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Mechanisms of Drug Interactions

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LEARNING OBJECTIVES

Upon completion of this module, the subscriber will be able to:

1. Give an example of the following types of interactions: drug-disease, drug-food, drug-herbal supplement, and drug-drug.
2. Describe different causes of drug interactions.
3. Explain how stomach acid can affect drug absorption and elimination.
4. Discuss the role of enzyme systems in the liver that result in drug interactions.
5. Describe characteristics of drugs and patients that increase the likelihood of a significant drug-drug interaction.

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Mechanisms of Drug Interactions

Introduction

The risk of dying from a drug-related incident now exceeds the risk of dying in a traffic accident. In 2008 (the most recent data available), 36,500 drug related deaths were reported. This statistic is a wide net and includes intentional overdose and illicit drug use, as well as adverse drug reactions, drug interactions, and other drug mishaps.[1]

In 2010, 3.7 billion prescriptions were filled, averaging about 12 prescriptions per person in the United States.[2] The risk of adverse drug effects and drug interactions increases with the number of drugs a patient is taking.[3] Forty percent of elderly patients take from 5 to 9 medications, and 18% take 10 or more. Researchers in a recent study estimated nearly 100,000 emergency hospitalizations per year related to adverse drug events.[2,4]

"Adverse drug event" is a broad term that encompasses several drug mechanisms. An adverse drug reaction is defined as any unexpected, unintended, undesired, or excessive response to a drug that requires discontinuing or changing the drug, or modifying the dose; causes hospital admission or prolongs stay; requires supportive treatment; complicates diagnosis or negatively affects prognosis; or results in harm, disability or death. Although the terms are sometimes used interchangeably, a "side effect" differs from an adverse drug reaction in that is it is an expected, well-known reaction resulting in little or no change in treatment (e.g., drowsiness with an antihistamine, nausea with chemotherapy).[5]

"Drug-drug interaction" is defined as the pharmacologic or clinical response to the administration of a drug combination that is different from the anticipated effects of the two drugs when given alone.[6] Drug-drug interactions may result in adverse drug reactions, decreased therapeutic benefit, or patient harm. More than 100,000 types of potential drug interactions have been documented, but most do not actually lead to adverse effects.[7] The actual frequency of drug-drug interactions is unknown. One survey of two large health plans using prescription drug claims data estimated the risk of potential drug interactions to be 6.2% to 6.7% per year.[8]

Not all drug interactions are bad. Some drug interactions are used therapeutically. Drugs used for numbing a specific area (local anesthetics) often contain a combination of lidocaine (or other "-caines") and epinephrine, which causes blood vessels to constrict, thereby prolonging the effect of lidocaine in the area of the injection. Reversing agents, such as naloxone (Narcan), are given after surgery to stop the effects of narcotics. Several drugs are given simultaneously for cancer treatment to provide effects at multiple sites of cancer cell growth. Beneficial drug interactions can improve treatment.

Knowledge of potential drug interactions is an important part of pharmaceutical care. The term "drug interactions" encompasses drug-disease interactions, drug-food interactions, drug-herb interactions, and drug-drug interactions.

Drug-disease (or -condition) interactions occur when a drug affects a preexisting disease or condition. Diseases can interact with drugs to increase the risk of adverse effects. For example, aspirin increases bleeding in patients with peptic ulcer disease; people with high blood pressure may be at greater risk for increased heart rate with oral decongestants found in over-the counter cough, cold and allergy products.

Advanced age is a condition that increases drug interaction risk. For example, sedatives increase the risk of falls in the elderly, and lower doses of narcotics are often effective for pain relief. The anticoagulant warfarin causes more bleeding in elderly patients and usually requires a lower dose.[9]

Drug-food (or -nutrient) interactions occur when a food changes the expected effect of a drug. For example, milk decreases the absorption of antibiotics such as tetracycline or ciprofloxacin; grapefruit juice increases the effect of some antihypertensive medicines.[10]

Drug-herb (or -supplement) interactions occur when an herb or dietary supplement changes the expected effect of a drug. For example, ginkgo biloba may increase the effect of anticoagulants; calcium supplements may reduce the absorption of thyroid supplements.[11] This review will focus on drug-drug interaction (DDI) mechanisms and will include examples of common drug interactions.

Drug-Drug Interaction Classification

DDIs can be classified according to where the interaction occurs: outside or inside of the body **(Figure 1)**. Most pharmaceutical drug interactions, often called incompatibilities, occur outside the body whereas pharmacological interactions occur within the body. Pharmaceutical interactions generally occur before drugs are actually administered to the patient.[12] We will briefly discuss pharmaceutical reactions, and the remainder of this review will focus on pharmacological interactions, which occur inside the body.

Pharmaceutical Interactions

Chemical DDI

Pharmaceutical drug interactions can be divided in to chemical and physical reactions. An example of a chemical reaction is the incompatibility of potassium phosphate and calcium chloride in total parenteral nutrition preparations, also known as TPNs or hyperalimentation. The two drugs may interact to form calcium phosphate, which will result in a precipitate ("snow") in the intravenous (IV) fluid bag. Persistent seizures (status epilepticus) is a life threatening condition that requires medication to stop the seizures as soon as possible. Two commonly used anticonvulsant drugs, phenytoin (Dilantin) and lorazepam (Ativan), become ineffective if mixed together in the same IV bag or syringe.[12,13]

Physical DDI

Physically altering a drug formulation such as by crushing a sustained-release tablet could result in the drug being released more quickly and/or in a larger amount. Alcohol or food given with some sustained release products may cause similar problems. Another example of a physical reaction includes the thyroid drug levothyroxine sticking to IV tubing and bags.[14] One drug can alter the formulation of another drug, such as the combination of diazepam (Valium) with the emulsion propofol (Diprivan). Diazepam destabilizes the propofol emulsion, causing it to "oil out" and making it dangerous to administer intravenously.[15]

Environmental conditions can adversely affect drugs. Light can cause some drugs to degrade and become less effective. This is why medicine bottles are usually amber or opaque. Humidity can have a similar effect on drugs. Other environmental conditions can affect drug absorption. For example, heating pads can increase the release of the narcotic fentanyl from transdermal patches.[16, 17]

Pharmacological Interactions

More commonly, DDIs are identified with reactions that occur inside the body, or pharmacological interactions. Pharmacological interactions are classified as pharmacodynamic interactions and pharmacokinetic interactions **(Figure 2).**

Figure 1. Classification of drug interactions[13]

