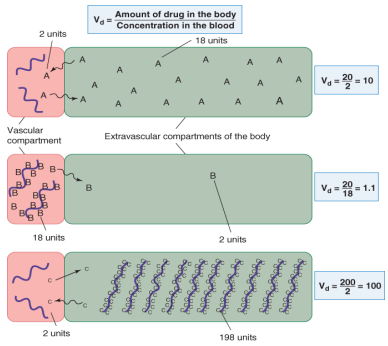
PHARMACOKINETICS

Volume and clearance are fundamental concepts in pharmacokinetics: volume represents the dilution of drug into fluids and tissues, and clearance is the flow of blood or plasma that is completely cleared of the drug.

Volume of distribution (apparent) The ratio of the amount of drug in the body divided by the drug concentration in the plasma or blood. This is shown graphically in the fig →



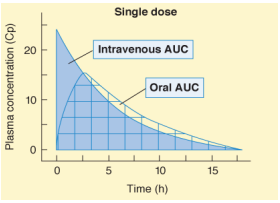
Clearance The ratio of the rate of elimination of a drug divided by the concentration of the drug in the plasma or blood

$$\text{Concentration} = \frac{\text{amount}}{\text{volume}}$$

$$\text{Volume} = \frac{\text{amount (dose)}}{\text{concenration}}$$

$$\text{Clearance} = \frac{\text{rate of elimination}}{\text{concentration}}$$

Metabolizing enzymes and transporters usually are not saturated, and thus the absolute rate of elimination of the drug is essentially a linear function (first-order kinetics) of its concentration in plasma, where a constant fraction of drug in the body is eliminated per unit of time. Most drugs obey first order kinetics. If mechanisms for elimination of a given drug become saturated, the kinetics approach zero order, in which a constant amount of drug is eliminated per unit of time. Three important drugs which use zero order kinetics are phenytoin, ethanol and aspirin.



The area under the blood concentration-time curve (area under the curve, or AUC, shaded in blue) can be used to calculate the clearance for first-order elimination.

$$\text{Clearance} = \frac{\text{Dose}}{\text{Area under Curve}}$$

The AUC is also used as a measure of bioavailability. It is defined as the fraction of unchanged drug reaching the systemic circulation by any route. By definition is is 100% for IV drugs.

For drug administration orally, the bioavailability is less than 100% for two main reasons:

1. Incomplete extent of absorption this is usually due to drugs being two hydrophilic (eg atenolol) or lipophilic (aciclovir). Drugs may also be actively transported back to the gut lumen by transporters such as P-glycoprotien (which is inhibited by grapefruit juice which leads to increased bioavailability)
2. First pass elimination following absortion from the gut wall the venous blood returns via the portal system via the liver which may metabolise a large portion of the drug (some metabolism also happens in tissues such as the gut wall). Morphine is well absorbed at the gut but metabolised extensively in the liver (Extraction ratio is 67%), therefore the bioavailability is only 33%.

Sublingual - Venous drainage from the mouth is to the superior vena cava, which protects highly soluble drugs like nitroglycerin from rapid hepatic first-pass metabolism.

Transdermal - Absorption of drugs able to penetrate the intact skin is dependent on the surface area over which they are applied and their lipid solubility

Rectally - Approx 50% of the drug that is absorbed from the rectum will bypass the liver, thus reducing the hepatic first-pass effect.

Pulmonary - Gaseous and volatile drugs may be inhaled and absorbed through the pulmonary epithelium and mucous membranes of the respiratory tract. Access to the circulation is rapid by this route because the lung's surface area is large (~140 m2) and first-pass metabolism is avoided.

Subcutaneous The rate of absorption following subcutaneous injection of a drug often is sufficiently constant and slow to provide a prolonged effect. Variations in particle size, protien complexation and pH can also vary absorption (eg insulin types)

Intramuscular Drugs in aqueous solution are absorbed rapidly after intramuscular injection depending on the rate of blood flow to the injection site and the fat versus muscular composition of the site. Gluteus maximus injections in women often lead to slower rates.

Intrathecal The blood–brain barrier and the blood–cerebrospinal fluid (CSF) barrier often preclude or slow the entrance of drugs into the CNS. Therefore, when local and rapid effects on the meninges or cerebrospinal axis are desired, drugs sometimes are injected directly into the spinal subarachnoid space. Some of the common local anesthetics (e.g., tetracaine) are esters; they are hydrolyzed and inactivated primarily by a plasma esterase, probably plasma cholinesterase. Hepatic enzymes also hydrolyze local anesthetic esters. Since spinal fluid contains little or no esterase, anesthesia produced persists until clearance by the systemic circulation.

Biotransformation of drugs typically reduces the lipophilicity, resulting in metabolites that are more likely to be excreted by the kidney, or discharged into the intestine. Biotransformation occurs in nearly all tissues, but the main site is the liver. Hepatic metabolism is responsible for systemic clearance of almost all IV drugs in anaesthesia. There are two types of biotransformation reactions:

Phase I Reactions: which expose a linking group (usually oxygen or nitrogen). This can be achieved by cleaving a a molecule (O-dealklation or N-dealkylation), altering an existing oxygen to increase reactivity (deamination) or by adding an OH group (hydroxylation) or double bonded O (s-oxidation). Phase 1 rxns are often catalysed by cytochrome P450 enzymes present in the smooth endoplasmic reticulum (others catalysers include Flavin-containing monooxygenases (FMO) and Epoxide hydrolases (mEH, sEH)). The most important is CYP3A4 which is responsible for metabolism of more than 50% of drugs including many anaesthetics such as (fentanyl, alfentanil, methadone, midazolam, diazepam, lignocaine, bupivacaine & ondansetron). CYP3A4 may be induced by rifampicin, glucocorticoids, barbituates, phenytoin and carbemazepine. It is inhibited by St Johns Wort, macrolide antibiotics (which are metabolised then bind tightly to P450 rendering it inactive) and the -azole antifungals. Grapefruit juice inhibits CYP3A4 at the intestinal lumen.

Phase II Reactions: the drug undergoes conjugation, typically by glucuronic acid (via UDP-glucuronosyltransferases (UGT)), acetate (N-acetyltransferases (NAT)), glutathione (Glutathione-S-transferases (GST)), sulfate (Sulfotransferases (SULT)) or an amino group. This may mask an exisiting functional group. The main purpose of this rxn is to transform hydrophobic molecules into hydrophilic molecules by addition of a polar group. Phase II rxns are relatively faster than P450 catalysed rxns, thus effectively accelerating drug biotransformation. Biotransformation may result in toxic metabolites. This is often exaberated when substrates are exhaused as occurs in paracetamol which is 95% conjugated by UGT or SULT and 5% by P450 dependent glutathione (GSH). When UGT & SULT are saturated GSH becomes dominant. As GSH is depleted a toxic metabolite accumulates causing liver death. This is neutralised by N-acetylcysteine.

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