of distribution and clearance can be altered and thus the $t_{1/2}$ will be altered. We can rewrite the equation as:

\[
t_{1/2} = \beta \cdot V_d = \frac{0.693 \cdot V_d}{Cl_B}
\]

f. Bioavailability ($F$) is a term that describes the fraction of drug entering the systemic circulation intact from the site of administration; it is the fraction absorbed or taken up.

By definition the bioavailability of an IV dose = 100% or 1. All other routes of administration will have a bioavailability of less than one. Knowledge of $F$
for oral dosage is particularly important. The presence of food may alter the bioavailability of some drugs.

\[ F = \frac{(AUC)_{nIV} \cdot \text{dose}_{IV} \cdot \beta_{nIV}}{(AUC)_{IV} \cdot \text{dose}_{nIV} \cdot \beta_{IV}}, \]

where AUC is the area under the plasma concentration curve; nIV is the non-intravenous route of administration; IV is the intravenous route of administration; and \( \beta \) is the slope of the elimination phase.

g. Determination of dosage

Knowledge of a drug’s bioavailability \( F \), clearance \( (Cl_B) \), and the average steady state concentration \( (C_{P\infty}) \) of a drug needed to produce the pharmacologic response permits dosage calculation.

\[ \frac{F \cdot \text{dose}}{\text{Dosing interval}} = C_{P\infty} \cdot Cl_B. \]

G. Species variation. Veterinarians must be aware of differences between species and also of differences that can occur among breeds.

1. Examples of species variation

a. It is recognized that xylazine (an \( \alpha_2 \)-adrenergic agonist) is a much more potent sedative in cattle than other species; the reason that ruminants are more sensitive to \( \alpha_2 \)-agonists such as xylazine is because the difference is at the pharmacodynamics level; ruminants have \( \alpha_{2D} \)-receptors and nonruminants have \( \alpha_{2A} \)-receptors.

b. It is recognized that morphine (a \( \mu \)-opoid agonist) is more potent in cats than dogs. In dogs, the dose is 1 mg/kg where it consistently produces sedation. In cats, the dose for analgesia is 0.1 mg/kg. Higher doses in cats may produce excitement. The excitement in cats appears to be mediated by central dopamine receptors and is inhibited by sedatives with dopamine antagonist actions like droperidol. The detailed explanation for this species difference between dogs and cats is not known.

c. Certain breeds of dog: Great Dane and Irish Setters are more sensitive to bloat following xylazine administration due to aerophagia.

d. Ivermectin can cause CNS depression in collies at normal doses due to a defect in the P-glycoprotein transporter which excludes ivermectin from the brain.

e. Ivermectin should not be used in tortoises or crocodiles because of potential toxic effects; it is possible that the BBB in these species against ivermectin maintained by the P-glycoprotein is not secure.

f. Succinlycholine, a depolarizing muscle relaxant, can be used in horses where it is broken down rapidly by the plasma esterases, but in ruminants where the esterase levels are much lower require only 0.02 mg/kg, but horses require 0.1 mg/kg.

g. Cats have a low level of glucuronyl transferase so that the \( t_{1/2} \) of many drugs that are conjugated to glucuronide by the liver is much longer. The classic example is aspirin where the \( t_{1/2} \) in cats is 25–35 hours compared to 8 hours in dogs and 1 hour in horses.

h. GI absorption will differ between nonherbivores animals and ruminant herbivores. The GI transit time in monogastrics animals means that oral suspensions are swept out of the intestine within 24 hours. The benzimidazoles are examples of drugs where the GI transit time in herbivores is longer than in nonherbivores. In most cases, benzimidazoles are administered once to herbivores, but to nonherbivores, in daily doses over a period of 3–5 days.

i. Most lipophilic organic bases, like ivermectin, lincosamide, tulathromycin, erythromycin, tylosin, ketamine, metronidazole, enrofloxacin, theophylline, and trimethoprim have larger volumes of distribution in ruminants than in monogastrics animals.
2. **Drug metabolism.** The differences in the rate of elimination for drugs that are metabolized by the liver usually accounts for most of the differences in the $t_{1/2}$ values between species. There is a wide variation in the $t_{1/2}$ of most drugs that are eliminated mainly by hepatic metabolism.