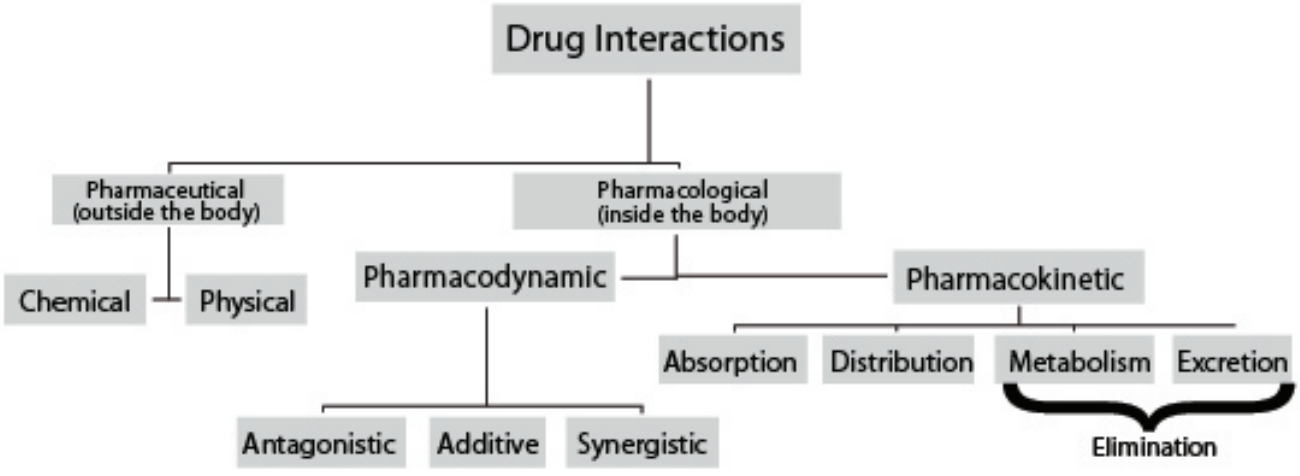
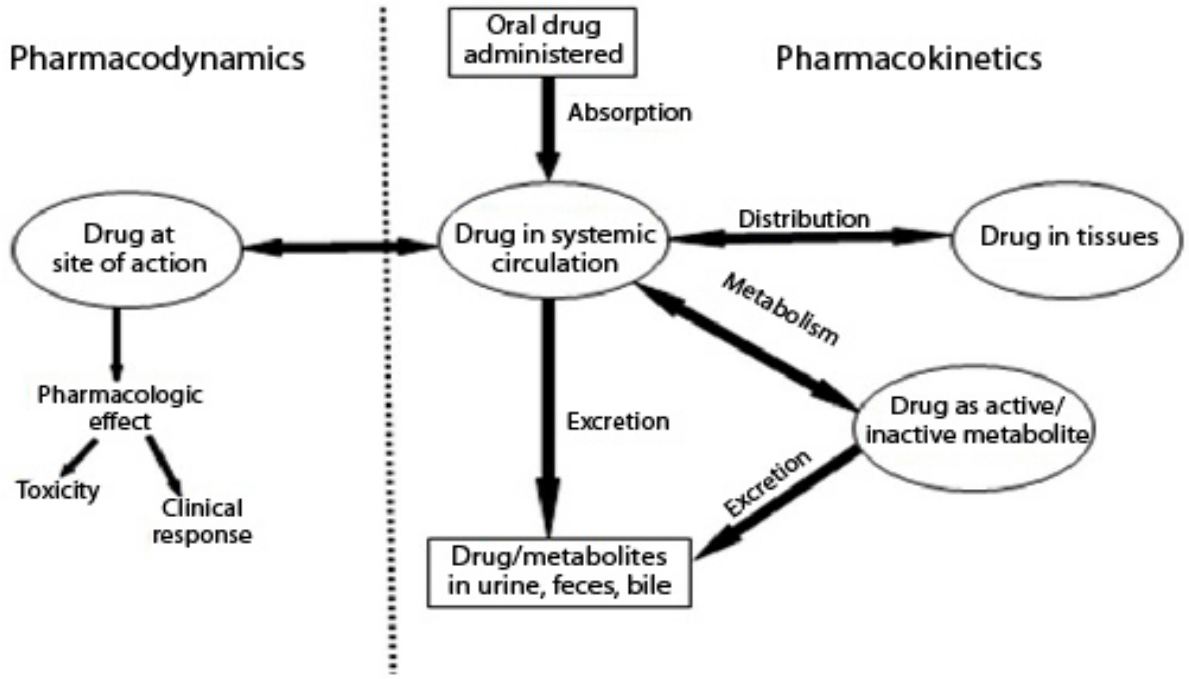


Figure 2. Pharmacodynamic and pharmacokinetic drug activity



Pharmacodynamic DDI

Drug receptors: agonists and antagonists

Pharmacodynamics is the term for the effect(s) that a drug has on the body. The pharmacodyamics of a drug are described in terms of pharmacological effect vs drug dose. Generally, as the dose or drug concentration increases, the pharmacological effect increases proportionately. The effect may be an intended therapeutic effect such as relieving pain, relaxing muscle, or killing bacteria. The effect might also be an unintended side effect such as headache with the use of nitroglycerin or discolored urine with the phenazoperidine (Pyridium). The effect could also be an adverse reaction such as birth defects with the acne drug isotretinoin (Accutane), rhabdomyolysis (muscle breakdown) with statins such as atorvastatin (Lipitor).[12,17]

Regardless of whether the pharmacological effect is intended or unintended, drugs work by interacting with receptors on the surface of a cell. The relationship between a receptor and drug is often compared with a lock and key. Cell receptor molecules bind with naturally occurring substances (eg, hormones, neurotransmitters) or drugs. Receptors may be thought of as keyholes that provide access to the cell with the correctly fitting key. The "key" may be a naturally occurring substance in the body such as epinephrine (adrenaline), or a drug or any other substance that is foreign to the body, such as an herb. Many drugs work by mimicking chemicals that occur naturally in the body. For pharmacological effect, a drug must bind to a cell receptor site.[17]

A drug that binds with a receptor (i.e., fits into the keyhole) and causes it to act in the same way as a naturally occurring

Pop Quiz #1

Why must nitroglycerin tablets (NitroStat) be dispensed in the original container?

A. Nitroglycerin will explode on impact if it is placed in another container.
B. The tablets are too easily lost if stored in a larger container.
C. Nitroglycerin decomposes easily and sticks to plastic so it must be stored in a dark glass container.
D. It is easier to get the tablets out of a smaller container in an emergency.

See page 24 for answer.

substance is called an agonist **(Figure 3)**. Drugs that bind with a receptor to prevent it from interacting with naturally occurring substances blocking the receptor (i.e., jamming the lock) are called antagonists **(Figure 4)**.[17] Examples of drugs that are agonists and antagonists are adrenergic agonists and adrenergic antagonists. "Adrenergic" refers to the so called "fight-or-flight" system of the body. Adrenergic receptors bind with epinephrine (adrenaline). Adrenergic receptors are classified as alpha or beta depending on their function and are found in various parts of the body. If you were being chased by a lion, the adrenal glands, which sit on top of the kidneys, would release epinephrine. Epinephrine binds to adrenergic receptors causing the heart to pump more blood, the lungs to take in more oxygen, and the blood vessels to constrict, raising the blood pressure. More oxygen-filled blood gets to the brain and muscles, allowing quick thinking and faster movement – hopefully avoiding lunch for the lion.

Mimicking some of the effects of epinephrine can be useful for specific diseases or conditions. During an asthma attack, muscles around the airways contract, causing the bronchial (breathing) tubes to narrow. A beta-agonist, such as albuterol or salmeterol, can bind with adrenergic receptors in the lungs and relax the bronchial tubes, which improves breathing. Patients with high blood pressure or other conditions may take beta-antagonists, also called beta-blockers, to reduce blood pressure or heart rate. Beta-blockers, such as propranolol (Inderal) or metoprolol (Toprol), block the beta adrenergic receptors from binding with naturally occurring substances such as epinephrine, thereby lowering the blood pressure and heart rate.[18] The combination of a beta-agonist with a beta-blocker could reduce the effects of both drugs by competing for the same cellular receptor **(Figure 4)**.

