Advanced Veterinary Pharmacology : Pharmacology and Veterinary Technicians

Lesson 1 Overview

Veterinary technicians enhance the veterinary field's ability to deliver healthcare to animals and protect public health. Part of this effort relies on the ability to apply appropriate and safe drug therapy. Therefore, they must understand the basis of drug action and how animals can respond to treatment. To do this, they need to have a working knowledge of pharmacology and how to apply it to the practice setting. This lesson covers the main areas of pharmacology knowledge (pharmacokinetics and pharmacodynamics), safe drug handling, dispensing, and administration.

Course Version: 1

1.3 Explain the principles of pharmacokinetics and pharmacodynamics

Pharmacokinetics and Pharmacodynamics

READING ASSIGNMENT

Read this assignment. Then, read Chapter 3 of your *Clinical Pharmacology and Therapeutics for Veterinary Technicians* textbook.

Pharmacokinetics is the study of the action of the body on drugs (how the drugs move through and out of the body), while *pharmacodynamics* is the action of drugs on the body. A solid understanding of these concepts will help the veterinary technician understand how dose, route of administration, and other drug administration factors are linked to how drugs work in the body. These principles are discussed in more detail later in this section after first addressing therapeutic concepts and mechanisms of drug movement.

Therapeutic Drug Concentration

For a drug to have a beneficial effect on an animal, it must reach a *therapeutic concentration*. This optimal concentration is derived from laboratory and clinical studies performed by the drug manufacturer. The therapeutic range, or window, describes this concentration and is lower than the levels that will cause toxicity. The highest drug concentration that provides beneficial effects without causing toxicity is the *maximum effective concentration*. The *minimum effective concentration* is the lowest concentration that will have beneficial effects.

Although therapeutic concentrations have been identified and associated with recommended dosing ranges, individual animals can and often do respond differently from others. Some may experience adverse effects with blood drug concentrations well within the proposed therapeutic range. Or, these concentrations may not be reached adequately despite receiving the recommended doses. Still others don't respond optimally when given the recommended doses.

Maintenance of therapeutic drug concentrations depends on an equilibrium between the amount of drug entering and exiting the body. There are several factors that affect this. Any modifications to any of those factors can disrupt the equilibrium and change how the drug behaves in the body.

When the maximum and minimum effective doses are close to each other, the drug is considered to have a *narrow therapeutic range.* A drug with a narrow therapeutic range has a minimum dose that isn't significantly less than the dose that can cause toxicity. These types of drugs have a higher potential for adverse effects, particularly in animals with conditions that affect the drug's excretion. Drug routes of administration influence the blood levels reached.

Dosing Regimen

To establish initial drug concentrations, some drugs are dosed at a higher *loading dose* or *bolus dose*. This allows a rapid achievement of therapeutic concentrations.

After that, only a smaller *maintenance dose* is needed. This is the dose to keep blood concentrations within the therapeutic range.

The total amount of drug per day associated with a drug regimen is called the *total daily dose.* The amount of drug per dose and frequency of dosing establishes the total daily dose. Many drugs are formulated to be time-released; this helps with client compliance because they require less frequent drug administration while maintaining therapeutic concentrations. If a drug must be given four or more times per day, a missed dose can significantly affect blood concentration levels.

There are various routes of parenteral administration, including intravenous (IV), intramuscular (IM), and subcutaneous (SC). Some drugs, such as vincristine, must be given IV because they're very damaging to the tissue if given by any other parenteral route. Administering this type of drug must be done with much skill to avoid accidental extravascular or perivascular administration that could cause damage to the tissues. Drugs that are very toxic to tissues could lead to damage such as *necrosis* (death of tissue) and skin sloughing.

The primary nonparenteral route is the oral route of administration. Others are rectal, aerosol (inhaled), and topical application. Giving drugs with these routes provide less than the 100 percent bioavailability seen with the IV route. *Bioavailability* refers to the percentage of the drug that will get to the site of action.

Read more about the various routes of drug administration. (www.msdvetmanual.com/pharmacology/pharmacology-introduction/routes-of-administration-and-dosage-forms)

Mechanism of Drug Movement

There are four primary mechanisms in the body to move drugs between different compartments and cells.

