Drug Action- The Therapeutic Effect

Abstract

In this article in the series of ‘bite sized’ pharmacology, we will look at the concept of drug action- the therapeutic effect of the medications we give. It is important that prescribers are aware of factors that can affect drug action and the time to onset of and subsequent duration of the desired therapeutic effect. We will look at factors that affect these two important areas of drug action. Knowledge of these factors can assist the prescriber when deciding on doses and dose schedules to ensure that patients receive their medications at the correct dosing, by the correct route and in the right formulation to ensure optimum therapeutic effect. It also helps the prescriber understand why dose adjustments are made or some drugs are avoided in patients with hepatic or renal impairment.

Time to Onset

The time to the onset of drug action is the time taken form the point of drug administration until the drug is delivered to its site of action. This is controlled by three main factors;

- The route of administration of the drug
- The rate of absorption of the drug
- The manner of distribution of the drug

We often want the drug we give to have its effect within a certain time frame. This is especially important in the cases of one off does of medication such as analgesia as it’s important to be able to monitor response and knowing when response is expected helps us assess our patients more accurately.

We can affect the time to the onset of drug action in many ways. The first is the route of administration. If drug action is needed more quickly, we can use the IM or IV route as

necessary. We can also delay drug onset by using transdermal or SC routes. Box 1 shows the main routes of drug administration and their advantages and disadvantages.

Box 1

ROUTE	ADVANTAGES	DISADVANTAGES
ENTERAL ROUTES		
ORAL	Convenient, non-sterile, good absorption for most drugs, medium onset of action	Gastrointestinal (GI) irritation, potential for interactions, first pass destruction, inactivated by acids, variable absorption
SUBLINGUAL/BUCCAL	Avoids first pass, avoids gastric acid, fast acting	Few preparations suitable
RECTAL	Avoids first pass, avoids gastric acid, medium onset of action	Less dignified for the patient
PARENTERAL (refers to IV, IM and SC) ROUTES		
INTRAVENOUS (IV)	Rapid action, complete availability	Increased drug levels to heart, must be sterile, risk of sepsis and embolism
INTRAMUSCULAR (IM)	Rapid absorption, fact action	Painful, risk of tissue damage
SUBCUTANEOUS (SC)	Good for slower absorption and where delayed onset may be advantageous	Absorption variable
INHALED (LUNGS)	Large absorption area, good for topical use, rapid onset of action	Few disadvantages

Adapted from Barber & Robertson (2015)

Exercise

Using pharmacologically available resources such as textbooks, the BNF or online electronic medicines compendium, find out the different routes of administration available for a drug from your area of practice. Use this information and your knowledge of patients you may prescribe for to reflect on what information you would need and how you would chose a route for a particular patient.

After we have chosen the route of administration best suited to the drug and patient we can use our knowledge of the pharmacological processes of Absorption and Distribution to predict and affect time to onset.

Absorption

The main factors that affect drug absorption that you may remember from our pharmacokinetics article are physiological and physicochemical. We will look at the oral route of administration as an example.

Physiological

Drug absorption by the oral route can be affected by the presence or absence of food in the stomach. Some drugs should be given on an empty stomach and therefore well before or after food. This is to maximise their absorption. Some drugs should be given with food, this often starts peristalsis and moves the drug to the small intestine where the majority of its absorption takes place. Drugs which are given orally that do not specify food timing can be absorbed well with or without food present.

Physicochemical

If the drug is given orally, we can use liquid or dispersible formulations instead of regular tablets. These are absorbed more quickly and readily form the gastrointestinal tract and can reduce the time to onset of drug action. We can also delay drug onset by using enteric coated or slow release preparations orally.

Exercise

Using pharmacologically available resources such as textbooks, the BNF or online electronic medicines compendium, look at the different preparations available for a drug from your area of practice. Use this information and your knowledge of patients you may prescribe for to reflect on what information you would need and how you would chose a preparation for a particular patient.

Distribution

The main factor that affect drug distribution that you may remember from our pharmacokinetics article is plasma protein binding.

Plasma Protein Binding

When a drug is absorbed and enters the plasma it will be subjected to binding to plasma proteins. Any drug bound to a plasma protein is pharmacologically inert, only the drug that is ‘free’ in the plasma can go on to its target site and have activity. The degree of binding is controlled by the amount of drug that has reached the systemic circulation (bioavailability), what affinity that drug has for the biding sites on the proteins, and the amount of plasma proteins present in the blood. Albumin is the most significant of the plasma proteins in terms of drug binding. Some drugs have a high affinity for the binding sites (warfarin is a good example) and some a much lower affinity (paracetamol at therapeutic doses) and this affects the amount of free drug available for action. Dosing and knowledge of absorption control the bioavailability. Affinity is predetermined and cannot be affected by the prescriber. In some patients on some medications it is advantageous to know the level of albumin before prescribing. Pregnant women, children and some elderly patients can have altered levels of plasma proteins.

