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MANUAL TO PRACTICAL CLASSES IN CLINICAL PHARMACOLOGY

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Рекомендовано Центральним методичним кабінетом з вищої медичної освіти МОЗ України як навчальний посібник для студентів вищих медичних навчальних закладів IV рівня акредитації, які опановують навчальну дисципліну англійською мовою.

Навчальний посібник затверджено на засіданні Комісії з медицини науково-методичної ради Міністерства освіти і науки України (Протокол №4 від 24.12 2007 року).

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Based on the requirements of the Clinical Pharmacology Course Programme, this book presents the main theoretical issues and provides tasks to check the students' acquisition. Designed in a clear fashion, the book contributes to the students' comprehension and visualization of Clinical Pharmacology. It also covers the issues of monitoring drug therapy, and drugs interaction. The book is designed to be used at the undergraduate or graduate levels.

У посібнику, відповідно до програми з фармакокінетики розглядаються головні теоретичні питання, необхідні для вивчення дисципліни, та подані навчальні завдання для контролю засвоєння матеріалу. Завдяки доступно викладеним основним принципам, це видання допоможе студентам у розумінні та візуалізації фармакокінетики. Книга містить принципи моніторингу фармакотерапії та взаємодії лікарських препаратів.

PREFACE

Drugs are the cornerstone of modern therapeutics. Nevertheless, it is well recognized among physicians that the outcome of drug therapy varies widely among individuals. Two important goals of the discipline of clinical pharmacology are (1) to provide a description of conditions under which drug actions vary among human subjects; and (2) to determine mechanisms underlying this variability, with the goal of improving therapy with available drugs as well as pointing to new drug mechanisms that may be effective in the treatment of human disease.

The use of pharmacokinetic and biopharmaceutic principles in predicting plasma drug concentrations, as well as the changes in plasma drug concentrations that accrue over time, are now widely accepted as useful adjuncts in patient care. With the continued advancement of analytical technology, every health care institution and practitioner has ready access to drug concentration assays, and for some drugs, monitoring serum drug concentrations has become the standard of practice. As we gain more knowledge about both the limitations and application of drug concentrations and their correlation with either efficacy or toxicity, concentration sampling strategies change. Appropriate use of serum drug concentrations, however, continues to be a major problem in the clinical setting. Basic pharmacokinetic principles must be applied rationally to specific patients.

The trend in patient care is towards cost containment. This includes everything from minimizing and streamlining drug therapy and laboratory testing to the increased use of automation. This book will help the pharmacist in the rational application of pharmacokinetics and therapeutic drug monitoring of patient care and will also contribute to ensuring that drug concentration monitoring is focused in an optimal way on the most appropriate patients.

For each of the drugs, examples of the most common pharmacokinetic manipulations, such as calculation of a loading dose and maintenance dose, are presented. In addition, pathophysiologic factors that influence the pharmacokinetics of these drugs and their significance are considered. Examples of the most common problems encountered in clinical practice are also given to help the reader recognize when caution should be used in making patient care decisions based upon serum drug concentrations and pharmacokinetic principles. Ultimately, it is hoped that the reader will be able to recognize the fundamental principles that are being applied to each of the drugs.

Although plasma drug concentrations are useful in evaluating drug therapy, they constitute only one source of information. They should not, therefore, be used as the sole criterion on which treatment is based. Pharmacokinetic calculations should be considered only as an adjunctive guide to the determination of dosing regimens.

The first steps in the discipline were empirical descriptions of the influence of disease on drug action or of individuals or families with unusual sensitivities to adverse drug effects. These important descriptive findings are now being replaced by an understanding of the molecular mechanisms underlying variability in drug actions. Thus, the effects of disease, drug coadministration, or familial factors in

modulating drug action can now be reinterpreted as variability in expression or function of specific genes whose products determine pharmacokinetics and pharmacodynamics. Nevertheless, it is the personal interaction of the patient with the physician that first identifies unusual variability in drug actions; maintained alertness to unusual drug responses continues to be a key component of improving drug safety.

Unusual drug responses, segregating in families, have been recognized for decades and initially defined the field of pharmacogenetics. Now, with an increasing appreciation of common polymorphisms across the human genome, comes the opportunity to reinterpret descriptive mechanisms of variability in drug action as a consequence of specific DNA polymorphisms, or sets of DNA polymorphisms, among individuals. This approach defines the nascent field of pharmacogenomics, which may hold the opportunity of allowing practitioners to integrate a molecular understanding of the basis of disease with an individual's genomic makeup to prescribe personalized, highly effective, and safe therapies.

The authors of this book have made every effort to ensure the information provided herein were accurate at the time of publication. It remains the responsibility of every practitioner to evaluate the appropriateness of a particular opinion or therapy in the context of the actual clinical situation and with due consideration of any new developments in the field. Although the authors have been careful to recommend dosages that are in agreement with current standards and responsible literature, the student or practitioner should consult several appropriate information sources when dealing with new and unfamiliar drugs.

Notices of errors and suggestions for improvement of the text will be greatly appreciated by the authors.

Lesson 1

PHARMACOKINETICS AND PHARMACODYNAMICS

QUESTIONS FOR IN-CLASS WORK

1. General principles of Clinical Pharmacology.
2. Principles of pharmacokinetics. The most important pharmacokinetic parameters (bioavailability, clearance, volume of distribution, half-life).
3. The most important pharmacokinetic processes (absorption, distribution, biotransformation, excretion).
4. Principles of pharmacodynamics.
5. Interactions between drugs (impaired gastrointestinal absorption, induction of CYP or transporter activity, inhibition of cellular uptake or binding, inhibition of drug metabolism, inhibition of drug transport).
6. Adverse reactions to drugs.

THEORETICAL ISSUES

It is well recognized among physicians that the outcome of drug therapy varies widely among individuals. Drugs interact with specific target molecules to produce their beneficial and adverse effects. The chain of events between administration of a drug and production of these effects in the body can be divided into two important components, both of which contribute to variability in drug actions.

The actions of the drug on the body are termed *pharmacodynamic* processes. These properties determine the group in which the drug is classified and often play the major role in deciding whether that group is appropriate therapy for a particular symptom or disease.

The actions of the body on the drug are called *pharmacokinetic* processes.

1. PRINCIPLES OF PHARMACOKINETICS

The processes of absorption, distribution, metabolism, and elimination – collectively termed drug disposition – determine the concentration of drug delivered to target effector molecules. Mathematical analysis of these processes can define specific, and clinically useful, parameters that describe drug disposition. This approach allows prediction of how factors such as disease, concomitant drug therapy, or genetic variants affect these parameters, and how dosages therefore should be adjusted.

1.1. The most important pharmacokinetic parameters

The three most important parameters are *clearance*, a measure of the body's ability to eliminate drug; *volume of distribution*, a measure of the apparent space in

the body available to contain the drug; and *bioavailability*, the fraction of drug absorbed as such into the systemic circulation. Of lesser importance are the rates of availability and distribution of the agent.

1.1.1. Bioavailability

Bioavailability (F) is the percentage or fraction of the administered dose that reaches the systemic circulation of the patient.

$$F = \frac{Amount\ of\ drug\ reaching\ the\ systemic\ circulation}{D} \times 100\%$$

Bioavailability (F) is defined as the area under the time-concentration curve (AUC) after a drug dose, divided by AUC after the same dose intravenously.

Examples of factors that can alter bioavailability include the inherent dissolution and absorption characteristics of the administered chemical form (e.g., salt, ester), the dosage form (e.g., tablet, capsule), the route of administration, the stability of the active ingredient in the gastrointestinal (GI) tract, and the extent of drug metabolism before reaching the systemic circulation. Drugs can be metabolized by GI bacteria, by the GI mucosa, and by the liver before reaching the systemic circulation.

For an intravenous dose of the drug, bioavailability is assumed to be equal to unity. For a drug administered orally, bioavailability may be less than 100% for two main reasons — incomplete extent of absorption and first-pass elimination.

First-Pass Elimination. Following absorption across the gut wall, the portal blood delivers the drug to the liver prior to entry into the systemic circulation. A drug can be metabolized in the gut wall or even in the portal blood, but most commonly it is the liver that is responsible for metabolism before the drug reaches the systemic circulation. In addition, the liver can excrete the drug into the bile. Any of these sites can contribute to this reduction in bioavailability, and the overall process is known as first-pass loss or elimination.

1.1.2. Clearance

Clearance is the most important concept to be considered when a rational regimen for long-term drug administration is to be designed.

Clearance can be thought of as the intrinsic ability of the body or its organs of elimination to remove drug from the blood or plasma. Clearance is expressed as a volume per unit of time. It is important to emphasize that clearance is not an indicator of how much drug is being removed; it only represents the theoretical volume of blood or plasma which is completely cleared of drug in a given period. The amount of drug removed depends on the plasma concentration of drug and the clearance.

The concept of clearance is extremely useful in clinical pharmacokinetics because clearance of a given drug usually is constant over the range of concentrations encountered clinically. This is true because systems for elimination of drugs usually are not saturated and, thus, the absolute rate of elimination of the drug is essentially a linear function of its concentration in plasma.

A synonymous statement is that the elimination of most drugs follows *first-order kinetics* — a constant fraction of drug is eliminated per unit of time.

If the mechanisms for elimination of a given drug become saturated, the elimination follows *zero-order kinetics* — a constant amount of drug is eliminated per unit of time. Under such a circumstance, clearance becomes variable.

Clearance usually is further defined as *blood clearance* (CL_b), *plasma clearance* (CL_p), or *clearance based on the concentration of unbound or free drug* (CL_u), depending *the concentration* measured (C_b, C_p, or C_u).

Clearance by means of various organs of elimination is additive. Elimination of drug may occur as a result of processes that occur in the kidney, liver, and other organs. Division of the rate of elimination by each organ by a *concentration of drug* (e.g., *plasma concentration*) will the respective clearance by that organ. Added together, these separate clearances will equal total systemic clearance:

$$CL_{renal} + CL_{hepatic} + CL_{other} = CL_{systemic}$$

Other routes of elimination could include that in saliva or sweat, partition into the gut, and metabolism at other sites.