Passive Diffusion or Transport

Passive diffusion or *transport* is the most common means by which drugs move across bodily tissues, fluids, and cells. With this mechanism, drugs move from an environment of high concentration to lower concentration. This concentration difference is referred to as a *concentration gradient.* Since no active transport mechanism requiring the expenditure of energy is involved, it's called a *passive* process.

The passage of molecules through a cell membrane depends on their interaction with the molecules that make up the cell membrane. Generally, the outside of a cell has molecules associated with it that are water-soluble, or *hydrophilic.* The inner membrane consists of fatty molecules or lipids and is therefore *lipophilic.* Therefore, drugs that can enter cells via passive diffusion are lipophilic.

Facilitated Diffusion

Facilitated diffusion is still a passive transport mechanism because it doesn't require expending energy. It's called *facilitated* because a specialized protein molecule in the cell membrane helps to allow entry of the molecule into the cell. When a molecule attaches to the protein in the membrane, the protein changes shape and enters through the pore of the protein structure. The pore or "door" closes again once the drug molecule passes through.

Active Transport

With the *active transport* mechanism, energy is spent to transport a molecule. It's the least common of the drug movement mechanisms. Molecules move in one direction only, unlike in passive and facilitated diffusion. Also, molecules can be moved against a concentration gradient and don't stop when there's an equilibrium between both sides of the membrane. For drugs moved by active transport, toxicity can occur more easily because of the potential of reaching high drug concentrations in the cells or tissue.

Rate of Drug Transport

The rate of drug transport across a cell membrane can be affected if carrier molecules are occupied or saturated. At this point, the *transportation maximum (t-max)* has been reached. A sort of a bottleneck in transport occurs, causing slower distribution and action in the body.

Although passive diffusion does not involve carrier molecules, the rate of drug molecule movement can still be affected by a number of factors:

- A difference in the concentration gradient across the cell membrane
- Drug's molecular size
- Level of drug lipophilicity
- Temperature (the lower the temperature, the slower the movement)
- Membrane thickness

Pharmacokinetics

Drug Absorption

For a drug to have an effect, it must be transported to the site of action. It then must be eliminated from the body to avoid toxicity. The process of drug movement through the body involves *absorption, distribution, metabolism, and excretion (ADME).* The drug is first absorbed into the body. In the case of IV administration, this is an extremely rapid process. As mentioned previously, bioavailability is the percentage of the drug that will actually get to the site of action. For drugs given by routes other than IV, the bioavailability is less than 100 percent.

Drugs entering through the gastrointestinal tract (such as oral drugs) enter the body through the *enteral route*. The amount of drug available after entering through this route can be decreased by the *first-pass effect.* This refers to the breakdown of some of the drug in the intestinal tract or liver.

Parenteral drugs enter through other routes, such as intravenous, intramuscular, or subcutaneous injections. These routes provide higher amounts of drug to the

site of action, and more rapidly, than the enteral route. Factors such as the lipophilic or hydrophilic nature of the drug and the pH of the environment (blood, tissue fluids) affect drug absorption. The pH is a measure of the number of protons in a solution. An acid drug releases protons in an alkaline (lower pH) environment and becomes ionized.

In an acidic environment, an acid drug will take up more hydrogen ions and become more lipophilic. Base drugs take up hydrogen ions in an acidic environment and release them in an alkaline environment. They become more ionized by taking up hydrogen ions and become more nonionized (lipophilic) when releasing them, the opposite situation to acid drugs. These factors affect the movement of the drugs through cell membranes.

pKa

The *pKa* is the acid-base dissociation constant of a drug. It's the pH at which there are equal numbers of nonionized and ionized forms of the drug. When the pKa of a drug is known, along with whether it's acid or base, calculation of the ratio of nonionized and ionized forms of the drug molecules is possible. This information indicates how a given drug will diffuse across membranes and be absorbed.

