4 Metabolism and Excretion of Drugs

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Both metabolism and excretion can be viewed as processes responsible for elimination of drug (parent and metabolite) from the body. Drug metabolism changes the chemical structure of a drug to produce a drug *metabolite,* which is frequently but not universally less pharmacologically active. Metabolism also renders the drug compound more water soluble and therefore more easily excreted.

Drug metabolism reactions are carried out by enzyme systems that evolved over time to protect the body from exogenous chemicals. The enzyme systems for this purpose for the most part can be grouped into two categories: phase I oxidative or reductive enzymes and phase II conjugative enzymes. Enzymes within these categories exhibit some limited specificity in relation to the substrates acted upon; a given enzyme may interact with only a limited number of drugs. Some nonspecific hydrolytic enzymes, such as esterases and amidases, have not received much research attention. The focus of this discussion therefore is on phase I and phase II reactions and the enzymes that carry out these processes.

OXIDATIVE AND REDUCTIVE ENZYMES: PHASE I REACTIONS

Phase I enzymes act by causing the drug molecule to undergo oxidation or more rarely, reduction. Examples of oxidation reactions carried out by phase I enzymes are listed in Table 4.1 and encompass a broad range of drugs with varying chemical structures. However, as discussed later, there is still a great deal of substrate specificity within a given enzyme family.

Cytochrome P450 Enzymes

The cytochrome P450 (CYP450) enzyme superfamily is the primary phase I enzyme system involved in the oxidative metabolism of drugs and other chemicals. These enzymes also are responsible for all or part of the metabolism and synthesis of a number of endogenous compounds, such as steroid hormones and prostaglandins.

Though it was originally described as the CYP450 enzyme, it is now apparent that it is a group of related enzymes, each with its own substrate specificity. To date, 12 unique isoforms (e.g., CYP3A4, CYP2D6) have been identified as playing a role in human drug metabolism, and others may be discovered. These isoforms, along with examples of compounds for which each isoform plays a substantial role in their metabolism, are listed in Table 4.2. More than one CYP isoform may be involved in the metabolism of a particular drug. For example, the calcium channel blocking drug verapamil is primarily metabolized by CYP3A4, but CYPs 2C9, 2C8 and 2D6 participate to some degree, particularly in the secondary metabolism of the verapamil metabolites. Thus, the degree to which a drug interaction involving competition for a CYP isoform may occur will depend on the extent of metabolism of each compound that can be attributed to that isoform. The more isoforms involved in the metabolism of a drug, the less likely is a clinically significant drug interaction.

Substrate Specificity of the CYP Enzymes

CYP3A4 is thought to be the most predominant CYP isoform involved in human drug metabolism, both in terms of the amount of enzyme in the liver and the variety of drugs that are substrates for this enzyme isoform.

TABLE 4.1 Types of Oxidation Reactions Involved in Enzymatic Drug Metabolism

Reaction	Examples
Aliphatic and aromatic hydroxylation	Ibuprofen, flurbiprofen
N-demethylation	Morphine
O-demethylation	Codeine
Epoxidation	Carbamazepine
N-Oxidation	Morphine
S-oxidation	Sulindac
Deamination	Amphetamine

This isoform may account for more than 50% of all CYP-mediated drug oxidation reactions, and CYP3A4 is likely to be involved in the greatest number of drug–drug interactions. The active site of CYP3A4 is thought to be large relative to other isoforms, as evidenced by its ability to accept substrates up to a molecular weight of 1200 (e.g., cyclosporine). This active site size allows drugs with substantial variation in molecular structure to bind within the active site. However, the fact that two drugs are metabolized predominantly by CYP3A4 does not mean that coadministration will result in a drug–drug interaction, since drugs can bind in different regions of the CYP3A4 active site, and these binding regions may be distinct. In fact, it is believed that two drugs (substrates) can occupy the active site simultaneously, with both available for metabolism by the enzyme. This finding helps account for a number of absent interactions that would have been predicted to occur based on strict substrate specificity rules.

CYP3A5, whose amino acid sequence is similar to that of CYP3A4, appears to possess roughly the same substrate specificity characteristics as CYP3A4. However, it differs in that it is not present in all individuals. Thus, patients expressing both CYP3A4 and CYP3A5 have the potential to exhibit increased metabolism of CYP3A substrates as compared to individuals expressing only the CYP3A4 isoform.

Levels of CYP enzyme expression of any isoform can vary substantially among individuals. The other identified human CYP3A isoform is CYP3A7, which appears to be expressed only in the fetus and rapidly disappears following birth, to be replaced by CYP3A4 and CYP3A5. It is becoming increasingly clear that different enzyme expression patterns, and thus different drug metabolism capabilities, are observed throughout the various stages of life. Neonates are different from 6-month-old infants, who differ from year-old infants, who differ from preadolescents, who differ from adolescents, who differ from adults, who differ from the elderly. Thus, consideration must be given to the person's age when assessing drug metabolism capacity.

The second most common CYP isoform involved in human drug metabolism is CYP2D6. It may account for 30% of the CYP-mediated oxidation reactions involving drugs, including the metabolism of drugs in such diverse therapeutic categories as antipsychotic agents, tricyclic antidepressants, β-blocking agents, and opioid analgesics. Though this isoform accepts a number of drugs as substrates, its relative abundance in the liver is quite low. CYP2D6 is most known for its propensity to exhibit genetic polymorphisms (see Pharmacogenetics, later in the chapter).

The other isoform responsible for a substantial portion (about 10%) of the CYP-mediated drug oxidation

TABLE 4.2 Representative Drugs Metabolized by Each of the CYP Isoforms in Human Drug Metabolism

CYP Isoform	Examples of Substrates	Comments
CYP1A1	Essentially same as CYP1A2	
CYP1A2	Polycyclic aromatic hydrocarbons, caffeine, theophylline	
CYP2A6	Nicotine, 5-fluorouracil, coumarin	
CYP2B6	Bupropion, cyclophosphamide, propofol	
CYP2C8	Paclitaxel	
CYP2C9	Phenytoin, warfarin, nonsteroidal antiinflammatory drugs	Polymorphic
CYP2C19	Omeprazole	Polymorphic
CYP2D6	Tricyclic antidepressants, codeine, dextromethorphan, some β-blockers, some antipsychotics, some antiarrhythmics	Polymorphic
CYP2E1	Acetaminophen, chlorzoxazone	
CYP3A4	Midazolam, triazolam, cyclosporine, erythromycin, HIV protease inhibitors, calcium channel blockers	Polymorphic
CYP3A5	Essentially same as CYP3A4	Polymorphic
CYP3A7	Unclear but may be similar to CYP3A4	Present only in the fetus

CYP, cytochrome P450.

reactions is CYP2C9. This isoform metabolizes several clinically important drugs with narrow therapeutic indices. Two of these drugs are the antiepileptic agent phenytoin and the anticoagulant warfarin. Any change in the metabolism of these two drugs, either increased or decreased, can have profound adverse effects. CYP2C9 appears to prefer weakly acidic drugs as substrates, which limits the number of drugs metabolized by this isoform, since most drugs are weak bases).