For a single dose of a drug with first-order kinetics of elimination, total systemic clearance may be determined:

$$CL = \frac{F \times Dose}{AUC}$$

where AUC is the total area under the curve that describes the concentration of drug in the systemic circulation as a function of time.

2.1.3. Volume of Distribution

Volume is a fundamental parameter that is useful in discussing processes of drug disposition. The volume of distribution (V_d) relates the amount of drug in the body to the concentration of drug (C) in the blood or plasma, depending upon the fluid measured. This volume does not necessarily refer to an identifiable physiological volume, but merely to the fluid volume that would be required to contain all of the drug in the body at the same concentration as in the blood or plasma:

$$V_d = \frac{D}{C},$$

where D – the total amount of drug in the body.

The volume of distribution may vary widely depending on the pKa of the drug, the degree of binding to plasma proteins, the partition coefficient of the drug in fat, the degree of binding to other tissues, and so forth. As might be expected, the volume of distribution for a given drug can change as a function of the patient's age, gender, disease, and body composition.

1.1.4. Half-Life

The half-life ($t_{1/2}$) is the time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

While the organs of elimination can only clear drug from the blood or plasma in direct contact with the organ, this blood or plasma is in equilibrium with the total volume of distribution. Thus, the time course of drug in the body will depend on both the volume of distribution and the clearance:

$$t1/2 = \frac{0{,}693}{K} = \frac{0{,}693 \times Vd}{CL}$$

The constant 0,693 in equation is an approximation to the natural logarithm of 2. Because drug elimination can be described by an exponential process, the time taken for a twofold decrease can be shown to be proportionate to ln(2).

Half-life is useful because it indicates the time required to attain 50% of steady state — or to decay 50% from steady-state conditions — after a change (ie, starting or stopping) in the rate of drug administration.

1.1.5. Maintenance dose

The clearance formula can be rearranged slightly and used to calculate the rate of administration or maintenance dose which will produce a desired average plasma concentration at steady state:

$$\text{Maintenance Dose} = \frac{CL \times Css \times \tau}{S \times F}$$

where CL is the clearance, Css is the steady state concentration, F is the bioavailability, S represents the fraction of the administrated dose that is the active drug.

1.1.6. Loading dose

Because the volume of distribution is the factor that accounts for all of the drug in the body, it is an important variable in estimating the loading dose necessary to rapidly achieve a desired plasma concentration:

$$Loding\ Dose = \frac{Vd \times C}{S \times F}$$

where Vd is the volume of distribution, C is the desired plasma level, F is the bioavailability, S represents the fraction of the administrated dose that is the active drug.

1.2. The most important pharmacokinetic processes

1.2.1. Absorption

Absorption describes the rate at which a drug leaves its site of administration and the extent to which this occurs. However, the clinician is concerned primarily with a parameter designated as bioavailability, rather than absorption.

Routes of administration such as the parenteral route avoid the absorption process and provide an immediate onset of action. For drugs that diffuse through a barrier, a delay in the onset action may occur, the magnitude of which depends on the complexity of the barrier and the physicochemical characteristics of the drug

and the dosage form. Moreover, factors that modify the absorption of a drug can change its bioavailability.

Many factors, in addition to the physicochemical factors that affect transport across membranes, influence the absorption of drugs.

1. Absorption, regardless of the site, is dependent upon *drug solubility*. Drugs given in aqueous or oily solution are more rapidly absorbed than those given in solid form, because they mix more readily with the aqueous phase at the absorptive site. For those given in solid form, the rate of dissolution may be the limiting factor in their absorption.
2. *Local conditions at the site of absorption* alter solubility, particularly in the gastrointestinal tract.
3. *The concentration of a drug* influences its rate of absorption. Drugs introduced at an administration site in solutions of high concentration are absorbed more rapidly than are drugs in solutions of low concentration.
4. *The circulation to the site of absorption* also affects drug absorption. Increased blood flow, brought about by massage or local application of heat, enhances the rate of drug absorption; decreased blood flow, produced by vasoconstrictor agents, shock, or other disease factors, can slow absorption.
5. *The area of the absorbing surface* to which a drug is exposed is one of the more important determinants of the rate of drug absorption. Drugs are absorbed very rapidly from large surface areas such as the pulmonary alveolar epithelium, the intestinal mucosa, or, in a few cases after extensive application, the skin. The absorbing surface is determined largely by the route of administration.

Each of these factors separately or in conjunction with one another may have profound effects on the clinical efficacy and toxicity of a drug.

1.2.2. Distribution of drugs

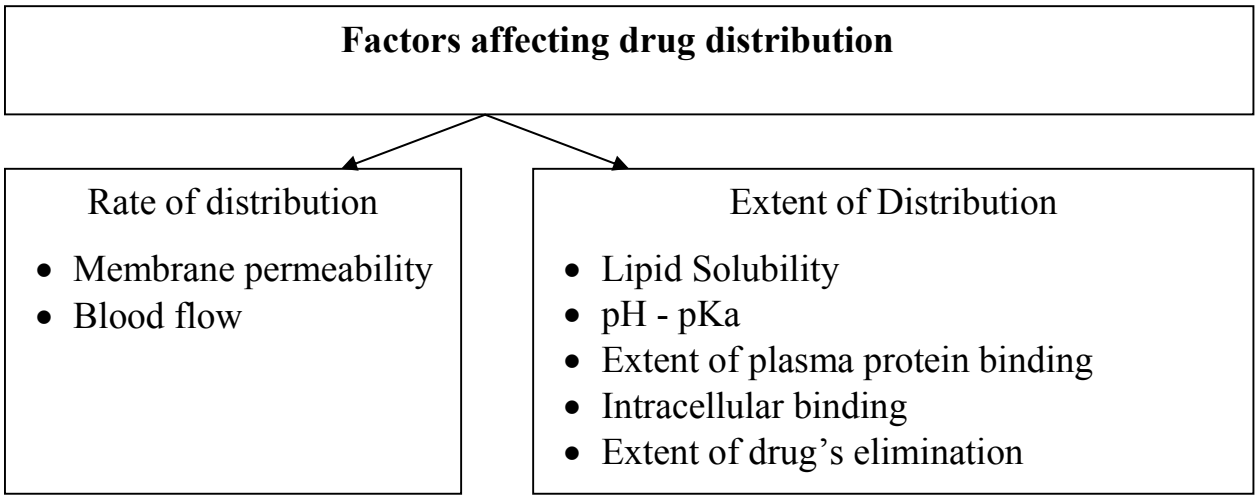
After gaining access to the systemic circulation through one of the routes of administration, drugs distribute in different tissues and organs of the body. Distribution can be thought of as following one of four types of patterns.

1. The drug may remain largely within the vascular system. Plasma substitutes such as dextran are an example of this type, but drugs which are strongly bound to plasma protein may also approach this pattern.
2. Some low molecular weight water soluble compounds such as ethanol and a few sulfonamides become uniformly distributed throughout the body water.
3. A few drugs are concentrated specifically in one or more tissues that may or may not be the site of action. Iodine is concentrated by the thyroid gland. The antimalarial drug chloroquine may be present in the liver at concentrations 1000 times those present in plasma. Tetracycline is almost irreversibly bound to bone and developing teeth. Consequently tetracyclines should only be given to young

children or infants in extreme conditions as it can cause discoloration and mottling of the developing second set of teeth. Another type of specific concentration may occur with highly lipid soluble compounds which distribute into fat tissue.

4. Most drugs exhibit a non-uniform distribution in the body with variations that are largely determined by the ability to pass through membranes and their lipid/water solubility. The highest concentrations are often present in the kidney, liver, and intestine usually reflecting the amount of a drug being excreted.

Depending on their physicochemical characteristics a series of physical and physiologic processes occur simultaneously that shape the distinctive pattern of their distribution in the body. Thus, in general the distribution of drugs can be influenced by some factors.



Several physiologic barriers (placental, blood-brain, blood-testis) affect the distribution of drugs in the body. The function of these barriers is essentially to protect different regions of the body from foreign substances.

1.2.3. Drug biotransformation

Drug metabolism is a mechanism for elimination of drugs from the body. Metabolism or biotransformation is the process of conversion of drugs to pharmacologically inactive metabolites.

The metabolites either can be water-soluble and leave the body or can be highly reactive and require further metabolism to become water-soluble. The reactive metabolites may also interact with cellular components such as membranes and macromolecules and cause repairable or nonrepairable lesions. Water-soluble metabolites leave the body by urinary and/or biliary elimination. The metabolic pathways catalyzed by the enzyme systems occur in two distinct phases known as Phase I and Phase II metabolism.

The enzyme systems involved in the biotransformation of drugs are localized in the liver, although every tissue examined has some metabolic activity. Other

organs with significant metabolic capacity include the kidneys, gastrointestinal tract, skin, and lungs. Following nonparenteral administration of a drug, a significant portion of the dose may be metabolically inactivated in either the liver or intestines before it reaches the systemic circulation. This first-pass metabolism significantly limits the oral availability of highly metabolized drugs. Within a given cell, most drug-metabolizing activity is found in the endoplasmic reticulum and the cytosol, although drug biotransformations also can occur in the mitochondria, nuclear envelope, and plasma membrane.

Genetic, environmental, and physiological factors are involved in the regulation of drug biotransformation reactions. The most important factors are genetically determined polymorphisms in drug oxidations and conjugations, concomitant use of other drugs, exposure to environmental pollutants and industrial chemicals, disease, state, and age. These factors have been thought responsible for decreased efficacy, prolonged pharmacological effects, and increased toxicity.

Genetic Polymorphisms. Genetic differences in the ability of individuals to metabolize a drug through a given pathway are recognized as an important contributor to the large interindividual differences in biotransformation. Phenotypic differences in the amount of drug excreted through a polymorphically controlled pathway lead to the classification of individuals as rapid or slow metabolizers.

Diseases. Impairment of normal liver function in patients with hepatitis, alcoholic liver disease, fatty liver disease, biliary cirrhosis, and hepatocarcinomas potentially can lead to alterations in hepatic drug biotransformation. The degree to which cytochrome P450 monooxygenase activity and hepatic elimination are decreased will be a function of the severity of the liver damage.

