DRUG METABOLISM AND PHARMACOKINETICS

Drug metabolism – physico chemical principles, radioactivity – pharmacokinetics-action of drugs on human bodies.

PHARMACOKINETICS

Pharmacokinetics, sometimes described as what the body does to a drug, refers to the movement of drug into, through, and out of the body—the time course of its absorption, bioavailability, distribution, metabolism, and excretion.

Pharmacokinetics of a drug depends on patient-related factors as well as on the drug's chemical properties. Some patient-related factors (eg, renal function, genetic makeup, sex, age) can be used to predict the pharmacokinetic parameters in populations. For example, the half-life of some drugs, especially those that require both metabolism and excretion, may be remarkably long in the elderly. In fact, physiologic changes with aging affect many aspects of pharmacokinetics. Other factors are related to individual physiology. The effects of some individual factors (eg, renal failure, obesity, hepatic failure, dehydration) can be reasonably predicted, but other factors are idiosyncratic and thus have unpredictable effects. Because of individual differences, drug administration must be based on each patient's needs—traditionally, by empirically adjusting dosage until the therapeutic objective is met. This approach is frequently inadequate because it can delay optimal response or result in adverse effects. Knowledge of pharmacokinetic principles helps prescribers adjust dosage more accurately and rapidly. Application of pharmacokinetic principles to individualize pharmacotherapy is termed therapeutic drug monitoring.

DRUG ABSORPTION

Drug absorption is determined by the drug's physicochemical properties, formulation, and route of administration. Dosage forms (eg, tablets, capsules, solutions), consisting of the drug plus other ingredients, are formulated to be given by various routes (eg, oral, buccal, sublingual, rectal, parenteral, topical, inhalational). Regardless of the route of administration, drugs must be in solution to be absorbed. Thus, solid forms (eg, tablets) must be able to disintegrate and deaggregate.

Unless given IV, a drug must cross several semipermeable cell membranes before it reaches the systemic circulation. Cell membranes are biologic barriers that selectively inhibit passage of drug molecules. The membranes are composed primarily of a bimolecular lipid matrix, which determines membrane permeability characteristics. Drugs may cross cell membranes by passive diffusion, facilitated passive diffusion, active transport, or pinocytosis. Sometimes various globular proteins embedded in the matrix function as receptors and help transport molecules across the membrane.

Passive diffusion

Drugs diffuse across a cell membrane from a region of high concentration (eg, GI fluids) to one of low concentration (eg, blood). Diffusion rate is directly proportional to the gradient but also depends on the molecule's lipid solubility, size, degree of ionization, and the area of absorptive surface. Because the cell membrane is lipoid, lipid-soluble drugs diffuse most rapidly. Small molecules tend to penetrate membranes more rapidly than larger ones.

Most drugs are weak organic acids or bases, existing in un-ionized and ionized forms in an aqueous environment. The un-ionized form is usually lipid soluble (lipophilic) and diffuses readily across cell membranes. The ionized form has low lipid solubility (but high water solubility—ie, hydrophilic) and high electrical resistance and thus cannot penetrate cell membranes easily. The proportion of the un-ionized form present (and thus the drug's ability to cross a membrane) is determined by the environmental pH and the drug's p K_a (acid dissociation constant). The p K_a is the pH at which concentrations of ionized and un-ionized forms are equal. When the pH is lower than the p K_a, the un-ionized form of a weak acid predominates, but the ionized form of a weak base predominates. Thus, in plasma (pH 7.4), the ratio of un-ionized to ionized forms for a weak acid (eg, with a p K_a of 4.4) is 1:1000; in gastric fluid (pH 1.4), the ratio is reversed (1000:1). Therefore, when a weak acid is given orally, most of the drug in the stomach is un-ionized, favoring diffusion through the gastric mucosa. For a weak base with a p K_a of 4.4, the outcome is reversed; most of the drug in the stomach is ionized. Theoretically, weakly acidic drugs (eg, aspirin) are more readily absorbed from an acid medium (stomach) than are weakly basic drugs (eg, quinidine). However, whether a drug is acidic or basic, most absorption occurs in the small intestine because the surface area is larger and membranes are more permeable.