Figure 3. Drug (agonist)-receptor interaction

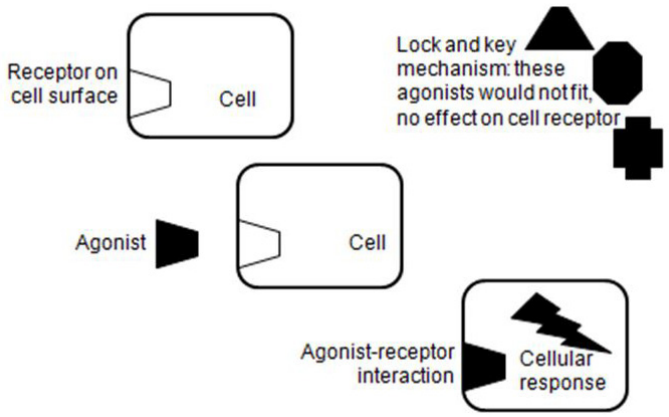
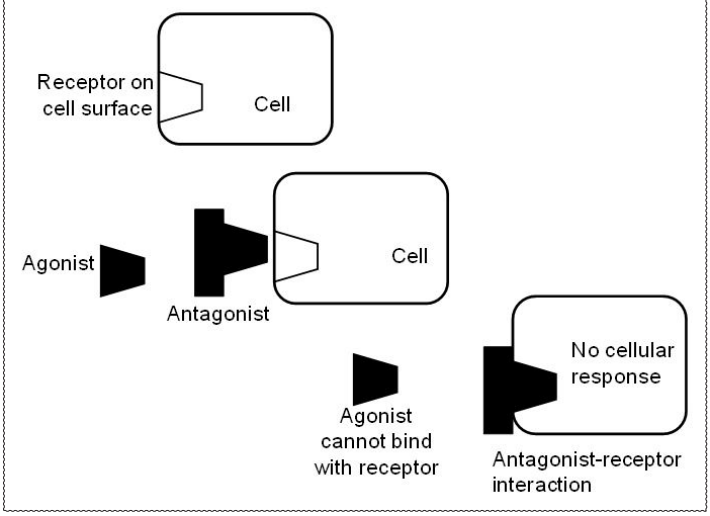


Figure 4. Drug (antagonist)-receptor interaction



Additive, Antagonistic, and Synergistic DDI

The combined effects of drugs may result in additive, antagonistic, or synergistic DDIs. Additive DDIs occur when the effect of two drugs results in a greater effect than the effect of each agent given alone (1+1=2). For example, alcohol plus sleep medicines cause increased (and sometimes dangerous) drowsiness, greater than the drowsiness caused by either alcohol or sleep medicine alone. Aspirin inhibits platelet aggregation (stops them from sticking together to form a clot) and heparin prevents blood from clotting; the combination of an antiplatelet drug and an anticoagulant may increase the risk of bleeding. High blood pressure is often treated with two or more antihypertensives to gain better control over blood pressure. The combination of drugs often lowers blood pressure more effectively than increasing the dose of one medication.[17]

Antagonistic DDIs occur when one drug reduces or eliminates the effect of another (1-1=0). This may occur at the receptor level, as with beta-blockers discussed above, or by other mechanisms. Antagonistic DDIs are the basis for antidotes in poisoning. For example, acetaminophen (Tylenol) overdoses may be treated with a drug called acetylcysteine (Mucomyst or Acetadote), which prevents the toxic effect on the liver by eliminating toxic metabolites (breakdown products) of acetaminophen. The narcotic antagonist naloxone (Narcan) is used for narcotic overdoses. Antagonistic drug interactions are often unwanted;

Pop Quiz #2

Flumazenil (Romazicon) is used to reverse the effects of diazepam (Valium) overdose. What type of pharmacodynamic interaction is it?

A. Synergistic
B. Antagonistic
C. Additive
D. Positive

See page 24 for answer.

for example, caffeine may reduce the effect of sleep aids. Antihypertensive medication is likely to be less effective when taken with many herbal weight loss products. These products often contain the stimulant bitter orange (synephrine) and various forms of caffeine such as guarana, which can increase blood pressure.[11,18]

Synergistic DDIs occur when the combined effect of two drugs exceeds the sum of the effects of each drug given alone (1+1=3). Antibiotics are often given together for a synergistic effect. For example, aminoglycosides such as gentamicin and penicillins such as ampicillin are often given for serious infections in hospitalized patients. Many pain medications use two or more analgesics (e.g., Percocet contains oxycodone and acetaminophen, Excedrin contains acetaminophen, aspirin, and caffeine) for greater pain relief than each individual component can provide. An example of an unwanted synergistic drug interaction is the combination of nitrates (e.g., nitroglycerin, isosorbide) and erectile dysfunction drugs such as sildenafil (Viagra), which may cause a potentially life-threatening drop in blood pressure when taken together.[19]

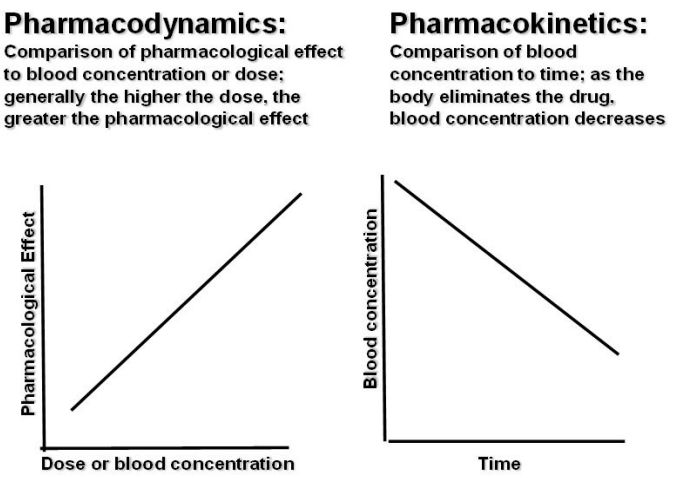
Pharmacokinetic DDI

Pharmacokinetics is defined as what the body does to a drug, or more formally, the movement of drugs through the body including the processes of absorption, distribution, metabolism, and excretion (ADME). The pharmacokinetics of a drug are described in terms of drug concentration in the blood or plasma vs. time **(Figure 5)**.The drug must achieve adequate concentration at the site of activity (cell receptor site) to exert a pharmacologic effect, which is dependent on ADME. Think of pharmacokinetics as the time course of the drug concentration from a particular dosage regimen. Pharmacokinetics can tell us how much of a drug to give and how often it must be given to reach the target drug concentration that causes the desired pharmacological effect. Drug interactions can occur at any point in ADME.[17,18]

Absorption

Absorption is the first process of pharmacokinetics. In general, drugs require absorption to have a pharmacologic effect. Drugs given by mouth must be absorbed through the stomach and/or intestine to reach the blood to be delivered to the site of action. Likewise, drugs given by intramuscular (IM) or subcutaneous (Sub-Q) injection or drugs administered nasally, sublingually (under the tongue), or by other non-oral routes must be absorbed from the administration site. Drugs given intravenously are given directly into the blood, bypassing absorption; thus, the onset of effect is almost immediate. Drugs given Sub-Q or IM and other non-oral routes exert a pharmacological effect more slowly than IV drugs, but usually

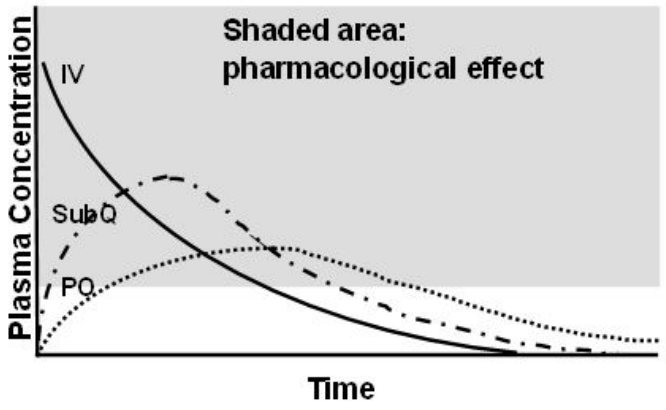
Figure 5. Comparison of pharmacokinetic and pharmacodynamic graphs



faster than oral drugs **(Figure 6)**. We will focus on oral drug absorption, where most absorption drug interactions occur.[17,18]

The cell membrane acts as a gate keeper for selective entrance and exit of nutrients, waste, drugs, and other substances foreign to the cell. Cell membranes are made up of phospholipid molecules: each molecule contains a phosphate (a molecule of the elements oxygen and phosphorus) end and a fatty acid (a string of carbons and hydrogens) end. Phospholipids form a bilayer so that their hydrophobic (from Greek words meaning "afraid of water") tails are projecting to the interior of the two layers and their hydrophilic (from Greek words meaning "water loving") heads are projecting outward **(Figure 7)**. This organization of phospholipids allows the cell membranes to selectively control the entrance and exit of molecules.[20]

