Principles of basic clinical pharmacokinetic parameters:

Clinical pharmacokinetics is the application of pharmacokinetic concepts and principles in humans in order to:

1. Design individualized dosage regimens which optimize the therapeutic response of a medication.
2. Minimizing the chance of an adverse drug reaction.
3. Monitor medications with a narrow therapeutic index.
4. Development and evaluation of new drugs.

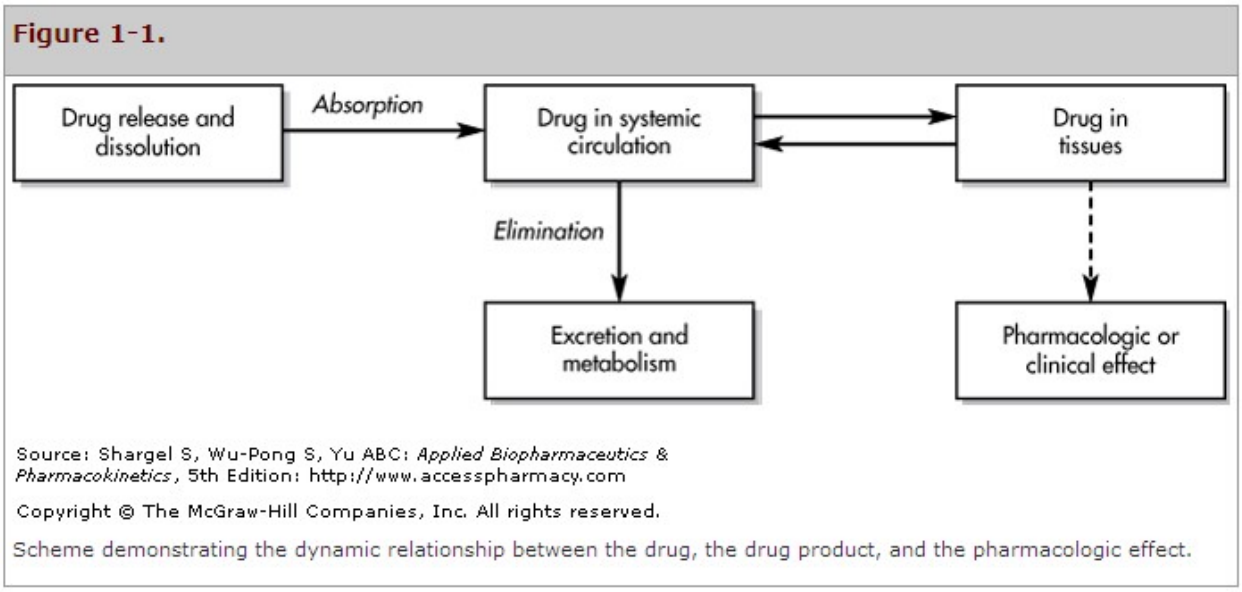
Pharmacokinetics is the study of the absorption, distribution, metabolism, and excretion of drugs. When drugs are given extravascularly (e.g., orally, intramuscularly, applied to the skin via a transdermal patch, etc.), absorption must take place for the drug molecules to reach the systemic circulation.

In order to be absorbed, the drug molecules must pass through several physiological barriers before reaching the vascular system. For example, when a medication is given orally, the drug dosage form must release drug molecules via dissolution, and the molecules must pass through the various layers of the gastrointestinal tract where they enter capillaries.

Distribution occurs when drug molecules that have entered the vascular system pass from the bloodstream into various tissues and organs such as the muscle or heart.

Metabolism is the chemical conversion of the drug molecule, usually by an enzymatically mediated reaction, into another chemical entity referred to as a metabolite. The metabolite may have the same, or different, pharmacological effect as the parent drug, or even cause toxic side effects.

Excretion is the irreversible removal of drug from the body and commonly occurs via the kidney or biliary tract.



