Chapter 5
Drug Elimination

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Abstract Most drugs, especially toxicants, are lipophilic in nature and once absorbed, would remain inside the body, distributing between tissues indefinitely unless they are converted to polar substances and excreted from the body. Drug elimination is the process that permanently removes drugs from the body. It may occur physically by excretion or chemically by metabolism, and is responsible for the termination of most drug actions. Drug metabolism is the single most important pharmacokinetic process that accounts for many of the inter-individual variations seen in therapeutic drug responses, and the liver is the main organ involved. Both internal (e.g., age, diseases or genetic factors) and external (e.g., diet or environment) factors may affect the rate or extent of drug metabolism. The metabolism of drugs usually results in water soluble metabolites which are readily excreted, and this generally occurs in the kidneys. The processes involved in the renal excretion of drugs are glomerular filtration, active tubular secretion and passive tubular reabsorption. While the former two processes facilitate drug excretion and are not affected by urine pH, the latter one decreases drug excretion and is pH-dependent. The two pharmacokinetic parameters that are related to drug elimination are drug clearance (*CL*) and plasma half-life ($t_{½}$). Drugs with high clearance (e.g., lidocaine, propranolol, morphine) display flow-dependent elimination, whereas drugs with low clearance (e.g., phenytoin, ethanol) exhibit capacity-limited elimination.

Keywords Drug elimination • Biotransformation (metabolism) • Excretion • Plasma clearance • Elimination half-life

Introduction

Most drugs, especially toxicants, are lipophilic in nature and once absorbed, would remain inside the body, distributing between tissues indefinitely unless they are converted to polar substances and excreted from the body. Drug elimination is the process that permanently removes drugs from the body. This may occur physically

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by excretion or chemically by metabolism and is responsible for the termination of most drug actions. Drug elimination especially metabolism, is also the single most important pharmacokinetic process that is responsible for many of the inter-individual variations seen in therapeutic drug responses. It is usually the slowest of the four major pharmacokinetic processes. Hence, the terminal plasma half-life of a drug usually describes its elimination half-life.

Drug Elimination by Metabolism or Biotransformation

Biotransformation and metabolism are often used synonymously in describing the disposition of a drug. However, biostransformation is a more accurate term as it describes the process by which a substance is chemically transformed into another entity by the body. On the other hand, the term metabolism is used frequently to describe also the total fate of a xenobiotic (drug or non-drug chemical) in the body. In pharmacokinetics, the term metabolism is commonly used to mean biotransformation from the standpoint that the products of drug biotransformation are called metabolites.

Sites of Drug Metabolism

Liver is the principal, but not the only, organ involved in metabolizing drugs since a large variety of enzymes reside there. Other important sites of drug metabolism include gastrointestinal tract (e.g., catecholamines), lungs (e.g., prostaglandins, angiotensins), kidneys (e.g., imipenem) and plasma (e.g., succinylcholine, procaine).

Process of Drug Metabolism

Drug metabolism involves chemical reactions (usually enzymatic) that produce metabolites that are frequently more polar, more readily excreted and often biologically inactive. But at times, active drugs (e.g., diazepam, aspirin, codeine) may be converted to active metabolites (e.g., oxazepam, salicylate, morphine, respectively), which will then prolong the pharmacological actions of the parent drugs. Drugs (e.g., acetaminophen, cyclophosphamide) may occasionally produce reactive metabolites (e.g., N-acetyl-p-benzoquinoneimine, acrolein, respectively) that may be toxic to intracellular components (see Fig. 27.2 in Chap. 27). Drug metabolism may also be used to convert an inactive precursor (called a prodrug) to the actual active drug in the body. Examples include:

(a) levodopa to dopamine (in the central nervous system)
(b) prednisone to prednisolone (in the liver)

(c) erythromycin succinate to erythromycin (in the gastrointestinal tract)
(d) zidovudine (AZT) to AZT-triphosphate (in infected cells)

Advantages of prodrugs include improved bioavailability, prolonged duration of action, and site-specific drug delivery.