The remaining CYP isoforms involved in human drug metabolism (Table 4.2) are present in the liver in varying amounts, and each is thought to contribute 2–3% or less of the CYP-mediated drug oxidation reactions. Though they may not be involved in the metabolism of a broad range or significant number of drugs, if they are the primary enzyme responsible for the metabolism of the drug of interest, then their importance in that instance is obviously increased.

Regulation of the CYP Enzymes

CYP450 enzymes can be regulated by the presence of other drugs or by disease states. This regulation can either decrease or increase enzyme function, depending on the modulating agent. These phenomena are commonly referred to as enzyme inhibition and enzyme induction, respectively.

TABLE 4.3 Representative Inhibitors for Each of the CYP Isoforms Involved in Human Drug Metabolism

CYP Isoform	Examples of Inhibitors
CYP1A1	Thought to be same as CYP1A2
CYP1A2	Amiodarone, fluoroquinolone antibiotics, fluvoxamine
CYP2A6	Tranylcypromine, methoxsalen
CYP2B6	Efavirenz, nelfinavir, ritonavir
CYP2C8	Probably similar to CYP2C9
CYP2C9	Amiodarone, fluconazole, fluvastatin, lovastatin, zafirlukast
CYP2C19	Cimetidine, ketoconazole, omeprazole, ticlopidine[a]
CYP2D6	Amiodarone, cimetidine, fluoxetine, paroxetine, quinidine
CYP2E1	Disulfiram[a]
CYP3A4	HIV antivirals (e.g., Ritonavir), amiodarone, cimetidine, diltiazem, erythromycin[a], grapefruit juice, ketoconazole
CYP3A5	Thought to be same as CYP3A4
CYP3A7	Unclear at this time but may be similar to CYP3A4

[a]Mechanism-based inactivator.
CYP, cytochrome P450.

Enzyme Inhibition

Enzyme inhibition is the most frequently observed result of CYP modulation and is the primary mechanism for drug–drug pharmacokinetic interactions. The most common type of inhibition is simple competitive inhibition, wherein two drugs are vying for the same active site and the drug with the highest affinity for the site wins out. In this scenario, addition of a second drug with greater affinity for the enzyme inhibits metabolism of the primary drug, and an elevated primary drug blood or tissue concentration is the result. In the simplest case, each drug has its own unique degree of affinity for the CYP enzyme active site, and the degree of inhibition depends on how avidly the secondary (or effector) drug binds to the enzyme active site. For example, ketoconazole and triazolam compete for binding to the CYP3A4 active site and thus exhibit their own unique rate of metabolism. However, when given concomitantly, the metabolism of triazolam by the CYP3A4 enzyme (essentially the only enzyme that metabolizes triazolam) is decreased to such a degree that the patient is exposed to 17 times as much of parent triazolam as when ketoconazole is not present. Table 4.3 lists the common CYP isoforms and representative inhibitory agents.

A second type of CYP enzyme inhibition is mechanism-based inactivation (or suicide inactivation). In this type of inhibition, the effector compound (i.e., the inhibitor) is itself metabolized by the enzyme to form a reactive species that binds irreversibly to the enzyme and prevents any further metabolism by the enzyme. This mechanism-based inactivation lasts for the life of the enzyme molecule and thus can be overcome only by the proteolytic degradation of that particular enzyme molecule and subsequent synthesis of new enzyme protein. A drug that is commonly used in clinical practice and yet is known to be a mechanism-based inactivator of CYP3A4 is the antibiotic erythromycin.

Enzyme Induction

Induction of drug-metabolizing activity can be due either to synthesis of new enzyme protein or to a decrease in the proteolytic degradation of the enzyme. Increased enzyme synthesis is the result of an increase in messenger RNA (mRNA) production (transcription) or in the translation of mRNA into protein. Regardless of the mechanism, the net result of enzyme induction is the increased turnover (metabolism) of substrate. Whereas one frequently associates enzyme inhibition with an increase in potential for toxicity, enzyme induction is most commonly associated with therapeutic failure due to inability to achieve required drug concentrations.

Table 4.4 lists representative inducers of each of the CYP isoforms. No inducers of CYP2D6 have been identified.

TABLE 4.4 Representative Inducers for Each of the CYP Isoforms Involved in Human Drug Metabolism

CYP Isoform	Examples of Inducers
CYP1A1	Smoking (polycyclic aromatic hydrocarbons), char-grilled meat, omeprazole
CYP1A2	Same as CYP1A1
CYP2A6	Phenobarbital, dexamethasone
CYP2B6	Phenobarbital, dexamethasone, rifampin
CYP2C8	Same as CYP2C9
CYP2C9	Rifampin, dexamethasone, phenobarbital
CYP2C19	Rifampin
CYP2D6	None known
CYP2E1	Ethanol, isoniazid
CYP3A4	Efavirenz, nevirapine, barbiturates, carbamazepine, glucocorticoids, phenytoin, pioglitazone, rifampin, St. John's wort
CYP3A5	Thought to be same as CYP3A4
CYP3A7	Unclear but may be similar to CYP3A4

The time course of enzyme induction is important, since it may play a prominent role in the duration of the effect and therefore the potential onset and offset of the drug interaction. Both time required for synthesis of new enzyme protein (transcription and translation) and the half-life of the inducing drug affect the time course of induction. An enzyme with a slower turnover rate will require a longer time before induction reaches equilibrium (steady state), and conversely, a faster turnover rate will result in a more rapid induction. With respect to the drug inducer, drugs with a shorter half-life will reach equilibrium concentrations sooner (less time to steady state) and thus result in a more rapid maximal induction, with the opposite being true for drugs with a longer half-life.

Flavin Monooxygenases

The flavin monooxygenases (FMOs) are a family of five enzymes (FMO 1–5) that operate in a manner analogous to the cytochrome P450 enzymes in that they oxidize the drug compound in an effort to increase its elimination. Though they possess broad substrate specificity, in general they do not play a major role in the metabolism of drugs but appear to be more involved in the metabolism of environmental chemicals and toxins.

CONJUGATIVE ENZYMES: PHASE II REACTIONS

Phase II conjugative enzymes metabolize drugs by attaching (conjugating) a more polar molecule to the original drug molecule to increase water solubility, thereby permitting more rapid drug excretion. This conjugation can occur following a phase I reaction involving the molecule, but prior metabolism is not required. The phase II enzymes typically consist of multiple isoforms, analogous to the CYPs, but to date are less well defined.

Glucuronosyl Transferases

Glucuronosyl transferases (UGTs) conjugate the drug molecule with a glucuronic acid moiety, usually through establishment of an ether, ester, or amide bond. Examples of each of these types of conjugates are presented in Figure 4.1. The glucuronic acid moiety, being very water soluble, generally renders the new conjugate more water soluble and thus more easily eliminated. Typically this conjugate is inactive, but sometimes it is active. For example, UGT-mediated conjugation of morphine at the 6- position results in the formation of morphine-6-glucuronide, which is 50 times as potent an analgesic as morphine.