Age and Gender. Functional cytochrome P450 enzymes can be detected relatively early in fetal development, although the oxidative metabolism rates are lower than those found postnatally. Glucuronidation, sulfation, glutathione conjugation, and epoxide hydrolysis also are active at low levels in the fetus. Newborns are able to catalyze efficiently most phase I biotransformation reactions, although the rate of these reactions is generally slower than that in adults. A marked impairment of bilirubin glucuronidation at birth contributes to hyperbilirubinemia in newborns. Both phase I and phase II enzyme systems begin to mature gradually following the first 2 weeks of life, although the pattern of the development is variable for the different enzymes.

In general, age-related decreases in liver mass, hepatic enzyme activity, and hepatic blood flow result in a decrease in the overall metabolic capacity of the liver in the elderly. Decreases in the hepatic biotransformalion of high hepatic extraction ratio drugs in the elderly are predicted from the decrease in liver blood flow, although the large degree of interindividual variability in age- and disease-related changes in organ function makes it difficult to make generalizations.

Diet and environmental factors. Diet and environmental factors also contribute to the individual variations in drug metabolism. Charcoal-broiled foods and cruciferous vegetables are known to induce CYP1A enzymes, whereas grapefruit juice is known to inhibit the CYP3A metabolism of coadministered drug

substrates. Cigarette smokers metabolize some drugs more rapidly than nonsmokers because of enzyme induction. Industrial workers exposed to some pesticides metabolize certain drugs more rapidly than nonexposed individuals. Such differences make it difficult to determine effective and safe doses of drugs that have narrow therapeutic indices.

Metabolic Drug Interactions. The coadministration of two or more drugs is often associated with a change in the clearance of one of the agents. Although drug interactions can lead to changes in absorption, protein binding, and urinary excretion, the effect on biotransformation generally is more pronounced.

Interactions between drugs and endogenous compounds. Various drugs require conjugation with endogenous substrates such as glutathione, glucuronic acid, and sulfate for their inactivation. Consequently, different drugs may compete for the same endogenous substrates, and the faster-reacting drug may effectively deplete endogenous substrate levels and impair the metabolism of the slower-reacting drug. If the latter has a steep dose-response curve or a narrow margin of safety, potentiation of its pharmacologic and toxic effects may result.

1.2.4. Excretion of drugs

The body eliminates xenobiotics predominantly by excretion and metabolism. Drugs are eliminated from the body either unchanged or as metabolites. Excretory organs, the lung excluded, eliminate polar compounds more efficiently than substances with high lipid solubility. Lipid-soluble drugs are thus not readily eliminated until they are metabolized to more polar compounds.

The kidney is the most important organ for elimination of drugs and their metabolites. Substances excreted in the feces are mainly unabsorbed orally ingested drugs or metabolites excreted in the bile and not reabsorbed from the intestinal tract. Excretion of drugs in breast milk is important, not because of the amounts eliminated, but because the excreted drugs are potential sources of unwanted pharmacological effects in the nursing infant. Pulmonary excretion is important mainly for the elimination of anesthetic gases and vapors; occasionally, small quantities of other drugs or metabolites are excreted by this route.

2. PRINCIPLES OF PHARMACODYNAMICS

Once a drug accesses a molecular site of action, it alters the function of that molecular target, with the ultimate result of a drug effect. For drugs used in the urgent treatment of acute symptoms, little or no delay is anticipated between the drug-target interaction and the development of a clinical effect. For many conditions, however, the indication for therapy is less urgent, and in fact a delay between the interaction of a drug with its pharmacologic target(s) and a clinical effect is common.

A therapeutic drug effect assumes the presence of underlying pathophysiology. Thus, a drug may produce no action, or a different spectrum of actions, in unaffected individuals compared to patients. Further, concomitant disease can complicate interpretation of response to drug therapy, especially adverse effects.

The concept that a drug interacts with a specific molecular receptor does not imply that the drug effect will be constant over time, even if stable drug and metabolite concentrations are maintained. The drug-receptor interaction occurs in a complex biologic milieu that itself can vary to modulate the drug effect. For example, ion channel blockade by drugs, an important anticonvulsant and antiarrhythmic effect, is often modulated by membrane potential, itself a function of factors such as extracellular potassium or ischemia. Thus, the effects of these drugs may vary depending on the external milieu.

3. INTERACTIONS BETWEEN DRUGS

Drug interactions can complicate therapy by adversely increasing or decreasing the action of a drug; interactions may be based on changes in drug disposition or in drug response in the absence of changes in drug levels.

Prescribers should recognize that patients often come to them with a legacy of drugs acquired during previous medical experiences, often with multiple physicians who may not be aware of all the patient's medications. A drug history should include examination of the patient's medications. It should also address the use of agents not often volunteered during questioning, such as over-the-counter (OTC) drugs, health food supplements, and topical agents such as eye drops. Lists of interactions are available from a number of electronic sources. The practicing physician cannot be expected to memorize these. However, certain drugs consistently run the risk of generating interactions, through mechanisms that are well understood.

3.1. Impaired Gastrointestinal Absorption

Aluminum ions, present in antacids, can form insoluble chelates with the tetracyclines, preventing their absorption. Kaolin-pectin suspensions bind digoxin, and when the substances are administered together, digoxin absorption is reduced by about one-half. Resins that sequester bile acids in the gut can bind other drugs, such as digoxin. Ketoconazole is a weak base that dissolves well only at acidic pH. Histamine H2 receptor antagonists and proton pump inhibitors reduce gastric acidity and thus impair the dissolution and absorption of ketoconazole.

3.2. Induction of CYP or transporter activity

Expression of some genes responsible for drug elimination, notably CYP3A and MDR1, can be markedly increased by “inducing” drugs, such as rifampin, carbamazepine, phenytoin, St. John's wort, and glutethimide and by smoking, exposure to chlorinated insecticides such as DDT, and chronic alcohol ingestion.

One mechanism for this coordinate induction of multiple pathways is increased expression of common transcription factors. Administration of inducing agents lowers plasma levels over 2 to 3 weeks as gene expression is increased.

This alters the effects of many drugs, including warfarin, quinidine, mexiletine, verapamil, ketoconazole, itraconazole, cyclosporine, dexamethasone,

methylprednisolone, prednisolone, oral contraceptive steroids, methadone, and metronidazole.

If a drug dose is stabilized in the presence of an inducer which is subsequently stopped, major toxicity can occur as clearance returns to preinduction levels and drug concentrations rise. This is a particular problem with narrow-therapeutic-ratio drugs such as warfarin and some antiarrhythmics. Individuals vary in the extent to which drug metabolism can be induced, likely through genetic mechanisms.

3.3. Inhibition of Cellular Uptake or Binding

Tricyclic antidepressants, doxepin, and chlorpromazine are potent inhibitors of norepinephrine uptake into adrenergic neurons and prevent the uptake of the guanidinium antihypertensive agents (such as guanethidine and guanadrel), thereby abolishing their antihypertensive effects. Similarly, the antihypertensive effect of clonidine is partially antagonized by tricyclic antidepressants.

3.4. Inhibition of Drug Metabolism

Inhibition of drug metabolism can lead to reduced clearance, prolonged half-life, accumulation of drug during maintenance therapy, and thus adverse effects. In contrast to induction, new protein synthesis is not involved, and the effect develops as drug and any inhibitor metabolites accumulate. Since shared substrates of a single enzyme can compete for access to the active site of the protein, many CYP substrates can also be considered inhibitors. However, some drugs are especially potent as inhibitors; it is in the use of agents of the latter type that clinicians must be most alert to the potential for interactions.

Cimetidine is a potent inhibitor of the oxidative metabolism of many drugs, including warfarin, quinidine, nifedipine, lidocaine, theophylline, and phenytoin. Severe adverse reactions can develop as a consequence.

The antifungal agents ketoconazole and itraconazole are potent inhibitors of enzymes in the CYP3A family. When fluconazole levels are elevated as a result of higher doses and/or renal insufficiency, this drug can also inhibit CYP3A. The macrolide antibiotics erythromycin and clarithromycin inhibit CYP3A4 to a clinically significant extent, but azithromycin does not. Some of the calcium channel blockers, including diltiazem, nicardipine, and verapamil can also inhibit CYP3A, as can some of the enzyme's substrates, such as cyclosporine. Examples of CYP3A substrates also include quinidine, lovastatin, simvastatin, atorvastatin, nifedipine, lidocaine, erythromycin, methylprednisolone, carbamazepine.

Phenytoin, an inducer of many systems including CYP3A, inhibits CYP2C9. CYP2C9 metabolism of losartan to its active metabolite is inhibited by phenytoin, with potential loss of antihypertensive effect.

Accumulation of the prokinetic drug cisapride and the antihistamine terfenadine due to CYP3A inhibition led to QT prolongation and torsades de pointes. Measures to prevent co-prescription of these agents with CYP3A inhibitors were unsuccessful, and alternative safer agents were developed, so these drugs were eventually withdrawn.

Cyclosporine can cause serious toxicity when its metabolism via CYP3A4 is inhibited by erythromycin, ketoconazole, diltiazem, nicardipine, or verapamil. The risk of myopathy with some HMG-CoA reductase inhibitors (lovastatin, simvastatin, atorvastatin) is thought to be increased by CYP3A4 inhibition. One agent in this class, cerivastatin, was withdrawn because of an especially high incidence of this adverse effect, although cellular studies suggest inhibition of other pathways may have also contributed in this case. The antiviral ritonavir is a very potent CYP3A4 inhibitor that is often added to anti-HIV regimens not because of its antiviral effects but because it decreases clearance, and hence increases efficacy, of other anti-HIV agents. Grapefruit juice inhibits CYP3A, especially at high doses; patients receiving drugs where even modest CYP3A inhibition may increase the risk of adverse effects (e.g., cyclosporine, some HMG-CoA reductase inhibitors) should therefore avoid grapefruit juice.

