Veterinary Bioscience: Metabolism

WEEK 4 – DRUGS, TOXINS AND TUMOURS

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INTENDED LEARNING OUTCOMES

At the end of these two lectures, you should be able to:

- describe the major components of pharmacokinetics – administration, absorption, distribution and elimination
- describe the difference between local and systemic routes of administration, and the advantages and disadvantages of each
- describe the means by which drugs undergo absorption, allowing them to enter the systemic administration, in particular the role of lipid diffusion in crossing cell membranes
- describe the concept of first pass hepatic metabolism, and how, along with extent of absorption, it influences the bioavailability of drugs administered orally
- describe the concept of volume of distribution, and how it can be used to quantitate the distribution of a drug, and assist in the calculation of dose
- describe how the elimination of drugs is dependent on metabolism and excretion, and how these two processes work in concert to result in elimination
- describe the three processes in the kidney – glomerular filtration, tubular secretion and tubular reabsorption – that lead to drug excretion from this organ
- describe how changing the pH of urine can lead to changes in the excretion of both endogenous compounds and drugs
- describe how compounds can compete for tubular secretion, and thus how one compound can mask the appearance of another compound in the urine
- describe the two phases of drug metabolism reaction that occur largely in the liver.

KEYWORDS

absorption, administration, bioavailability, elimination, excretion, first pass hepatic metabolism, glomerular filtration, metabolism, pharmacokinetics, phase 1 and phase 2 metabolism, tubular reabsorption, tubular secretion, volume of distribution

LECTURES 12 AND 13 – INTRODUCTION TO PHARMACOKINETICS 1 AND 2

In previous lectures, you have come across a variety of drugs. If these agents are to be used appropriately in the clinic, it is necessary for them to get to their site of action. How do you know how to do this? By what means should you administer a drug? What dose should you give of a drug? How often should you give it? Pharmacokinetics, the science of how drugs get into and out of the body, provides the basis for the answers to these questions, and thus for the effective use of drugs in the clinic.

ADMINISTRATION

The first question to be dealt with is whether a drug is to have a local or a systemic action. With local administration, drugs act somewhere at or near the site where they are administered. Local routes of administration include the skin (e.g. for anti- inflammatory agents), the lungs (e.g. for bronchodilator drugs) and the eye (e.g. for antibiotic drugs). The advantage of local administration is that it can be used as a means to reduce side effects, as a locally administered drug will have limited access to tissues. In contrast, with systemic administration, the drug enters the blood circulation, and will gain access to many tissues, as determined by the extent to which the drug distributes. The most common route of systemic administration is oral administration, largely because it is the most convenient (although is has issues, discussed below). Other routes of systemic administration include the skin (e.g. for nicotine patches), the lungs (e.g. for gaseous anaesthetic drugs). The injectable routes of administration (e.g. subcutaneous, intramuscular) form a special group, requiring penetration of the skin. Of this group, intravenous administration is special, in that it does not require absorption for the drug to enter the systemic circulation.

BIOVAILABILITY AND FIRST PASS HEPATIC METABOLISM

Bioavailability is a measure of the proportion of active drug that enters the systemic circulation. It is important to know, as it determines how much of a drug will actually be experienced by a patient. Bioavailability is determined by the extent of absorption of a drug, and the extent of metabolism of a drug prior to it reaching the systemic circulation. Thus a drug administered intravenously will show 100% bioavailability. Other routes may show 100% or less. For drugs administered orally, first pass hepatic metabolism can play a major role in determining bioavailability. Drugs administered orally are absorbed from the small intestine and enter the hepatic portal vein – which leads directly to the liver – prior to them entering the systemic circulation. If the drug undergoes significant metabolism in this first pass through the liver, and the metabolism renders the drug inactive, then the amount of active drug that comes out the other side (and is thus able to enter the systemic circulation) may be reduced. When bioavailability is low and/or variable, then generally one needs to choose an alternative route to administer the drug.

ABSORPTION

Absorption of drugs generally requires them to cross a series of cell membranes, which present themselves as a succession of lipid barriers. The main mechanism by which drugs do this is via a process of lipid diffusion, which requires that the drug is partially soluble in lipid. Many drugs are weak acids or weak bases. As a result, they will exist in equilibrium in solution between ionised (charged) species and unionised (uncharged species). The position of the equilibrium will depend on the pH of the solution. As the unionised form of a drug will generally be more lipid soluble than the ionised species, the unionised species will be better able to cross cell membranes. Thus, pH (for example in the gastrointestinal tract) can affect the ability of compounds to undergo absorption. The same phenomenon affects the ability of drugs to undergo tubular reabsorption in the kidney.