It is now apparent that UGTs are also a superfamily of enzyme isoforms, each with differing substrate specificities and regulation characteristics. Of the potential products of the UGT1 gene family, only expression of UGT1A1, 3, 4, 5, 6, 9 and 10 occurs in humans. Depending on the isoform, these enzymes have varying reactivity toward a number of pharmacologically active compounds, such as opioids, androgens, estrogens, progestins, and nonsteroidal antiinflammatory drugs; UGT1A1 is the only physiologically significant enzyme involved in the conjugation of bilirubin. UGT1A4 appears to be inducible by phenobarbital administration, and UGT1A7 is induced by the chemopreventive agent oltipraz.

UGT2B7 is probably the most important of the UGT2 isoforms and possibly of all of the UGTs. It exhibits broad substrate specificity encompassing a variety of pharmacological agents, including many already mentioned as substrates for the UGT1A family. Little is known about the substrate specificities of the other UGT2B isoforms or the inducibility of this enzyme family.

N-Acetyltransferases

As their name implies, the *N*-acetyltransferase (NAT) enzymes catalyze to a drug molecule the conjugation of an acetyl moiety derived from acetyl coenzyme A. Examples of this type of reaction are depicted in Figure 4.1. The net result of this conjugation is an increase in water solubility and increased elimination of the compound. The NATs identified to date and involved in human drug metabolism include NAT-1 and NAT-2. Little overlap in substrate specificities of the two isoforms appears to exist. NAT-2 is a polymorphic enzyme, a

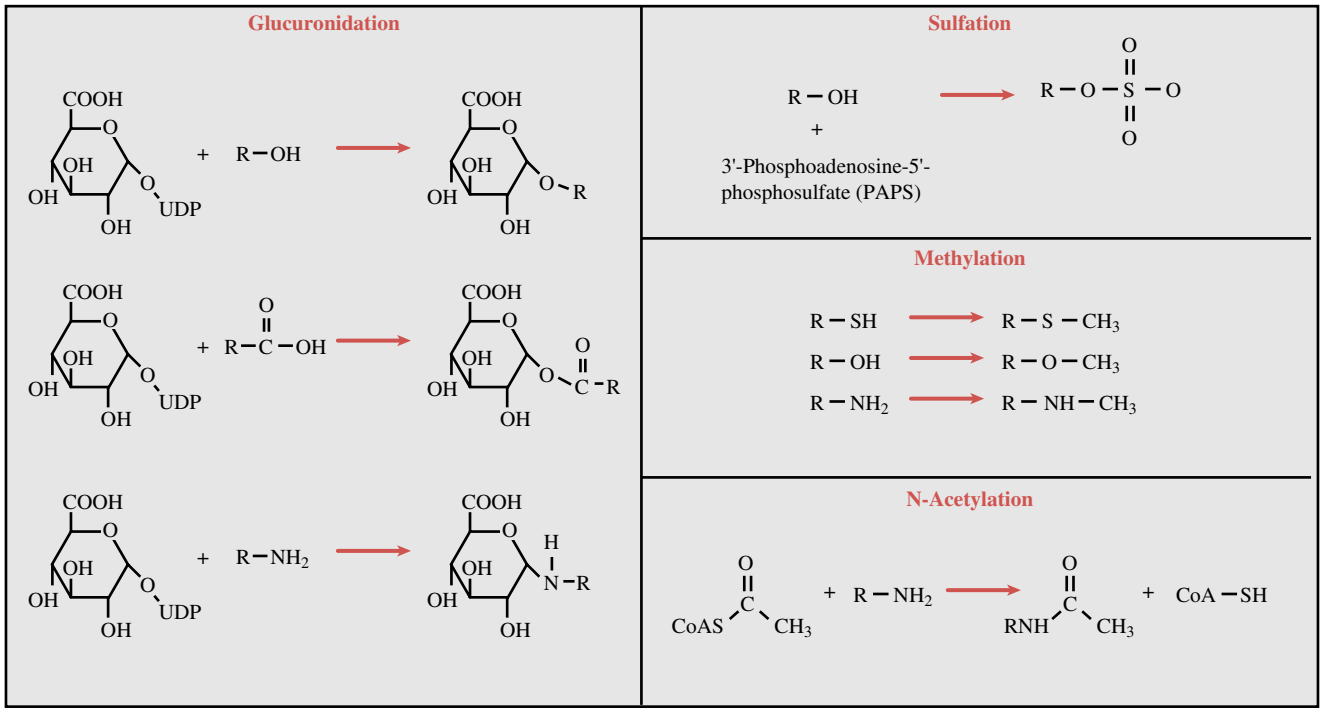

FIGURE 4.1
Examples of phase II conjugation reactions in drug metabolism.

property found to have important pharmacological consequences (discussed later). To date, little information exists on the regulation of the NAT enzymes, such as whether they can be induced by chemicals. However, reports have suggested that disease states such as acquired immunodeficiency syndrome (AIDS) may down-regulate NAT-2, particularly during active disease.

Sulfotransferases and Methyltransferases

Sulfotransferases (SULTs) are important for the metabolism of a number of drugs, neurotransmitters, and hormones, especially the steroid hormones. The cosubstrate for these reactions is 3′-phosphoadenosine 5′-phosphosulfate (PAPS) (Fig. 4.1). Like the aforementioned enzymes, sulfate conjugation typically renders the compound inactive and more water soluble. However, this process can also result in the activation of certain compounds, such as the antihypertensive minoxidil and several of the steroid hormones. Seven SULT isoforms identified in humans, including SULTs 1A1 to 1A3, possess activity toward phenolic substrates such as dopamine, estradiol, and acetaminophen. SULT1B1 possesses activity toward such endogenous substrates as dopamine and triiodothyronine. SULT1E1 has substantial activity toward steroid hormones, especially estradiol and dehydroepiandrosterone, and toward the antihypertensive minoxidil. SULT2A1 also is active against steroid hormones. Little is known about the substrate specificity of SULT1C1. Regulation of the SULT enzymes appears to be controlled by levels of the available sulfate pool in the body or that of PAPS. Patients who consume a low-sulfate diet or have ingested multiple SULT substrates may be susceptible to inadequate metabolism by this enzyme and thus drug toxicity.

The methyltransferases (MTs) catalyze the methyl conjugation of a number of small molecules, such as drugs, hormones, and neurotransmitters, but they are also responsible for the methylation of such macromolecules as proteins, RNA, and DNA. A representative reaction of this type is shown in Figure 4.1. Most of the MTs use *S*-adenosyl-L-methionine (SAM) as the methyl donor, and this compound is now being used as a dietary supplement for the treatment of various conditions. Methylations typically occur at oxygen, nitrogen, or sulfur atoms on a molecule. For example, catechol-*O*-methyltransferase (COMT) is responsible for the biotransformation of catecholamine neurotransmitters such as dopamine and norepinephrine. *N*-methylation is a well established pathway for the metabolism of neurotransmitters, such as conversion of norepinephrine to epinephrine and methylation of nicotinamide and histamine. Possibly the most clinically relevant example of MT activity involves *S*-methylation by the enzyme thiopurine methyltransferase (TPMT). Patients who are low or lacking in TPMT (i.e., are polymorphic) are at

high risk for development of severe bone marrow suppression when given normal doses of the chemotherapeutic agent 6-mercaptopurine. Patients are now studied for TPMT activity prior to administration of 6-mercaptopurine so that the dose may be adjusted downward if they are found to be deficient in this enzyme.