**a.** The general trend is that cattle and horses have shorter $t_{1/2}$ values than the dog and cats which often have longer $t_{1/2}$ values. Cattle and horses oxidize drugs more efficiently than dogs and cats.

**b.** Because pharmacokinetic parameters including $t_{1/2}$ values are more available for humans, it is important to appreciate that human values are usually longer than those of domestic animals (except cats), because the oxidation of drugs by liver P450 oxidative enzymes in domestic animals is usually faster than in humans.

**c.** The exceptions include the methylxanthines (e.g., theophylline) in horses and phenylbutazone in cattle, which have longer $t_{1/2}$ values in these animals than in humans.

**d.** There are also differences between more closely related species. Cefitofur, trimethoprim, and sulfamethazine have a shorter $t_{1/2}$ value in goats than sheep, while $t_{1/2}$ of phenylbutazone is shorter in donkeys than horses.

**e.** The $t_{1/2}$ of extensively metabolized drugs is shorter in mice, rats, rabbits, and guinea pigs (lab animals) than in domestic animals.

**f.** It is also important to be careful about comparing duration of action between different species of birds. There is significant variation between $t_{1/2}$ values of chickens, turkeys, and different wild birds which is again related to differences in metabolism.

**g.** Although there are different types of cholinesterase in the tissues and blood, the overall levels in ruminants are lower than in horses and humans. This means that sheep, goats, calves, and cattle, are more sensitive to organophosphorous compounds than horses and humans. Sheep have been suggested as possible “sentinel” animals for the detection of toxic anticholinesterase (organophosphate nerve gases) because of their sensitivity.

3. **Ionized drugs.** There is much less variation in the $t_{1/2}$ values between the species for drugs that are more ionized, and have a lower volume of distribution: renal excretion is the main route of elimination. For example, the $t_{1/2}$ of gentamicin for cats is 82 minutes, for dogs it is very similar, 75 minutes. Penicillins and cephalosporins also have short $t_{1/2}$ values of 30–90 minutes in different species. Thus, highly “ionized drugs” are less likely to show species variation.

4. **Cold-blooded animals.** Fish and reptiles have longer $t_{1/2}$ values compared to mammalian species due to the much lower metabolic rates. However, the temperature of the ambient environment affects the metabolic rate of the animals and this, in turn, affects the $t_{1/2}$ values of the drug. The $t_{1/2}$ value of trimethoprim given IV to carp is 41 hours at $10\degree C$ but 20 hours at $24\degree C$. Fish also have a lower renal function and more enterohepatic recycling than warm-blooded animals.

5. **Distribution and species variation.** Distribution does vary with species, but less so than $t_{1/2}$ values. There is a significant difference between nonruminant and ruminants in the distribution of lipid-soluble organic base drugs. The rumen has a pH of 5.5–6.5 and is a large volume relative to the whole body water; because of the large capacity of the rumen, which is up to 25 liters in sheep and up to 220 liters in cattle, the phenomenon of “ion-trapping” leads to the accumulation of weak bases in the rumen fluids. This means that xylazine, furosemide, and phenylbutazone have larger volumes of distribution in ruminants so that these compounds have a greater clearance in ruminants than nonruminants.

**H. Effect of disease states on pharmacokinetic parameters.** We have seen above that the distribution of drugs ($V_d$) and $t_{1/2}$ values are key factors that affect access, concentration, and duration of action of drugs. These parameters are usually determined in healthy animals. However, veterinarians need to treat sick animals with these drugs, so how do the pharmacokinetics change in diseased animals?

1. **Effects of fever.** Endotoxin-induced fever can increase the extravascular distribution of ionized drugs like penicillins, cephalosporins, and aminoglycosides,
although without much effect on $t_{1/2}$ values and renal clearance. Bacterial infections induced experimentally in pigs can increase the volume of distribution of penicillin G, ampicillin, and decrease that of oxytetracycline. The volume of distribution of the penicillins probably increases because the permeability of the inflamed tissue barriers to penicillins increases. The distribution of oxytetracycline may decrease because of binding to inflammatory exudates.

