Unless administered by IV, drugs need to diffuse across many semi-permeable cell membranes before entering the bloodstream. Biological membranes are barriers that allow the diffusion of drug molecules. Drugs may cross cell membranes by passive diffusion, facilitated diffusion, active transport, or pinocytosis. Proteins embedded in the phospholipid membrane act as receptors to also help transport molecules across the cell membrane.

Pharmacokinetics is divided into four areas including the rate of absorption, distribution, metabolism and excretion, commonly referred to as ADME.

On successful completion of this topic you will:
- understand factors that affect pharmacokinetic processes (LO2).

To achieve a Pass in this unit you need to show that you can:
- discuss factors affecting absorption, distribution, metabolism and excretion of drugs (2.1)
- explain how factors influence dosage regimes, including those for patients with renal and hepatic impairment (2.2)
- explain types of drug interactions arising from pharmacokinetic mechanisms (2.3).
1 Absorption

Absorption of drugs can be affected by many factors such as the solubility of the compound once the drug enters the body. The less soluble the compound is, the longer it will take to diffuse into the bloodstream – very hydrophilic drugs are not absorbed well because of the nature of the lipid membrane.

Drugs can cross biological membranes by facilitated diffusion down a concentration gradient. Integral membrane proteins provide a protein-lined pathway through the bilayer.

There are two types of membrane transport proteins:
- carrier proteins, which carry specific molecules across
- channel proteins, which form a path that molecules can pass through.

Carrier and channel proteins carry out facilitated diffusion, in which molecules travel down concentration gradients. Some carrier proteins carry out active transport, in which a molecule is transported against its concentration gradient, with an input of energy to power the movement.

Decreased blood flow may lower concentration gradients required for diffusion and therefore may reduce absorption of drugs.

The rate of absorption may also be affected by gastric emptying time. This depends on the contents and amount of food in the stomach. The stomach has a large surface area of epithelial cells, which are excellent for rapid diffusion as they are one cell thick. However, its thick mucosa layer slows the rate down. Most absorption occurs in the small intestine so gastric emptying is a limiting factor – fatty foods slow down the rate of gastric emptying and therefore the rate of absorption of any drugs. However, food being present can help drugs that are not very soluble to be absorbed, hence why some drugs state ‘to be taken with food’.

The acidic environment of the stomach means that some chemicals are not stable. Penicillin, for example, is unstable in the low pH of the stomach and insulin is destroyed in the gastrointestinal tract by degradative enzymes, this being the reason that insulin is not administered orally because it would not be absorbed.

The surface area of the small intestine is the largest for drug absorption because of the many microvilli present; it has the ability to absorb even acidic drugs. The intestinal transit time affects the rate of absorption of drugs that dissolve slowly – the slower the drug is to be absorbed, the less will be absorbed. If the transit time of the products in the intestines is quick, those drugs that are polar and those that are absorbed by active transport will not be absorbed as readily. During diarrhoea, for example, drug absorption is reduced and the drug may not work effectively.

2 Distribution

Once absorbed, drugs are carried in the bloodstream to the effector site; they may also distribute to muscle and organs. A drug’s efficiency to distribute may be affected by its ability to bind to plasma proteins. The lower the amount of drug that binds to proteins in the blood plasma, the more efficiently it can diffuse across cell membranes.
Common proteins that drugs bind to in the blood include: human serum albumin, lipoprotein, glycoprotein, and α, β, and γ globulins. When drugs enter the bloodstream they either bind or they do not. It is the unbound portion of the drug that exhibits its pharmacological effect on the body. For example, 97% of the anticoagulant warfarin binds to plasma proteins in the blood. This means that the remaining 3% is unbound and only this small amount is actually active and may be excreted.

For a drug to pass through a membrane by passive diffusion it must dissolve in the lipophilic membrane – this requires the drug molecule to have some lipophilic character. For efficient absorption and distribution to target organs, the drug molecule must possess solubility – in lipid phases of the body and in water. Solubility in just one phase generally results in the drug exhibiting limited effects because of poor membrane penetration.

Distribution in pharmacokinetics is the reversible transfer of a drug from one compartment to another to make molecules available to be metabolised. The central compartment consists of the heart, blood, liver, brain and kidneys, where drugs are brought to equilibrium quickly. The peripheral compartment consists of tissues (e.g. adipose and skeletal muscle) that are less well perfused, and where drugs reach equilibrium at a slower rate. Entry of drugs into special compartments, such as cerebrospinal fluid (CSF) and the central nervous system (CNS), is restricted by the structure of the capillaries and pericapillary glial cells.