TISSUE SPECIFICITY OF HUMAN DRUG METABOLISM ENZYMES

Though most drug metabolism enzymes reside in the liver, other organs may also play an important role. All of the enzymes previously mentioned are found in the human liver, but other tissues and organs may have some complement of these enzymes. CYP3A4 and CYP3A5 have been found in the human gut and can contribute to substantial metabolism of orally administered drugs, even before the compound reaches the liver. For example, CYP3A4 may play a substantial role in the low bioavailability of cyclosporine. Drug-metabolizing enzymes have also been found in measurable quantities in the kidney, brain, placenta, skin, and lungs.

PHARMACOGENETICS OF DRUG-METABOLIZING ENZYMES

One of the most interesting and heavily researched areas of drug metabolism today is genetic polymorphism of drug-metabolizing enzymes (pharmacogenetics). As early as the late 1950s it was recognized that individuals might differ in whether they could acetylate certain drugs, such as isoniazid (see Chapter 49). In this case, the individuals studied appeared to segregate into two distinct groups, rapid acetylators and slow acetylators.

It was later discovered that this polymorphism existed in the *N*-acetyltransferase-2 gene and thus the NAT-2 enzyme. More important, it has become clear that slow acetylators (about 50% of the caucasian population) are more prone to adverse effects following administration of certain drugs than fast acetylators. For example, it is well established that slow acetylators receiving the antiarrhythmic drug procainamide are much more likely to develop the systemic lupus erythematosus–like syndrome that has been described as a characteristic and therapy-limiting event associated with this drug. In fact, this adverse event is rare in fast acetylators. Fortunately, the number of drugs that depend on NAT-2 for their primary metabolic fate is small, so this polymorphism is clinically relevant only in certain situations.

Possibly the most studied genetic polymorphism is that associated with CYP2D6. At least 17 variant alleles of this enzyme have been identified, most being associated with a deficiency in the ability to carry out CYP2D6-mediated oxidation reactions. Approximately 7% of the caucasian population is CYP2D6 deficient, whereas only 1–3% of African Americans and Asians are deficient in this enzyme. CYP2D6 is responsible for about 30% of the CYP-mediated reactions (Table 4.2) and exhibits this polymorphism. Likelihood of adverse events, such as the dyskinesias associated with certain antipsychotic agents, have been linked to this polymorphism, since individuals who are CYP2D6 deficient have a higher incidence of these side effects. To minimize adverse events and toxicity, care should be exercised when prescribing drugs that depend on CYP2D6 metabolism.

Recently, variant alleles (and thus polymorphisms) have been elucidated for most of the CYP isoforms. For example, six alleles of CYP2C9 have been discovered, and several of them profoundly affect therapy. The variant allele CYP2C9*3 occurs in fewer than 1% of the population, but affected individuals generally require doses of the anticoagulant warfarin that are 10–25% of those required by unaffected individuals. A CYP2C19 polymorphism also has been identified in 2–3% of caucasians and 20–30% of Asians. In this case, individuals who are CYP2C19 deficient are more likely to have complete ulcer healing after therapy with omeprazole (a proton pump inhibitor that reduces gastric acid) than are extensive metabolizers, a positive benefit.

EXCRETION OF DRUGS

Despite the reduction in activity that occurs as a drug leaves its site of action, it may remain in the body for a considerable period, especially if it is strongly bound to tissue components. Thus, reduction in pharmacological activity and drug elimination are to be seen as related but separate phenomena.

Excretion, along with metabolism and tissue redistribution, is important in determining both the duration of drug action and the rate of drug elimination. Excretion is a process whereby drugs are transferred from the internal to the external environment, and the principal organs involved in this activity are the kidneys, lungs, biliary system, and intestines.

The physicochemical considerations discussed in Chapter 3 that govern the passage of drugs across biological barriers are applicable to both excretory and absorptive phenomena.

RENAL EXCRETION

Although some drugs are excreted through extrarenal pathways, the kidney is the primary organ of removal for most drugs (Figure 4.2), especially for those that are water soluble and not volatile. *The three principal processes that determine the urinary excretion of a drug are glomerular filtration, tubular secretion, and tubular reabsorption (mostly passive back-diffusion).* Active

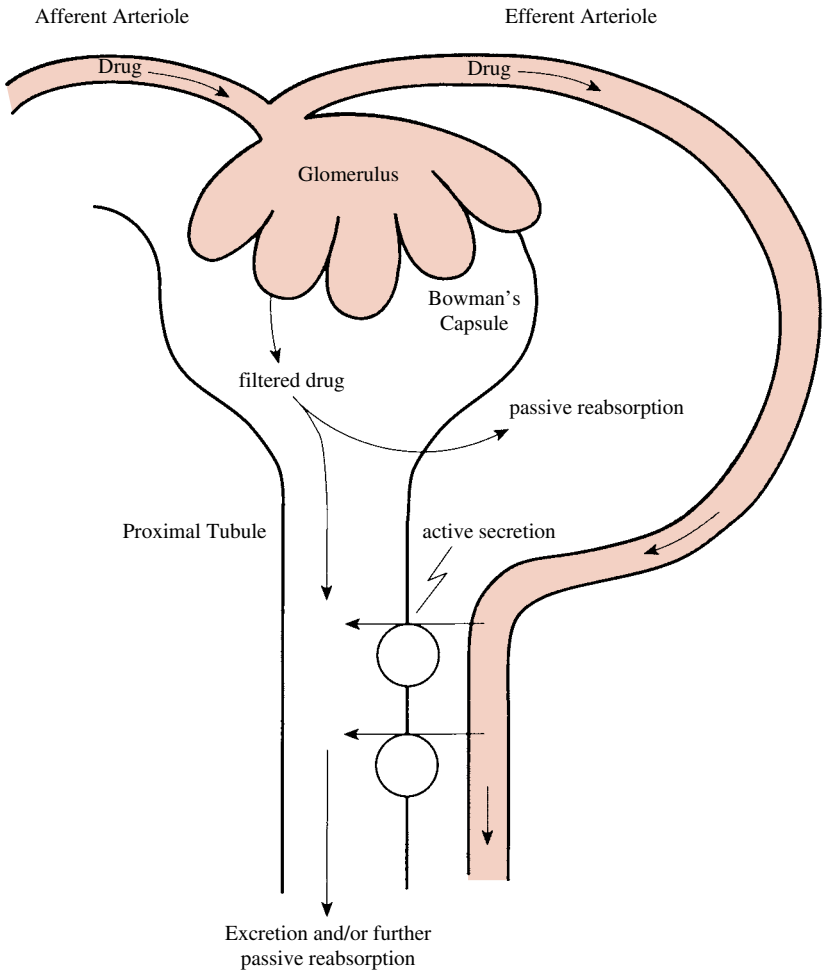

FIGURE 4.2
Renal excretion of drugs. Filtration of small non–protein-bound drugs occurs through glomerular capillary pores. Lipid-soluble and un-ionized drugs are passively reabsorbed throughout the nephron. Active secretion of organic acids and bases occurs only in the proximal tubular segment.

tubular reabsorption also may have some influence on the rate of excretion for a limited number of compounds.