Figure 6. Effect of route of administration on onset of pharmacological effect



IV = intravenous; SubQ= subcutaneous; PO = by mouth

Substances that are lipid soluble (hydrophobic) can move from outside the cell through the cell membrane by a process called diffusion – movement from high concentration to lower concentration – into the inside of the cell **(Figure 7)**. Most oral drugs are designed to be lipid soluble and are absorbed by passive diffusion so they easily pass through the membrane. Other substances diffuse through the cell membrane, but require help getting into the cell. Larger molecules or non-lipid soluble (hydrophilic) substances enter the cell via carrier proteins in a process called facilitated diffusion. The sugar glucose enters cells by facilitated diffusion. Less commonly, substances enter the cell via active transport, a process that requires energy and may involve movement from a lower concentration to a higher concentration. For example, vitamin B12 (cyanocobalamin) is absorbed partially by active transport. In addition to the role these processes play in drug absorption, passive and facilitated diffusion and active transport also play a role in drug excretion.[18,20]

In order to be absorbed, a tablet or capsule must disintegrate and dissolve in the stomach. This presents a dilemma for the chemist designing a drug formulation: water solubility is best for the dissolution of the drug in the stomach, but lipid solubility is best for absorption. Thus, drugs are usually weak acids or weak bases, designed to dissolve and thus promote absorption. Many drugs are formulated as salts (e.g., morphine sulfate, potassium penicillin) to improve water solubility without negatively affecting absorption or changing other characteristics of the drug. The dissolved drug in the gastrointestinal tract exists in two forms, the water-soluble ionized (having a positively or negatively charged molecule) and lipid-soluble non-ionized form. The proportion of each form is dependent on pH, the acidity or alkalinity of the environment (most acidic = pH 1, neutral = pH 7, most alkaline [basic] = pH 12). The stomach is very acidic with a pH of 1-2; the intestine is less acidic with a pH of 6 in the duodenum, where the stomach connects to the small intestine. The pH increases to become more alkaline, about 7.4 farther along in the small intestine.

In the acidic stomach, weak acids are more non-ionized, and therefore lipid soluble and readily absorbed. Weak bases are

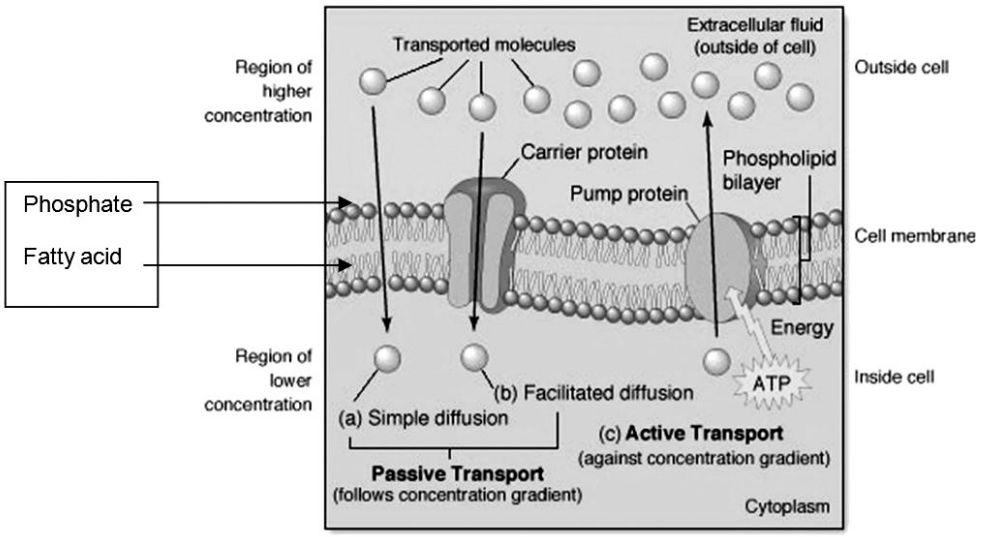
Pop Quiz #3

Which of the following routes of drug administration is not affected by absorption?

A. oral
B. subcutaneous
C. intramuscular
D. intravenous

See page 24 for answer.

Figure 7. Cell membrane structure and cellular membrane transport



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more ionized in the acidic stomach, limiting absorption. In the alkaline small intestine, drugs that are weak bases become more non-ionized, and therefore more lipid soluble and readily absorbed. For example, aspirin, a weak acid, is more non-ionized (lipid soluble) in the stomach and is partially absorbed there; caffeine, a weak base, is ionized (water soluble) in the stomach and thus not well absorbed. In the more alkaline small intestine, caffeine becomes a more non-ionized, lipid-soluble molecule, so it is absorbed better in the intestine than in the stomach. Aspirin is a weak acid and is more readily absorbed in the stomach. A good tip to remember is "like absorbs like," as an acidic stomach more readily absorbs weak acids and a basic (alkaline) intestine more readily absorbs weak bases. Most drug absorption takes place in the small intestine. Absorption in the stomach is hindered by the mucous layer that coats the surface of the stomach to protect it from the acid other stomach cells secrete. Also, the surface area of the stomach is relatively small compared with the small intestine, whose surface area would be the size of a tennis court if stretched out.[17,18,20]

DDIs involving absorption can occur by several mechanisms. Some drugs require an acidic or basic environment for absorption. Drugs that increase the pH of the stomach (i.e., make it less acidic) can change the absorption of drugs that are best absorbed in an acidic environment. For example, absorption of the antifungal drug, itraconazole, is decreased when taken with an antacid (e.g. Maalox, Mylanta), which increases the pH of the stomach. Enteric-coated aspirin has a coating that is designed to dissolve at a higher pH (more alkaline) so that it will not dissolve in the stomach and cause problems for patients with ulcer disease. Giving enteric aspirin with a drug that increases the pH of the stomach, such as ranitidine (Zantac), can cause the enteric coating to dissolve in the stomach instead of the intestine. The auxiliary label, "take on an empty stomach," usually means the drug is better absorbed in a more acidic environment.[17,18]

Another mechanism of DDI involves reduced absorption through binding and chelation (formation of an insoluble complex) mechanisms. For example, the combination of the antibiotic ciprofloxacin (Cipro) and iron or calcium supplements (or the calcium in milk, yogurt, ice cream, etc.) results in lower ciprofloxacin absorption. Bile acid sequestrants such as cholestyramine (Questran) and colestipol (Colestid) are designed to bind with bile acids, which reduces the production of cholesterol. In addition to bile acids, these drugs bind many other drugs such as the diuretic, furosemide (Lasix).[21]

Pop Quiz #4
Match the term to its definition.