Again, there are factors that affect the rate of distribution. Regional blood flow affects the rate of distribution – the higher the blood flow and the availability of capillaries, the faster the rate of distribution.

Molecular size affects the rate of distribution – larger molecules find it difficult to cross biological membranes while smaller ones pass through more easily, and therefore have an increased rate of distribution.

Polar drugs (e.g. penicillin) are unable to cross biological barriers unless they make use of carrier proteins or are taken across by pinocytosis (e.g. insulin).

Finally, distribution into the interstitial fluid surrounding tissues and organs occurs quickly if the drug is not bound to any plasma proteins.

### 3 Metabolism

As soon as a drug enters the body it begins to break down into metabolites, reducing the effect of the drug on the body. The main aim of drug metabolism is to change chemical compounds into more polar, water-soluble products so that they can be eliminated from the body.

Metabolism phase I reactions often occur in the liver by oxidation, reduction, hydrolysis, cyclisation, and decyclisation, addition of oxygen or removal of hydrogen, carried out by mixed function oxidases.

Phase I oxidation converts a C–H bond to a C–OH. This converts an inactive compound to an active one, which exhibits pharmacological effects. It can also convert a non-toxic molecule into a poisonous molecule.
Phase II reactions involve interactions of the polar functional groups of phase I products. These include carboxyl (–COOH), hydroxyl (–OH), amino (NH₂), and sulfhydryl (–SH) groups. Products of phase II reactions are less active, unlike phase 1 products. Phase II metabolic reactions involve the addition of highly polar molecules to a functional group making the metabolites more soluble and therefore more easily excreted.

The liver is the primary site for drug metabolism although other organs such as the kidneys and lungs can carry out metabolism of drugs too. Cytochrome P450 enzymes present in the liver carry out phase I oxidation reactions – the amount of the enzymes present will affect the rate of metabolism. The activity of these enzymes can be affected by food, chemicals and other drugs, which can potentially slow the rate of reaction.

**4 Excretion**

The newly synthesised metabolites must be excreted; this is usually through the kidneys as urine or in faeces (see Case study). Three processes occur in the kidney: glomerular filtration excretes unbound drugs; active secretion of free and protein-bound drugs occurs; and filtrate concentrated in the tubules of the kidney produces a concentration gradient for reabsorption and excretion in urine.

If excretion does not take place and substances build up it can affect the body. The liver and the lungs also play a role in excretion.

Renal impairment is a problem associated with age and disease – it is a medical problem whereby the kidneys are not able to filter toxins out of the body as efficiently. Renal failure results in decreased drug excretion from the body. It also reduces the plasma protein binding of drugs, which can affect their distribution and elimination and therefore may cause toxicity. A change in dosage must be considered in order to avoid toxic levels of drugs in the body. Dosage adjustment is calculated by remaining kidney function, based on the patient’s glomerular filtration rate (GFR).

If a patient has hepatic dysfunction, this means that the liver is not working to its full potential. The liver plays a major role in the metabolism of substances and breaking them down into their metabolites; therefore this medical issue may also cause a build-up of toxic substances and may slow down the body’s ability to metabolise chemicals.

**Checklist**

In this topic you should now be familiar with the following ideas about factors affecting pharmacokinetics:

- the absorption of drugs is necessary for them to have an effect on the desired area of the body
- the rate of absorption can be affected by many factors such as gastric emptying, chemical balance of the stomach and surface area
- distribution is the movement of chemicals from the site of absorption to their site of action
- metabolism is the breakdown of substances into smaller products called metabolites
- excretion is the removal of substances from the body, mainly by the kidneys.
Take it further
To find more information about dosage change for patients with renal impairment, check out the journal article in the link: http://www.farm.ucl.ac.be/Full-texts-FARM/Verbeeck-2009-1.pdf.

Portfolio activity (2.1, 2.2)
- Produce a list of all of the factors that may affect absorption, distribution, metabolism and excretion.
- Research how nurses would change their dosage if their patient was diagnosed with renal or hepatic impairment.

Further reading

Case study
The elimination time of illicit drugs and their metabolites is of both clinical and forensic interest. The knowledge of how drugs are absorbed, distributed and excreted plays an important role in the analysis of illegal drugs.
Blood and urine samples can be used to determine how long it takes for different drugs to be eliminated from the human body. This can be important for drugs in sport, crime and in workplace drug testing and plays an important part in society.

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