Drug Disposition, Bioavailability and Efficacy

Abstract

In this article in the series of 'bite sized' pharmacology, we will look at the concepts of drug disposition, bioavailability and efficacy. Drug distribution can be defined as getting a drug into its appropriate position in the body and in an appropriate concentration. This is represented by pharmacokinetic properties such as absorption, distribution, metabolism and excretion that we have looked at in previous articles in this series. Here we will concentrate on the movement of drug molecules at a tissue and cellular level to discover how drug molecules cross membranes and are distributed into the relevant body compartments to have their effect. We will also look at the concept of bioavailability- which is the fraction of an administered dose of unchanged drug that reaches the systemic circulation and efficacy that is maximum response achievable to elicit a therapeutic response.

Drug Disposition

Once a drug has been administered, by whatever route, it has to be distributed to its site of action, and as you will remember form previous articles, these can be receptors, ion channels, enzymes or transport systems located in various compartments of the body. To reach these targets drugs have to cross cell membranes or tissue membranes during distribution. These mechanisms of drug transport can be looked at in detail.

Drugs can use many biochemical mechanisms and influences to cross biological membranes. These include the mechanisms in box 1.

Passive Diffusion
Passive Transport
Active Transport
Receptor Mediated Endocytosis
pH effects

Box 1- Types of Membrane Transport

Passive diffusion

Cellular membranes within the body are made up of a lipid bilayer. Chemicals and drug molecules can diffuse across this bilayer by the mechanism of passive diffusion. This passive diffusion allows for very small molecules to pass through any ‘gaps’ in the lipid bilayer. Diffusion can also occur down a concentration gradient from a high concentration to a low concentration seeking to create an equal concentration on both sides of the membrane. (See figure 1, 1- passive diffusion)

Passive Transport

Passive transport differs from passive diffusion in that the crossing of membranes is mediated in this case by carrier proteins. This mechanism allows for the passive transport of larger molecules or molecules that are charger (have polar groups) or are water soluble. They provide a protein lined ‘pathway’ through the cell membrane for these larger molecules to enter and are carried in a spontaneous manner. (See figure 1, 2-3 passive transport)

Active Transport

This is when chemicals or drug molecules require the input of energy and an active protein carrier molecule. This normally occurs when the molecules are being moved *against* their

concentration gradient (from a low concentration to a high concentration). This form of transport is important as it can help drugs to enter cells and tissues that they may not be able to enter in either of the passive mechanisms. (See figure 1, 4 active transport)

Receptor Mediated Endocytosis

This mechanism of transport across membranes is used for very large molecules or drugs. Like active transport it requires an energy input from the cell. Essentially the cell membrane expands to engulf the molecule and absorb it into the cell. This process is often referred to a bulk transport.

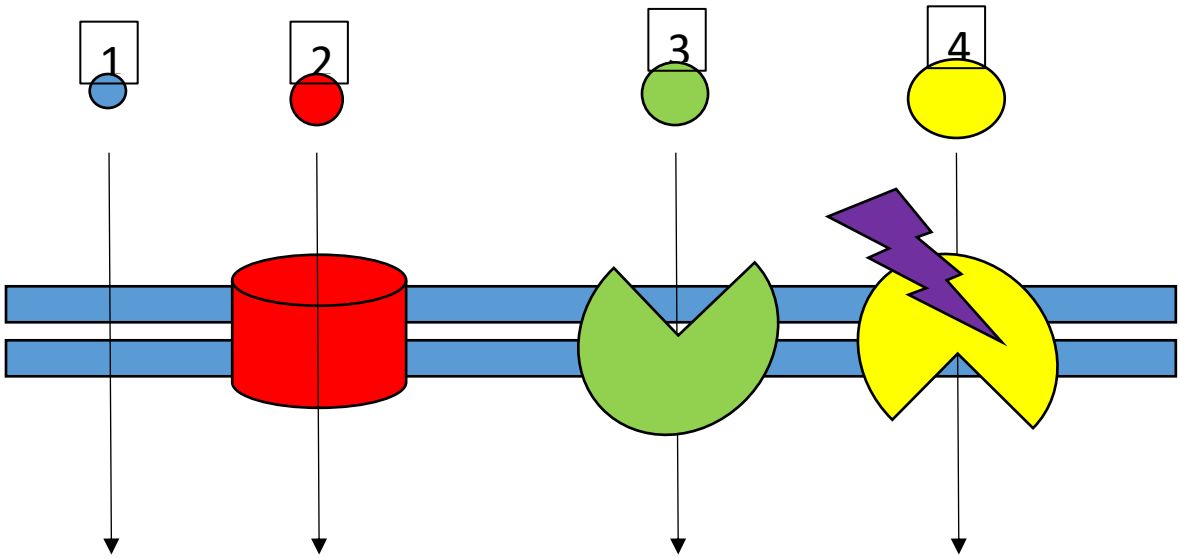

Figure 1 Cell membrane transport (I drew this myself, can we tidy this up???)

pH Effects

The pH of body compartments such as cells and tissues can affect how chemicals diffuse or are transported across membranes. Body fluids in compartments can hold onto drug

molecules dependent on the charge of the molecule and the PH of the environment it is moving from.

