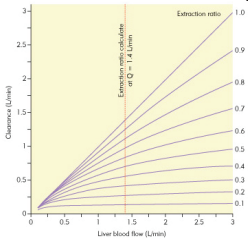
Extraction ratio is the fraction of drug flowing into the liver which is removed. Clearance can therefore also be expressed as blood flow times extraction ratio. In drugs with a high extraction ratio such as propofol, clearance is flow dependent, in drugs with a low ER such as alfentanil the capacity of the liver is the rate limiting factor. This is shown graphically in the image adjacent. As previously noted systemic clearance of anesthetic drugs generally occurs by means of hepatic metabolism. Other mechanisms include plasma and tissue ester hydrolysis (e.g., remifentanil, succinylcholine,esmolol), renal elimination (e.g., pancuronium), and nonspecific, "extrahepatic" metabolism for drugs whose clearance exceeds hepatic blood flow (e.g., propofol).



Renal excretion of drugs and metabolites in the urine involves three distinct processes: glomerular filtration, active tubular secretion, and passive tubular reabsorption. Changes in overall renal function generally affect all three processes to a similar extent. Almost all drugs are filtered at the glomerulus. Filtration is directly related to the rate and unlike the liver it is possible to estimate filtration rate using the cockroff-gault formula or eGFR. If a drug is in a lipid soluble form during its passage down the tubules a significant portion will be reabsorbed by simple passive diffusion. It may be therefore advantageous to have a drug in its ionised form which will increase removal of a drug in an overdose situation by alkanising or acidifying the urine. Pancuronium is the only anaethetic extensively execreted renally.

$$\log \frac{(\text{protonated})}{(\text{unprotonated})} = pK_a - pH$$

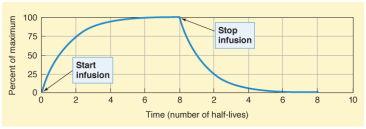
recall that log 1 equals 0 therefore when the protonanted and unprotonated forms are equal pKa and pH are the same

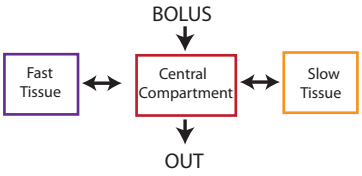
Most drugs are weak acids or bases that are present in solution as both the lipid-soluble and diffusible nonionized form, and the relatively lipid-insoluble nondiffusible ionized species. Therefore, the transmembrane distribution of a weak electrolyte is determined by its pKa (pH at which 50% is ionized) and the pH gradient across the membrane.. The ratio of nonionized to ionized drug at each pH is readily calculated from the Henderson–Hasselbalch equation:

Virtually all anaesthetic drugs are reversibly bound to plasma protiens. Acidic drugs (salicylates and barbituates) bind to albumin, basic drugs (fentanyl, diazepam and propanolol) also bind mainly to alpha1-acid glycoprotien. Only free unbound drugs may diffuse accross the membrane. The extent of plasma protein binding may be affected by disease-related factors (e.g., hypoalbuminemia). Conditions resulting in the acute-phase reaction response (e.g.,cancer, arthritis, myocardial infarction, and Crohn's disease) lead to elevated levels of alpha1-acid glycoprotein and enhanced binding of basic drugs. Decreases in protien binding can increase the clearance of drugs with low extraction rations by driving gradient into the liver (high extraction ratio drugs are not affected as all of the drug is metabolised whether it is bound or not). Decreases in protien binding may also increase the apparent potency of a drug by increasing free drug at the site of action.

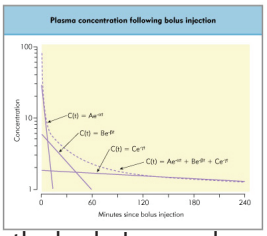
Half life is the time required to change the amount of drug in the body by one half. Using a single compartment model the half life depends on the volume of distribution and the clearance. It may be represented by the following formula (0.693 is the log of 2). It can be used to describe change to steady state or rate of elimination. Note that after one half life the amount is 0.5, then 0.5+0.25, then 0.75+0.125, then 0.875+0.0612. This means steady state basically occurs after 4-5 half lives (greater than 94%).

$$t_{1/2} = \frac{0.693 \times V_d}{CL}$$





Many drugs in anaesthesia are not easily described as single compartments. Whilst it is possible to create models with ten or more compartments they are cumbersome mathematically. Frequently a three compartment model is used with the central compartment (plasma), fast tissues (roughly correlating to muscles and splancic) and slow tissues (fat). Although this is gross simplification of what is actually happening, polyexponential pharmacokinetic models are useful because the models describe the data.



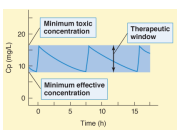
This adjacent picture shows the plasma concentration following a bolus injection into a three compartment model. This is described as the algerbraic sum of three exponential functions. The solid lines are the exponential fns and the dotted line is their sum (and the measured amount). An example of a drug that follows this behaviour is fentanyl.

When an infusion is given at an input rate of I, the plasma concentration rises as long as the rate of drug going into the body, I, exceeds the rate at which drug leaves the body, $C \times Cl$, in which C is the drug concentration. When $I = C \times Cl$, drug is going in and coming out at the same rate, and drug concentration in the body is at steady state. Clearance is the most important pharmacokinetic term to be considered when defining a rational steady state drug dosing regime. Because the maintenance rate of drug administration is equal to the rate of elimination at steady state (this is the definition of steady state), the maintenance dosage is a function of clearance

$$\text{Dosing rate} = \frac{\text{CL x Desired Plasma Concentration}}{\text{Bioavailability}}$$

If the therapeutic concentration must be achieved rapidly and the Vd is large, a large loading dose may be needed at the onset of therapy. This can be calculated from the following equation noting that unlike maintenence dose it is the volume of distribution which is most important. It is often prudent to give doses as a slow infusion to avoid toxic plasma concetrations as the drug distributes.

$$\text{Loading dose} = \frac{V_d \text{ x Desired Plasma Concentration}}{\text{Bioavailability}}$$



The therapeutic window is the safe range between the minimum therapeutic concentration and the minimum toxic concentration of a drug. The concept is used to determine the acceptable range of plasma levels when designing a dosing regimen. Thus, the minimum effective concentration usually determines the desired trough levels of a drug given intermittently, whereas the minimum toxic concentration determines the permissible peak plasma concentration

When drugs are administered there is a delay from peak plasma concentrations to drug effect. This represents the time taken to transit to the effect site (or biophase). K_{e0} is a constant which determines elimination from the effect site, and in combination with plasma pharmacokinetics determine the time to plasma-effect site equilibrium. Drugs with a high K_{e0} such as thiopental, propofol, and alfentanil reach rapid plasma effect site equilibrium. Intermediate medications include midazolam, fentanyl, vec and pancuronium and slow for morphine.

Christopher Andersen 2012