Drug handling

After completing this tutorial, you will be able to:

- Explain the difference between pharmacokinetics and pharmacodynamics, and terms such as half-life.
- Recognise the roles played by patient age and changes to kidney or liver function in determining drug clearance.
- Know the right questions to ask when managing a patient who requires monitoring of drug levels for therapeutic reasons.

Why this subject matters…

Many clinical problems require a basic understanding of pharmacokinetics. These range from predicting how quickly a patient will respond to a change in drug regimen, to estimating doses in patients at extremes of weight or age.

This tutorial covers the key terminology and some practical tips on problem solving in clinical practice.

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[Last updated: 18 December 2018]

Explaining some concepts

We start by describing the difference between two similar-sounding words, that you'll need to be confident you understand...

Pharmacokinetics

The time course of absorption, distribution, metabolism and excretion of a medicine. Think of this as: '*what the body does to the medicine*'.

Pharmacodynamics

The biochemical and physiological effects of medicines and their mechanisms of action. This includes all the actions of a medicine not just the desirable ones – so it's about side effects too. To help you remember the difference from pharmacokinetics you could say pharmacodynamics is '*what a medicine does to the body*'.

Bioavailability (F)

The fraction of a medicine's dose that reaches the systemic circulation as intact drug. It depends on how well the drug is absorbed and how much is removed by the liver during 'first-pass clearance'.

Steady-state

The equilibrium achieved after multiple dosing when the rate of drug administration equals the rate of drug elimination. At steady-state the amount of drug in the body, and the plasma concentration, are constant.

Volume of distribution (V_d)

A hypothetical volume that relates the concentration of drug in the plasma to the total amount of drug in the body. It illustrates the distribution of the drug in a patient. The equation for the volume of distribution is expressed as follows:

$$V_d(L) = \text{Total amount of drug in the body (mg)} \div \text{Plasma drug concentration (mg/L)}$$

The volume of distribution is determined by physiological factors such as the size of the patient. For example a 160kg young male athelete would be expected to have a larger V_d than a 40kg lady aged 83 because his blood volume and tissue size will be larger.

Pharmacodynamic factors such as the affinity of the drug for the tissues compared with the plasma may also affect the V_d. Digoxin is very tightly bound by the tissues and not held in the plasma: the drug appears to be dissolved in a large volume and thus the V_d is large (6L/kg).

In contrast warfarin is held in the plasma by proteins and does not distribute to the tissues. The V_d in this case is smaller and approximates to the actual blood volume (0.08 – 0.27L/kg). V_d helps to determine the loading dose of a drug when rapid therapeutic plasma levels are required e.g. digoxin, theophylline.

Clearance (Cl)

This is defined as the volume of blood cleared of drug per unit time, and the units are normally litres per hour or ml per minute. It describes the ability of the body to remove a drug from the blood either unchanged in the urine, gut or sweat or after metabolic conversion. It is not an indicator of how much drug is being removed but the theoretical volume of blood or plasma that is completely cleared of drug in a given time. Clearance is important because it helps to determine the maintenance dose of a drug to achieve the desired plasma concentration.