Facilitated passive diffusion

Certain molecules with low lipid solubility (eg, glucose) penetrate membranes more rapidly

than expected. One theory is facilitated passive diffusion: A carrier molecule in the membrane combines reversibly with the substrate molecule outside the cell membrane, and the carrier-substrate complex diffuses rapidly across the membrane, releasing the substrate at the interior surface. In such cases, the membrane transports only substrates with a relatively specific molecular configuration, and the availability of carriers limits the process. The process does not require energy expenditure, and transport against a concentration gradient cannot occur.

Active transport

Active transport is selective, requires energy expenditure, and may involve transport against a concentration gradient. Active transport seems to be limited to drugs structurally similar to endogenous substances (eg, ions, vitamins, sugars, amino acids). These drugs are usually absorbed from specific sites in the small intestine.

Pinocytosis

In pinocytosis, fluid or particles are engulfed by a cell. The cell membrane invaginates, encloses the fluid or particles, then fuses again, forming a vesicle that later detaches and moves to the cell interior. Energy expenditure is required. Pinocytosis probably plays a small role in drug transport, except for protein drugs.

ORAL ADMINISTRATION

To be absorbed, a drug given orally must survive encounters with low pH and numerous GI secretions, including potentially degrading enzymes. Peptide drugs (eg, insulin) are particularly susceptible to degradation and are not given orally. Absorption of oral drugs involves transport across membranes of the epithelial cells in the GI tract. Absorption is affected by

- Differences in luminal pH along the GI tract
- Surface area per luminal volume
- Blood perfusion
- Presence of bile and mucus
- The nature of epithelial membranes

The oral mucosa has a thin epithelium and rich vascularity, which favor absorption; however, contact is usually too brief for substantial absorption. A drug placed between the gums and cheek (buccal administration) or under the tongue (sublingual administration) is retained longer, enhancing absorption.

The stomach has a relatively large epithelial surface, but its thick mucous layer and short transit time limit absorption. Because most absorption occurs in the small intestine, gastric emptying is often the rate-limiting step. Food, especially fatty food, slows gastric emptying (and rate of drug absorption), explaining why taking some drugs on an empty stomach speeds absorption. Drugs that affect gastric emptying (eg, parasympatholytic drugs) affect the absorption rate of other drugs. Food may enhance the extent of absorption for poorly soluble drugs (eg, griseofulvin), reduce it for drugs degraded in the stomach (eg, penicillin G), or have little or no effect.

The small intestine has the largest surface area for drug absorption in the GI tract, and its membranes are more permeable than those in the stomach. For these reasons, most drugs are absorbed primarily in the small intestine, and acids, despite their ability as un-ionized drugs to readily cross membranes, are absorbed faster in the intestine than in the stomach. The intraluminal pH is 4 to 5 in the duodenum but becomes progressively more alkaline, approaching 8 in the lower ileum. GI microflora may reduce absorption. Decreased blood flow (eg, in shock) may lower the concentration gradient across the intestinal mucosa and reduce absorption by passive diffusion.
Intestinal transit time can influence drug absorption, particularly for drugs that are absorbed by active transport (eg, B vitamins), that dissolve slowly (eg, griseofulvin), or that are polar (ie, with low lipid solubility; eg, many antibiotics).

To maximize adherence, clinicians should prescribe oral suspensions and chewable tablets for children < 8 yr. In adolescents and adults, most drugs are given orally as tablets or capsules primarily for convenience, economy, stability, and patient acceptance. Because solid drug forms must dissolve before absorption can occur, dissolution rate determines availability of the drug for absorption. Dissolution, if slower than absorption, becomes the rate-limiting step. Manipulating the formulation (ie, the drug's form as salt, crystal, or hydrate) can change the dissolution rate and thus control overall absorption.

PARENTERAL ADMINISTRATION

Drugs given IV enter the systemic circulation directly. However, drugs injected IM or sc must cross one or more biologic membranes to reach the systemic circulation. If protein drugs with a molecular mass > 20,000 g/mol are injected IM or sc, movement across capillary membranes is so slow that most absorption occurs via the lymphatic system. In such cases, drug delivery to systemic circulation is slow and often incomplete because of first-pass metabolism (metabolism of a drug before it reaches systemic circulation) by proteolytic enzymes in the lymphatics.