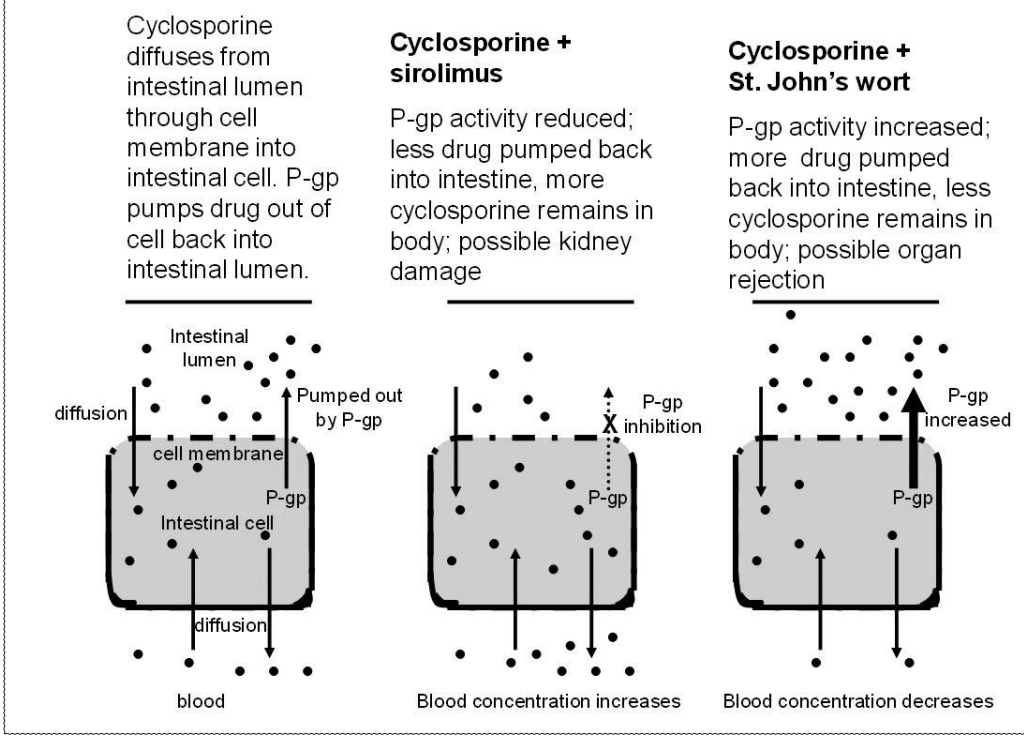
A. Ionized	1. Having a pH greater than 7
B. Alkaline	2. Movement through a cell membrane
C. Hydrophobic	3. "Water fearing," lipid soluble
D. Diffusion	4. Positively or negatively charged molecule

See page 24 for answers.

Cell transporters such as P-glycoprotein (P-gp) may also contribute to absorption DDI **(Figure 8)**. P-gp acts as sort of a "cellular vacuum cleaner" and pumps foreign substances out of the cell. Cyclosporine is used to suppress the immune system to prevent the body from rejecting transplanted organs. Cyclosporine is transported across cell membranes by P-gp. Some drugs and herbs such as St. John's wort increase the activity of P-gp causing cyclosporine that has been absorbed into intestinal cells to be pumped back out into the intestinal lumen (the inside of the "pipe") and excreted. Episodes of organ rejection have occurred when cyclosporine and St. John's wort are taken together. Drugs that inhibit the activity of P-gp such as the anti-rejection drug sirolimus (Rapamune) or the antibiotic erythromycin can cause higher amounts of cyclosporine to remain in the body, resulting in kidney damage.[22]

A therapeutic use of adsorption DDI is the use of charcoal for drug poisoning. Charcoal adsorbs some drugs to its surface so that the drug cannot be absorbed. Accidental or suicidal overdoses of the antidepressant drug amitriptyline (Elavil) are sometimes treated with charcoal to decrease the amount of amitriptyline that is absorbed. The amitriptyline is adsorbed to the charcoal and stays in the intestine, rather than being absorbed into the bloodstream where it can cause irregular heartbeat and other problems. Don't confuse the terms aBsorb and aDsorb. An example of aBsorption is the action of a sponge soaking up water,

Figure 8. Drug interactions involving P-glycoprotein (P-gp)



or a drug passing through a cell membrane. An example of aDsorption is the action of a cigarette filter trapping tars and other substances on its surface, or a drug being adsorbed to the surface of charcoal.[18]

Drugs may affect the rate of absorption by altering the movement of the gastrointestinal tract. For example, narcotics slow the motility (movement) of substances through the intestine. Theoretically, greater absorption might occur because the intestine has a longer period of time in which to absorb the narcotic or other drugs given concurrently. On the other hand, laxatives could increase the movement of drugs through the intestinal tract, and theoretically reduce absorption. Usually, given the huge surface area of the intestine available for absorption, changes in the motility of the intestinal tract do not affect drug absorption to a clinically noticeable degree.[17,18]

Drug absorption may be changed by a process called enterohepatic circulation, circulation between the liver and intestine **(Figure 9)**. Some drugs that enter the liver are secreted into bile, which the liver produces. Bile plus drug are secreted into the small intestine. Drugs (and/or metabolites) are absorbed again in the intestine and circulated back to the liver. Some fraction of what is absorbed will be secreted into the bile again, while the rest will enter the systemic circulation (bloodstream). Enterohepatic circulation is the reason for warnings about the concomitant use of oral contraceptives and antibiotics **(Figure 9)**. The estrogen in oral contraceptives is transformed to an inactive metabolite in the liver and secreted into bile. Beneficial bacteria that live in the intestine restore estrogen to its active form, and active estrogen is reabsorbed. Antibiotics can kill the bacteria in the intestine; instead of being reactivated, the inactive estrogen stays in the intestine to be excreted. As a result, estrogen levels could decrease, causing an unplanned pregnancy. The clinical importance of this interaction is debatable and usually is significant only when other factors such as genetic differences or concurrent metabolic interactions are involved.[12,23]

Figure 9. Enterohepatic circulation

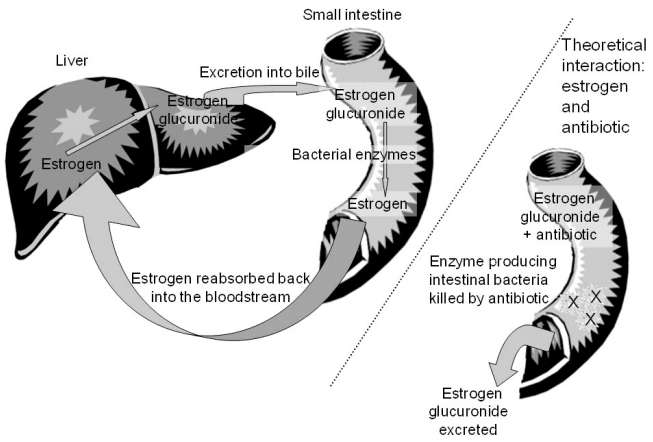
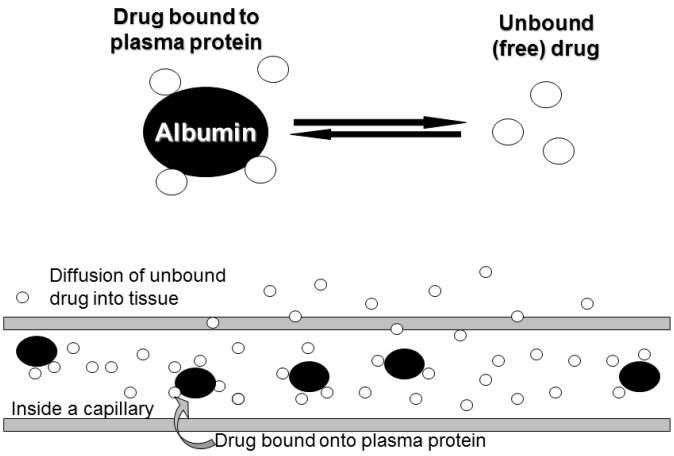


Figure 10. Plasma protein binding[12,23]



Distribution

After a drug is absorbed or injected into the bloodstream, it is distributed to various body tissues. DDIs can occur at the distribution phase of pharmacokinetics. Distribution differs among drugs and depends on factors such as lipid solubility and blood flow to the specific tissue. Organs that receive higher blood flow such as the liver, heart, and kidney receive larger amounts of drug more quickly than organs with lower blood flow such as muscle, fat, and peripheral tissues.[23]

One factor that affects drug distribution is the extent of binding with plasma and tissue proteins. Drugs bind at varying degrees to plasma proteins such as albumin. Protein-bound drugs are not available to exert pharmacologic effects. Only the portion of the drug that is not protein bound is available for diffusion to tissue sites and pharmacological effects **(Figure 10)**.[23]

Two drugs that are highly plasma protein bound may compete for the same binding sites causing high concen-

Pop Quiz #5

What is the most likely reason for advising patients with a prescription for alendronate (Fosamax) for osteoporosis to take the drug on an empty stomach?