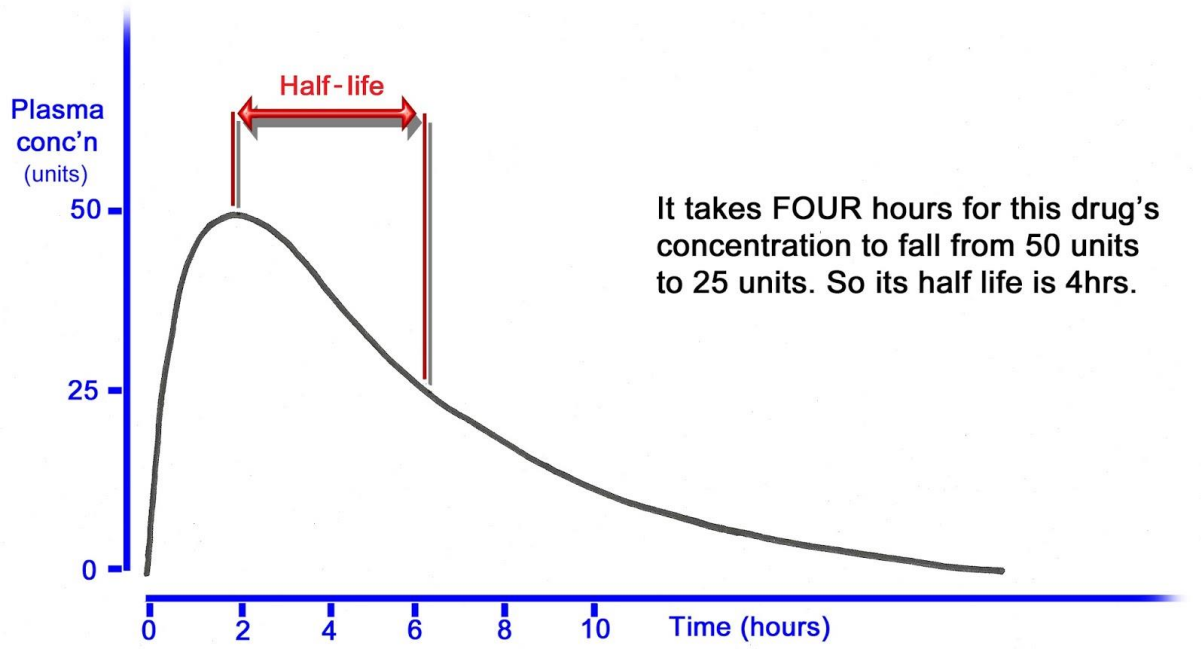
Half-life

This is a particularly important concept. It is the time taken for the amount of drug in the body (or the plasma concentration) to fall by half. The elimination of a drug is usually an exponential process meaning that a constant proportion of the drug is eliminated per unit time.

Half-life is important because it determines both the time to reach steady-state conditions with chronic dosing and the time for elimination. As a rule of thumb it takes approximately 3-5 half-lives to achieve steady-state conditions. Drug elimination is the mirror image: it normally takes 3-5 half-lives for a drug to be completely eliminated from the plasma. Half-life also helps to determine the frequency of dosing.

Half-life is proportional to V_d and inversely proportional to clearance:

$$\text{Half-life (hrs)} = 0.693 \times \text{Volume of distribution (L)} \div \text{Clearance (L/hr)}$$



Courtesy of Simon Wills

The larger the V_d, the more the drug is concentrated in the tissues and not in the blood. It is only the drug in the blood that is exposed to clearance by the liver or the kidneys. Therefore increasing Vd increases half-life. A decrease in the efficiency of elimination (i.e. the clearance) will obviously increase the half-life as well.

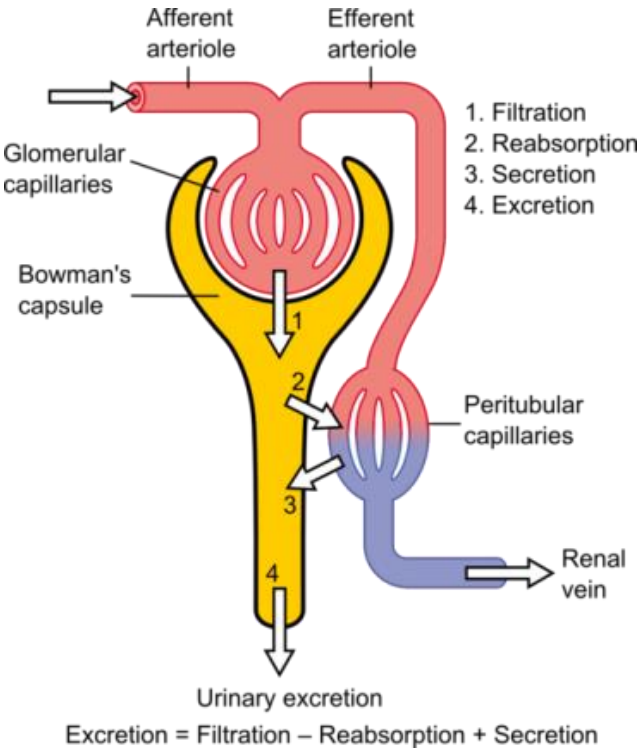
Kidney and liver clearance

These two topics are covered in more detail in later tutorials on prescribing in renal disease and in liver disease.

Clearance by the kidney

Three processes determine the amount of drug cleared by the kidneys: glomerular filtration, active tubular secretion and passive tubular reabsorption.