Phases of Drug Metabolism

Drug metabolism reactions are broadly divided into two phases: Phase I (or functionalization) reactions and phase II (or conjugative) reactions. Examples of drugs undergoing the various phase I and II reactions are given in Table 5.1.

Phase I reactions add or unmask functional groups (e.g., –OH, $-NH_2$, $-SH$, $-COOH$, etc.), which can then participate in phase II reactions. These are non-synthetic reactions. Oxidation reactions occur mainly on the smooth endoplasmic reticulum (sER) and are catalyzed by a family of enzymes known as microsomal "mixed-function oxidases" (MFO, so called because they catalyze a large range of oxidation reactions on a variety of substrates). These microsomal oxidative enzymes are also known as "monooxygenases". Other phase I reactions (including some oxidation reactions) take place in the cytosol, plasma and mitochondria. Phase I metabolites are usually not much more polar than their parent drugs, but they are often chemically reactive and may even be toxic (e.g., acetaminophen-induced liver toxicity or cyclophosphamide-induced bladder toxicity).

Table 5.1 Examples of drugs undergoing phase I and II drug metabolism reactions

Phase I reactions	Drugs
Oxidation (involving cytochrome P450)	Amphetamine, codeine, diazepam, ethanol, lignocaine, phenobarbital, phenytoin
Oxidation (others)	Epinephrine, ethanol, theophylline, tyramine
Reduction	Chloramphenicol, halothane, methadone
Hydrolysis	Esters: procaine, succinylcholine Amides: lignocaine, procainamide

Phase II reactions	Drugs
Glucuronide conjugation	Acetaminophen, morphine
Sulfate conjugation	Acetaminophen, sex steroids
Glutathione conjugation	Acetaminophen
Glycine conjugation	Salicylates
Acetylation	Isoniazid
Methylation	Catecholamines

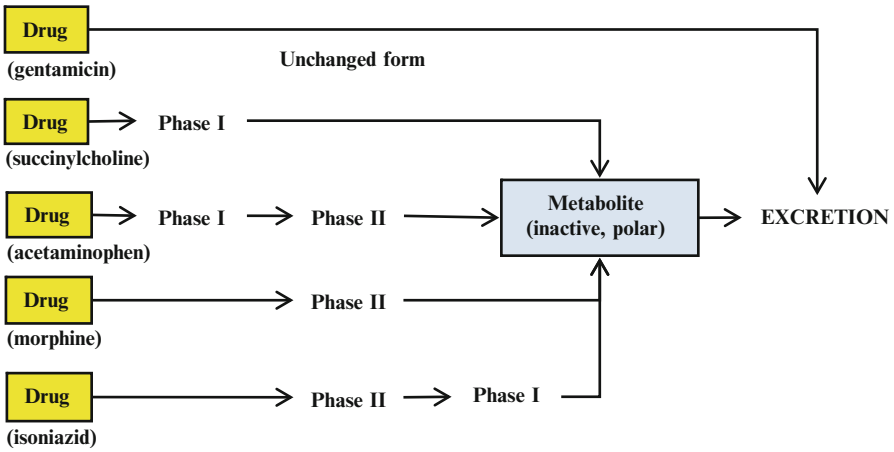

Fig. 5.1 Schematic diagram showing different pathways of drug metabolism

Phase II reactions are synthetic and involves the addition of a large endogenous substrate to the drug or its phase I metabolite to form a conjugate. Thus, phase II metabolites are frequently much more polar and almost always inactive, except for a few drug metabolites (e.g., morphine 6-glucuronide, N-acetylprocainamide or minoxidil sulfate). These conjugation reactions occur mainly in the cytosol, except for glucuronide conjugation reactions, which occur on sER and thus glucuronyl-transferases are microsomal enzymes. Generally speaking, only the microsomal enzymes are inducible.