Glomerular Filtration

The ultrastructure of the glomerular capillary wall is such that it permits a high degree of fluid filtration while restricting the passage of compounds having relatively large molecular weights. This selective filtration is important in that it prevents the filtration of plasma proteins (e.g., albumin) that are important for maintaining an osmotic gradient in the vasculature and thus plasma volume.

Several factors, including molecular size, charge, and shape, influence the glomerular filtration of large molecules. The restricted passage of macromolecules can be thought of as a consequence of the presence of a glomerular capillary wall barrier with uniform pores. Since approximately 130 mL of plasma water is filtered across the porous glomerular capillary membranes each minute (190 L/day), the kidney is admirably suited for its role in drug excretion. As the ultrafiltrate is formed, any drug that is free in the plasma water, that is, not bound to plasma proteins or the formed elements in the blood (e.g., red blood cells), will be filtered as a result of the driving force provided by cardiac pumping.

All unbound drugs will be filtered as long as their molecular size, charge, and shape are not excessively large. Compounds with an effective radius above 20 Å may have their rate of glomerular filtration restricted; hindrance to passage increases progressively as the molecular radius increases, and passage approaches zero when the compound radius becomes greater than about 42Å.

Charged substances (e.g., sulfated dextrans) are usually filtered at slower rates than neutral compounds (e.g., neutral dextrans), even when their molecular sizes

are comparable. The greater restriction to filtration of charged molecules, particularly anions, is probably due to an electrostatic interaction between the filtered molecule and the fixed negative charges within the glomerular capillary wall. These highly anionic structural components of the wall contribute to an electrostatic barrier and are most likely in the endothelial or glomerular basement membrane regions.

Molecular configuration also may influence the rate of glomerular filtration of drugs. Differences in the three-dimensional shape of macromolecules result in a restriction of glomerular passage of globular molecules (e.g., proteins) to a greater extent than of random coil or extended molecules (e.g., dextrans). Thus, the efficient retention of proteins within the circulation is attributed to a combination of factors, including their globular structure, their large molecular size, and the magnitude of their negative charge.

Factors that affect the glomerular filtration rate (GFR) also can influence the rate of drug clearance. For instance, inflammation of the glomerular capillaries may increase GFR and hence drug filtration. Most drugs are at least partially bound to plasma proteins, and therefore their actual filtration rates are less than the theoretical GFR. Anything that alters drug–protein binding, however, will change the drug filtration rate. The usual range of half-lives seen for most drugs that are cleared solely by glomerular filtration is 1 to 4 hours. However, considerably longer half-lives will be seen if extensive protein binding occurs.

Also, since water constitutes a larger percentage of the total body weight of the newborn than of individuals in other age groups, the apparent volume of distribution of water-soluble drugs is greater in neonates. This results in a lower concentration of drug in the blood coming to the kidneys per unit of time and hence a decreased rate of drug clearance. The lower renal plasma flow in the newborn also may decrease the glomerular filtration of drugs.

Passive Diffusion

An important determinant of the urinary excretion of drugs (i.e., weak electrolytes) is the extent to which substances diffuse back across the tubular membranes and reenter the circulation. In general, the movement of drugs is favored from the tubular lumen to blood, partly because of the reabsorption of water that occurs throughout most portions of the nephron, which results in an increased concentration of drug in the luminal fluid. The concentration gradient thus established will facilitate movement of the drug out of the tubular lumen, given that the lipid solubility and ionization of the drug are appropriate.

The pH of the urine (usually between 4.5 and 8) can markedly affect the rate of passive back-diffusion. The back-diffusion occurs primarily in the distal tubules and collecting ducts, where most of the urine acidification takes place. Since it is the un-ionized form of the drug that diffuses from the tubular fluid across the tubular cells into the blood, it follows that acidification increases reabsorption (or decreases elimination) of weak acids, such as salicylates, and decreases reabsorption (or promotes elimination) of weak bases, such as amphetamines. However, should the un-ionized form of the drug not have sufficient lipid solubility, urinary pH changes will have little influence on urinary drug excretion.

Effects of pH on urinary drug elimination may have important applications in medical practice, especially in cases of overdose. For example, one can enhance the elimination of a barbiturate (a weak acid) by administering bicarbonate to the patient. This procedure alkalinizes the urine and thus promotes the excretion of the now more completely ionized drug. The excretion of bases can be increased by making the urine more acidic through the use of an acidifying salt, such as ammonium chloride.

Active Tubular Secretion

A number of drugs can serve as substrates for the two active secretory systems in the proximal tubule cells. These transport systems, which actively transfer drugs from blood to luminal fluid, are independent of each other; one secretes organic anions (Figure 4.3), and the other secretes organic cations. One drug substrate can compete for transport with a simultaneously administered or endogenous similarly charged compound; this competition will decrease the overall rate of excretion of each substance. The secretory capacity of both the organic anion and organic cation secretory systems can be saturated at high drug concentrations. Each drug will

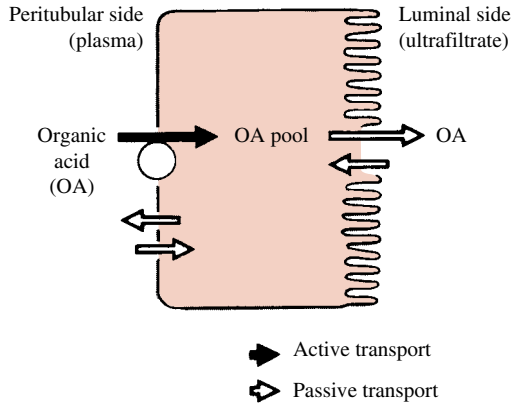

FIGURE 4.3
Active renal elimination of an organic anion. The transport mechanism is in the peritubular portion of the membrane of the proximal tubular cell.

have its own characteristic maximum rate of secretion (transport maximum, T_m).

Some drugs that are not candidates for active tubular secretion may be metabolized to compounds that are. This is often true for metabolites that are formed as a result of conjugative reactions. Because the conjugates are generally not pharmacologically active, increases in their rate of elimination through active secretion usually have little effect on the drug's overall duration of action.

These active secretory systems are important in drug excretion because *charged anions and cations are often strongly bound to plasma proteins* and therefore are not readily available for excretion by filtration. However, since the protein binding is usually reversible, the active secretory systems can rapidly and efficiently remove many protein-bound drugs from the blood and transport them into tubular fluid.