Drug Distribution in to Compartments

The body is composed of many compartments that drugs can be distributed into. Most drugs will be distributed into all compartments to a greater or lesser degree.

The 4 main body fluid compartments are

Plasma water

Interstitial water and lymph

Intracellular Water (all fluid within cells)

Transcellular water (includes CSF, intraocular, peritoneal, pleural and synovial fluids)

Drugs can be found in all of these compartments in either free or bound form. Distribution into each compartment is controlled by the mechanisms above and dependent on drug molecule size, charge, concentration and solubility. The amount of drug contained within any fluid compartment can be calculated with reference to its concentration in plasma to give an apparent volume of distribution. These values are theoretical figures that estimate how much of the drug is in plasma compared to the amount in the other compartments. Drugs that do not leave the plasma have a volume of distribution similar to plasma volume. The higher the volume of distribution, the more of the drug is distributed into the tissues and other compartments. Warfarin has a volume of distribution of 0.14 l/kg indicating a low distribution into tissues.

Exercise

Using pharmacologically available resources such as textbooks, the BNF or online electronic medicines compendium, find out, for a drug from your area of practice the volume of distribution in litres/kg.

Bioavailability

In pharmacology, bioavailability is considered under the pharmacokinetic process of absorption and is defined as

“The fraction of an administered dose of unchanged drug that reaches the systemic circulation”

When a drug is given intravenously, its bioavailability is 100%. This means it has bypassed the absorption step of pharmacokinetics and therefore none of the drug has been lost or changed prior to arrival in the systemic circulation. If we give a drug via another route of administration (orally, rectally etc.) then its bioavailability usually decreases. Bioavailability should be considered when deciding upon route of administration, calculating dosages for non-intravenous routes of administration, and switching drugs from one route of administration to another.

Exercise

Using pharmacologically available resources such as textbooks, the BNF or online electronic medicines compendium, find out, for a drug from your area of practice what the bioavailability is for the oral route of administration and compare this to the 100% of Intravenous administration. Reflect on how this affects the dose you will give by each of the routes.

Efficacy and Effectiveness

The word efficacy is derived from and is often used synonymously with, "effectiveness". We use the term efficacy in pharmacology to refer to the maximum response that can be obtained from a given drug and its subsequent therapeutic effect. This maximum effect is independent of dose. So although a graded response can be seen when a dose of a drug in increased, there comes a maximum level of response that cannot be increased regardless of any increase in dose. This is all relative to the drugs pharmacological ability to produce a response, so for example the ability of an antihypertensive drug to reduce blood pressure. There are many drugs developed for use as antihypertensives that have been demonstrated to be efficacious at lowering blood pressure. Effectiveness in medicine and therapeutics has a slightly different meaning to efficacy. Many drugs can be efficacious but have low effectiveness because, for example, although they may reduce blood pressure, they may cause too many side effects to be considered effective in clinical use.

It is important for the prescriber to consider a drug's efficacy but also to look at its effectiveness in a patient they are likely to prescribe for. Comorbidities, cautions and contraindications and drug interaction may lower the effectiveness of a drug without reducing its efficacy.

Exercise

Using pharmacologically available resources such as textbooks, the BNF or online electronic medicines compendium, find out, for a drug class from your area of practice if there are differences in prescribing for drugs within that group. Look at doses needed, any cautions or contraindications, interactions and the side effect profiles of each drug. Reflect on how the

drugs available for prescribing for the condition you have selected are narrowed down as you make a prescribing choice.

I hope you have enjoyed this bite sized pharmacology article. In the next in the series we will look at side effects and adverse drug reactions.

References & Further Reading

Barber and Robertson (2015) Essentials of Pharmacology for Nurses 3rd Edition McGraw Hill London

BNF Online https://www.bnf.org/products/bnf-online/

Electronic Medicines Compendium https://www.medicines.org.uk/emc/

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