A. To prevent the drug from dissolving in the stomach
B. The drug is better absorbed in an acidic environment
C. To slow the absorption of the drug
D. The drug may become too potent when taken with food

See page 24 for answer.

trations of unbound (free) pharmacologically active drug. For example, the antiseizure drug phenytoin (Dilantin) may be more pharmacologically active and require a dosage adjustment when given with valproic acid (Depakote), another antiseizure medication **(Figure 11)**.[21] In terms of clinical significance, protein-binding DDIs are the least important of the 4 pharmacokinetic parameters. These interactions are likely to be most noticeable when a new drug is added or a drug is discontinued. Often, the increased amount of unbound drug available is not clinically apparent because of increased elimination of the drug.

Metabolism

While drug absorption and distribution are still occurring, the body begins the process of elimination – getting rid of the drug. (Elimination is also called clearance, and metabolism is sometimes called biotransformation.) Drugs that are water soluble (i.e., hydrophilic, ionized) are most easily excreted by the body. The two major pathways of drug elimination from the body are metabolism by liver enzymes and excretion through the kidneys. DDIs that speed up or slow down these processes are important sources of both adverse and therapeutic effects.[17]

The enzyme-producing liver is the major player in drug metabolism, which is classified as phase I and phase II metabolism. In phase I metabolism, the liver produces various enzymes to metabolize (break down) drugs and make them more water soluble and easier to eliminate. A drug that is broken down by an enzyme is called a metabolite. Metabolites may be active with similar or dissimilar pharmacological activity as the parent drug (i.e., the original drug), or pharmacologically inactive. A drug may undergo several types of metabolism **(Figure 12)**.

Phase I metabolism involves chemical reactions resulting in a metabolite that is a different molecule from the parent drug. Phase II metabolism is simpler. A drug (or a phase I metabolite) is conjugated (Latin for "joined together") with a molecule produced by the body such as glucuronide, glutathione, or sulfate; this process is called conjugation. For example, aspirin undergoes phase I metabolism to salicylic acid; salicylic acid is joined (conjugated) with

Figure 11. Competition for plasma protein binding sites[12,23]

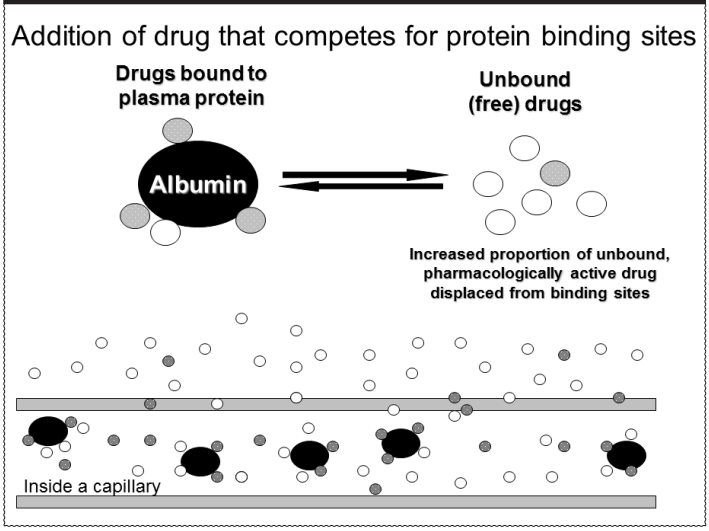
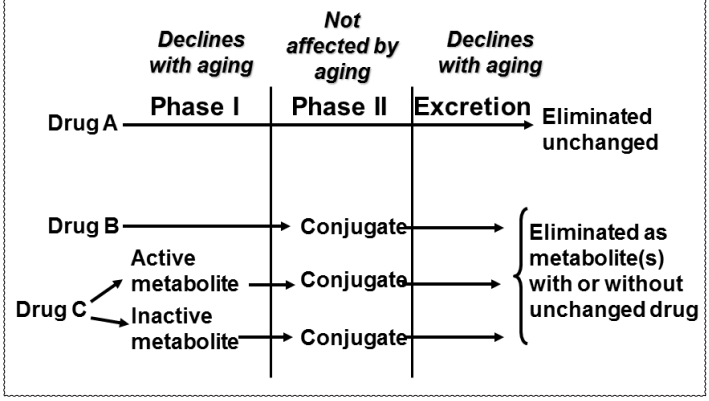


Figure 12. How drugs are eliminated[18,23]



glucuronide by phase II metabolism; the glucuronide metabolite is excreted by the kidneys as an inactive metabolite. Phase I metabolism is affected by aging whereas aging has little effect on phase II metabolism. Phase I metabolism is a huge source of DDIs.[18,23]

Different enzymes metabolize different drugs; however, a drug may be metabolized by several enzymes. Hepatic (liver) enzymes probably developed through the process of evolution to protect the body from foreign substances. Early humans without enzymes to metabolize foreign substances died. For example, after eating a toxic root or herb, cavemen with protective enzymes lived on to produce offspring; unfortunate individuals without protective enzymes did not survive. This evolutionary process is likely responsible for genetic differences in drug metabolism (more on this later).[18]

The major drug-metabolizing enzymes are the cytochrome P-450 enzymes. These enzymes are located throughout the body, but are present in highest concentrations in the liver and intestine – the sites that serve as first line of defense for the body to protect itself from foreign substances. More than 50 cytochrome P-450 enzymes have been identified in humans, but only six are significantly involved in DDIs **(Figure 13)**. The enzymes are named by family, subfamily, and individual gene, e.g., CYP2D6 or CYP3A4. CYP, which is pronounced "sip," identifies the enzyme group, cytochrome P-450; the first number identifies the family of genes; the letter is the subfamily; and the last number is the individual gene. CYP3A4 is involved in the greatest number of DDIs.[17,18,23]

Metabolism DDIs can occur when a drug that affects the activity or production of a CYP enzyme is given with a drug that is metabolized by the CYP enzyme. The drug metabolized by the CYP enzyme is called the "substrate" (think of it as the "victim" that is metabolized by an enzyme). Drugs that inhibit the activity of CYP enzymes are called "inhibitors" and increase the effect of the substrate drug. Drugs that induce (cause) the production of larger amounts of enzyme are called "inducers," which decrease the effect of the substrate drug **(Figure 14)**.

Figure 13. Proportion of drugs metabolized by various CYP-450 enzymes[17]

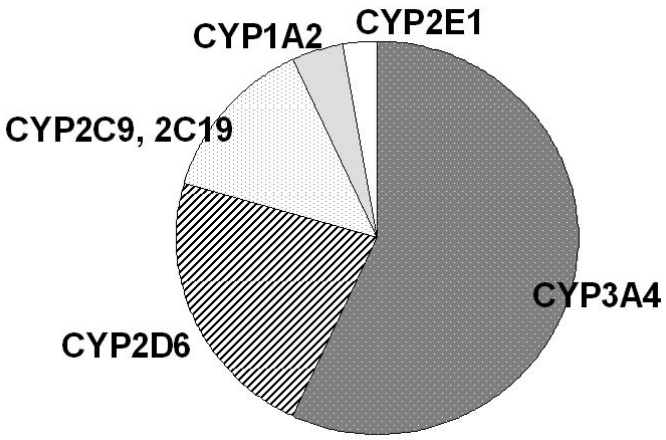
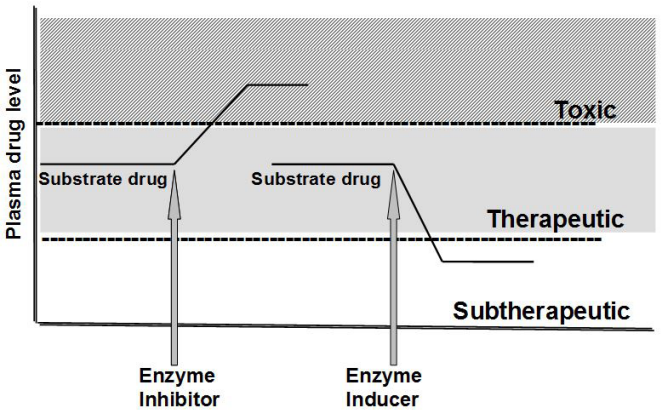