Any drug known to be largely excreted by the kidney that has a body half-life of less than 2 hours is probably eliminated, at least in part, by tubular secretion. Some drugs can be secreted and have long half-lives, however, because of extensive passive reabsorption in distal segments of the nephron (see Passive Diffusion, earlier in the chapter). Several pharmacologically active drugs, both anions and cations, known to be secreted are listed in Table 4.5.

It is important to appreciate that these tubular transport mechanisms are not as well developed in the neonate as in the adult. In addition, their functional capacity may be diminished in the elderly. Thus, *compounds normally eliminated by tubular secretion will be excreted more slowly in the very young and in the older adult.* This age dependence of the rate of renal drug secretion may have important therapeutic implications and must be considered by the physician who prescribes drugs for these age groups.

Finally, compounds that undergo active tubular secretion also are filtered at the glomerulus (assuming protein binding is minimal). Hence, a reduction in secretory activity does not reduce the excretory process to zero but rather to a level that approximates the glomerular filtration rate.

Active Tubular Reabsorption

Some substances filtered at the glomerulus are reabsorbed by active transport systems found primarily in the proximal tubules. Active reabsorption is particularly important for endogenous substances, such as ions, glucose, and amino acids (Fig. 4.4), although a small number of drugs also may be actively reabsorbed. The probable location of the active transport system is on the luminal side of the proximal cell membrane. *Bidirectional* active transport across the proximal tubule also occurs for some compounds; that is, a drug may be both actively reabsorbed and secreted. The occurrence of such bidirectional active transport mechanisms across the proximal tubule has been described for several organic anions, including the naturally occurring uric acid (see Chapter 37). The major portion of *filtered* urate is probably reabsorbed, whereas that eventually found in the urine is mostly derived from active tubular secretion.

Most drugs act by reducing active transport rather than by enhancing it. Thus, drugs that promote uric acid loss (uricosuric agents, such as probenecid and sulfinpyrazone) probably inhibit active urate reabsorption, while pyrazinamide, which reduces urate excretion, may block the active tubular secretion of uric acid. A complicating observation is that a drug may primarily inhibit active reabsorption at one dose and active secretion at another, frequently lower, dose. For example, small amounts of salicylate will decrease total urate ex-

TABLE 4.5 Compounds Secreted by Renal Tubular Transport Systems

Organic Anion Transport	Organic Cation Transport
Acetazolamide	Acetylcholine
Bile salts	Atropine
Hydrochlorothiazide	Cimetidine
Furosemide	Dopamine
Indomethacin	Epinephrine
Penicillin G	Morphine
Prostaglandins	Neostigmine
Salicylate	Quinine

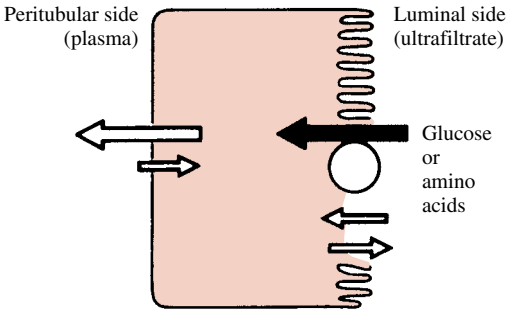

FIGURE 4.4
Active reabsorption of important substances that have been filtered at the glomerular membranes. The transport mechanism is in the luminal portion of the membrane of the proximal tubular cell. *Solid arrow* indicates active transport.

cretion, while high doses have a uricosuric effect. This is offered as an explanation for the apparently paradoxical effects of low and high doses of drugs on the total excretory pattern of compounds that are handled by renal active transport.

Clinical Implications of Renal Excretion

The rate of urinary drug excretion will depend on the drug's volume of distribution, its degree of protein binding, and the following renal factors:

1. Glomerular filtration rate
2. Tubular fluid pH
3. Extent of back-diffusion of the unionized form
4. Extent of active tubular secretion of the compound
5. Possibly, extent of active tubular reabsorption

Changes in any of these factors may result in clinically important alterations in drug action. In the final analysis, the amount of drug that finally appears in the urine will represent a balance of filtered, reabsorbed (passively and actively), and secreted drug. For many drugs, the duration and intensity of pharmacological effect will be influenced by the status of renal function, because of the major role played by the kidneys in drug and metabolite elimination. Ultimately, whether or not dosage adjustment (e.g., prolongation of dosing interval, reduction in the maintenance dose, or both) becomes necessary will depend on an assessment of the degree of renal dysfunction, the percentage of drug cleared by the kidney, and the potential for drug toxicity, especially if renal function is reduced.

Biliary Excretion

The liver secretes about 1 L of bile daily. Bile flow and composition depend on the secretory activity of the hepatic cells that line the biliary canaliculi. As the bile flows through the biliary system of ducts, its composition can be modified in the ductules and ducts by the processes of reabsorption and secretion, especially of electrolytes and water. For example, osmotically active compounds, including bile acids, transported into the bile promote the passive movement of fluid into the duct lumen. In the gallbladder, composition of the bile is modified further through reabsorptive processes.

The passage of most foreign compounds from the blood into the liver normally is not restricted because the endothelium of the hepatic blood sinusoids behaves as a porous membrane. Hence, drugs with molecular weights lower than those of most protein molecules readily reach the hepatic extracellular fluid from the plasma. A number of compounds are taken up into the liver by carrier-mediated systems, while more lipophilic drugs pass through the hepatocyte membrane by diffusion. The subsequent passage of substances into the bile, however, is much more selective.

At least three groups of compounds enter the bile. Compounds of group A are those whose concentration in bile and plasma are almost identical (bile–plasma ratio of 1). These include glucose, and ions such as Na^+, K^+, and Cl^-. Group B contains the bile salts, bilirubin glucuronide, sulfobromophthalein, procainamide, and others, whose ratio of bile to blood is much greater than 1, usually 10 to 1,000. Group C is reserved for compounds for which the ratio of bile to blood is less than 1, for example, insulin, sucrose, and proteins. Drugs can belong to any of these three categories. Only small amounts of most drugs reach the bile by diffusion. However, biliary excretion plays a major role (5–95% of the administered dose) in drug removal for some anions, cations, and certain un-ionized molecules, such as cardiac glycosides. In addition, biliary elimination may be important for the excretion of some heavy metals.

Cardiac glycosides, anions, and cations are transported from the liver into the bile by three distinct and independent carrier-mediated active transport systems, the last two closely resembling those in the renal proximal tubules that secrete anions and cations into tubular urine. As is true for renal tubular secretion, protein-bound drug is completely available for biliary active transport. In contrast to the bile acids, the *actively secreted drugs* generally do not recycle, because they are not substrates for the intestinal bile acid transport system, and they are generally too highly charged to back-diffuse across the intestinal epithelium. Thus, the ability of certain compounds to be actively secreted into bile accounts for the large quantity of these drugs removed from the body by way of the feces.