Perfusion (blood flow/gram of tissue) greatly affects capillary absorption of small molecules injected IM or sc. Thus, injection site can affect absorption rate. Absorption after IM or sc injection may be delayed or erratic for salts of poorly soluble bases and acids (eg, parenteral form of phenytoin) and in patients with poor peripheral perfusion (eg, during hypotension or shock).

CONTROLLED-RELEASE FORMS

Controlled-release forms are designed to reduce dosing frequency for drugs with a short elimination half-life and duration of effect. These forms also limit fluctuation in plasma drug concentration, providing a more uniform therapeutic effect while minimizing adverse effects. Absorption rate is slowed by coating drug particles with wax or other water-insoluble material, by embedding the drug in a matrix that releases it slowly during transit through the GI tract, or by complexing the drug with ion-exchange resins. Most absorption of these forms occurs in the large intestine. Crushing or otherwise disturbing a controlled-release tablet or capsule can often be dangerous.

Transdermal controlled-release forms are designed to release the drug for extended periods, sometimes for several days. Drugs for transdermal delivery must have suitable skin penetration characteristics and high potency because the penetration rate and area of application are limited.

Many non-IV parenteral forms are designed to sustain plasma drug concentrations. Absorption of antimicrobials can be extended by using their relatively insoluble salt form (eg, penicillin G benzathine) injected IM. For other drugs, suspensions or solutions in nonaqueous vehicles (eg, crystalline suspensions for insulin) are designed to delay absorption.

DRUG BIOAVAILABILITY

Bioavailability refers to the extent and rate at which the active moiety (drug or metabolite) enters systemic circulation, thereby accessing the site of action.

Bioavailability of a drug is largely determined by the properties of the dosage form, which depend partly on its design and manufacture. Differences in bioavailability among formulations of a given drug can have clinical significance; thus, knowing whether drug formulations are equivalent is essential.

Chemical equivalence indicates that drug products contain the same active compound in the same amount and meet current official standards; however, inactive ingredients in drug products may differ. **Bioequivalence** indicates that the drug products, when given to the same patient in the same dosage regimen, result in equivalent concentrations of drug in plasma and tissues. **Therapeutic**

equivalence indicates that drug products, when given to the same patient in the same dosage regimen, have the same therapeutic and adverse effects.

Bioequivalent products are expected to be therapeutically equivalent. Therapeutic nonequivalence (eg, more adverse effects, less efficacy) is usually discovered during long-term treatment when patients who are stabilized on one formulation are given a nonequivalent substitute. Sometimes therapeutic equivalence is possible despite differences in bioavailability. For example, the therapeutic index (ratio of the minimum toxic concentration to the median effective concentration) of penicillin is so wide that efficacy and safety are usually not affected by the moderate differences in plasma concentration due to bioavailability differences in penicillin products. In contrast, for drugs with a relatively narrow therapeutic index, bioavailability differences may cause substantial therapeutic nonequivalence.

Causes of low bioavailability

Orally administered drugs must pass through the intestinal wall and then the portal circulation to the liver; both are common sites of first-pass metabolism (metabolism that occurs before a drug reaches systemic circulation). Thus, many drugs may be metabolized before adequate plasma concentrations are reached. Low bioavailability is most common with oral dosage forms of poorly water-soluble, slowly absorbed drugs.

Insufficient time for absorption in the GI tract is a common cause of low bioavailability. If the drug does not dissolve readily or cannot penetrate the epithelial membrane (eg, if it is highly ionized and polar), time at the absorption site may be insufficient. In such cases, bioavailability tends to be highly variable as well as low.

Age, sex, physical activity, genetic phenotype, stress, disorders (eg, achlorhydria, malabsorption syndromes), or previous GI surgery (eg, bariatric surgery) can also affect drug bioavailability.