Figure 14. Enzyme inhibitors and inducers[12]



The asthma drug, theophylline, is a substrate of CYP1A2. If a patient with therapeutic blood levels of theophylline begins taking cimetidine (Tagamet), used for gastroesophageal reflux disease (GERD, heartburn), theophylline levels may increase to toxic concentrations because cimetidine inhibits the effect of CYP1A2 and theophylline is metabolized more slowly **(Figure 14)**. Conversely, if a patient with therapeutic blood levels of theophylline begins smoking cigarettes, theophylline levels may decline to subtherapeutic levels because tobacco causes the body

Pop Quiz #6
True or False:
Only unbound drug (i.e., drug that is not bound to plasma proteins) is pharmacologically active.
See page 24 for answer.

to produce more CYP1A2, so theophylline is metabolized more quickly **(Figure 14)**. Generally, inhibition DDIs take place within hours or a day or so; induction DDIs take longer, days to a couple of weeks, because of the time required for the inducing drug to cause the body to produce more enzyme.[12,21,24]

Drugs may affect metabolism by different pathways depending on dosage and other conditions. For example, 95% of a therapeutic dosage of acetaminophen (Tylenol, 650–1000 mg tid to qid) is metabolized by phase II metabolism and eliminated as acetaminophen glucuronide and sulfate conjugates. The remaining 5% is metabolized via phase I metabolism by CYP2E1, which produces a metabolite that is hepatotoxic (damaging to the liver). The toxic metabolite is further metabolized by phase II metabolism to a glutathione metabolite, which does not harm the liver. In cases of acetaminophen overdose, the body uses up all the available glucuronide and sulfate, so metabolism shifts from phase II metabolism to phase I. Phase I metabolism produces so much of the toxic liver metabolite that the protective glutathione is also depleted, and severe liver damage can occur. Acetylcysteine is sometimes given in the emergency room to replenish glutathione and prevent the toxic metabolite from accumulating, thereby decreasing liver toxicity. Chronic alcohol abuse, particularly in acetaminophen overdose, induces the production of CYP2E1, favoring development of the hepatotoxic metabolite. Interestingly, acute alcohol ingestion seems to inhibit the activity of CYP2E1 and may actually protect the liver in cases of acetaminophen overdose.[25,26]

Excretion

Excretory mechanisms combine with metabolic processes to eliminate foreign substances such as drugs from the body. The kidney is the most important organ for drug excretion. Minor routes of excretion include the breath (how the breathalyzer works to detect alcohol), breast milk (drugs taken by the mother can affect the nursing baby), feces, and perspiration.[18]

The kidneys are fist-sized organs located on each side of the spinal column in the lower back. Blood flows from the body into the renal arteries into the glomerulus (filtration capsule) through the kidneys where it is filtered **(Figure 15)**. Sugars, amino acids, water, and electrolytes such as sodium and potassium are reabsorbed, and urine is produced and sent through the ureters for collection in the bladder. Filtered blood is returned to the heart. Among its many functions, the kidney regulates fluid balance, blood pressure, and maintains acid-base balance.[20]

At the microscopic level, the kidney is made up of millions of nephrons. Each nephron consists of a long tubule **(Figure 16)**. Blood enters a group of capillaries called the glomerulus where pressure from the heart forces fluid out of the blood into the glomerular or Bowman's capsule, the part of the nephron tubule that surrounds the glomerulus. The efficiency of this process of blood filtering is called the glomerular filtration rate and is a measure of renal (kidney) function. Renal function is also determined by the ability of the kidney to filter creatinine, a natural byproduct of muscle contractions. This indicator of renal function is called creatinine clearance. Renal function and thus the ability of the body to excrete drugs declines with age, about 1% per year during adulthood.[18,20]

The kidney excretes drugs via three processes: glomerular filtration, tubular secretion and tubular reabsorption **(Figure 16)**. Glomerular filtration and tubular secretion remove drugs from the body. Tubular reabsorption prevents a drug from being excreted into the urine. The processes involved in excretion of drugs overlap with the absorption of drugs. Lipophillic, non-ionized drugs are reabsorbed from the glomerular filtrate back into the blood. Conversely, hydrophilic, ionized drugs are not reabsorbed and

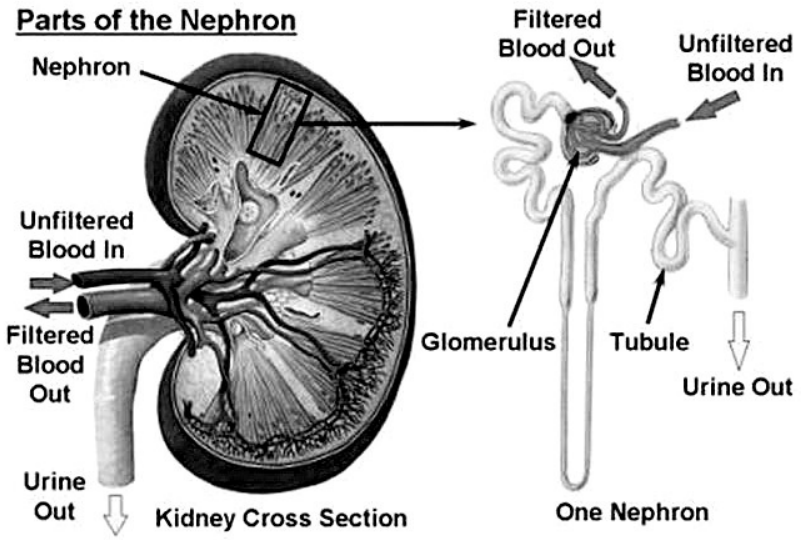
Pop Quiz #7

One of the breakdown products of codeine is the narcotic, morphine. In this case, morphine is a _____.

A. CYP enzyme
B. Parent drug
C. Dreamy molecule
D. Metabolite

See page 24 for answer.

Figure 15. Parts of the nephron



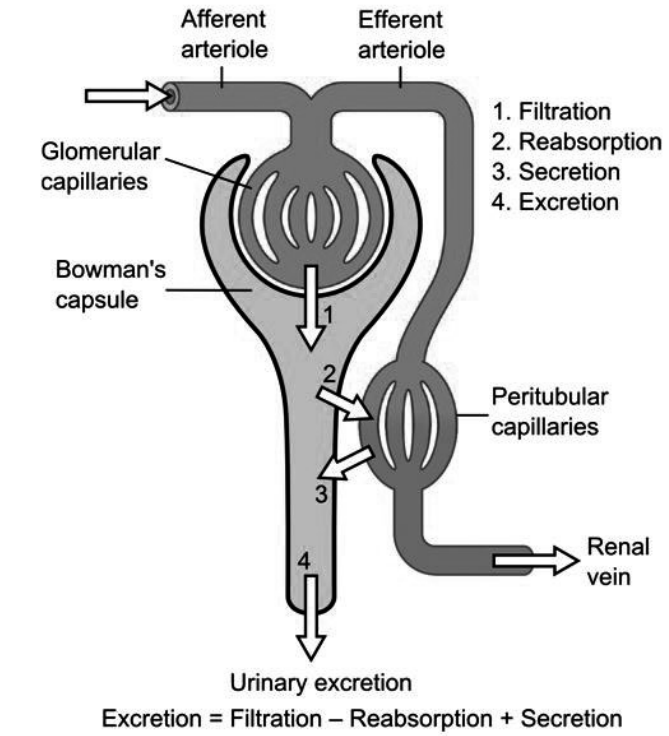
From UNC Kidney Center. Glomerular disease – Part of the Nephron. http://www.unckidneycenter.org/kidneyhealthlibrary/glomerulardisease.html. Copyright © UNC Kidney Center. Reprinted by permission of UNC Kidney Center. February 21, 2012.