Ion Trapping

The ratio of nonionized and ionized forms of a drug changes as it moves through different bodily compartments with different pH. If a nonionized or ionized form of a drug moves to a compartment with markedly different pH, it will shift to the opposite form and get "trapped" in the compartment—unable to move out via the cell membrane. As some of the unchanged forms move out, gradual changes in ratio of the drug forms allow the eventual movement out of the compartment. This concept of ion trapping is exploited to remove drugs or toxicants from the body via the kidneys. However, side effects can be caused by this effect as well.

Active Transport Pumps

An example of an active transport pump is P-glycoprotein, which exists in the epithelium of the gastrointestinal tract (GI) wall. This pump prevents certain molecules from entering the systemic circulation and is a mechanism to prevent toxic drugs coming into circulation.

GI Tract Mobility and Drug Dissolution

Solid orally administered drugs are broken into smaller particles (dissolution) to enhance absorption. Gastric and intestinal mobility (peristaltic, wave-like contractions) further facilitate drug movement and absorption. After this phase, the oral drugs are subjected to the first-pass effect. Blood from the GI tract passes to the liver. Here, the liver removes toxins from the blood. A portion of drug doses is subject to this process, lowering the amount of drug available to the systemic circulation and to reach the site of action. Drugs with a substantial first-pass effect are not given orally.

In the case of parenteral injection of drugs (other than IV injections), the degree of tissue perfusion by blood vessels influences the rate of absorption. The better the tissue perfusion, the more rapid and thorough the absorption. Blood flow reduced by vasoconstriction lowers absorption, while vasodilation improves blood flow and thus absorption. This also applies to the distribution of drugs throughout the body.

Distribution and Metabolism

Distribution is the process by which the bloodstream transports drugs throughout the body. Certain tissue factors can hinder drug absorption, such as the *blood-brain barrier*. This barrier limits access of certain drugs to the brain tissue.

As mentioned, liver enzymes can metabolize drugs and lower the amount of active drug that reaches the site of action. Blood proteins such as albumin can bind certain drugs. Since proteins of this class are too large to pass through capillary pores, the bound drug will remain in the circulation instead of being distributed. However, some drugs are changed to their bioactive form within the liver.

The extent to which a drug is distributed throughout the body is the *volume of distribution* and is expressed in liters. The higher the volume of distribution, the more tissues contain the drug. Higher than normal volumes of distribution require changes in dose to ensure that drugs reach therapeutic concentrations.

Excretion or Elimination

Excretion or elimination is the final stage in the pharmacokinetic process. The kidneys, liver, lungs, and intestinal tract are the primary organs of drug elimination. Care must be taken to adjust dose levels (or avoid a drug altogether) in patients with kidney and liver impairment. This is necessary to prevent toxicity in these patients because of the buildup of toxic metabolites. Another important concept regarding elimination is the *half-life.* This is the time it takes for half of the drug to be eliminated from the body. For drugs excreted by the kidneys, this value increases, leading to a longer time for the drug to be eliminated from the body.

In food animals, the *withdrawal time* of drugs must be understood to prevent prohibited drug residues in animal-derived food products. The withdrawal time is the time that must pass from the last dosing to the day of market or slaughter. These values (measured normally in days) are based on the elimination half-life.

Pharmacodynamics

Pharmacodynamics is the study of the mechanism by which a drug produces its effects. Drugs interact with specific targets at the sites of action to produce their effects. Many drugs bind to specialized protein receptors located on or inside cells. Once a drug molecule binds to a receptor, it will cause a change in the *conformation* (shape) of the receptor. This then provokes a chain of molecular events in the cell to mediate the drug's effects.

The concept of the lock and key model for drug-receptor interaction is a classic mechanism of drug actions. The substance or drug (key) that binds or inserts into the receptor (lock) is called a *ligand*. A receptor *agonist* mimics an endogenous

substance that normally interacts with the receptor. The degree of binding, or how tight the drug binds to the receptor, indicates how strong the agonist action will be. If a drug-ligand blocks the normal action of the receptor, it's a *receptor antagonist*. This is like putting in the wrong key that fits but doesn't open the door.