2. Liver disease. Drugs whose $t_{1/2}$ values are determined by liver metabolism, that is, lipophilic drugs in general, and which undergo conjugation to convert them to more polar drugs can be affected by liver disease. Liver microsomal activity can be reduced in the presence of moderate or severe liver damage and so the effect and duration of drugs metabolized by the liver can be increased.

3. Kidney disease. The rates of elimination of drugs that are eliminated mostly via the kidney are decreased with renal disease. Renal blood flow affects all three renal excretion mechanisms of glomerular filtration, carrier-mediated secretion, and pH-dependent passive reabsorption.

I. Effect of stereoisomers. Many of the drugs that are used for therapeutic purposes have a chiral carbon so that a number of stereoisomers are possible; they are produced during the chemical synthesis of the compounds. Many of the commonly used therapeutic drugs are produced as a mixture of racemates. Because of the stereoselective nature of drug receptors, the mixture of racemates will contain the active moiety and the isomeric ballast (reduced activity racemates).

1. Tetramisole was originally produced by Jansen Pharmaceutical and subsequently the l-isomer, levamisole, was produced as the active compound and the d-isomer, dexamisole, found to be less active but contributed to toxicity of the racemic mixture.

2. Medetomidine is a racemate mixture, whereas dexmedetomidine, the d-isomer, has much more potent $\alpha_2$-agonistic activity than the l-isomer of medetomidine.

3. The metabolism of the stereoisomers may also be selective, favoring one isomer over others. The more potent isomer is referred to as the eutomer and the less potent enantiomer as the distomer. The stereoselective processes involved in the pharmacokinetic processes can be species-dependent and so concentration–time plots may vary between enantiomers and between the different species of animal.

III. PHARMACODYNAMICS: MECHANISMS OF DRUG–RECEPTOR INTERACTIONS

A. Drugs and drug receptors

1. Many drug receptors are protein macromolecules present in cell membranes, which when activated initiate a biochemical change within the cell/tissue that in turn produces a pharmacologic response.
   a. Receptors bind ligands (drugs) and transduce signals (a process referred to as signal transduction)
   b. Drug binding to receptors uses similar chemical bonds as that used for enzyme–substrate interaction: hydrogen bonds coordinate covalent bonding and Vander Waals forces. Examples of covalent bonding involved in drug–receptor interactions are few in number.
   c. Drugs have two identifiable properties: affinity for the receptor and intrinsic activity.
      (1) Intrinsic activity is the property of the drug that permits it to initiate post-receptor processes, which lead to a response.
      (a) Agonists are drugs that have both affinity and intrinsic activity. Examples: epinephrine, acetylcholine, angiotensin, and prostaglandin $F_{2\alpha}$.
         i. Full agonists versus partial agonists. A full agonist is a drug that appears able to produce the full cell/tissue response. A partial agonist is a drug that provokes a response, but the maximum response is less than the maximum response to a full agonist; this is because a partial
FIGURE 1-5. Ligands may be classified as agonists (full, partial, and inverse) and antagonists. Both full and partial agonists stabilize the active state (R*) and thus increase receptor signaling, whereas inverse agonists stabilize the inactive state and thus decrease basal receptor signaling. Antagonists, which have equal affinity for both R* and R and thus do not affect the equilibrium between the two states, but will reduce the ability of full, partial, and inverse agonists to bind to the receptor. (Modified from Leurs R. et al., Clin. Exp. Allergy, 32:4989–498, 2002.)

agonist has much higher affinity for the receptor, but less intrinsic activity than a full agonist. Concurrent administration of a partial agonist can reduce/antagonize the effect of a full agonist (Figure 1-5).

ii. Inverse agonists. In the context of receptors which exert constitutive signaling activity, even in the absence of an agonist, inverse agonists are drugs that bind to the receptor, suppressing the constitutive signaling activity. Recent evidence suggests that propranolol and antihistamines are inverse agonists (Figures 1-5 and 1-6).