Drugs may be excreted without being metabolized (e.g., gentamicin). However, the majority of drugs undergo some form of metabolism (whether phase I or phase II, or more commonly, both) before excretion. While most drugs undergo phase I and phase II reactions in that order, in some cases (e.g., isoniazid), phase II reactions precede phase I reactions (Fig. 5.1).

Cytochrome P450

Cytochrome P-450 (P450) is a heme-containing enzyme, which is part of the MFO system, and can exist in many isoforms (e.g., CYP1A2, CYP2D6, CYP3A4). These P450 enzymes are predominantly expressed in the liver and are extremely important in drug metabolism. They are essential for most drug metabolism, contribute to most of the observed variations in drug response of differing ethnic origins (due to genetic polymorphism of P450 isozymes), account for many of the important drug interactions (Table 5.2), and are responsible for a number of serious adverse effects. In view of this, physicians should be cautious in prescribing drugs known to be P450 inducers or inhibitors, especially to critically ill patients.

Table 5.2 Important P450 enzymes and examples of drugs which require dose adjustment to prevent adverse effects resulting from drug interaction involving enzyme inhibition or induction

Enzymes	Potent inhibitor	Potent inducer	Affected drug
CYP1A2	Amiodarone Cimetidine Ciprofloxacin Fluvoxamine	Carbamazepine Phenobarbital Rifampin Cigarette smoke	Clozapine Haloperidol Propranolol Theophylline
CYP2D6	Amiodarone Cimetidine Diphenhydramine Fluoxetine Quinidine Ritonavir	No significant inducers	Amitriptyline Carvedilol Codeine Donepezil Haloperidol Metoprolol Propranolol Risperidone Tramadol
CYP3A4	Clarithromycin Cimetidine Erythromycin Fluconazole Indinavir Omeprazole Sertraline	Carbamazepine Phenobarbital Phenytoin Rifampin St. John's wort	Alprazolam Amiodarone Astemizole Carbamazepine Cyclosporine Diazepam Fentanyl Simvastatin Zolpidem

Factors Affecting Drug Metabolism

Both internal (e.g., age, diseases or genetic factors) and external (e.g., diet or environment) factors may affect the rate or extent of drug metabolism.

1. **Age:** The activity of hepatic microsomal enzymes is low in both the very young and the elderly patients resulting in impaired drug metabolism. Hence there is an increased risk of drug toxicity with reduced inactivation of drugs. For example, the grey baby syndrome associated with the use of chloramphenicol in neonates is the result of an inadequate amount of glucuronyl transferases to conjugate the drug in the immature liver. On the other hand, phenobarbital, a potent enzyme inducer, can be given to accelerate the clearance of bilirubin in jaundiced neonates by enhancing bilirubin conjugation.
2. **Diseases:** Chronic liver diseases (e.g., cirrhosis) markedly affect the hepatic metabolism of certain drugs (e.g., diazepam) and prolong their duration of action in the body, leading to potential risk of overdose. Therefore, drugs which are highly dependent on liver for their elimination (e.g., opioids, acetaminophen, and propranolol) should be used with caution in patients with liver diseases and their dosages reduced accordingly.

3. **Genetic variation:** The metabolism of certain drugs (e.g., succinylcholine and isoniazid) is significantly reduced in susceptible people who have either a defective enzyme (e.g., atypical pseudocholinesterase for hydrolyzing succinylcholine) or abnormally low level of an enzyme (e.g., acetylation of isoniazid).
4. **Diet:** Certain plant foods (e.g., cabbage and cauliflower) and barbecued foods contain bioactive compounds which are enzyme inducers. Regular ingestion of such foods can significantly increase the metabolism of administered drugs and reduce their therapeutic effectiveness. On the other hand, grapefruit juice is known to inhibit certain P450 enzymes that metabolize a number of drugs and may result in increased risk of toxicity.
5. **Environment:** Cigarette smoke and dichlorodiphenyltrichloroethane (DDT, a banned insecticide in many countries) are also powerful inducers of drug-metabolizing enzymes.