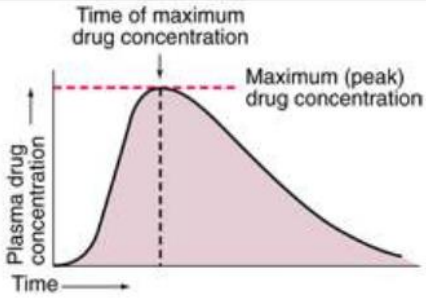
Chemical reactions that reduce absorption can decrease bioavailability. They include formation of a complex (eg, between tetracycline and polyvalent metal ions), hydrolysis by gastric acid or digestive enzymes (eg, penicillin and chloramphenicol palmitate hydrolysis), conjugation in the intestinal wall (eg, sulfoconjugation ofisoproterenol), adsorption to other drugs (eg, digoxin to

cholestyramine), and metabolism by luminal microflora.

Assessing bioavailability

Bioavailability is usually assessed by determining the area under the plasma concentration–time curve (AUC—seeFIG :1 Representative plasma concentration–time relationship after a single oral dose of a hypothetical drug.). The most reliable measure of a drug's bioavailability is AUC. AUC is directly proportional to the total amount of unchanged drug that reaches systemic circulation. Drug products may be considered bioequivalent in extent and rate of absorption if their plasma concentration curves are essentially superimposable.

FIG 1: Representative plasma concentration–time relationship after a single oral dose of a hypothetical drug



Plasma drug concentration increases with extent of absorption; the maximum (peak) plasma concentration is reached when drug elimination rate equals absorption rate. Bioavailability determinations based on the peak plasma concentration can be misleading because drug elimination begins as soon as the drug enters the bloodstream. Peak time (when maximum plasma drug concentration occurs) is the most widely used general index of absorption rate; the slower the absorption, the later the peak time.

For drugs excreted primarily unchanged in urine, bioavailability can be estimated by measuring the total amount of drug excreted after a single dose. Ideally, urine is collected over a period of 7 to 10 elimination half-lives for complete urinary recovery of the absorbed drug. After multiple dosing, bioavailability may be estimated by measuring unchanged drug recovered from urine over a 24-h period under steady-state conditions.

DRUG DISTRIBUTION TO TISSUES

After a drug enters the systemic circulation, it is distributed to the body's tissues. Distribution is generally uneven because of differences in blood perfusion, tissue binding (eg, because of lipid content), regional pH, and permeability of cell membranes.

The entry rate of a drug into a tissue depends on the rate of blood flow to the tissue, tissue mass, and partition characteristics between blood and tissue. Distribution equilibrium (when entry and exit rates are the same) between blood and tissue is reached more rapidly in richly vascularized areas, unless diffusion across cell membranes is the rate-limiting step. After equilibrium, drug concentrations in tissues and in extracellular fluids are reflected by the plasma concentration. Metabolism and excretion occur simultaneously with distribution, making the process dynamic and complex.

For interstitial fluids of most tissues, drug distribution rate is determined primarily by perfusion. For poorly perfused tissues (eg, muscle, fat), distribution is very slow, especially if the tissue has a high affinity for the drug.

Volume of distribution

The apparent volume of distribution is the theoretical volume of fluid into which the total drug administered would have to be diluted to produce the concentration in plasma. For example, if 1000 mg of a drug is given and the subsequent plasma concentration is 10 mg/L, that 1000 mg seems to be distributed in 100 L (dose/volume = concentration; 1000 mg/ x L = 10 mg/L; therefore, x = 1000 mg/10 mg/L = 100 L). Volume of distribution has nothing to do with the actual volume of the body or its fluid compartments but rather involves the distribution of the drug within the body. For a drug that is highly tissue-bound, very little drug remains in the circulation; thus, plasma concentration is low and volume of distribution is high. Drugs that remain in the circulation tend to have a low volume of distribution. Volume of distribution provides a reference for the plasma concentration expected for a given dose but provides little information about the specific pattern of distribution. Each drug is uniquely distributed in the body. Some drugs distribute mostly into fat, others remain in extracellular fluid, and others are bound extensively to specific tissues.