CYP2D6 is markedly inhibited by quinidine and is also blocked by a number of neuroleptic drugs, such as chlorpromazine and haloperidol, and by fluoxetine. The analgesic effect of codeine depends on its metabolism to morphine via CYP2D6. Thus, quinidine reduces the analgesic efficacy of codeine. Since desipramine is cleared largely by metabolism via CYP2D6, its levels are increased substantially by concurrent administration of quinidine, fluoxetine, or the neuroleptic drugs that inhibit CYP2D6. Clinical consequences of fluoxetine's interaction with CYP2D6 substrates may not be apparent for weeks after the drug is started, because of its very long half-life and slow generation of a CYP2D6-inhibiting metabolite.

6-Mercaptopurine, the active metabolite of azathioprine, is metabolized by xanthine oxidase. When allopurinol, a potent inhibitor of xanthine oxidase, is administered with standard doses of azathioprine or 6-mercaptopurine, life-threatening toxicity (bone marrow suppression) can result.

3.5. Inhibition of Drug Transport

The best studied example is P-glycoprotein. Quinidine inhibits P-glycoprotein function in vitro, and it now appears that the long-recognized doubling of plasma digoxin when quinidine is coadministered reflects this action in vivo, particularly since the effects of quinidine (increased digoxin bioavailability and reduced renal and hepatic secretion) occur at the sites of P-glycoprotein expression. Many other drugs also elevate digoxin concentrations (e.g., amiodarone, verapamil, cyclosporine, itraconazole, and erythromcyin), and a similar mechanism seems likely. Reduced CNS penetration of multiple HIV protease inhibitors (with the attendant risk of facilitating viral replication in a sanctuary site) appears attributable to P-glycoprotein-mediated exclusion of the drug from the CNS; thus inhibition of P-glycoprotein has been proposed as a therapeutic approach to enhance drug entry to the CNS.

A number of drugs are secreted by the renal tubular transport systems for organic anions. Inhibition of these systems can cause excessive drug accumulation. Salicylate, for example, reduces the renal clearance of methotrexate, an interaction that may lead to methotrexate toxicity. Renal tubular secretion contributes substantially to the elimination of penicillin, which can be inhibited by probenecid.

Inhibition of the tubular cation transport system by cimetidine decreases the renal clearance of dofetilide and of procainamide and its active metabolite NAPA.

3.6. Drug interactions not mediated by changes in drug disposition

Drugs may act on separate components of a common process to generate effects greater than either has alone. For example, although small doses of aspirin (<1 g daily) do not alter the prothrombin time appreciably in patients who are receiving warfarin therapy, aspirin nevertheless increases the risk of bleeding in these patients because it inhibits platelet aggregation. Thus the combination of impaired functions of platelets and of the clotting system, while useful in some patients, also increases the potential for hemorrhagic complications. Similarly, the use of other anticlotting agents (heparin, glycoprotein IIb/IIIa inhibitors, clopidogrel) with aspirin improves outcomes in acute coronary syndromes, while exacerbating this bleeding tendency.

Nonsteroidal anti-inflammatory drugs (NSAIDs) cause gastric ulcers, and, in patients treated with warfarin, the risk of bleeding from a peptic ulcer is increased almost threefold by concomitant use of a NSAID.

Indomethacin, piroxicam, and probably other NSAIDs antagonize the antihypertensive effects of β-adrenergic receptor blockers, diuretics, ACE inhibitors, and other drugs. The resulting elevation in blood pressure ranges from trivial to severe. This effect is not seen with aspirin and sulindac but has been found with cyclooxygenase-2 inhibitors (celecoxib, rofecoxib).

Torsades de pointes during administration of QT-prolonging antiarrhythmics (quinidine, sotalol, dofetilide) occur much more frequently in those patients receiving diuretics, probably reflecting hypokalemia. In vitro, hypokalemia not only prolongs the QT interval in the absence of drug but also potentiates drug block of ion channels that results in QT prolongation. Also, some diuretics have direct electrophysiologic actions that prolong QT.

The administration of supplemental potassium leads to more frequent and more severe hyperkalemia when potassium elimination is reduced by concurrent treatment with ACE inhibitors, spironolactone, amiloride, or triamterene.

The pharmacologic effects of sildenafil result from inhibition of the phosphodiesterase type 5 isoform that inactivates cyclic GMP in the vasculature. Nitroglycerin and related nitrates used to treat angina produce vasodilation by elevating cyclic GMP. Thus, coadministration of these nitrates with sildenafil can cause profound hypotension.

Sometimes, combining drugs can increase overall efficacy and/or reduce drug-specific toxicity. Such therapeutically useful interactions are described in chapters dealing with specific disease entities, elsewhere in this text.

4. ADVERSE REACTIONS TO DRUGS

The beneficial effects of drugs are coupled with the inescapable risk of untoward effects. The morbidity and mortality from these untoward effects often present diagnostic problems because they can involve every organ and system of

the body and are frequently mistaken for signs of underlying disease. Major advances in the investigation, development, and regulation of drugs ensure in most instances that drugs are uniform, effective, and relatively safe and that their recognized hazards are publicized. However, prior to regulatory approval and marketing, new drugs are tested in relatively few patients who tend to be less sick and to have fewer concomitant diseases than those patients who subsequently receive the drug therapeutically. Because of the relatively small number of patients studied in clinical trials, and the selected nature of these patients, rare adverse effects may not be detected prior to a drug's approval, and physicians therefore need to be cautious in the prescription of new drugs and alert for the appearance of previously unrecognized adverse events. Often, these adverse reactions are rare, such as hematologic abnormalities, arrhythmias, hepatitis, or renal dysfunction. In these cases, often labeled “idiosyncratic,” elucidating underlying mechanisms can assist development of safer compounds or allow a patient subset at especially high risk to be excluded from drug exposure.

Adverse effects may be exploited to develop an entirely new indication for a drug. Unwanted hair growth during minoxidil treatment of severely hypertensive patients led to development of the drug for hair growth. Sildenafil was initially developed as an antianginal, but its effects to alleviate erectile dysfunction not only led to a new drug indication but also to increased understanding of the role of type 5 phosphodiesterase in erectile tissue. These examples further reinforce the concept that prescribers must remain vigilant to the possibility that unusual symptoms may reflect unappreciated drug effects.

The large number of drugs and herbal remedies available OTC as well as by prescription make it impossible for patient or physician to obtain or retain the knowledge necessary to use all drugs well. It is understandable, therefore, that many OTC drugs are used unwisely by the public and that restricted drugs may be prescribed incorrectly by physicians.

Some 25 to 50% of patients make errors in self-administration of prescribed medicines, and these errors can be responsible for adverse drug effects. Elderly patients are the group most likely to commit such errors, perhaps in part because they consume more medicines. One-third or more of patients also may not take their prescribed medications. Similarly, patients commit errors in taking OTC drugs by not reading or following the directions on the containers.

In hospital, drugs are administered in a controlled setting, and patient compliance is, in general, ensured. Errors may occur nevertheless – the wrong drug or dose may be given or the drug may be given to the wrong patient – and improved drug distribution and administration systems are addressing this problem. On the other hand, there are no easy means for controlling how ambulatory patients take prescription or OTC drugs.

EXERCISES FOR OUT-CLASS WORK

Exercise 1. Using the table 1, give your examples and explain advantages and disadvantages of oral rout of administration.

Table 1. Advantages and disadvantages of oral administration.

Advantages	Disadvantages
Convenient – portable, no pain, easy to take. Cheap – compact, multi-dose bottles, automated machines produce tablets in large quantities. Variety – fast release tablets, capsules, enteric coated, layered tablets, slow release, suspensions, mixtures	Sometimes inefficient - high dose or low solubility drugs may suffer poor availability, only part of the dose may be absorbed.

Exercise 2. Using the table 2, give your examples and explain advantages and disadvantages of buccal/sublingual rout of administration.

Table 2. Advantages and disadvantages of Buccal/Sublingual administration.

Advantages	Disadvantages
• First pass - The liver is by-passed thus there is no loss of drug by first pass effect for buccal administration. • Bioavailability is higher. • Rapid absorption - Because of the good blood supply to the rate of absorption is usually quite high. • Drug stability - pH in mouth relatively neutral. A drug may be more stable.	• Holding the dose in the mouth is inconvenient. If any is swallowed that portion must be treated as an oral dose and subject to first pass metabolism. • Small doses only can be accommodated easily.

Exercise 3. Using the table 3, give your examples and explain advantages and disadvantages of subcutaneous rout of administration.

Table 3. Advantages and disadvantages of Subcutaneous administration.

Advantages	Disadvantages
• Can be given by patient, e.g. in the case of insulin. • Absorption slow but usually complete. • Improved by massage or heat. • Vasoconstrictor may be added to reduce the absorption of a local anesthetic agent.	• Can be painful. • Irritant drugs can cause local tissue damage. • Maximum of 2 ml injection thus often small doses limit use.

Exercise 4. Using the table 4, give your examples and explain advantages and disadvantages of intramuscular rout of administration.

Table 4. Advantages and disadvantages of intramuscular administration.

Advantages	Disadvantages
• Larger volume, than by subcutaneous rout, can be given by IM rout. • A depot or sustained release effect is possible with IM injections, e.g. procaine penicillin	• Trained personnel required for injections. • The site of injection will influence the absorption, the deltoid muscle is the best site. • Absorption is sometimes erratic, especially for poorly soluble drugs, e.g. diazepam, phenytoin. • The solvent maybe absorbed faster than the drug causing precipitation of the drug.

Exercise 5. Using the table 5, explain the rate of distribution and pharmacological effect of drugs in different organs.

Table 5. Blood perfusion rate.

.Organ	Perfusion Rate (ml/min/ml of tissue)	% of Cardiac Output
Bone	0.02	5
Brain	0.5	14
Fat	0.03	4
Heart	0.6	4
Kidneys	4.0	22
Liver	0.8	27
Muscle	0.025	15
Skin	0.024	6

Exercise 6. Using the table 6, explain the rate of distribution and pharmacological effect of drugs depending on the plasma level of albumins and globulins.

Table 6. Proteins with potential binding sites for various drugs.