Drug Elimination by Excretion

The metabolism of drugs usually results in water soluble metabolites which are readily excreted. Some drugs, however, are directly eliminated without metabolism. While the liver is the major organ for eliminating drugs by metabolism, it is the kidneys which are responsible for eliminating most drugs and metabolites by excretion. Besides the kidneys, the intestine, the biliary system and the lungs are also involved in excreting many drugs, while a small amount of drugs may be excreted in the saliva, sweat and milk.

Renal Excretion

Three processes are involved in the renal excretion of drugs (Fig. 5.2). They are glomerular filtration, active tubular secretion and passive tubular reabsorption. While the former two processes facilitate drug excretion and are not affected by urine pH, the latter one decreases drug excretion and is pH-dependent.

1. *Glomerular filtration*: Drugs with MW <5,000 are readily filtered. The concentration of drugs in the filtrate is directly proportional to the glomerular filtration rate (GFR) and the fraction of unbound drug in the plasma.
2. *Active tubular secretion*: Active secretion of acidic drugs (e.g., penicillin, salicylates, furosemide, probenecid, sulfonamides) and basic drugs (e.g., amphetamine, quinine, procaine, morphine) occur in the proximal renal tubules. These transport systems are saturable and subject to competition by drugs with similar physicochemical properties. Thus, probenecid may competitively inhibit the active secretion of penicillin, thereby prolonging the duration of penicillin action. On the other hand, competitive inhibition of the tubular secretion of methotrexate by probenecid and salicylates contributes to its increased risk of nephrotoxicity.

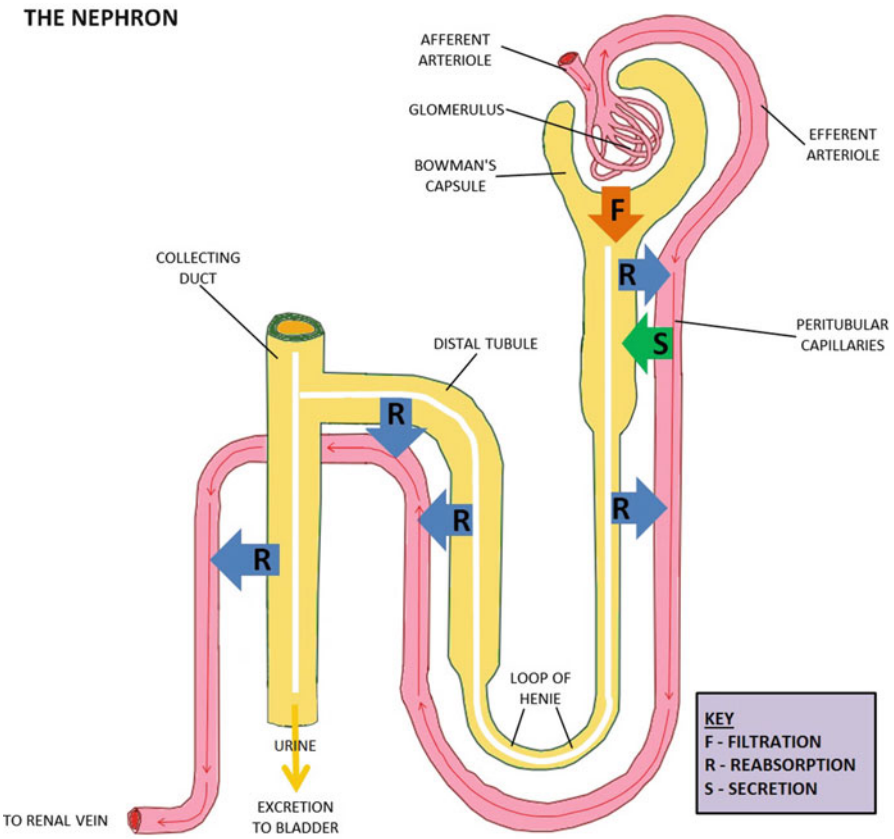

Fig. 5.2 The nephron showing the three processes (filtration, reabsorption and secretion) involved in the excretion of drugs

