Modes of drug elimination and bioactive metabolites

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Abstract

Drug elimination is the removal of active drug from the body. Metabolism takes place largely in the liver and produces water soluble metabolites which can be excreted in the bile or urine. Metabolism may also produce active or toxic metabolites or a pharmacologically active drug from an inactive prodrug. Most volatile anaesthetics are excreted unchanged via the lungs. Drug elimination can be affected by factors such as first-pass metabolism, genetic variants and various disease processes. Knowledge of these processes will allow better prediction of pharmacokinetics in practice.

Keywords Clearance; excretion; metabolism; pharmacokinetics

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Learning objectives

After reading this article, you should be able to:

- describe the phases of metabolism
- list the routes of drug excretion
- discuss the factors which affect these processes

Drug elimination is the removal of active drug from the body and comprises the pharmacokinetic processes of metabolism and excretion. In most cases, the role of drug metabolism is to produce a more polar (water soluble) molecule that can then be excreted in the bile or urine, the main routes of drug excretion. However, not all drugs are metabolized; some are excreted unchanged. Other routes of drug excretion include the lungs, saliva, sweat, tears, breast milk and hair.

Clearance

Clearance represents the notional volume of blood cleared of the drug per unit time. Drug elimination is often a first order process, such that the rate of drug removal depends upon its plasma concentration. For most drugs, the total body clearance is the sum of hepatic and renal clearance, but for some drugs clearance by the lungs may be significant (e.g. volatile anaesthetic agents).

Total clearance (Cl) is calculated by dividing the mass of drug that enters the systemic circulation by the area under its plasma concentration vs. time curve (AUC).

$$\mathrm{Cl} = \frac{\mathrm{DOSE}}{\mathrm{AUC}}$$

At steady state, when the blood concentration of a drug is constant, the amount entering the blood per unit time (i.e. the dose) must be the same as the amount leaving the body (i.e. the clearance). Thus, for infused drugs, the clearance can be calculated from the infusion rate and the steady state concentration.

Clearance = Drug infusion rate/Steady state drug concentration.

For intermittent drug dosing, a similar relationship exists.

Metabolism

Drug metabolism is largely (though not exclusively) handled by the liver. There are 2 phases of metabolism, I and II (Figure 1).

Phase I (non-synthetic)

Phase I reactions include oxidation, reduction and hydrolysis. The most important of these is oxidation. Many oxidative phase I reactions result from the activity of cytochrome P450, a non-specific enzyme system residing in the endoplasmic reticulum. Other enzymes involved in phase I metabolism include the mono-oxygenase system, alcohol dehydrogenase, aldehyde dehydrogenase, monoamine oxidase, peroxidase, NADPH-cytochrome P450 reductase, reduced cytochrome P450, esterases and amidases.

Some phase I processes take place in either the plasma or in other tissues. Suxamethonium is metabolized by hydrolysis in the plasma, catalysed by plasma cholinesterase. Genetic variants of this enzyme may lead to prolonged drug action and are discussed in greater detail below. Atracurium is metabolized by lung and plasma esterases but also undergoes spontaneous degradation in a pH and temperature dependent manner (Hoffman elimination) to form a tertiary amine (laudanosine). Remifentanil is metabolized by non-specific plasma and tissue esterases. Other tissues, including gastric mucosa and the lung, also metabolize drugs (Table 1).

Phase II (conjugation or synthetic)

Phase II reactions involve conjugation of the drug; such reactions occur after phase I chemical modification and render the drug metabolite water soluble. The drug molecule becomes chemically bound to a small molecular group (e.g. amino, hydroxyl, thiol, sulphate, glutamate, acetate, methyl and most commonly, glucuronide).

The enzymes involved in drug metabolism can be induced or inhibited by certain drugs and other substances (Table 2). This can give rise to clinically important drug interactions leading to therapeutic failure, drug toxicity or tolerance.

Bioactive metabolites

Metabolism usually reduces the activity of a drug. However, in some cases, it leads to the conversion of one pharmacologically active substance to another active substance. This has the effect

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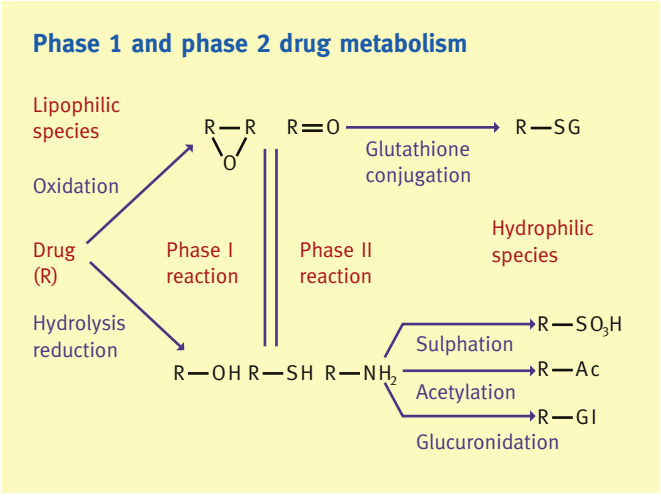

Figure 1

of prolonging drug action. An example of this is in morphine metabolism. One of its metabolites, morphine-6-glucuronide, is 13 times more potent than morphine and has a similar duration of action. Metabolism may also lead to the conversion of a pharmacologically inactive substance to an active one. These inactive substances, reliant on metabolism for their pharmacological effects, are termed prodrugs. Examples include diamorphine, parecoxib and enalapril.