Many acidic drugs (eg, warfarin, aspirin) are highly protein-bound and thus have a small apparent volume of distribution. Many basic drugs (eg, amphetamine, meperidine) are extensively taken up by tissues and thus have an apparent volume of distribution larger than the volume of the entire body.

Binding

The extent of drug distribution into tissues depends on the degree of plasma protein and tissue binding. In the bloodstream, drugs are transported partly in solution as free (unbound) drug and partly reversibly bound to blood components (eg, plasma proteins, blood cells). Of the many plasma proteins that can interact with drugs, the most important are albumin, α1-acid glycoprotein, and lipoproteins. Acidic drugs are usually bound more extensively to albumin; basic drugs are usually bound more extensively to α1-acid glycoprotein, lipoproteins, or both.

Only unbound drug is available for passive diffusion to extravascular or tissue sites where the pharmacologic effects of the drug occur. Therefore, the unbound drug concentration in systemic circulation typically determines drug concentration at the active site and thus efficacy.

At high drug concentrations, the amount of bound drug approaches an upper limit determined by the number of available binding sites. Saturation of binding sites is the basis of displacement interactions among drugs.

Drugs bind to many substances other than proteins. Binding usually occurs when a drug associates with a macromolecule in an aqueous environment but may occur when a drug is partitioned into body fat. Because fat is poorly perfused, equilibration time is long, especially if the drug is highly lipophilic.

Accumulation of drugs in tissues or body compartments can prolong drug action because the tissues release the accumulated drug as plasma drug concentration decreases. For example, thiopental is highly lipid soluble, rapidly enters the brain after a single IV injection, and has a marked and rapid anesthetic effect; the effect ends within a few minutes as the drug is redistributed to more slowly perfused fatty tissues. Thiopental is then slowly released from fat storage, maintaining subanesthetic plasma levels. These levels may become significant if doses of thiopental are repeated, causing large amounts to be stored in fat. Thus, storage in fat initially shortens the drug's effect but then prolongs it. Some drugs accumulate within cells because they bind with proteins, phospholipids, or nucleic acids. For example, chloroquine concentrations in WBCs and liver cells can be thousands of times higher than those in plasma. Drug in cells is in equilibrium with drug in plasma and moves into plasma as the drug is eliminated from the body.

Blood-brain barrier

Drugs reach the CNS via brain capillaries and CSF. Although the brain receives about one sixth of cardiac output, drug penetration is restricted because of the brain's permeability characteristics. Although some lipid-soluble drugs (eg, thiopental) enter the brain readily, polar compounds do not. The reason is the blood-brain barrier, which consists of the endothelium of brain capillaries and the astrocytic sheath. The endothelial cells of brain capillaries, which appear to be more tightly, joined to one another than those of most capillaries, slow the diffusion of water-soluble drugs. The astrocytic sheath consists of a layer of glial connective tissue cells (astrocytes) close to the basement membrane of the capillary endothelium. With aging, the blood-brain barrier may become less effective, allowing increased passage of compounds into the brain.

Drugs may enter ventricular CSF directly via the choroid plexus, then passively diffuse into brain tissue from CSF. Also in the choroid plexus, organic acids (eg, penicillin) are actively transported from CSF to blood.

The drug penetration rate into CSF, similar to other tissue cells, is determined mainly by the extent of protein binding, degree of ionization, and lipid-water partition coefficient of the drug. The penetration rate into the brain is slow for highly protein-bound drugs and nearly nonexistent for the ionized form of weak acids and bases. Because the CNS is so well perfused, the drug distribution rate is determined primarily by permeability.

DRUG METABOLISM

The liver is the principal site of drug metabolism. Although metabolism typically inactivates drugs, some drug metabolites are pharmacologically active—sometimes even more so than the parent compound. An inactive or weakly active substance that has an active metabolite is called a prodrug, especially if designed to deliver the active moiety more effectively.

Drugs can be metabolized by oxidation, reduction, hydrolysis, hydration, conjugation, condensation, or isomerization; whatever the process, the goal is to make the drug easier to excrete. The enzymes involved in metabolism are present in many tissues but generally are more concentrated in the liver. Drug metabolism rates vary among patients. Some patients metabolize a drug so rapidly that therapeutically effective blood and tissue concentrations are not reached; in others, metabolism

may be so slow that usual doses have toxic effects. Individual drug metabolism rates are influenced by genetic factors, coexisting disorders (particularly chronic liver disorders and advanced heart failure), and drug interactions (especially those involving induction or inhibition of metabolism).