The average glomerular filtration rate in young adults is 80 to 120 ml/min and approximates to creatinine clearance. Only unbound drugs are able to pass into the glomeruli: drugs bound to plasma proteins are not filtered.



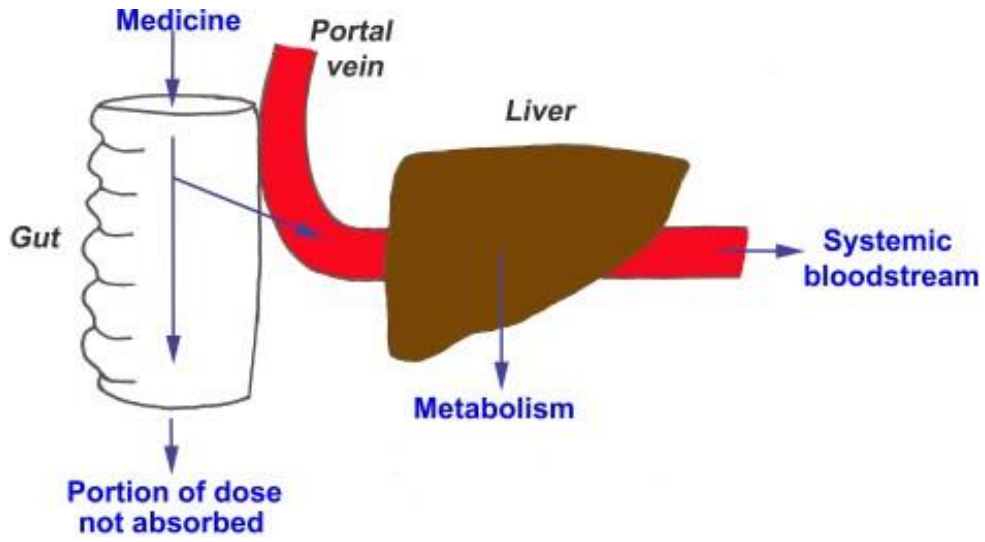
Courtesy of Madhero88, Wikimedia Commons

Although the glomeruli filter about 120ml of blood per minute, most is reabsorbed, resulting in 1-2 ml of urine being produced per minute. This leads to a drug concentration gradient between the tubular fluid and the blood. If the drug is physically able to travel back across the tubular membrane down the concentration gradient, it will diffuse back to the blood. The physical characteristics of the drug and the size of the concentration gradient determine how much drug is reabsorbed.

Clearance by the liver

The major organ of drug metabolism is the liver. Traditionally, drug metabolism is characterised as phase I reactions that oxidise drug molecules, or phase II reactions that link drug molecules to soluble compounds (e.g. glucuronides). In either case the resulting metabolite is more water-soluble than the parent drug and is more likely to be eliminated in the urine as described above.

The extent to which a drug is metabolised by the liver during its *first* passage through the portal blood vessels after absorption from the gut is called '**first-pass metabolism'**. For example, glyceryl trinitrate cannot be administered orally because first-pass clearance removes 99% of the dose. When administered sublingually, the drug is absorbed directly into the systemic circulation thereby avoiding the first-pass effect.



Courtesy of Simon Wills

The 'extraction ratio' of a drug, which is related to its first-pass clearance, is defined as 'the fraction of drug entering the liver which is irreversibly extracted from the blood during one pass through the liver'. The ratio can range from zero (no drug is removed by the liver) to one (all the drug entering the liver is removed in one pass). The hepatic blood flow via the portal vein is an important factor in determining how much drug the liver removes.

Some drugs are wholly or partly excreted directly by the liver in bile (e.g. rifampicin).

Changes with age

Elderly patients

Pharmacokinetic and pharmacodynamic changes in the elderly may lead to altered drug response. All aspects of pharmacokinetics (absorption, distribution, metabolism and excretion) may be affected, although clinically significant effects due to changes in oral absorption are rare.

Changes in **drug distribution** with ageing are due to:

- Differences in body composition in the elderly (*e.g.* reduced body water and increased body fat).
- Reduced serum albumin levels.
- Alterations in organ perfusion, such as reduced liver and kidney blood flow due to decreased cardiac output and increased peripheral vascular resistance.