Phase I oxidation may also lead to the formation of highly reactive, toxic metabolites (epoxides) that bind irreversibly to cell constituents. Glutathione in the liver combines with epoxides rendering them inactive and is an important defence mechanism against hepatic damage.

First-pass effects

Oral bioavailability (the proportion of orally administered drug entering the systemic circulation compared with the same dose given intravenously) depends not only upon the ability of a drug to penetrate the gut mucosa, but also upon the extent to which the drug is metabolized either by enzymes in the gut wall or in the liver. This metabolism, which occurs before oral drugs are able to reach the systemic circulation, is known as first-pass metabolism. Drugs with significant first-pass metabolism include morphine, lidocaine, glyceryl trinitrate and salbutamol.

Genetic variants

Drug responses are sometimes governed by heredity. Some of the variations which are relevant to anaesthetists are listed below.

Acetylator status

Acetylation is a phase II metabolic pathway in the liver for many drugs that possess a $-NH_2$ group and include isoniazid, hydralazine, and sulphasalazine. Different isoenzymes acetylate at either a fast or slow rate, leading to pharmacokinetic differences between individuals.

Pseudocholinesterase deficiency

Suxamethonium is hydrolysed in the plasma by plasma pseudocholinesterase. However, genetic variability can lead to prolonged neuromuscular block. Ten different genotypes are known. Heterozygotes for the normal gene have a mildly prolonged block, whereas a small fraction of the population have a genotype which may confer a block of several hours.

Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency

G-6-PD activity maintains erythrocyte glutathione in its reduced form, which is necessary to keep haemoglobin in its reduced (ferrous) rather than ferric state (methaemoglobin). Individuals who are G-6-PD deficient may suffer acute haemolysis if exposed to certain oxidant drugs, including quinolones, sulphonamides and sometimes aspirin.

Biliary excretion

The bile is the route of excretion for high molecular weight compounds (generally greater than 300) such as the steroid-based muscle relaxants. Secretion into the biliary canaliculus is an active process and therefore subject to inhibition and competition. Drugs may be excreted unchanged or as conjugated metabolites. Once in the digestive tract, lipid soluble drugs may be reabsorbed unchanged and glucuronide conjugates may be hydrolysed by bacterial glucuronidase and reabsorbed. The drug can then be extracted from the portal circulation by the liver and re-excreted in the bile. This is known as the enterohepatic circulation. Drugs and metabolites that do not recirculate are excreted in the faeces.

Reactions taking place in the lungs

Reaction	Drug	Metabolite
Phase 1 reactions		
Oxidation	Phenobarbitone	5-ethyl-5-barbituric acid
	Nortryptyline	Desmethylnortryptyline
Reduction	Nitrazepam	7-aminonitrazepam
Hydrolysis	Acetylcholine	Choline & acetate
Phase 2 reactions		
Methyltransferase	5-hydroxytryptamine	5-N-methyl-5-hydroxytryptamine
Catechol-O-methyltransferase	Isoprenaline	3-O-methylisoprenaline

Table 1

List of liver enzyme inducers and inhibitors

Enzyme inducers	Enzyme inhibitors
Alcohol (chronic)	Alcohol (acute)
Barbiturates	Amiodarone
Carbemazepine	Cimetidine
Griseofulvin	Ciprofloxacin
Phenytoin	Dextropropoxyphene
Rifampicin	Etomidate
Volatiles	Erythromycin
	Fluconazole
	Metronidazole

Table 2

The extraction ratio is the fraction of drug removed from the plasma by the liver. It depends upon hepatic blood flow, uptake into the hepatocyte and enzyme metabolic capacity within the hepatocyte. Drugs for which the hepatocyte has a high metabolic capacity (e.g. propranolol) will have an extraction ratio dependent upon blood flow. Those for which there is a low metabolic capacity (e.g. warfarin, phenytoin) will have an extraction ratio dependent upon protein binding as the enzymes rapidly become saturated once the free drug concentration increases and the concentration gradient into the hepatocyte is reduced.

Renal excretion

To be extensively excreted in the urine, a drug or metabolite must not only be water soluble (polar), but also must not be too large or bound too strongly to proteins in the bloodstream. Three processes are important:

Glomerular filtration: drugs pass through the membrane of Bowman's capsule, to be excreted in the urine. Drugs that are too large to pass through the membrane (e.g. heparin) cannot be filtered.