For many drugs, metabolism occurs in 2 phases. Phase I reactions involve formation of a new or modified functional group or cleavage (oxidation, reduction, hydrolysis); these reactions are nonsynthetic. Phase II reactions involve conjugation with an endogenous substance (eg, glucuronic acid, sulfate, glycine); these reactions are synthetic. Metabolites formed in synthetic reactions are more polar and thus more readily excreted by the kidneys (in urine) and the liver (in bile) than those formed in nonsynthetic reactions. Some drugs undergo only phase I or phase II reactions; thus, phase numbers reflect functional rather than sequential classification.

Rate

For almost all drugs, the metabolism rate in any given pathway has an upper limit (capacity limitation). However, at therapeutic concentrations of most drugs, usually only a small fraction of the metabolizing enzyme's sites are occupied, and the metabolism rate increases with drug concentration. In such cases, called first-order elimination (or kinetics), the metabolism rate of the drug is a constant fraction of the drug remaining in the body (ie, the drug has a specific half-life). For example, if 500 mg is present in the body at time zero, after metabolism, 250 mg may be present at 1 h and 125 mg at 2 h (illustrating a half-life of 1 h). However, when most of the enzyme sites are occupied, metabolism occurs at its maximal rate and does not change in proportion to drug concentration; instead, a fixed amount of drug is metabolized per unit time (zero-order kinetics). In this case, if 500 mg is present in the body at time zero, after metabolism, 450 mg may be present at 1 h and 400 mg at 2 h (illustrating a maximal clearance of 50 mg/h and no specific half-life). As drug concentration increases, metabolism shifts from first-order to zero-order kinetics.

Cytochrome P-450

The most important enzyme system of phase I metabolism is cytochrome P-450 (CYP450), a microsomal superfamily of isoenzymes that catalyzes the oxidation of many drugs. The electrons are supplied by NADPH–CYP450 reductase, a flavoprotein that transfers electrons from NADPH (the reduced form of nicotinamide adenine dinucleotide phosphate) to CYP450. CYP450 enzymes can be induced or inhibited by many drugs and substances resulting in drug interactions in which one drug enhances the toxicity or reduces the therapeutic effect of another drug. For examples of drugs that

interact with specific enzymes, see Table:1 Common Substances That Interact With Cytochrome P-450 Enzymes and Some Drugs With Potentially Serious Drug-Drug Interactions*.

TABLE 1: Common Substances That Interact With Cytochrome P-450 Enzymes

Enzyme	Substrates	Inhibitors	Inducers
CYP1A2	Acetaminophen Caffeine Clarithromycin Estradiol Haloperidol Lidocaine Methadone Olanzapine Propranolol	Amiodarone Cimetidine Ciprofloxacin Erythromycin Fluvoxamine Ticlopidine	Charcoal-broiled beef Cigarette smoke Omeprazole Phenobarbital Phenytoin Rifampin
	Ritonavir Tacrine Theophylline Tricyclic antidepressants Verapamil *(R)* –Warfarin		
CYP2C9	Celecoxib Diclofenac Fluoxetine Glipizide Glyburide Indomethacin Nifedipine	Amiodarone Cimetidine Fluconazole Lovastatin Ritonavir Sertraline Sulfamethoxazole	Dexamethasone Phenobarbital Other barbiturates Phenytoin Rifampin

	Phenytoin Piroxicam Progesterone Testosterone Tricyclic antidepressants Valproate *(S)* –Warfarin	Topiramate Trimethoprim Zafirlukast	
CYP2C19	Diazepam *(S)* -Mephenytoin Omeprazole Pentamidine Propranolol *(R)* –Warfarin	Cimetidine Fluoxetine Fluvoxamine Ketoconazole Lansoprazole Omeprazole Paroxetine Ticlopidine	Carbamazepine Phenobarbital Prednisone Rifampin
CYP2D6	β-Blockers Codeine Dextromethorphan Flecainide	Amiodarone Bupropion Celecoxib Cimetidine	Carbamazepine Dexamethasone Phenobarbital Phenytoin