On the other hand, most drugs that are secreted by the liver into the bile and then into the small intestine are not eliminated through the feces. The physicochemical properties of most drugs are sufficiently favorable for passive intestinal absorption that the compound will reenter the blood that perfuses the intestine and again be carried to the liver. Such recycling may continue (*enterohepatic cycle* or *circulation*) until the drug either undergoes metabolic changes in the liver, is excreted by the kidneys, or both. This process permits the conservation of such important endogenous substances as the bile acids, vitamins D_3 and B_{12}, folic acid, and estrogens (Table 4.6).

Extensive enterohepatic cycling may be partly responsible for a drug's long persistence in the body. Orally administered activated charcoal and/or anion exchange resins have been used clinically to interrupt enterohepatic cycling and trap drugs in the gastrointestinal tract.

As stated earlier, many foreign compounds are either partially or extensively metabolized in the liver.

TABLE 4.6 Drugs that Undergo Enterohepatic Recirculation

Adriamycin	Methadone
Amphetamine	Metronidazole
Chlordecone	Morphine
1,25-Dihydroxyvitamin D_3	Phenytoin
Estradiol	Polar Glucuronic Acid Conjugates
Indomethacin	Polar Sulfate Conjugates
Mestranol	Sulindac

Conjugation of a compound or its metabolites is especially important in determining whether the drug will undergo biliary excretion. Frequently, when a compound is secreted into the intestine through the bile, it is in the form of a conjugate. *Conjugation generally enhances biliary excretion,* since it both introduces a strong polar (i.e., anionic) center into the molecule and increases its molecular weight. Molecular weight may, however, be less important in the biliary excretion of organic cations. Conjugated drugs will not be reabsorbed readily from the gastrointestinal tract unless the conjugate is hydrolyzed by gut enzymes such as β-glucuronidase. Chloramphenicol glucuronide, for example, is secreted into the bile, where it is hydrolyzed by gastrointestinal flora and largely reabsorbed. Such a continuous recirculation may lead to the appearance of drug-induced toxicity.

The kidney and liver are, in general, capable of actively transporting the same organic anion substrates. However, the two organs have certain quantitative differences in drug affinity for the transporters. It has been suggested that several subsystems of organic anion transport may exist and that the binding specificities of the transporters involved are not absolute but overlapping.

Liver disease or injury may impair bile secretion and thereby lead to accumulation of certain drugs, for example probenecid, digoxin, and diethylstilbestrol. Impairment of liver function can lead to decreased rates of both drug metabolism and secretion of drugs into bile. These two processes, of course, are frequently interrelated, since many drugs are candidates for biliary secretion only after appropriate metabolism has occurred.

Decreases in biliary excretion have been demonstrated at both ends of the age continuum. For example, ouabain, an unmetabolized cardiac glycoside that is secreted into the bile, is particularly toxic in the newborn. This is largely due to a reduced ability of biliary secretion to remove ouabain from the plasma.

Increases in hepatic excretory function also may take place. After the chronic administration of either phenobarbital or the potassium-sparing diuretic spironolactone, the rate of bile flow is augmented. Such an increase in bile secretion can reduce blood levels of drugs that depend on biliary elimination.

Finally, the administration of one drug may influence the rate of biliary excretion of a second coadministered compound. These effects may be brought about through an alteration in one or more of the following factors: hepatic blood flow, uptake into hepatocytes, rate of biotransformation, transport into bile, or rate of bile formation. In addition, antibiotics may alter the intestinal flora in such a manner as to diminish the presence of sulfatase and glucuronidase-containing bacteria. This would result in a persistence of the conjugated form of the drug and hence a decrease in its enterohepatic recirculation.

PULMONARY EXCRETION

Any volatile material, irrespective of its route of administration, has the potential for pulmonary excretion. Certainly, gases and other volatile substances that enter the body primarily through the respiratory tract can be expected to be excreted by this route. *No specialized transport systems are involved in the loss of substances in expired air; simple diffusion across cell membranes is predominant.* The rate of loss of gases is not constant; it depends on the rate of respiration and pulmonary blood flow.

The degree of solubility of a gas in blood also will affect the rate of gas loss. Gases such as nitrous oxide, which are not very soluble in blood, will be excreted rapidly, that is, almost at the rate at which the blood delivers the drug to the lungs. *Increasing cardiac output has the greatest effect on the removal of poorly soluble gases;* for example, doubling the cardiac output nearly doubles the rates of loss. Agents with high blood and tissue solubility, on the other hand, are only slowly transferred from pulmonary capillary blood to the alveoli. Ethanol, which has a relatively high blood gas solubility, is excreted very slowly by the lungs. *The arterial concentration of a highly soluble gas falls much more slowly, and its rate of loss depends more on respiratory rate than on cardiac output.*

A more detailed discussion of the uptake, distribution, and elimination of compounds administered by inhalation can be found in Chapter 25.

EXCRETION IN OTHER BODY FLUIDS

Sweat and Saliva

Excretion of drugs into sweat and saliva occurs but has only minor importance for most drugs. The mechanisms involved in drug excretion are similar for sweat and

saliva. Excretion mainly depends on the diffusion of the un-ionized lipid-soluble form of the drug across the epithelial cells of the glands. Thus, the pK_a of the drug and the pH of the individual secretion formed in the glands are important determinants of the total quantity of drug appearing in the particular body fluid. It is not definitely established whether active drug transport occurs across the ducts of the glands.

Lipid-insoluble compounds, such as urea and glycerol, enter saliva and sweat at rates proportional to their molecular weight, presumably because of filtration through the aqueous channels in the secretory cell membrane. Drugs or their metabolites that are excreted into sweat may be at least partially responsible for the dermatitis and other skin reactions caused by some therapeutic agents. Substances excreted into saliva are usually swallowed, and therefore their fate is the same as that of orally administered drugs (unless expectoration is a major characteristic of a person's habits). The excretion of a drug into saliva accounts for the drug taste patients sometimes report after certain compounds are given intravenously.

Milk

Many drugs in a nursing mother's blood are detectable in her milk (Table 4.7). The ultimate concentration of the individual compound in milk will depend on many factors, including the amount of drug in the maternal blood, its lipid solubility, its degree of ionization, and the extent of its active excretion. Thus, the physicochemical properties that govern the excretion of drugs into saliva and sweat also apply to the passage of drugs into milk.

Since milk is more acidic (pH 6.5) than plasma, basic compounds (e.g., alkaloids, such as morphine and codeine) may be somewhat more concentrated in this fluid. In contrast, the levels of weak organic acids will probably be lower than those in plasma. In general, a high maternal plasma protein binding of drug will be associated with a low milk concentration. A highly lipid-soluble drug should accumulate in milk fat. Low-molecular-weight un-ionized water-soluble drugs will diffuse passively across the mammary epithelium and transfer into milk. There they may reside in association with one or more milk components, for example, bound to protein such as lactalbumin, dissolved within fat globules, or free in the aqueous compartment. Substances that are not electrolytes, such as ethanol, urea, and antipyrine, readily enter milk and reach approximately the same concentration as in plasma. Compounds used in agriculture also may be passed from cows to humans by this route. Finally, antibiotics such as the tetracyclines, which can function as chelating agents and bind calcium, have a higher milk than plasma concentration.