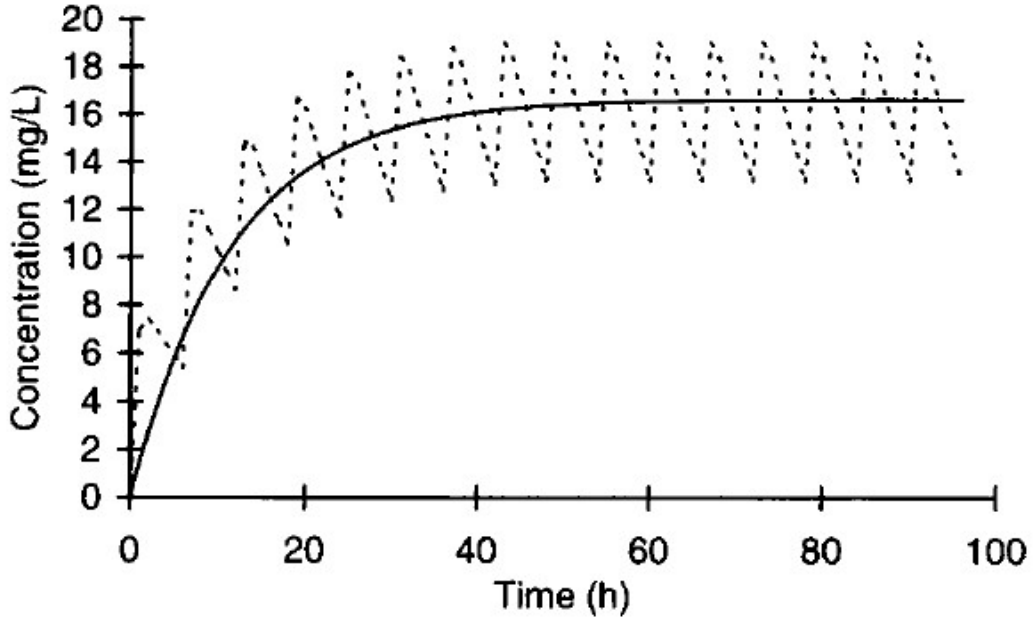
Pharmacokinetic principles

steady state concentration:

Regardless of the mode of drug administration, when the rate of drug administration equals the rate of drug removal, the amount of drug contained in the body reaches a constant value. This equilibrium condition is known as steady state and is extremely important in clinical pharmacokinetics because usually steady-state serum or blood concentrations are used to assess patient response and compute new dosage regimens.

Drugs with short half-life reach Css rapidly, while drugs with long half-life takes days to weeks to reach steady state.

When drugs are given on a constant basis, such as a continuous intravenous infusion or an oral medication given every 12 hours, serum drug concentrations increase until the rate of drug administration equals the rate of drug metabolism and excretion. At that point, serum drug concentrations become constant during a continuous intravenous infusion or exhibit a repeating pattern over each dosage interval for medications given at a scheduled time (Figure 1-2). For example, if theophylline is given as a continuous infusion at a rate of 50 mg/h, theophylline serum concentrations will increase until the removal of theophylline via hepatic metabolism and renal excretion equals 50 mg/h.



Half-life (t1/2):

The time required for serum concentrations to decrease by one half (50%).

Drug needs (t1/2) to reach Css.