Drugs	Binding Sites
Acidic Agents: Bilirubin, Bile acids, Fatty acids,Vitamin C, Salicylates, Sulfonamides, Barbiturates, Phenylbutazone, Penicillins, Tetracyclines, Probenecid	Albumins
Basic Agents: Adenisine, Quinacrine, Quinine, Streptomycin, Chloramphenicol, Digitoxin, Ouabain, Coumarin	Globulins (α_1, α_2, β_1, β_2, γ)

Exercise 7. What is your conclusions about the data presented in table 7.

Table 7. Drugs and fu Values for Plasma Protein Binding.

Drug	fu Value	Drug	fu Value
Amitriptyline	0.04	Salicylic Acid	0.16
Cyclosporine	<0.1	Carbamazepine	0.2
Diazepam	0.01	Quinidine	0.20
Warfarin	0.03	Lidocaine	0.30
Chlorpromazine	0.04	Methotrexate	0.5
Imipramine	0.04	Phenobarbital	0.5
Chlordiazepoxide	0.05	Digoxin	0.70
Propranolol	0.06	Procainamide	0.84
Digitoxin	0.10	Gentamicin	0.9
Nafcillin	0.10	Vancomycin	0.9
Phenytoin	0.10	Gabapentin	0.97
Methadone	0.13	Ethosuximide	1.0
Valproic Acid	0.15	Lithium	1.0

Exercise 8. Using the table 8, explain interactions of drugs with inducers. Discuss the changes of pharmacological effects due to these interactions.

Table 8. Partial list of drugs that enhance drug metabolism in humans.

Inducer	Drug whose metabolism is enhanced
Benzopyrene	Theophylline
Chlorcyclizine	Steroid hormones
Ethchlorvynol	Warfarin
Glutethimide	Antipyrine, glutethimide, warfarin
Griseofulvin	Warfarin
Barbiturates	Barbiturates, chloramphenicol, chlorpromazine, cortisol, coumarin anticoagulants, digitoxin, estradiol, phenytoin, quinine, testosterone
Phenylbutazone	Aminopyrine, cortisol, digitoxin
Phenytoin	Cortisol, dexamethasone, digitoxin, theophylline
Rifampin	Coumarin anticoagulants, digitoxin, glucocorticoids, methadone, metoprolol, oral contraceptives, prednisone, propranolol, quinidine

Exercise 9. Using the table 9, explain interactions of drugs with inhibitors. Discuss the changes of pharmacological effects due to these interactions.

Table 9. Molecular pathways mediating drug disposition.

Molecule	Substrates	Inhibitors
CYP3A	Calcium channel blockers; antiarrhythmics (lidocaine, quinidine, mexiletine); HMG-CoA reductase inhibitors; cyclosporine, tacrolimus; indinavir, saquinavir, ritonavir	Amiodarone; ketoconazole; itraconazole; erythromycin, clarithromycin; ritonavir
CYP2D6	Timolol, metoprolol, carvedilol; phenformin; codeine; propafenone, flecainide; tricyclic antidepressants; fluoxetine, paroxetine	Quinidine; tricyclic antidepressants; fluoxetine, paroxetine
CYP2C9	Warfarin; phenytoin; glipizide; losartan	Amiodarone; fluconazole; phenytoin
CYP2C19	Omeprazole; mephenytoin	
Thiopurine *S*-methyltransferase	6-Mercaptopurine, azathioprine	
N-acetyl transferase	Isoniazid; procainamide; hydralazine; some sulfonamides	
UGT1A1	Irinotecan	
Pseudocholinesterase	Succinylcholine	
P-glycoprotein	Digoxin; HIV protease inhibitors; many CYP3A substrates	Quinidine; amiodarone; verapamil; cyclosporine; itraconazole; erythromycin

Exercise 10. Using the table 10, discuss mechanisms of pharmacokinetic interactions of drugs. Explain the changes of pharmacological effects due to these interactions.

Table 10. Drugs with a high risk of generating pharmacokinetic interactions.

Drug	Mechanism	Examples
Antacids; bile acid sequestrants	Reduced absorption	Antacids/tetracyclines; cholestryamine/digoxin
Proton pump inhibitors; H2-receptor blockers	Altered gastric pH	Ketoconazole absorption decreased
Rifampin; carbamazepine; barbiturates; phenytoin; St. John's wort; glutethimide	Induction of hepatic metabolism	Decreased concentration and effects of: warfarin; quinidine; cyclosporine; losartan
Tricyclic antidepressants; fluoxetine; quinidine	Inhibitors of CYP2D6	Increased beta blockade; decreased codeine effect
Cimetidine	Inhibitor of multiple CYPs	Increased concentration and effects of: warfarin; theophylline; phenytoin
Ketoconazole, itraconazole; erythromycin, clarithromycin; calcium channel blockers; ritonavir	Inhibitor of CYP3A	Increased concentration and toxicity of: statins; cyclosporine; cisapride, terfenadine (now withdrawn) Increased concentration and effects of: indinavir (with ritonavir); Decreased clearance and dose requirement for: cyclosporine (with calcium channel blockers)
Allopurinol	Xanthine oxidase inhibitor	Azathioprine and 6-mercaptopurine toxicity
Amiodarone	Inhibitor of many CYPs and of P-glycoprotein	Decreased clearance (risk of toxicity) for: warfarin; digoxin; quinidine
Gemfibrazol (and other fibrates)	CYP3A inhibition	Rhabdomyolysis when co-prescribed with some HMG-CoA reductase inhibitors
Quinidine; amiodarone; verapamil; cyclosporine; itraconazole; erythromycin	P-glycoprotein inhibition	Risk of digoxin toxicity
Phenylbutazone, probenecid; salicylates	Inhibition of renal tubular transport	Salicylates → increased risk of methotrexate toxicity

CLINICAL EXERCISES FOR OUT-CLASS WORK

1. A nurse is to give an SC injection of heparin to a patient. Determine what information the nurse needs to know about the patient before preparing the injection. Discuss how this information would affect the preparation of the injection and the technique used to give the SC injection.

2. A postoperative patient requires analgesia. We choose a drug that has the following pharmacokinetics properties: half-life 12 h, clearance 0.08 L/min, volume of distribution 60 L. The patient has and indwelling venous catheter with a slow drip 0.9% NaCl, and you use this line to administer intermittent injections of the drug every 4 h. The target blood level of the drug, following each injection, is 8 mcg/ml. What dose should be injected every 4 h, if all administrated drug is active. Which would be the correct loading dose?

3. A hypothetical aminoglycoside antibiotic was injected intravenously (5 mg/kg) into a 70-kg volunteer. The plasma concentrations of the drug were measured at various times after the end of the injection, as recorded in the table 3.3. Calculate elimination half-life, elimination rate constant, volume of distribution, total body clearance of aminoglycoside.

Table 3.3. Plasma concentration (mcg/mL) of hypothetical aminoglycoside antibiotic that was injected intravenously (5 mg/kg) into a 70-kg volunteer.

Time after dosing stopped (h)	**Plasma aminoglycoside concentration (mcg/mL)**
0.0	18.0
0.5	10.0
1.0	5.8
2.0	4.6
3.0	3.7
4.0	3.0
5.0	2.4
6.0	1.9
8.0	1.3

4. A 60-year-old man with aggressive rheumatoid arthritis will be started on an anti-inflammatory drug to suppress the joint inflammation. Published pharmacokinetic data for this drug include:

   Bioavailability (F): 1.0 (100%)

   Plasma half-life ($t_{1/2}$) = 0.5 h

   Volume of distribution (Vd): 45 L

For this drug it is important to maintain an average steady state concentration 2.0 mcg/mL in order to ensure adequate and continued anti-inflammatory activity. The drug will be given every 4 hours. What dose will be needed to obtain an average steady-state drug concentration of 2.0 mcg/mL?

REVIEW QUESTIONS

1. What substances are eliminated more efficiently?
    A) Polar compounds
    B) Lipid-soluble compounds
    C) Weak acidic compounds
    D) Weak basic compounds
    E) Acidic compounds
    F) Basic compounds
    G) a, b, c, d, e, f
2. What major processes in the nephron are considered?
    A) Glomerular filtration
    B) Active tubular secretion
    C) Passive tubular reabsorption
    D) Crossing the glomerular membrane by active transport
    E) Crossing the glomerular membrane by pinositosis
    F) a, b, c
    G) a, b, c, d, e
3. What substances are used for determining the glomerular filtration rate?
    A) Inulin
    B) Creatinine
    C) p-aminohippuric acid
    D) Tetraethylammonium
    E) a, b
    F) a, b, c
    G) a, b, c, d
4. When are weak acids excreted more rapidly?
    A) When the tubular urine is made more alkaline
    B) When the tubular urine is made more acidic
    C) When the concentration of the output approaches the input
    D) When the extraction ratio approaches zero
    E) a, b
    F) a, b, c
    G) a, b, c, d
5. When are weak basics excreted more rapidly?
    A) When the tubular urine is made more alkaline
    B) When the tubular urine is made more acidic
    C) When the concentration of the output approaches the input
    D) When the extraction ratio approaches zero
    E) a, b
    F) a, b, c
    G) a, b, c, d

6. What drugs are able to be excreted by the lung?
    A) Acidic drugs
    B) Gaseous substances
    C) Volatile substances
    D) Ethanol
    E) Basic drugs
    F) a, b, c, d
    G) b, c
7. What compounds may be concentrated in milk?
    A) Acidic compounds
    B) Basic compounds
    C) Ethanol
    D) Urea
    E) Volatile substances
    F) a, b, c
    G) a, b, c, d
8. What compounds reach the concentration in milk equal to the concentration in plasma?
    A) Acidic compounds
    B) Basic compounds
    C) Ethanol
    D) Urea
    E) Volatile substances
    F) a, b, c
    G) c, d
9. What compounds reach the concentration in milk lower than in plasma?
    A) Acidic compounds
    B) Basic compounds
    C) Ethanol
    D) Urea
    E) Volatile substances
    F) a, b, c
    G) a, b, c, d
10. What substances are used for determining the renal plasma flow rate?
    A) Inulin
    B) Creatinine
    C) p-aminohippuric acid
    D) Tetraethylammonium
    E) a, b
    F) a, b, c
    G) a, b, c, d
11. What is the biotransformation?
    A) Process of conversion of metabolites to drugs