Enzyme	**Substrates**	**Inhibitors**	**Inducers**
	Haloperidol Lidocaine Mexiletine Morphine Omeprazole Phenothiazines Quinidine Risperidone SSRIs Tamoxifen Testosterone Tramadol Trazodone Tricyclic antidepressants	Fluoxetine Fluvoxamine Metoclopramide Methadone Paroxetine Quinidine Ritonavir Sertraline	Rifampin

CYP2E1	Acetaminophen Alcohol	Disulfiram	Alcohol Isoniazid
CYP3A4	Amiodarone Azole antifungals Benzodiazepines Ca channel blockers Caffeine Carbamazepine Clarithromycin Cyclosporine Delavirdine Enalapril Estradiol Estrogen Erythromycin	Amiodarone Amprenavir Atazanavir Azole antifungals Cimetidine Ciprofloxacin Clarithromycin Delavirdine Diltiazem Erythromycin Fluoxetine Fluvoxamine Grapefruit juice	Carbamazepine Dexamethasone Isoniazid Phenobarbital Phenytoin Prednisone Rifampin
	Erythromycin Fentanyl Finasteride	Grapefruit juice Indinavir Metronidazole	

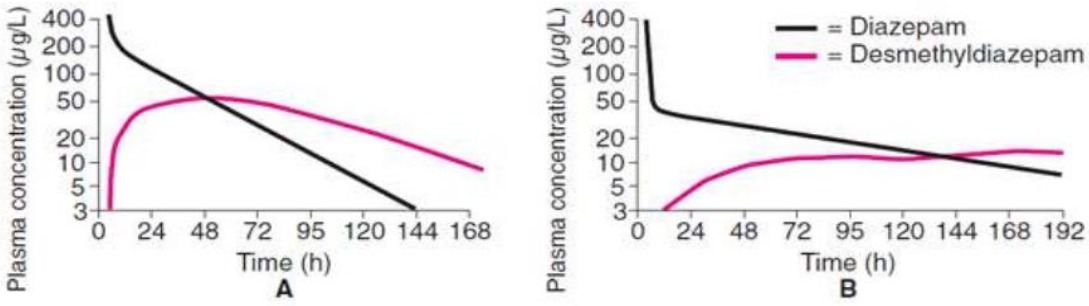
Enzyme	**Substrates**	**Inhibitors**	**Inducers**
	Indinavir Lidocaine Lopinavir Loratidine Methadone Nelfinavir Omeprazole Prednisone Progesterone Ritonavir Saquinavir Sildenafil Sirolimus Statins	Nefazodone Nelfinavir Nifedipine Omeprazole Paroxetine Propoxyphene Ritonavir Saquinavir Sertraline Verapamil	

	Tacrolimus Tamoxifen *(R)* –Warfarin		

With aging, the liver's capacity for metabolism through the CYP450 enzyme system is reduced by ≥ 30% because hepatic volume and blood flow are decreased. Thus, drugs that are metabolized through this system reach higher levels and have prolonged half-lives in the elderly (see Figure: 2 Comparison of pharmacokinetic outcomes for diazepam in a younger man (A) and an older man (B).). Because neonates have partially developed hepatic microsomal enzyme systems, they also have difficulty metabolizing many drugs.

FIG :2Comparison of pharmacokinetic outcomes for diazepam in a younger man (A) and an older man (B).

Diazepam is metabolized in the liver to desmethyldiazepam through P-450 enzymes. Desmethyldiazepam is an active sedative, which is excreted by the kidneys. Elimination half-life is inversely proportional to the terminal slopes of the curves; flat slopes correspond to long half-lives. 0 = time of dosing. (Adapted from Greenblatt DJ, Allen MD, Harmatz JS, Shader RI: Diazepam disposition determinants. Clinical Pharmacology and Therapeutics 27:301–312, 1980.)