Receptor agonists and antagonists are further broken down as follows:

- ***Endogenous agonist.*** Natural bodily molecule that binds to and activates its receptor
- ***Full agonist.*** Binds and activates the receptor with a potency equal to that of the natural ligand
- ***Superagonist.*** Binds to the receptor but produces a more potent action than that of the endogenous ligand
- ***Partial agonist.*** Causes effects with a lower potency than that of the natural ligand (and may be seen as a partial antagonist)
- ***Inverse agonist.*** Both inhibits the function of the natural ligand and causes an effect opposite to that produced by the natural ligand
- ***Competitive antagonists.*** Bind to the same site on the receptor as the endogenous ligand without causing an action
- ***Noncompetitive.*** Bind to the active site or another site on the receptor (*allosteric site*, and therefore would be an *allosteric antagonist*). The binding of this type of antagonist decreases the level of maximum response normally possible with the agonist.

There are many drugs that produce nonreceptor-mediated effects. Examples are the diuretic mannitol, the chelator EDTA, and magnesium sulfate (osmotic activity as a laxative). These and other nonreceptor-mediated drugs act physically, chemically (antacids), through inhibition of certain enzymes (nonsteroidal anti-inflammatory drugs), and by affecting bacterial metabolism and reproduction (antibiotics).

Homework Assignment

After reading this chapter, complete the self-assessment questions at the end of the chapter. You can check your answers with the answers provided in the back of your textbook. Don't submit your answers to the school. This is for your benefit and will help ensure you understand the material.

Lab: Pharmcokinetics and Pharmacodynamics

Complete the following lab by listening to and reading the information provided, then choose the best answer to fit each question.

Lab: Pharmcokinetics and Pharmacodynamics (lessons.pennfoster.edu/savi/INA0006/story.html)

Key Points and Links

READING ASSIGNMENT

Key Points

- Pharmacokinetics is the study of the action of the body on drugs (how the drugs move through and out of the body).
- Pharmacodynamics is the action of drugs on the body.

Links

- Routes of administration and dosage forms (www.msdvetmanual.com/pharmacology/pharmacology-introduction/routes-of-administration-and-dosage-forms)

Pharmcokinetics and Pharmacodynamics

1. A drug changes the conformation (shape) of a receptor. The study of this phenomenon is called _____.
2. What type of drug movement is characterized by movement across a concentration gradient?
3. Which of the following is a term that describes the pH at which there are equal numbers of the nonionized and ionized form of a drug?

a. Thermodynamic constant
b. [H+]
c. Kinetic binding rate
d. pKa

4. What is the anatomical structure that limits passage of drugs to the central nervous system?

Discover More Answer Key:
Pharmcokinetics and Pharmacodynamics

1. pharmacodynamics
2. Passive diffusion
3. d
4. Blood-brain barrier

Lesson 1 Review

Self-Check

1. Which of the following is one of the four basic rules for safe drug usage?
a. All drugs are poisonous.
b. Some drugs are silver bullets.
c. All doses are perfect amounts based on patient need.
d. All drugs heal.

2. Which of the following is a trade name for amoxicillin?
a. Atroban
b. Biomox
c. Defend
d. Ketaset

3. _____ is an example of a nonproprietary name of a drug.

a. Permethirin insecticide

b. Atroban

c. Defend

d. Flysect

4. _____ are often cloudy, opaque liquids in which the drug is "hanging" in the liquid medium.

a. Suspensions

b. Solutions

c. Syrups

d. Elixirs

5. The _____ is the complete information needed to determine the mass of drug to be given to the animal, the route by which the drug is to be given, and how often it’s to be administered.

a. dose interval

b. dosage form

c. dosage regimen

d. dosage range

6. According to the National Coordinating Council for Medication Error and Reporting, which of the following is a useful rule to avoid writing confusing drug orders or dosing information?

a. Avoid the use of trailing zeros after the decimal point.

b. Never put a zero in front of any decimal number less than zero.

c. Abbreviate "grains" instead of writing out the full word.

d. Recognize that "s.i.d" is universally used outside of the veterinary profession.

7. PRN is the abbreviation for

a. as needed.

b. by mouth.

c. both eyes.

d. once a day.