3. *Passive tubular reabsorption*: This process is affected by urinary pH and the degree of ionization of a drug. Weakly acidic drugs such as aspirin and phenobarbital are more ionized in alkaline urine and therefore more likely to be excreted because the ionized drugs are not reabsorbed from the tubule. The same is true with weakly basic drugs such as amphetamine and quinine in the presence of acidic urine. This property is used in the treatment of poisoning where forced alkaline diuresis is employed to hasten excretion of salicylates and barbiturates, whereas forced acid diuresis can be used to enhance the excretion of amphetamine and quinine.

Biliary and Fecal Excretion

There is a portion of orally administered drugs that are not absorbed and these are excreted in the feces. These are often large polar drugs. Large water-soluble

conjugates produced in the liver are excreted via the bile into the intestine. Some of these conjugated metabolites may get broken down in the lower portion of the gastrointestinal tract to release more lipid soluble drugs, which are reabsorbed and carried back to the liver. This cycle is then repeated. Such recycling is known as "enterohepatic circulation" and is responsible for prolonging the duration of action of drugs such as oral contraceptive steroids, morphine and erythromycin. It also explains the presence of some unusual metabolites in the urine, which could have originated from the gut microbial metabolism during the enterohepatic circulation. It has been suggested that failure of oral contraception may be due to a disruption of enterohepatic circulation following antibiotic therapy which removes the bacteria from the lower intestine that hydrolyze estrogen conjugates.

Pulmonary Excretion

The lungs are the main portal of excretion for gaseous and volatile agents such as alcohol and inhaled general anesthetic agents. The majority of these agents are excreted unchanged in the exhaled air and this allows for the anesthetic gas to be recycled in an anesthetic low flow system.

Other Routes of Excretion

Small amounts of drugs and metabolites may be excreted in sweat, saliva, tears and milk. Excretion in the saliva may impart some unique taste, such as metallic taste with metronidazole. A metabolite of rifampicin imparts an orange tinge to the sweat, tears, saliva and urine, and may sometimes be mistaken as blood in these body fluids. Milk has a slightly acidic pH, and basic drugs such as diazepam, chloramphenicol, morphine and tetracycline, are more likely to be excreted in milk, albeit in small amount. Since neonates have immature eliminating mechanisms, suckling infants may therefore be exposed to potentially dangerous levels of drugs.

Drug Clearance and Plasma Half Life

The two pharmacokinetic parameters that are related to drug elimination are clearance (CL) and plasma half-life ($t_{½}$). Plasma clearance of a drug is the volume of plasma cleared of the drug (by all elimination processes) per unit time. It is the sum of all the clearances ($CL_{\text{plasma}} = CL_{\text{hepatic}} + CL_{\text{renal}} + CL_{\text{others}}$), and can be calculated by the ratio of the rate of elimination to the plasma concentration.

$$CL = \frac{Rate\,of\,elimination}{Plasma\,concentration}$$

Clearance is the most important factor in determining the plasma concentration of a drug and should be taken into consideration when long-term treatment with the drug is required. Thus, when a drug is given on a regular basis,

$$\text{Dosing rate} \;=\; CL \cdot C_{\text{p,ss}}$$

where $C_{\text{p,ss}}$ is the plasma concentration at steady-state.

The general equation describing hepatic clearance is $CL_{\text{h}} = QE$, where CL_{h}, Q and E represent total hepatic drug clearance, total hepatic blood flow and the hepatic extraction ratio, respectively.