subsequently excreted. Drug reabsorption is also affected by urine pH and cellular transporters.[18]

Glomerular filtration is affected by many factors. Blood pressure must be high enough to force blood from the glomerulus into the tubule. Dehydration, extreme blood loss, and heart failure can lower blood pressure. Drugs such as nonsteroidal anti-inflammatory drugs (e.g., ibuprofen) can reduce the glomerular filtration rate, resulting in slowed excretion of drugs that are eliminated by the kidneys. Aminoglycoside antibiotics (e.g., gentamicin) are eliminated almost entirely by the kidney. The blood levels of aminoglycosides must be carefully monitored in patients with reduced glomerular filtration rate (creatinine clearance) to avoid toxicity to auditory (hearing) and vestibular (balance) function.[18,27]

Moving further down the nephron, drugs can compete with each other for secretion. For example, the anti-gout drug probenecid, is sometimes given with oral penicillin to increase the penicillin drug levels. Probenecid and penicillin compete for the same cellular transporters in the tubule, so more penicillin is retained in the body. Drugs such as erythromycin that inhibit P-gp may increase levels of P-gp substrates, such as digoxin by preventing the secretion of digoxin into the tubule.[28,29]

Figure 16. Mechanisms of drug excretion



Source: http://en.wikipedia.org/wiki/Glomerular_filtration. Physiology of the Nephron. March 6, 2010. Madhero88.

Pop Quiz #8
Which organ is the most important in the excretion of drugs?

A. Stomach
B. Kidney
C. Intestine
D. Brain

See page 24 for answer.

Excretion of drugs can be altered by changing the pH of the urine. Weakly acidic drugs become more ionized in alkaline urine. Ionized drugs are not reabsorbed back into the blood and are excreted in the urine. In cases of aspirin overdose, IV sodium bicarbonate is given to alkalinize the urine so that a greater amount of aspirin, a weak acid, will stay in the ionized state. Ionized aspirin is not reabsorbed and toxic aspirin levels are reduced.[30]

Clinical Effect of Drug Interactions

In the US, 48% of the population takes at least one prescription medicine; more than 10% of the population takes five or more prescription medications.[31] Given the thousands of prescription, over-the-counter, and dietary supplement products available, the number of possible combinations and potential DDIs is staggering. Fortunately, many potential DDIs do not have a noticeable clinical effect. For the interaction to be clinically important, the interaction must cause a change in the expected response to the drug. DDIs may cause different responses in different people. The risk of a significant DDI is affected by many factors. Logically, the risk of a DDI is higher with increased numbers of drugs a patient is taking. The elderly, who have more chronic diseases, are at particular risk for DDIs.[32] Compared with younger patients, patients aged 44-64 years have double the risk of taking potentially interacting drugs. Patients older than 74 years of age are six times more likely to be taking potentially interacting drugs.[33]

Women seem to have a higher risk of experiencing adverse effects from DDIs than men.[34] This may be because women generally weigh less than men, but are usually given the same dose of drug; however, other factors such as differences in the way women metabolize or eliminate drugs may also be involved.

Genetic factors are becoming increasingly recognized contributors to adverse drug reactions and metabolic DDIs. The CYP enzymes 2D6, 2C19, 2C9, 1A2, and 3A4 exhibit genetic polymorphism. Genetic polymorphism means that within the population, some people have genes producing functional enzymes and others do not. People who have genetically determined low levels of enzyme activity are poor metabolizers. Other people produce more enzyme than most of the population and are called ultra-metabolizers. For CYP1A2 and 3A4, most people produce intermediate amounts of enzyme; these are the so-called normal population. A few people have very low or very high activity. Genetic variations of CYP2D6, 2C19, and 1A2 are considerable and may explain some differences in response to drugs among individual patients **(Table 1)**.[35,36]

Some drugs, called prodrugs, rely on the body for conversion to an active form. The antiplatelet drug clopidogrel (Plavix) is an example of a prodrug: it has no pharmacological activity until it is metabolized to its active form by CYP2C19. A significant number of people do not adequately produce CYP2C19, so the clopidogrel might not be as effective in preventing clotting in these groups

Table 1. Genetic differences in CYP activity[27,28]

	2C9	2C19	2D6
African Americans	<0.01% PM	4-7% PM	8% PM
Whites	7-11% PM	2-4% PM	7-10% PM 1% UM
Asians	<0.1% PM	12-22% PM	1% PM 1% UM
Chinese	<0.1% PM	5-17% PM	--
Japanese	--	18-23% PM	--

PM, poor metabolizer
UM, ultra metabolizer

Pop Quiz #9

Factors that may affect DDI development include which of the following?

A. Genetics
B. Gender
C. Age
D. All of the above

See page 24 for answer.

of people. Proton pump inhibitors such as omeprazole (Prilosec), which are taken to reduce the secretion of acid in the stomach, also inhibit the activity of CYP2C19 and decrease the metabolism of clopidogrel to its active form. The interaction between drugs that inhibit CYP2C19 and clopidogrel might be particularly important in people who do not adequately produce CYP2C19.[37]

Other factors that can increase the risk for DDIs include patient-specific issues such as decreased kidney or liver function, which may reduce the ability of the body to eliminate the drugs. Concomitant diseases or conditions such as malnutrition, severe heart failure, and dehydration could also increase DDI risk.[38] Drug-specific factors, such as dose of a drug or drugs with a high risk for toxicity (e.g., warfarin, digoxin, and cyclosporine) can increase DDI risk.[38]

Computer programs are widely available to identify potential drug interactions. Although this seems like a useful tool, computerized DDI alerts have not been shown to decrease the risk of adverse events caused by DDIs. Alerts are triggered so frequently that they are largely ignored. To prevent a single adverse drug reaction of any severity, an estimated 331 DDI alerts must be reviewed. To prevent a single serious adverse drug reaction, an estimated 2,715 alerts must be reviewed. To prevent a single event leading to death, disability or prolonged symptoms, the clinician would need to review between 4,292 to 44,350 alerts! Efforts to eliminate alerts with little clinical value are underway.[39]

Many of the online pharmacy references such as Lexi-Comp[40] and Micromedex[41] include drug interaction checkers. For non-oral drugs, an online resource and book, Trissel's Stability of Compounded Formulations[42] (simply known as Trissel's), gives specific compatibility and stability data. None of these resources cover all potential DDIs, but provide information about the interactions of particular clinical concern.

Summary

DDIs can occur via a variety of mechanisms, both pharmacokinetic and pharmacodynamic. The number of potential DDIs is staggering, but not all DDIs have clinically significant consequences, particularly those involving drugs with a wide range between effectiveness and toxicity. Moreover, a potential DDI does not necessarily occur in all patients. Patient- or drug-specific factors may increase or reduce risk of clinically important DDIs. Anyone starting a new medication, whether prescription, over-the-counter, or dietary supplement should ask their pharmacist about drug interactions with their current medications or supplements. Vigilance is important in preventing adverse effects caused by DDIs, but hyper-anxiety about all potential DDIs is not warranted.

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Pop Quiz Answers:

#1 - C
#2 - B
#3 - D
#4 - A,4; B,1; C,3; D,2
#5 - B
#6 - True
#7 - D
#8 - B
#9 - D