Decreased hepatic blood flow leads to a reduction in first-pass **metabolism**. Together with reduced microsomal oxidation, the capacity of the liver to handle drugs may be significantly impaired in elderly patients. This can lead to increased half-lives and higher steady-state levels of some hepatically metabolised drugs.

Renal excretion of drugs may be reduced in the elderly due to a decrease in kidney size and loss of functioning glomeruli. Actual renal impairment on top of age-related reductions in function will obviously make drug clearance even worse. Note that elderly patients may have a normal plasma creatinine but still have a reduced creatinine clearance. Their decreased muscle mass produces less creatinine which can be balanced out by a decreased renal clearance, resulting in plasma levels within the normal range. Reduced renal excretion is particularly significant for drugs with a narrow therapeutic index (e.g. digoxin).

There are also **pharmacodynamic** changes with age such as an increased sensitivity to the sedating or hypotensive effects of medicines.

Children as patients

Altered pharmacokinetics in paediatric patients may have a significant effect on drug response.

There are probably no significant differences between adults and children in terms of oral absorption of medicines, but the distribution of drugs may be affected by changes in body composition. As a percentage of body weight, total body water and extracellular fluid volume *decrease* with age. This is important for water-soluble drugs such as gentamicin, where a larger dose on a milligram per kilogram basis is used in the neonate compared to an older child, to achieve the same plasma concentration.

In premature babies, plasma protein binding is reduced resulting in higher concentrations of free (active) drug. This also leads to medicines having a higher apparent volume of distribution in premature babies compared to adults.

At birth, the capacity of the neonate to metabolise drugs is significantly lower compared to adults. However there is a large rise in metabolic capacity in the older infant and young child. For some drugs, such as theophylline, the metabolic clearance in children may be greater than that seen in adults. This necessitates a larger dose on a milligram per kilogram basis in children to achieve plasma concentrations similar to adults. Metabolic pathways that make a minor contribution to adult metabolic capacity may be used more in children to compensate for their less developed systems.

Renal excretion of drugs in young infants is reduced due to anatomical and functional immaturity of the kidneys. However, towards 6-8 months of age, the glomerular and tubular function develops; by 8 months the renal elimination of drugs is approaching that seen in older children and adults.

For more information about the use of medicines in children, follow the link to the tutorial on this subject.

Therapeutic drug monitoring

One application of pharmacokinetics in practice is therapeutic drug monitoring (TDM). TDM is useful for drugs that have a **narrow therapeutic index** and a good concentration-response relationship. It can be helpful to monitor a patient's drug levels after the initiation of therapy; following a change in drug dosage; when a potentially interacting drug is introduced; to assess toxicity or overdose; and to monitor drug compliance.

Look at a table of drugs for which therapeutic drug monitoring is used here: consult it alongside the relevant SPC and any local guidelines you have.

The correct **time of sampling** is important because drug concentrations vary over the dosing interval and with duration of therapy. For drugs with short half-lives (e.g. oral theophylline), samples should be taken pre-dose. For drugs with long half-lives (e.g. phenytoin), timing is less critical and samples may be taken at any point in the dosage interval.

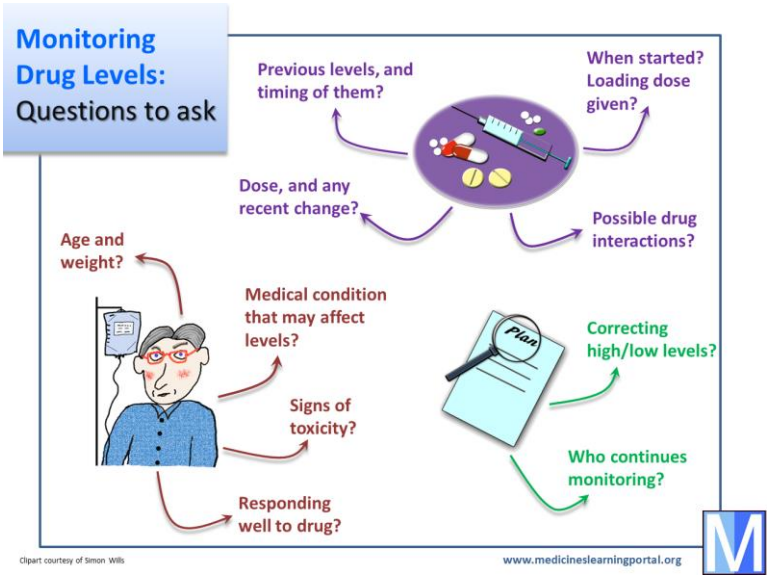
Courtesy of Stephanie Rubi www.manas.afcent.af.mil, Wikimedia Commons