8. 1 grain is equal to _____ mg.

a. 64.8

b. 30

c. 21.5

d. 84.5

9. A $70 bottle of 200 tablets calculates to _____ per tablet.

a. $0.35

b. $0.70

c. $2.85

d. $0.5

10. Which of the following is the layer of skin directly above the subcutis (SQ)?

a. Dermis

b. Epidermis

c. Muscle

d. Intradermal

11. _____ injections use very small needles to place the drug into, but not below, the narrow layers of the skin.

a. Intramuscular

b. Intraperitoneal

c. Intradermal

d. Intra-arterial

12. Which of the following actually means "cell drinking"?

a. Phagocytosis

b. Endocytosis

c. Pinocytosis

d. Intracytosis

13. _____ indicates that a molecule contains positive and negative charges at its ends.

a. Polarized

b. Ionized

c. Neutral

d. Nonpolarized

14. A/An _____ drug is defined as a drug whose chemical structure causes it to release a hydrogen ion into its liquid environment as the drug is placed into increasingly alkaline environments.

a. basic
b. acid
c. polarized
d. alkaline

Self-Check Answer Key

1. All drugs are poisonous.
   Explanation: There are four basic rules to keep in mind to ensure the safe use of drugs: 1. All drugs are poisonous; 2. No drug is a silver bullet; 3. All doses are guesses; 4. Complacency kills
   Reference: Section 1.1

2. Biomox
   Explanation: Biomox is a trade name for amoxicillin.
   Reference: Section 1.1

3. Permethirin insecticide
   Explanation: Permethirin insecticide is the nonproprietary name for Atroban, Defend, and Flysect.
   Reference: Section 1.1

4. Suspensions
   Explanation: Suspensions are often cloudy, opaque liquids in which the drug is "hanging" in the liquid medium.
   Reference: Section 1.1

5. dosage regimen

Explanation: The dosage regimen is the complete information needed to determine the mass of drug to be given to the animal, the route by which the drug is to be given, and how often it's to be administered.
Reference: Section 1.2

6. Avoid the use of trailing zeros after the decimal point.
   Explanation: Avoid the use of trailing zeros after the decimal point. If the decimal point is overlooked, the number could be interpreted to be much higher.
   Reference: Section 1.2

7. as needed.
   Explanation: PRN is the abbreviation for "as needed."
   Reference: Section 1.2

8. 64.8
   Explanation: 1 grain (gr) = 64.8 milligrams (mg)
   Reference: Section 1.2

9. $0.35
   Explanation: A $70 bottle of 200 tablets calculates to $0.35 per tablet. $70 ÷ 200 tablets = $0.35 per tablet
   Reference: Section 1.2

10. Dermis
    Explanation: The dermis is the layer of skin directly above the subcutis (SQ).
    Reference: Section 1.3

11. Intradermal
    Explanation: Intradermal injections use very small needles to place the drug into, but not below, the narrow layers of the skin.

Reference: Section 1.3

12. Pinocytosis
    Explanation: Pinocytosis actually means "cell drinking."
    Reference: Section 1.3

13. Polarized
    Explanation: Polarized indicates that a molecule contains positive and negative charges at its ends.
    Reference: Section 1.3

14. acid
    Explanation: An acid drug is defined as a drug whose chemical structure causes it to release a hydrogen ion into its liquid environment as the drug is placed into increasingly alkaline environments.
    Reference: Section 1.3

Flash Cards

1. Term: Chemical Name
Definition: Describes the structure of a drug

2. Term: Legend Drug
Definition: Drug that requires a prescription

3. Term: Paste
Definition: A semisolid drug form that remains solid at body temperature

4. Term: Schedule V
Definition: Controlled drug schedule that has the least potential for abuse

5. Term: Dosage

Definition: The amount of drug given per unit weight of an animal

6. Term: Total Daily Dose

Definition: The total amount of drug per day associated with a drug regimen

7. Term: Active Transport System

Definition: Movement of drugs in the body that requires energy

8. Term: Competitive Antagonist

Definition: An interaction where the drug binds to the same receptor site as the natural ligand but doesn't activate the receptor