1. *High clearance, flow-dependent elimination*: For some drugs (e.g., lidocaine, morphine, nitroglycerin, propranolol, and verapamil), the extraction ratio is high (E >0.7), and the drug is removed by the liver almost as rapidly as the organ is perfused by the blood containing the drug. Consequently, the hepatic clearance of these drugs approaches hepatic blood flow and the rate of their elimination is sensitive to changes in hepatic blood flow (i.e., flow-dependent elimination). Many ingested drugs that demonstrate significant first-pass effect are drugs with high hepatic extraction ratio.
2. *Low clearance, capacity-limited elimination*: For drugs with low extraction ratio (E <0.3), the hepatic clearance is less affected by liver blood flow (i.e., flow-independent elimination). Instead the elimination of these drugs is affected more by the intrinsic activities of the metabolizing enzymes (especially the CYP 450 enzymes). Hence, drugs with low hepatic clearance display capacity-limited elimination, which is sensitive to changes in intrinsic activity (e.g., enzyme induction). Examples of low clearance drugs include phenytoin, procainamide, and theophylline.

Renal clearance is measured by the equation, $CL_{\text{r}} = Q_{\text{u}}C_{\text{u}}/C_{\text{P}}$, where CL_{r}, Q_{u}, C_{u}, and C_P represent total renal drug clearance, urinary flow rate, urine concentration, and plasma concentration, respectively.

Plasma half-life ($t_{½}$) is the time taken for the plasma drug concentration to fall to half of its original concentration. It takes 4–5 half-lives to completely eliminate a drug from the body, and it also takes the same amount of time to reach its steady state when a drug is given repeatedly. It is important to realize that the plasma half-life of a drug may change as a result of changes to either its clearance or volume of distribution according to the formula below.

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

An increase in plasma clearance of a drug (e.g., as a result of enzyme induction) will result in a decrease of the plasma half-life of the drug, whereas an increase in the volume of distribution (e.g., pregnancy, edema) will result in an increase in the plasma half-life.

Key Concepts

- Elimination is the process that permanently removes substances from the body and this may occur physically by excretion or chemically by metabolism (biostransformation).
- Most drugs are metabolized before being excreted from the body, but polar drugs may be excreted unchanged.
- Drug metabolites are frequently more polar, more readily excreted and often biologically inactive compared to their parent compounds.
- Concurrent administration of two drugs may result in one drug affecting the rate of metabolism of the other drug.
- Renal excretion is the most important route for drug excretion.
- For weak acids and weak bases, the renal tubular pH can significantly affect the fraction of these drugs excreted unchanged in the urine.
- Enterohepatic recycling of drugs generally prolongs the duration of drug action.
- Plasma clearance of a drug is the volume of plasma cleared of the drug (by all elimination processes) per unit time. It is the most important pharmacokinetic parameter.
- Drugs with high clearance (e.g., lidocaine, propranolol, morphine) display flow-dependent elimination, whereas drugs with low clearance (e.g., phenytoin, ethanol) exhibit capacity-limited elimination.

Summary

Drug elimination may occur physically by excretion or chemically by metabolism. It is responsible for the termination of most drug actions. Drug metabolism accounts for many of the inter-individual variations seen in therapeutic drug responses, and liver is the main organ involved. Both internal and external factors may affect the rate or extent of drug metabolism. The metabolism of drugs usually results in water soluble metabolites which are readily excreted, and this generally occurs in the kidneys. The processes involved in the renal excretion of drugs are glomerular filtration, active tubular secretion and passive tubular reabsorption. While the former two processes facilitate drug excretion and are not affected by urine pH, the latter one decreases drug excretion and is pH-dependent. The two pharmacokinetic parameters that are related to drug elimination are drug clearance (CL) and plasma half-life ($t_{½}$). Drugs with high clearance display flow-dependent elimination, whereas drugs with low clearance exhibit capacity-limited elimination.

Further Reading

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