Tubular secretion: this is an active process whereby molecules are transported against a chemical gradient. Tubular secretion in combination with absence of tubular reabsorption may cause the renal clearance to exceed glomerular filtration rate (GFR: 100 ml kg^{-1} h^{-1}). Active secretion occurs via a carrier mechanism and binding to plasma proteins does not prevent it. Basic carriers transport basic drugs such as amiloride and dopamine; acidic carriers transport drugs such as furosemide and penicillin. Agents that block active secretion will increase the plasma concentration (and therapeutic effect) of drug (e.g. probenecid).

Tubular reabsorption: this occurs by diffusion, is a passive process and takes place along with normal water reabsorption within the nephron. It depends on the drug's ability to diffuse through the tubule. Very lipid soluble drugs (e.g. thiopentone and phenytoin) pass freely back into plasma, with little loss into the urine. Polar drugs cannot passively equilibrate between plasma and urine and so the entire mass that has been ultrafiltered into the nephron is passed into the urine (e.g. vecuronium). Some drugs may be reabsorbed actively; drugs that resemble essential amino acids (levodopa, α-methyldopa, and thyroxine) are actively reabsorbed.

The acidity of urine, which is affected by diet, drugs, and kidney disorders, can affect the rate at which the kidneys excrete some drugs. In the treatment of some poisonings, the acidity of the urine may be manipulated to accelerate the drug's elimination.

Other routes of excretion

The lungs are the main route of excretion of volatile anaesthetics. Most are excreted unchanged, the exceptions being halothane (up to 25% metabolized) and sevoflurane (2–3% metabolized).

Drug metabolites may also be found in the skin, sweat, tears, hair, saliva and breast milk. Non-ionized, lipid soluble drugs diffuse through glandular and epithelial cells. Hair testing focuses upon what is found inside the hair shaft. Metabolites for drugs, including cannabis, become lodged within the shaft and are thus detectable. Poisons such as mercury, lead and arsenic can also be detected years after death.

Chelation

Drug elimination may be enhanced pharmacologically by the use of chelating agents. Penicillamine may be used for copper chelation in Wilson's disease and desferrioxamine for iron chelation in haemochromatosis. Of particular interest to anaesthetists is sugammadex. This molecule is a 'doughnut' shaped cyclodextran possessing a lipophilic centre and a negatively charged hydrophilic outer core. The positive charges on rocuronium (quaternary ammonium compound) are attracted to this negative charged and the molecule is tightly bound, through van der Waal's forces, within the 'doughnut'. The molecular structure was designed to bind specifically to rocuronium forming a very stable complex. Vecuronium and pancuronium, which possess similar amino-steroidal structures are also bound, though less well. As a consequence of the chelation, the concentration of free rocuronium diminishes leading to termination of its effects. The resulting complex diffuses through Bowman's capsule, and is eliminated from the body in the urine.

Drug elimination and disease states

Liver disease: in pathological liver states, there may be profound alterations in drug handling. Some drugs, (e.g. morphine), are very effectively removed by the liver and enzyme activity is not close to maximal. Therefore, clearance is relatively robust to changes in hepatic function, but may be affected by reductions in hepatic blood flow. Other drugs, with low intrinsic clearance are much more affected by hepatic enzyme activity.

Heart failure: Hepatic or intestinal wall drug-metabolizing activity may be reduced in CHF patients due to forward flow failure or increased venous pressure. First-pass metabolism may be reduced, resulting in increased bioavailability of drugs with high hepatic extraction ratios. Conversely, it lowers the concentration and/or delays the appearance of pro-drug agents that undergo hepatic metabolism to an active form.

Renal disease: most drugs are at least partially excreted by the kidney. The altered biochemical milieu imposed by chronic renal failure may lead to adverse effects with many commonly prescribed drugs. If drug metabolites are in themselves nephrotoxic, a vicious cycle with consequent worsening renal failure may result.

For prescribing purposes renal impairment is usually divided into three grades:

1. Mild: GFR 20–50 ml min^{-1}; serum creatinine 150–300 μmol l^{-1}
2. Moderate: GFR 10–20 ml min^{-1}; serum creatinine 300–700 μmol l^{-1}
3. Severe: GFR less than 10 ml min^{-1}; serum creatinine >700 μmol l^{-1}

Patients with a GFR more than 50 ml min^{-1} do not usually require any dosage adjustment. Dialysis may lead to the loss of therapeutic effect for some drugs due to their removal. Drugs to which particular attention must be given include many antibiotics, H_2 blockers, digoxin, anticonvulsants and non-steroidal anti-inflammatory drugs (comprehensive lists are found in most drug formularies such as the BNF). Drugs with minimal dose-related side effects only require a simple scheme for dose reduction. For more toxic drugs with a small safety margin, dose regimens based on glomerular filtration rate should be used.

Renal impairment may not affect drug metabolism directly, but for some drugs, it may delay excretion of toxic metabolites, which are normally cleared rapidly e.g. Norpethidine, a demethylated metabolite of pethidine which is toxic and has convulsant and hallucinogenic effects. ◆

FURTHER READING

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