Remember that assays measure the amount of **unbound and bound** drug in the blood or plasma but it is only the unbound drug that interacts with the drug receptor to produce a pharmacological effect. Therefore changes in protein binding should be taken into account when interpreting a drug level. For example, if a patient is hypoalbuminaemic, the number of protein binding sites is reduced, resulting in an increase in unbound (free) concentrations of highly protein-bound drugs such as phenytoin.

Concurrent disease other than impaired renal and hepatic function can alter the pharmacokinetic profile of a drug. For example, hypothyroidism decreases digoxin's volume of distribution and decreases its clearance. Therefore patients with hypothyroidism normally require lower doses of digoxin compared to euthyroid patients. The opposite can be true for patients with hyperthyroidism.

Suggested questions

They may not apply to every situation you come across, but here are some questions you should be thinking about if tackling a problem about monitoring drug levels:



The Medicine

- When was the medicine started, and was a loading dose given? *If started very recently, then there may not have been time for the drug to reach steady state.*
- What is the current dose, and have there been any changes in the dose? *You need to know if the levels represent a long-term stable dosing regimen or a changing one that might not be at steady state.*
- Check if any previous drug levels have been taken and if so, check the time they were taken in relation to dosing. *This allows you to see any patterns in levels related to dose and whether they reflect peak levels. Be careful to confirm the units of measurement.*
- Are there any drug interactions that might affect clearance? *A key factor that can cause drug levels to fall or increase.*

The Patient

- What is the patient's age and weight? *To help in determining suitable dosage on the basis of body size and age. Age may affect clearance or response.*
- Any medical conditions that might affect levels? *Does the patient have kidney or liver dysfunction that might affect the clearance of the medicine? Are there any other medical conditions that might affect levels or drug response (e.g. low albumin levels may increase the amount of free phenytoin in the plasma)?*

- Is the patient responding well to their treatment? *Suggests that levels may be therapeutically adequate.*
- Do they have potential signs of toxicity? *Suggests that levels may be too high. The nature and severity of any reactions will help determine if a dose reduction is a suitable way forward or if treatment must be stopped (temporarily or permanently).*

Going Forward

- What will be done if the patient's drug levels are too high or too low? *Have the probable reasons been ascertained, is there a plan to manage the situation, and how will this be prevented in future?*
- Who will monitor drug response and any drug levels after today? *Maybe this is a junior doctor over the weekend, or a GP after discharge. Has this responsibility been communicated properly, and does the person know what they must do?*

Information sources

Drug handling problems can be complex, but for straightforward clinical situations concerned with sampling times and so forth, check to see if you have an in-house policy at your hospital. Alternatively try the TDM table we have produced here for general guidance. SPCs often have TDM information for drugs with a narrow therapeutic range, and will also provide some basic pharmacokinetic data for most drugs.

Martindale, Micromedex and similar sources can be helpful for determining a range of kinetic data including time to onset of action, protein binding, Vd, metabolism and excretion.

There are a number of kinetics books available, most are fairly in-depth and so consult these only after you've tried the above. An example is **Winter's Basic Clinical Pharmacokinetics** by Paul Beringer (Lippincott Williams and Wilkins).

Be careful about conducting a general internet search on this subject. If you do, you may like to look at our brief guide to evaluating websites about medicines.

Presenting your answer

Once you've asked sufficient questions, gathered the information required and assessed it, you'll need to provide an **answer**. We can offer you some general guidance on answering clinical problems.

Next steps in learning...

CPPE
CENTRE FOR PHARMACY POSTGRADUATE EDUCATION

CPPE hosts a Pharmacology e-learning programme developed at the University of Leiden. It teaches basic pharmacodynamics, pharmacokinetics, and drug mechanisms of action.
Their Older People distance learning programme covers the changes with ageing that affect health and medicines.

The online version of the Merck Manual has a helpful Introduction to Pharmacokinetics, which links to further learning on drug absorption, bioavailablity, distribution, metabolism, and excretion.