Conjugation

Glucuronidation, the most common phase II reaction, is the only one that occurs in the liver microsomal enzyme system. Glucuronides are secreted in bile and eliminated in urine. Thus, conjugation makes most drugs more soluble and easily excreted by the kidneys. Amino acid conjugation with glutamine or glycine produces conjugates that are readily excreted in urine but not extensively secreted in bile. Aging does not affect glucuronidation. However, in neonates, conversion

to glucuronide is slow, potentially resulting in serious effects (eg, as with chloramphenicol). Conjugation may also occur through acetylation or sulfoconjugation. Sulfate esters are polar and readily excreted in urine. Aging does not affect these processes.

DRUG ELIMINATION

The kidneys are the principal organs for excreting water-soluble substances. The biliary system contributes to excretion to the degree that drug is not reabsorbed from the GI tract. Generally, the contribution of intestine, saliva, sweat, breast milk, and lungs to excretion is small, except for exhalation of volatile anesthetics. Excretion via breast milk may affect the breastfeeding infant. Hepatic metabolism often increases drug polarity and water solubility. The resulting metabolites are then more readily excreted.

Renal excretion

Renal filtration accounts for most drug excretion. About one fifth of the plasma reaching the glomerulus is filtered through pores in the glomerular endothelium; nearly all water and most electrolytes are passively and actively reabsorbed from the renal tubules back into the circulation. However, polar compounds, which account for most drug metabolites, cannot diffuse back into the circulation and are excreted unless a specific transport mechanism exists for their reabsorption (eg, as for glucose, ascorbic acid, and B vitamins). With aging, renal drug excretion decreases; at age 80, clearance is typically reduced to half of what it was at age 30.

The principles of transmembrane passage govern renal handling of drugs. Drugs bound to plasma proteins remain in the circulation; only unbound drug is contained in the glomerular filtrate. Un-ionized forms of drugs and their metabolites tend to be reabsorbed readily from tubular fluids. Urine pH, which varies from 4.5 to 8.0, may markedly affect drug reabsorption and excretion because urine pH determines the ionization state of a weak acid or base. Acidification of urine increases reabsorption and decreases excretion of weak acids, and, in contrast, decreases reabsorption of weak bases. Alkalinization of urine has the opposite effect. In some cases of overdose, these principles are used to enhance the excretion of weak bases or acids; eg, urine is alkalinized to enhance excretion of acetylsalicylic acid. The extent to which changes in urinary pH alter the rate of drug elimination depends on the contribution of the renal route to total elimination, the polarity of the un-ionized form, and the molecule's degree of ionization.

Active tubular secretion in the proximal tubule is important in the elimination of many drugs. This energy-dependent process may be blocked by metabolic inhibitors. When drug concentration is high, secretory transport can reach an upper limit (transport maximum); each substance has a characteristic transport maximum.

Anions and cations are handled by separate transport mechanisms. Normally, the anion secretory system eliminates metabolites conjugated with glycine, sulfate, or glucuronic acid. Anions compete with each other for secretion. This competition can be used therapeutically; eg, probenecid blocks the normally rapid tubular secretion of penicillin, resulting in higher plasma penicillin concentrations for a longer time. In the cation transport system, cations or organic bases (eg, pramipexole, dofetilide) are secreted by the renal tubules; this process can be inhibited by cimetidine, trimethoprim, prochlorperazine, megestrol, or ketoconazole.

Biliary excretion

Some drugs and their metabolites are extensively excreted in bile. Because they are transported across the biliary epithelium against a concentration gradient, active secretory transport is required. When plasma drug concentrations are high, secretory transport may approach an upper limit (transport maximum). Substances with similar physicochemical properties may compete for excretion.

Drugs with a molecular weight of > 300 g/mol and with both polar and lipophilic groups are more likely to be excreted in bile; smaller molecules are generally excreted only in negligible amounts. Conjugation, particularly with glucuronic acid, facilitates biliary excretion.

In the enterohepatic cycle, a drug secreted in bile is reabsorbed into the circulation from the intestine. Biliary excretion eliminates substances from the body only to the extent that enterohepatic cycling is incomplete—when some of the secreted drug is not reabsorbed from the intestine.