B) Process of conversion of drugs to metabolites
C) Binding of drugs to proteins
D) Actions of food on the drug
E) Area of the absorbing surface

12. What are the organs with significant metabolic capacity?
A) Liver
B) Kidneys
C) Gastrointestinal tract
D) Skin
E) Lungs

13. The drug-metabolizing activity is found in:
A) endoplasmic reticulum
B) cytosol
C) mitochondria
D) nuclear envelope
E) plasma membrane
F) a, c, d, e
G) a, b, c, d, e

14. What reactions of Phase I do you know?
A) Oxidations
B) Reductions
C) Hydrolyse
D) Acetylation, methylation
E) Conjugations with glucuronic acid, gutathione, glycine, sulfate
F) a, b, c
G) d, e

15. What reactions of Phase II do you know?
A) Oxidations
B) Reductions
C) Hydrolyse
D) Acetylation, methylation
E) Conjugations with glucuronic acid, gutathione, glycine, sulfate
F) a, b, c
G) d, e

16. What reactions does the cytochrome P450 enzyme family catalyze?
A) Dehydrogenation
B) Hydroxylation
C) Epoxidation
D) Oxygenation
E) Dealkylation
F) a, d
G) a, b, c, d, e

17. What cytochrome P450 enzyme is involved in the biotransformation of a majority of all drugs and is expressed at significant levels extrahepatically?
    A) CYP1A1
    B) CYP2A5
    C) CYP2B6
    D) CYP2C19
    E) CYP2D6
    F) CYP3A4
    G) CYP4A9

18. What is the enterohepatic recirculation?
    A) Most important hepatic reaction
    B) Phenomenon during which conjugates excreted in the bile are subject to enzymatic cleavage of the conjugate bond by intestinal microflora and release of the parent drug back into the systemic circulation.
    C) Major reactions of drug biotransformation in the liver
    D) Reactions of drug biotransformation in the GI tract
    E) a, b
    F) a, d
    G) a, b, c

19. What substances enhance the drug metabolism in humans?
    A) Allopurinol, chloramphenicol, isoniazid
    B) Barbiturates, phenytoin
    C) Cimetidine, ketoconazole, oral contraceptives
    D) Grapefruit juice
    E) Griseofulvin, rifampin
    F) a, c, d
    G) b, e

20. What substances inhibit the drug metabolism in humans?
    A) Allopurinol, chloramphenicol, isoniazid
    B) Barbiturates, phenytoin
    C) Cimetidine, ketoconazole, oral contraceptives
    D) Grapefruit juice
    E) Griseofulvin, rifampin
    F) a, c, d
    G) b, e

21. What are the common factors that modify distribution?
    A) Membrane permeability
    B) Blood flow
    C) Lipid solubility
    D) pH - pKa
    E) Extent of plasma protein binding and intracellular binding
    F) Extent of drug's elimination

G) a, b, c, d, e, f

22. What organs are well-perfused?
    A) Heart
    B) Liver
    C) Kidney
    D) Brain
    E) Skin
    F) a, b, c, d
    G) a, b, c, d, e

23. What drugs commonly bind to albumin?
    A) Acidic drugs
    B) Basic drugs
    C) Steroids
    D) Vitamins
    E) Metal ions
    F) a, b, d
    G) a, b, c, d, e

24. What drugs commonly bind to alpha$_1$-acid glycoproteins and lipoproteins?
    A) Acidic drugs
    B) Basic drugs
    C) Steroids
    D) Vitamins
    E) Metal ions
    F) a, b, d
    G) c, d, e

25. What drugs commonly bind to globulins?
    A) Acidic drugs
    B) Basic drugs
    C) Steroids
    D) Vitamins
    E) Metal ions
    F) a, b, d
    G) c, d, e

26. What drugs have the highest fraction unbound for plasma protein binding?
    A) Amitriptyline
    B) Cyclosporine
    C) Diazepam
    D) Ethosuximide
    E) Lithium
    F) Vancomycin
    G) d, e, f

27. What drugs have the lowest fraction unbound for plasma protein binding?
    A) Amitriptyline

B) Cyclosporine
C) Diazepam
D) Ethosuximide
E) Lithium
F) Vancomycin
G) a, b, c

28. How do endothelial cells of the brain capillaries differ from their counterparts in most tissues?
A) By the absence of intercellular pores
B) By the absence of pinocytotic vesicles
C) By the tight junctions of endothelial cells
D) Drugs cross the barrier primarily by active transport
E) The Sertoli cells are tightly joined together and form an additional layer to the endothelium of capillaries
F) a, b, c
G) a, b, c, d, e

29. What are the features of placental barrier?
A) First-pass effect of the placenta because of the presence of metabolic enzyme system
B) Placental barrier is thinner at the early phase of pregnancy and becomes gradually thicker near term
C) Water-soluble, ionized drugs readily enter the fetal blood from the maternal circulation
D) Placental barrier is thicker at the early phase of pregnancy and becomes gradually thinner near term
E) Lipid-soluble, nonionized drugs readily enter the fetal blood from the maternal circulation
F) a, b, c
G) a, d, e

30. What are the features of blood-testis barrier?
A) Sertoli cells, which have an important role in spermatogenesis, are tightly joined together and form an additional layer to the endothelium of capillaries
B) Testis is not able of metabolizing molecules
C) P-glycoprotein is localized significantly in testicular endothelium and contributes to the exclusion of a wide range of xenobiotics
D) Drugs cross the barrier primarily by active transport
E) a, c
F) a, b, d
G) a, b, c, d, e

Lesson 2

CLINICAL PHARMACOLOGY OF DRUGS USED FOR THE TREATMENT OF MYOCARDIAL ISCHEMIA

QUESTIONS FOR IN-CLASS WORK

7. General principles of the treatment of myocardial ischemia.
8. Nitrates: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
9. Calcium channel blocking drugs: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
10. Beta-adrenergic blocking drugs: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
11. Drugs used for dyslipidemia: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
12. Anticoagulant: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
13. Thrombolytic: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
14. Antiplatelet drugs: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.

THEORETICAL ISSUES

ANTIANGINAL DRUGS

Angina is a disorder characterized by atherosclerotic plaque formation in the coronary arteries, which causes decreased oxygen supply to the heart muscle and results in chest pain or pressure. Any activity that increases the workload of the heart, such as exercise or simply climbing stairs, can precipitate an angina attack. Antianginal drugs relieve chest pain or pressure by dilating coronary arteries, increasing the blood supply to the myocardium.

The antianginal drugs include the nitrates, the calcium channel blockers, and the beta-blockers.

1. NITRATES

Actions. The nitrates, such as isosorbide and nitroglycerin, have a direct relaxing effect on the smooth muscle layer of blood vessels. The result of this effect is an increase in the lumen of the artery or arteriole and an increase in the amount of blood flowing through these vessels. An increased blood flow results in an increase in the oxygen supply to surrounding tissues.

Uses. The nitrates are used to treat angina pectoris. Some of these drugs, such as isosorbide dinitrate, are used for prophylaxis and long-term treatment of angina, whereas others, such as sublingual nitroglycerin, are used to relieve the pain of acute anginal attacks when they occur. Intravenous nitroglycerin is used to control perioperative hypertension associated with surgical procedures.

The nitrates are available in various forms (eg, sublingual, transmucosal, translingual spray, and inhalation).

Adverse reactions. The nitrate antianginal drugs all have the same adverse reactions, although the intensity of some reactions may vary with the drug and the dose. A common adverse reaction seen with these drugs is headache, especially early in therapy. Hypotension, dizziness, vertigo, and weakness may also be associated with headache. Flushing caused by dilatation of small capillaries near the surface of the skin may also be seen.

Some adverse reactions are a result of the method of administration. For example, sublingual nitroglycerin may cause a local burning or tingling in the oral cavity. However, the patient must be aware that an absence of this effect does not indicate a decrease in the drug's potency. Contact dermatitis may occur from use of the transdermal delivery system.

In many instances, the adverse reactions associated with the nitrates lessen and often disappear with prolonged use of the drug. However, for some patients, these adverse reactions become severe, and the doctor may lower the dose until symptoms subside. The dose may then be slowly increased if the lower dosage does not provide relief from the symptoms of angina.

Contraindications, precautions, and interactions. The nitrates are contraindicated in patients with known hypersensitivity to the drugs, severe anemia, closed angle glaucoma, postural hypertension, head trauma, cerebral hemorrhage (may increase intracranial hemorrhage), allergy to adhesive (transdermal system), or constrictive pericarditis.

The nitrates are used cautiously in patients with severe hepatic or renal disease, severe head trauma, acute myocardial infarction, hypothyroidism, and during pregnancy or lactation.

If the nitrates are administered with the antihypertensives, alcohol, calcium channel blockers, or the phenothiazines, there may be an increased hypotensive effect. When nitroglycerin is administered intravenously, the effects of heparin may be decreased. Increased nitrate serum concentrations may occur when the nitrates are administered with aspirin.

2. CALCIUM CHANNEL BLOCKERS

Actions. Systemic and coronary arteries are influenced by movement of calcium across cell membranes of vascular smooth muscle. The contractions of cardiac and vascular smooth muscle depend on movement of extracellular calcium ions into these walls through specific ion channels. Calcium channel blockers, such as amlodipine, diltiazem, nicardipine, nifedipine, and verapamil, inhibit the movement of calcium ions across cell membranes. This results in less calcium

available for the transmission of nerve impulses. This drug action of the calcium channel blockers has several effects on the heart, including an effect on the smooth muscle of arteries and arterioles. These drugs dilate coronary arteries and arterioles, which in turn deliver more oxygen to cardiac muscle. Dilation of peripheral arteries reduces the workload of the heart.

Uses. Calcium channel blockers are primarily used to prevent anginal pain associated with certain forms of angina, such as vasospastic angina and chronic stable angina. They are not used to stop anginal pain once it has occurred. When angina is caused by coronary artery spasm, these drugs are recommended when the patient cannot tolerate therapy with the beta-adrenergic blocking drugs or the nitrates. Some calcium channel blocking drugs have additional uses. Verapamil affects the conduction system of the heart and may be used to treat cardiac arrhythmias. Diltiazem, nicardipine, nifedipine, and verapamil also are used in the treatment of essential hypertension.