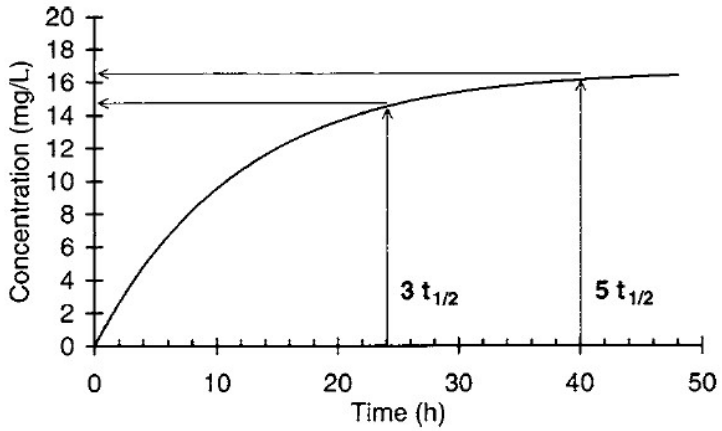


FIGURE 1-9 Serum concentration/time graph for a drug that has a half-life equal to 8 hours. The arrows indicate concentrations at 3 half-lives (24 hours, ~90% of Css) and at 5 half-lives (40 hours, ~95% of Css). Since most drug assays have 5–10% measurement error, serum concentrations obtained between 3–5 half-lives after dosing commenced can be considered to be at steady state for clinical purposes and used to adjust drug doses.

linear versus nonlinear pharmacokinetics

Linear pharmacokinetics:

If a plot of steady state concentration versus dose yields a straight line, the drug is said to follow linear pharmacokinetics. In this situation, steady-state serum concentrations increase or decrease proportionally with dose.

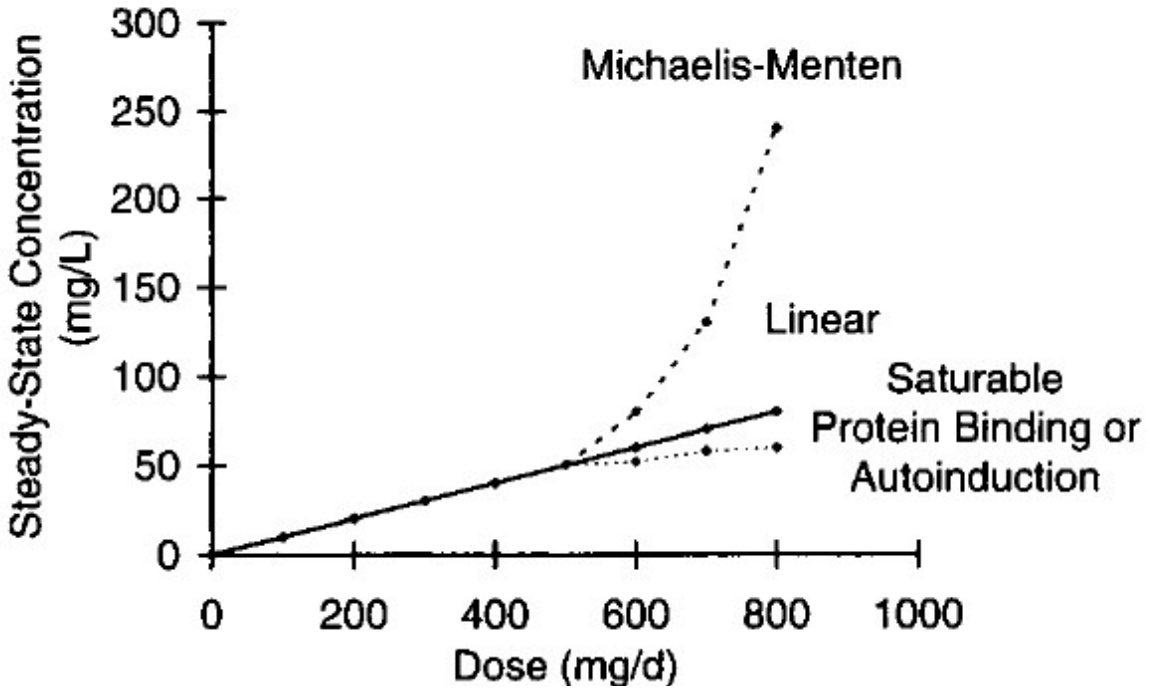
For example, if theophylline is given as a continuous infusion at a rate of 50 mg/h, theophylline serum concentrations will increase until the removal of theophylline via hepatic metabolism and renal excretion equals 50 mg/h.