DISTRIBUTION

Once a drug enters the systemic circulation, it begins to spread around the body, in the process known as distribution. Distribution is faster process than elimination, meaning that drugs reach a so-called distribution equilibrium. Distribution can be split into series of steps: dilution in the blood, movement into extracellular fluid, binding to/uptake into cells. As most blood vessels are leaky, most drugs are able to escape the vasculature and enter the extracellular fluid compartment. The binding of a drug to plasma protein tends to retard this. Movement into cells requires the drug to cross cell membranes, again typically via lipid diffusion. The volume of distribution (Vd) is an apparent volume used to quantitate the distribution of a drug. It is defined as the ratio of the amount of drug in the body (X) at a given time to the concentration of drug in the blood (C). Vd is small for drugs that do not distribute widely, such as those drugs that bind to plasma proteins, and is larger for drugs that distribute more widely. Vd occasionally corresponds to a physiological volume, such as plasma volume or total body water. Curiously, drugs that bind extensively to tissues, particularly to muscle or fat, can show volumes of distribution orders of magnitude greater than total body water. As far as clinical use of drugs is concerned, Vd is used to determine the amount of drug you need in order to get a particular concentration of drug in the plasma, i.e. it is used to determine the dose of drug.

METABOLISM

Metabolism is defined as making a chemical change to a drug, typically as a result of an enzyme catalysed reaction. While most tissues in the body can carry out drug metabolism reactions, the liver has the greatest concentration of drug metabolism reactions, and is thus considered to be the major site of drug metabolism. Drug metabolism reactions can have a variety of consequences on the pharmacological activity of a drug: they can render a compound inactive, they can have little or no effect, they can make an inactive compound active, or they can make a compound toxic. Drug metabolism reactions are grouped into two classes on the basis of the sort of chemical reaction that takes place. Phase 1 reactions involve the creation of a chemical functional group on a drug. Typically, they are oxidation reactions carried out by members of the cytochrome P450 superfamily of enzymes. Phase 2 reactions involve the conjugation of a water-soluble molecule onto a drug. The general outcome of drug metabolism reactions, whether phase 1 or 2, is to create compounds that are more water soluble (and therefore less lipid-soluble) than the parent. As a result, the products of drug metabolism are generally less able to undergo tubular reabsorption than the parent compounds, and are therefore more readily excreted. In this manner, metabolism and excretion work in concert to lead to the elimination of a drug.

EXCRETION

Excretion, the physical expulsion of drug from the body, takes place predominately in the kidneys. Here, three processes occur to affect the elimination of a drug: glomerular filtration, whereby drug is passively filtered from the blood into the kidney tubule via the leaky glomerulus. Plasma protein bound drugs are not readily filtered; tubular secretion, whereby active carrier mechanisms transport specific drugs from the blood into the tubule. Drugs can compete for these processes. The agent probenecid is banned in many sports because it can prevent the appearance of other banned substances in the urine, by competing for tubular secretion processes; tubular reabsorption, which is a passive process that takes drugs from the tubular fluid back into the blood. This requires a drug to cross cell membranes at the tubule-peritubular capillary junction, and thus requires a degree of lipid solubility of a drug, which can be influenced by the pH of the tubular fluid. The sum of glomerular filtration, tubular secretion and tubular reabsorption is referred to as renal clearance, defined as the volume of blood from which drug is removed in a given time period, i.e. it has units of flow e.g. mL/min.

FURTHER READING

Rang and Dale's Pharmacology. Elsevier (2020) (Chapters 9 and 10) (Available as e-Book from Unimelb Library)

Katzung and Trevor's Pharmacology. 12th ed. (2019) (Chapters 6-10) (Available as e-Book from Unimelb Library)

Riviere JE and Papich MG. *Veterinary Pharmacology and Therapeutics*. 9th ed., Wiley-Blackwell (2008) (Chapters 5 and 6)

Hsu WH. *Handbook of Veterinary Pharmacology*. 1st ed., Blackwell (2008) (Chapter 2)