Adverse reactions to the calcium channel blocking drugs usually are not serious and rarely require discontinuation of the drug therapy. The more common adverse reactions include dizziness, light-headedness, nausea, diarrhea, constipation, peripheral edema, headache, bradycardia, flushing, dermatitis, skin rash, and nervousness.

Contraindications, precautions, and interactions. Calcium channel blockers are contraindicated in patients who are hypersensitive to the drugs and those with sick sinus syndrome, second- or third-degree AV block (except with a functioning pacemaker), hypotension, ventricular dysfunction, or cardiogenic shock. The calcium channel blockers are used cautiously during pregnancy and lactation and in patients with congestive heart failure, hypotension, or renal or hepatic impairment.

The effects of the calcium channel blockers are increased when administered with cimetidine or ranitidine. A decrease in effectiveness of the calcium channel blockers may occur when the agents are administered with phenobarbital or phenytoin. The calcium channel blockers have an antiplatelet effect (inhibition of platelet function) when administered with aspirin, causing easy bruising, petechiae, and bleeding. There is an additive depressive effect on the myocardium when the calcium channel blockers are administered with the beta-adrenergic blocking drugs. When the calcium channel blockers are administered with digoxin, there is an increased risk for digitalis toxicity.

EXERCISES FOR OUT-CLASS WORK

Exercise 1. Using the table 1, administrate nitrates for:

1) treatment of angina pectoris;
2) prevention of angina pectoris;
3) control of blood pressure in perioperative hypertension;
4) control of blood pressure in immediate post-operative period;
5) CHF associated with acute MI.

Exercise 2. Using the table 2, explain interactions of nitrates.

Exercise 3. Using the table 3, administrate calcium channel blocking drugs for the patient with:

1) atrial fibrillation;
2) atrial flutter;
3) chronic stable angina;
4) hypertension;
5) paroxysmal supraventricular tachycardia;
6) temporary control of rapid ventricular rate in atrial flutter/fibrillation;
7) vasospastic angina (Prinzmetal's angina).
8) unstable angina;
9) chronic heart failure.

Table 1. Uses, adverse reactions and dosage ranges of nitrates.

Drugs	Uses	Adverse reactions	Dosage ranges
Nitroglycerin sublingual	Acute relief of an attack of angina pectoris or prophylaxis of angina pectoris	Headache, hypotension, dizziness, vertigo, weakness, flushing	1 tablet under tongue or in buccal pouch at first sign of an acute anginal attack; may repeat q5 min until relief or 3 tablets have been taken
Nitroglycerin, intravenous (Perlinganit)	Control of blood pressure in perioperative hypertension, CHF associated with MI, angina pectoris unresponsive to nitrates or beta blockers	Headache, hypotension, dizziness, vertigo, weakness, flushing	Initially 5 mcg/min via IV infusion pump; may increase to 20 mcg/min
Nitroglycerin, sustained release (Nitrong)	Prevention of angina pectoris	Headache, hypotension, dizziness, vertigo, weakness, flushing	2.5–2.6 mg TID, QID PO up to 26 mg QID
Nitroglycerin transdermal systems (Deponit)	Prevention of angina pectoris	Headache, hypotension, dizziness, vertigo, weakness, flushing	One system daily 0.2–0.8 mg/h
Nitroglycerin, topical (Nitrobid)	Prevention and treatment of angina pectoris	Headache, hypotension, dizziness, vertigo, weakness, flushing	1–5 inches q4–8h
Isosorbide dinitrate (Cardiket)	Treatment and prevention of angina pectoris	Headache, hypotension, dizziness, vertigo, weakness, flushing	Initial dose 5–20 mg PO; maintenance dose 10–40 mg BID, TID; sustained release: 40 mg/d; daily maximum dose, 160 mg/d PO
Isosorbide mononitrate (Efox long)	Prevention of angina pectoris	Headache, hypotension, dizziness, vertigo, weakness, flushing	20 mg BID PO with the two doses given 7h apart; extended-release tablets: 30–60 mg once daily may be increased to 240 mg/d PO

Table 2. Interactions and dosage ranges of nitrates.

Interacted drugs		Pharmacological effect
Nitrates	Antihypertensives, alcohol, calcium channel blockers, or the phenothiazines	Increased hypotensive effect
	Aspirin	Increased nitrate serum concentrations
Nitroglycerin administered intravenously	Heparin	effects of heparin may be decreased

Table 3. Uses, adverse reactions and dosage ranges of calcium channel blocking drugs.

Drugs	Uses	Adverse reactions	Dosage ranges
Amlodipine (Norvasc)	Hypertension, chronic stable angina, vasospastic angina (Prinzmetal's angina)	Dizziness, light-headedness, headache, nervousness, nausea, diarrhea, constipation, peripheral edema, angina, bradycardia, AV block, flushing, rash, nasal congestion, cough	Individualize dosage; 5–10 mg PO once daily
Nifedipine (Adalat)	Vasospastic angina (Prinzmetal's angina), chronic stable angina, hypertension (sustained-release only)	Dizziness, light-headedness, headache, nervousness, nausea, diarrhea, constipation, peripheral edema, angina, bradycardia, AV block, flushing, rash, nasal congestion, cough	10–20 mg TID PO; may increase to 120 mg/d; sustained release: 30–60 mg/d PO; may increase to 120 mg/d
Diltiazem HCl	Oral: Angina pectoris, chronic stable angina, essential hypertension. Parenteral: atrial fibrillation or flutter, paroxysmal supraventricular tachycardia	Dizziness, light-headedness, headache, nervousness, nausea, diarrhea, constipation, peripheral edema, angina, bradycardia, AV block, flushing, rash, nasal congestion, cough	Tablets: 30–360 mg/d in divided doses; sustained-release: 120–360 mg/d. Parenteral: 0.25 mg/kg IV bolus; 5–15 mg/h IV
Verapamil HCl	Superventricular tachyarrhythmias, temporary control of rapid ventricular rate in atrial flutter/fibrillation, angina, unstable angina, hypertension	Constipation, dizziness, light-headedness, headache, asthenia, nausea, peripheral edema, hypotension, proarrhythmias, CHF	Oral: initial dose 80–120 mg TID; maintenance 320–480 mg/d. Parenteral: IV use only; initial dose 5–10 mg over 2 min; may repeat 10 mg 30 min later.

Table 4. Interactions and dosage ranges of calcium channel blockers.

Interacted drugs		Pharmacological effect
Calcium channel blockers	Cimetidine or ranitidine	The effects of the calcium channel blockers are increased
	Phenobarbital or phenytoin	A decrease in effectiveness of the calcium channel blockers
	Aspirin	Inhibition of platelet function, causing easy bruising, petechiae, and bleeding.
	Beta-adrenergic blocking drugs	The additive depressive effect on the myocardium
	Digoxin	Increased risk for digitalis toxicity

Exercise 4. Using the table 4, explain interactions of calcium channel blockers**.**

Exercise 5. Using the table 5, administrate beta-adrenergic blocking drugs for the patient with:

1) angina pectoris;
2) glaucoma (ophthalmic);
3) heart failure;
4) hypertension;
5) myocardial infarction.

Table 5. Uses, and adverse reactions of beta-adrenergic blocking drugs.

Drugs	Uses	Adverse reactions	Dosage ranges
Atenolol	Angina pectoris, hypertension, myocardial infarction (MI)	Fatigue, hypotension, weakness, blurred vision, stuffy nose, impotence, decreased libido, rash, CHF, bradycardia, pulmonary edema, myopathy	50—100 mg/d PO in single dose; 5 mg IV; may repeat every 10 min up to 2 times
Betaxolol HCl (Lokren)	Hypertension, glaucoma (ophthalmic)	Fatigue, weakness, drowsiness, impotence, hypotension, CHF, bradycardia, pulmonary edema, myopathy	10—20 mg once daily PO
Bisoprolol fumarate	Hypertension	Fatigue, hypotension, weakness, blurred vision, stuffy nose, rash, CHF, bradycardia, pulmonary edema, myopathy	2.5–20 mg once daily PO
Labetalol HCl	Hypertension	Fatigue, weakness, orthostatic hypotension, impotence, drowsiness, bradycardia, pulmonary edema, CHF, myopathy	200—400 mg BID up to 2400 mg/d; 20–80 mg IV; may give q 10 min up to 300 mg
Metoprolol	Hypertension, angina pectoris, MI, heart failure (HF)	Fatigue, weakness, orthostatic hypotension, impotence, drowsiness, bradycardia, pulmonary edema, CHF, myopathy	Hypertension angina, 100–400 mg/d PO; extended-release products are given once daily; MI: 25—100 mg BID PO; 5 mg q 2 min IV for 3 doses

Exercise 6. Using the table 6, explain interactions of beta-adrenergic blockers**.**

Table 6. Interactions and dosage ranges of beta-adrenergic blockers.

Interacted drugs		Pharmacological effect
Beta-adrenergic blockers	Verapamil	The effects of the beta- blockers are increased
	Indomethacin, ibuprofen, sulindac, or barbiturates	The effects of the beta- blockers are decreased
	Diuretics	The hypotensive effects of the beta- blockers are increased
	Clonidine	Paradoxical hypertensive effect
	Lidocaine and cimetidine	The risk of increased serum levels and toxic effects of the beta-adrenergic blocking drugs

Exercise 7. Using the table 7, administrate HMG-CoA reductase inhibitors for the patient with:

1) hyperlipidemia;
2) reduction of elevated total and LDL cholesterol levels;
3) prevention of first MI;
4) CAD;
5) stroke;
6) TIA.

Table 7. Uses, and adverse reactions of HMG-CoA reductase inhibitors.