nonlinear pharmacokinetics:

When steady-state concentrations change in a disproportionate fashion after the dose is altered, a plot of steady-state concentration versus dose is not a straight line and the drug is said to follow nonlinear pharmacokinetics, which is either:

1. When steady-state concentrations increase more than expected after a dosage increase, the most likely explanation is that the processes removing the drug from the body have become saturated. This phenomenon is known as saturable or Michaelis-Menten pharmacokinetics. Both phenytoin and salicylic acid follow Michaelis-Menten pharmacokinetics.
2. When steady-state concentrations increase less than expected after a dosage increase, there are two typical explanations.
    a) Some drugs, such as valproic acid, saturate plasma protein binding sites so that as the dosage is increased steady-state serum concentrations increase less than expected.

b) Other drugs, such as carbamazepine, increase their own rate of metabolism from the body as dose is increased so steady-state serum concentrations increase less than anticipated. This process is known as autoinduction of drug metabolism.



Therapeutic drug monitoring

The measurement of medication levels in blood. Its main focus is on drugs with a narrow therapeutic range, i.e. drugs that can easily be under- or overdosed.

In pharmacology, many medications are used without monitoring of blood levels, as their dosage can generally be varied according to the clinical response that a patient gets to that substance. In a small group of drugs, this is impossible, as insufficient levels will lead to under treatment or resistance, and excessive levels can lead to toxicity and tissue damage.

Indications for therapeutic drug monitoring include:

- There is an experimentally determined relationship between plasma drug concentration and the pharmacological effect.

Clinical pharmacokinetics

- Knowledge of the drug level influences management.
- There is narrow therapeutic window
- There are potential patient compliance problems.
- The drug dose cannot be optimized by clinical observation alone.

Examples of drugs analyzed by therapeutic drug monitoring:

- Aminoglycoside antibiotics (gentamicin)
- Antiepileptics (such as carbamazepine, phenytoin and valproic acid)
- Mood stabilisers, especially lithium citrate)
- Antipsychotics (such as pimozide and clozapine)

Clearance

- The volume of serum or blood completely cleared of the drug per unit time.
- Clearance (Cl) is the most important pharmacokinetic parameter because it determines the maintenance dose (MD) that is required to obtain a given steady-state serum concentration (Css):

  MD = Css · Cl.
- The dimension of clearance is volume per unit time, such as L/h or mL/min.
- The ***therapeutic range*** should be considered as an initial guideline for drug concentrations in a specific patient; drug dose and steady-state concentrations should then be titrated and individualized based on therapeutic response.
- **Clearance**
- The **liver** is most often the organ responsible for drug metabolism while in most cases the kidney is responsible for drug elimination. The gastrointestinal wall, lung, and kidney can also metabolize some drugs, and some medications are eliminated unchanged in the bile. (examples)
- The majority of drug metabolism is catalyzed by enzymes contained in the microsomes of hepatocytes known as the **cytochrome P-450 (CYP) enzyme system**. This family of enzymes is very important to understand because specific enzymes are responsible for the metabolism of each drug entity.
- If a metabolic drug interaction occurs between one medication and another known to be a substrate for a specific enzyme, it can be assumed that a drug interaction will occur between that drug and other substrates of the same enzyme.

Clinical pharmacokinetics

- The kidney eliminates drugs by glomerular filtration and tubular secretion in the nephron. Once drug molecules have entered the urine by either of these processes, it is possible that the molecules may reenter the blood via a process known as ***tubular reabsorption***. Glomerular filtration and, usually, tubular reabsorption are passive processes. ***Tubular secretion*** is an active process usually mediated by a transport molecule which facilitates the transfer of drug across the kidney tubule. The majority of drug tubular secretion takes place in the proximal tubule of the nephron while tubular reabsorption usually takes place in the distal tubule of the nephron.