(b) Receptor antagonists are drugs which have an affinity for the receptor site but which lack intrinsic activity. Antagonists block or reduce the effects of agonists (Figure 1-5).

Examples:

\[
\begin{array}{ll}
\text{Antagonists} & \text{Agonists} \\
atropine (M_1–M_5) & \text{cholinergic agonists} \\
yohimbine (\alpha_2) & \text{\(\alpha_2\)-adrenergic agonists} \\
phenoxybenzamine (\alpha_1) & \text{epinephrine} \\
diphenhydramine (H_1) & \text{histamine} \\
cimetidine (H_2) & \text{histamine} \\
naloxone & \text{opioids} \\
naltrexone & \text{carfentanil} \\
flumazenil & \text{benzodiazepines} \\
spiroloactone & \text{aldosterone}
\end{array}
\]

i. Antagonists may act in a competitive (these are reversible on removal, washout) manner. Example: phentolamine-norepinephrine.

ii. Noncompetitive (these may be reversible or irreversible on removal, washout) manner. The noncompetitive antagonism may be due to the antagonist binding to separate site to the agonist or due to covalent bonding. Examples: phenoxybenzamine blockade of \(\alpha_1\)-adrenergic receptors are irreversible due to covalent bonding with the receptor protein; picrotoxin antagonism of GABA receptors is reversible but noncompetitive because picrotoxin blocks the open Cl\(^-\) channel pore not the GABA binding site.

2. Antagonism

a. Antagonism is the interaction between two drugs such that the response of one drug (the agonist) is reduced in the presence of the second drug (the antagonist).
There are three types of antagonism in pharmacology: receptor, physiologic, and chemical.

1. **Receptor antagonism** occurs on the same receptor protein such that two drugs, an agonist and an antagonist, compete and bind to the same receptor protein. See above for examples.

2. **Physiologic antagonism** occurs as the result of activating receptors with opposite physiological effects.

   **Examples:**
   
   - acetylcholine $\rightarrow$ ↓ heart rate
   - epinephrine $\rightarrow$ ↑ heart rate
   - histamine $\rightarrow$ bronchoconstriction
   - epinephrine $\rightarrow$ bronchodilation
   - histamine $\rightarrow$ ↓ blood pressure
   - epinephrine $\rightarrow$ ↑ blood pressure

3. **Chemical antagonism** occurs as the result of a drug combining with two or more molecules via the formation of chemical bonds. This type of antagonism often does not require animal tissue to be demonstrated, and has been used to treat heavy metal intoxication.

   **Examples:**
   
<table>
<thead>
<tr>
<th>Drug</th>
<th>Metal chelated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimercaprol (BAL)</td>
<td>Hg, As</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>Cu, Pb, Hg</td>
</tr>
</tbody>
</table>
3. **Signal transduction.** Four general types of receptor mechanism can be described (Figure 1-7):

   a. **Ligand-gated ion channels** (Type 1 receptor mechanisms) regulate the flow of ions through the cellular plasma membrane channels.

      (1) Response time is very rapid, for example, milliseconds, once the drug/ligand binds to the receptor.

      (2) Examples of synaptic transmitters which act via ion channels: acetylcholine (at nicotinic receptors), gamma-aminobutyric acid (GABA<sub>A</sub> receptors), glycine, and glutamate (ionotropic receptors).

   b. **GTP-binding proteins (G proteins, Type 2)** couple the binding of the ligand on the cell surface receptor to intracellular second messengers. These receptors are 7-transmembrane (serpentine) receptors, which cross the plasma membrane seven times. More than 80% of receptors in animals are G protein-coupled receptors (Figure 1-8).

      (1) Agonists (acetylcholine—on muscarinic receptor, catecholamines—on α- and β-adrenergic receptors, and many others) acting on receptors cause the displacement of guanosine diphosphate (GDP) from the G protein and its replacement by guanosine triphosphate (GTP).

      (2) The G protein–GTP complex in turn regulates the activity of enzymes (e.g., adenylyl cyclase, phospholipase C-β) or ion channels (e.g., Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup>).

---

**FIGURE 1-7.** General structure of four receptor families.