Both maternal and infant factors determine the final amount of drug present in the nursing child's body at any particular time. Variations in the daily amount of milk formed within the breast (e.g., changes in blood flow to the breast) as well as alterations in breast milk pH will affect the total amount of drug found in milk. In addition, composition of the milk will be affected by the maternal diet; for example, a high-carbohydrate diet will increase the content of saturated fatty acids in milk.

The greatest drug exposure occurs when feeding begins shortly after maternal drug dosing. Additional factors determining exposure of the infant include milk volume consumed (about 150 mL/kg/day) and milk composition at the time of feeding. Fat content is highest in the morning and then gradually decreases until about 10 P.M. A longer feed usually results in exposure of the infant to more of a fat-soluble drug, since milk fat content increases somewhat during a given nursing period.

Whether or not a drug accumulates in a nursing child is affected in part by the infant's ability to eliminate via metabolism and excretion the ingested compound. In general, the ability to oxidize and conjugate drugs is low in the neonate and does not approach full adult rates until approximately age 6. It follows, therefore, that drug accumulation should be less in an older infant who breast-feeds than in a suckling neonate.

Although abnormalities in fetal organ structure and function can result from the presence of certain drugs in breast milk, it would be quite inappropriate to deny the breast-feeding woman appropriate and necessary drug therapy. A pragmatic approach on the part of both the physician and patient is necessary. *Breast-feeding should be discouraged when inherent drug toxicity is known or when adverse pharmacological actions of the drug on the infant are likely.* Infant drug exposure can be minimized, however, through short intermittent maternal drug use and by drug dosing immediately after breast-feeding.

TABLE 4.7 Examples of Drugs That Appear in Breast Milk

Acetylsalicylic acid
Antithyroid uracil compounds
Barbiturates
Caffeine
Ethanol
Glutethimide
Morphine
Nicotine

Study Questions

1. Concerning regulation of CYP-mediated drug metabolism, all of the following statements are true EXCEPT
   (A) Drugs that competitively inhibit CYP enzymes cause a decrease in concentrations of the object (original) drug.
   (B) Induction of drug-metabolizing enzymes results in a decrease in concentrations of the object (original) drug, thus potentially reducing efficacy.
   (C) Induction of drug-metabolizing enzymes frequently requires the synthesis of new enzyme protein and thus may not occur immediately upon introduction of the inducing agent.
   (D) Mechanism-based inactivation results in irreversible inactivation of the enzyme that lasts for the duration of the enzyme molecule.
2. Which of the following CYP enzymes is associated with metabolism of the greatest number of drugs and thus most likely to be involved in drug–drug interactions?
   (A) CYP3A4
   (B) CYP2C9
   (C) CYP2D6
   (D) CYP2E1
   (E) CYP1A2
3. Conjugation of a drug with glucuronic acid via the glucuronosyl transferases will result in all of the following EXCEPT
   (A) Production of a more water-soluble moiety that is more easily excreted
   (B) A new compound that may also possess pharmacological activity
   (C) A drug molecule that may be more susceptible to biliary elimination
   (D) A drug molecule that may undergo enterohepatic recirculation and reintroduction into the bloodstream
   (E) A drug with a different pharmacological mechanism of action
4. Concerning the renal excretion of drugs:
   (A) Drugs that are ionized in the renal tubule are more likely to undergo passive reabsorption than those that are unionized
   (B) Low-molecular-weight drugs are much more likely to be actively secreted than filtered.
   (C) Only drug that is not bound to plasma proteins (i.e., free drug) is filtered by the glomerulus.
   (D) Decreasing renal tubular fluid pH will increase elimination of weakly acidic drugs.
5. Drug presence in breast milk is most likely for:
   (A) Drugs highly bound to plasma proteins
   (B) Lipid-soluble molecules
   (C) Large ionized water-soluble molecules
   (D) Acidic compounds

ANSWERS

1. **A.** When one inhibits the action of a drug-metabolizing enzyme (A), one would expect an increase instead of a decrease in drug concentrations, since less is being metabolized. Induction of an enzyme (B) would have the opposite effect, since there would be more enzyme available to metabolize the drug. C is correct, since the most common mechanism of enzyme induction is through synthesis of new enzyme protein, which does not occur immediately. Finally, mechanism-based inactivation (D) is also correct, since this is irreversible, leaving the enzyme inactive and eventually it is degraded by the body.
2. **A.** CYP3A4 is the predominant cytochrome P450 drug-metabolizing enzyme in the body, both in terms of amount of enzyme and the number of drugs that it metabolizes. It has been estimated to carry out approximately 50% of the cytochrome P450–mediated reactions observed. The other enzymes have been reported to carry out 30% (CYP2D6), 15–20% (CYP2C9) and 1–2% (both CYP2E1 and CYP1A2).
3. **E.** Most glucuronic acid conjugates are less effective than the parent drug. The conjugate, however, usually maintains the same pharmacological mechanism of action, although frequently of a lesser magnitude. Conjugation with glucuronic acid makes a drug molecule more water soluble (A), and glucuronic acid conjugates are more likely to be eliminated by secretion into the bile (C) than are unconjugated compounds. These glucuronide conjugates, once secreted into the bile, may be cleaved by β-glucuronidases to liberate the parent compound, which can then be reabsorbed (D). Several glucuronic acid conjugates of drugs (e.g., morphine 6-glucuronide) possess pharmacological activity (B).
4. **C.** Plasma proteins are too large to be filtered by the glomerulus, so that any drug molecules bound to these plasma proteins will not undergo filtration. A is not correct: ionized drugs are *less* likely to undergo reabsorption, since this is generally thought to be a passive process. B is also not correct: low-molecular-weight drugs are more likely to be filtered, since they can easily pass through the glomerulus filter. Finally, weakly acidic drugs will be un-ionized at a low (acidic) pH, hence more likely to undergo reabsorption, thus *reducing* the net elimination (D).

5. B. Lipid-soluble molecules are more likely to be excreted in breast milk because it is primarily a passive diffusion process. A, C, and D are not correct because they are opposite of the typical characteristics of drugs excreted into breast milk.

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CASE Study Why am I not getting pain relief?

A 37-year-old woman visited her dentist for removal of her wisdom teeth. The teeth were found to be impacted, and removal necessitated extensive surgery. Following completion of the procedure on one side of the mouth, the patient was given a prescription for acetaminophen 300 mg with codeine 30 mg (combination product) for the relief of pain. The patient took the prescription as prescribed for approximately 2 days, but little pain relief was achieved. She called the dentist to get a prescription for another analgesic. What is a possible explanation for this lack of efficacy?

ANSWER: Codeine itself is a very weak analgesic but is metabolized to morphine, which produces most of the analgesic effect following codeine administration. The metabolism of codeine to morphine is carried out by cytochrome P450 2D6, an enzyme that exhibits genetic polymorphism. The patient may be deficient in CYP2D6 and thus unable to convert codeine into its active metabolite, morphine; hence analgesic efficacy is lacking.