Exercise

Using pharmacologically available resources such as textbooks, the BNF or online electronic medicines compendium, find the plasma protein binding for a drug from your area of practice.

Duration of Effect

The duration of drug is the period from the time of onset to the time at which sufficient drug has been removed from the body to render it as therapeutically ineffective.

This is largely controlled by hepatic metabolism and renal excretion

It is important to know how long a drug will have its effect for. This decides the dosing schedules. Drugs need to be given more than once to have continued effect. Some drugs need to be given daily, but some need to be given more often to maintain effective drug action. This can be deduced from the duration of action of the drug.

Hepatic Metabolism

Enzymes within the microsomes of the liver, including cytochrome P450's are responsible for drug metabolism. Anything that affects the function or number of these enzymes can affect drug metabolism. These can involve physiological factors, pathological factors, genetics, and drug interactions.

Physiological, Pathological & Genetic

Age, diet, smoking and alcohol intake can all affect hepatic function. In babies and children we have an immature liver and must take this reduced metabolic activity into account when prescribing. In the elderly we can see reduced liver size and function as a consequence of normal ageing. Chemicals in cigarette smoke can affect the ability of liver enzymes to metabolise some drugs, theophylline being the most notable. Excessive alcohol consumption can cause liver damage and greatly reduce the function of the organ.

Factors such as liver disease, cirrhosis, and fatty accumulations in the liver can affect the ability of the microsomal enzymes.

The main genetic factors that can influence drug metabolism are the presence of polymorphisms in the enzymes themselves. These are genetic variations that can change the ability of the enzyme to metabolise drugs and affect response, action and duration.

Common and well documented polymorphisms exist, for example the variant of cytochrome P450 known as 2D6 is subject to polymorphism. This enzyme metabolises many drugs including some antidepressants.

These factors can reduce live enzyme function and mean that drugs metabolised by the liver are done so less efficiently. This can lead to a build-up of the parent drug and may cause side effects or toxicity. It will also prolong the level of the drug at or above its therapeutic effect in the body to an extent which may be undesirable. It is often necessary to reduce doses in liver compromise or even avoid certain drugs.

Drug Interactions

Some drugs are inducers or inhibitors of the hepatic microsomal enzyme systems. This means they can speed up or slow down the metabolism of other drugs and change their therapeutic duration of effect. This can prolong or shorten the therapeutic effect of a drug and may have a clinical significance. Prescribers should be aware of common inducers and inhibitors in their area of practice and also check interactions of drugs in the BNF before prescribing if unsure. Some common inducer and inhibitors are listed in Box2 but this is not exhaustive.

Box 2

Inducers	Inhibitors
Carbamazepine	Cimetidine
Rifampicin	Erythromycin
St Johns Wort	Grapefruit juice
Phenytoin	Valproate

Renal Excretion

The kidney excretes drugs and metabolites via the two processes of active glomerular filtration and passive tubular secretion. Factors that affect renal function can have an effect on the ability of the kidneys functional unit, the nephron, to perform these activities. If the activity is compromised then excretion of active drug, active and non-active metabolites can lead to an increased duration of action, an increase in plasma concentrations of drug molecules and potential side effects, adverse effects and toxicity. The extremes of age have significant bearing on renal function and should always be considered when prescribing. In babies we have an immature renal system and in the elderly the kidneys reduce in size and function as a manifestation of ageing therefore excretion of drugs can be compromised. The estimation of glomerular filtration rate (eGFR) is a commonly measured feature of renal function that can help determine the effectiveness of the kidney. It should be measured in any drug which requires extensive renal excretion or in patients where renal compromise is suspected. Dosing of drugs in mild, moderate and severe renal failure should be prescribed as per guidance in the British National Formulary (BNF).

Exercise

Using pharmacologically available resources such as textbooks, the BNF or online electronic medicines compendium, find the prescribing information for a drug from your area of practice in patients with hepatic or renal impairment.

This has been a brief introduction to the concepts of onset and duration of drug action. In future articles in this series we will explore aspects of pharmacodynamic actions in more detail, looking at first pass metabolism and in more detail at agonists and antagonists.

References & Further Reading

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

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

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