Drugs	Uses	Adverse reactions	Dosage ranges
Atorvastatin (Liprimar)	Hyperlipidemia, reduction of elevated total and LDL cholesterol levels; increase HDL-C in patients with hypercholesterolemia	(Usually mild) headache, flatulence, abdominal pain, cramps, constipation, nausea	10—80 mg/d PO
Fluvastatin (Lescol)	Hyperlipidemia and dyslipidemia, reduction of elevated total and LDL cholesterol levels, to slow progression of coronary artery disease (CAD), along with diet and exercise	(Usually mild) headache, flatulence, abdominal pain, cramps, constipation, nausea	20–80 mg/d PO
Lovastatin (Mevacor)	Hyperlipidemia, reduction of elevated total and LDL cholesterol levels, to slow progression of CAD along with diet and excercise	(Usually mild) headache, flatulence, abdominal pain, cramps, constipation, nausea	10–80 mg/d PO in single or divided doses
pravastatin (Lipostat)	Hyperlipidemia, reduction of elevated total and LDL cholesterol levels, prevention of first MI, to slow progression of CAD, reduce risk of stroke, TIA	(Usually mild) headache, flatulence, abdominal pain, cramps, constipation, nausea	10–40 mg/d PO
simvastatin (Zocor)	Hyperlipidemia, reduction of elevated total and LDL cholesterol levels	(Usually mild) headache, flatulence, abdominal pain, cramps, constipation, nausea	5–80 mg/d PO

Exercise 8. Using the table 8, explain interactions of HMG-CoA reductase inhibitors.

Table 8. Interactions and dosage ranges of HMG-CoA reductase inhibitors.

Interacted drugs		Pharmacological effect
HMG-CoA reductase inhibitors	Bile acid sequestrants	Additive antihyperlipidemic effect
	Erythromycin, niacin, or cyclosporine	Increased risk of myopathy
	Oral anticoagulants	Increased anticoagulant effect

Exercise 9. Using the table 9, explain interactions of anticoagulants.

Table 9. Interactions and dosage ranges of anticoagulants.

Interacted drugs		Pharmacological effect
Warfarin	Acetaminophen, NSAIDs, beta blockers, disulfiram, isoniazid, chloral hydrate, loop diuretics, aminoglycosides, cimetidine, tetracyclines, and cephalosporins	The effects of warfarin are increased
	Oral contraceptives, ascorbic acid, barbiturates, diuretics, and vitamin K	The effects of warfarin are decreased
Heparin	NSAIDs, aspirin, penicillin, or the cephalosporins	May be an increase in clotting times, thereby increasing the risk for bleeding
LMWHs	Aspirin, salicylates, NSAIDs, and thrombolytics	The risk of bleeding is increased

Exercise 10. Using the table 10, administrate anticoagulants for the patient with:

1) atrial fibrillation with embolism;
2) deep vein thrombosis (DVT);
3) disseminated intravascular coagulation;
4) prophylaxis of systemic embolism after acute MI;
5) pulmonary embolism;
6) thrombosis/embolism;
7) unstable angina/non Q-wave MI;
8) venous thrombosis.

Table 10. Uses, adverse reactions and dosage ranges of anticoagulants.

Drugs	Uses	Adverse reactions	Dosage ranges
Coumadin and Indandione Derivatives			
Warfarin	Venous thrombosis, atrial fibrillation with embolism, pulmonary embolism (PE), prophylaxis of systemic embolism after acute MI	Nausea, alopecia, hemorrhage, urticaria, dermatitis, vomiting, anorexia, abdominal cramping, priapism	2—10 mg/d PO, IV; individualized dose based on PT or INR
Unfractionated Heparin			
Heparin	Thrombosis/embolism, diagnosis and treatment of disseminated intravascular coagulation (DIC), prophylaxis of deep vein thrombosis (DVT), clotting prevention	Hemorrhage, chills, fever, urticaria, local irritation, erythema, mild pain, hematoma or ulceration at the injection site (IM or SC), bruising	10,000–20,000 units SC in divided doses q8—12h; 5000–10,000 units q4—6h intermittent IV; 5000–40,000 units/d IV infusion; 5000 units SC q2h before surgery and 5000 units SC after surgery q8—12h
Fractionated Heparins: Low-Molecular-Weight Heparins (LMWHs)			
Dalteparin sodium Fragmin	Unstable angina/non Q-wave MI, DVT prophylaxis	Hemorrhage, bruising, thrombocytopenia, chills, fever, pain, erythema and irritation at site of injection	Angina/MI: 120 IU/kg, SC q12h with concurrent oral aspirin; DVT: 2500 IU SC daily
Enoxaparin sodium (Klexane)	DVT and prophylaxis, DVT and pulmonary embolism (PE) treatment, unstable angina/non—Q-wave MI	Hemorrhage, bruising, thrombocytopenia, hyperkalemia, hypersensitivity, fever, pain and erythema at injection site	DVT prophylaxis: 30 mg q12h SC or 40 mg once daily SC; in abdominal surgery for patients at risk for thromboembolic complications: 40 mg/d SC; DVT/PE treatment: 1 mg/kg SC q12h; unstable angina, non—Q-wave MI: 1 mg/kg SC q12h

Exercise 11. Using the table 11, administrate thrombolytics for the patient with:

1) acute ischemic stroke;
2) acute myocardial infarction;
3) coronary artery thrombi;
4) IV catheter;
5) pulmonary embolism.

Table 11. Uses, adverse reactions and dosage ranges of thrombolytics.

Drugs	Uses	Adverse reactions	Dosage ranges
Alteplase (Actilyse)	Acute myocardial infarction (AMI), acute ischemic stroke, pulmonary embolism (PE)	Bleeding (GU, gingival, retroperitoneal), and epistaxis, ecchymosis	AMI: total dose of 100 mg IV given as 60 mg 1st h, 20 mg 2nd h and 20 mg over 3rd h; for patients < 65 kg, decrease dose to 1.25 mg/kg
Streptokinase (Streptase)	AMI, DVT, PE, embolism	Minor bleeding (superficial and surface) and major bleeding (internal and severe)	Lysis of coronary artery thrombosis, 20,000 IU directly into vein; PE, DVT, embolism: 250,000 IU IV over 30 min followed by 100,000 IU for 24—72 h
Tenecteplase (Metalize)	AMI	Bleeding (GI, GU, or at injection site), intracranial hemorrhage, anemia	Dosage based on weight, not to exceed 50 mg IV
Urokinase	PE, lysis of coronary artery thrombi, IV catheter clearance	Minor bleeding (superficial and surface) and major bleeding (internal and severe)	PE: 4400 IU/kg IV over 10 min, followed by 4400 IU/kg/hr for 12 h; lysis of thrombi: 6000 IU/min IV for 2 h; IV catheter clearance: see packaged instructions

Exercise 12. Using the table 12, explain interactions of thrombolytics.

Table 12. Interactions and dosage ranges of thrombolytics.

Interacted drugs		Pharmacological effect
Thrombolytics	Aspirin, dipyridamole, or the anticoagulants	The risk of bleeding is increased

CLINICAL EXERCISES FOR OUT-CLASS WORK

1. Ms. Moore is admitted with severe chest pain and a possible myocardial infarction. After tests are done, her doctor prescribes transdermal nitroglycerin for her angina. Develop a teaching plan that will show Ms. Moore how and when to apply the transdermal form of nitroglycerin.
2. Mr. Billings is prescribed sublingual nitroglycerin for his angina. Develop a teaching plan that incorporates when and how to take the drug and what precautions he should take regarding handling and storage of the drug.
3. Mr. Crawford has peripheral vascular disease and is prescribed propranolol. Discuss the important aspects of his administration and ongoing assessment for Mr. Crawford.
4. Ms. Jackson, age 56 years, is hospitalized with a venous thrombosis. The doctor orders SC heparin. In developing a care plan for Ms. Jackson, discuss the

interventions that would be most important to prevent complications while administering heparin. Provide a rationale for each intervention.

5. Mr. Harris, age 72 years, is a widower who has lived alone since his wife died 5 years ago. He has been prescribed warfarin to take at home after his dismissal from the hospital. Determine which questions concerning the home environment would be important to ask Mr. Harris to prepare him to care for himself and prevent any complications associated with the warfarin.
6. A patient enters the emergency department with an acute MI. Thrombolytic therapy is begun with streptokinase. Discuss ongoing assessments that are important for the nurse to perform. Discuss the use of laboratory tests in monitoring heparin administration.

REVIEW QUESTIONS

1. When administering the nitrates for angina pectoris, the doctor monitors the patient for the most common adverse reaction, which is:
   A) hyperglycemia;
   B) headache;
   C) fever;
   D) anorexia.
2. When teaching a patient about prescribed sublingual nitroglycerin, the doctor informs the patient that if pain is not relieved, the dose can be repeated in minute(s):
   A) 1
   B) 5
   C) 15
   D) 30
3. When administering nitroglycerin ointment, the doctor:
   A) rubs the ointment into the skin;
   B) applies the ointment every hour or until the angina is relieved;
   C) applies the ointment to a clean, dry area;
   D) rubs the ointment between her palms and then spreads it evenly onto the patient's chest.
4. A patient taking a calcium channel blocker experiences orthostatic hypotension. The nurse instructs the patient with orthostatic hypotension to:
   A) remain in a supine position until the effects subside;
   B) make position changes slowly to minimize hypotensive effects;
   C) increase the dosage of the calcium channel blocker;
   D) discontinue use of the calcium channel blocker until the hypotensive effects diminish.
5. The peripheral vasodilating drugs are contraindicated in patients:
   A) with arthritis;

B) with hypertension;
C) with elevated blood cholesterol levels;
D) during the immediate postpartum period.

6. The patient is receiving the first dose of warfarin. Before administering the drug, the nurse:
A) administers a loading of heparin
B) has the laboratory draw blood for a serum potassium level
C) takes the apical pulse
D) checks to see that blood has been drawn for a baseline prothrombin time

7. The doctor monitors the prothrombin time (PT) during therapy. Optimal PT for warfarin therapy is:
A) more than 15 seconds;
B) less than 25 seconds;
C) 1.8 to 2 times the control value;
D) 1.2 to 1.5 times the control value.

8. There is an increased risk for bleeding when the patient receiving heparin is also taking:
A) allopurinol;
B) NSAID;
C) digoxin;
D) furosemide.

9. In which of the following situations would the doctor expect a LMWH to be prescribed?
A) To prevent a DVT.
B) For a patient with disseminated intravascular coagulation.
C) To prevent hemorrhage.
D) For a patient with atrial fibrillation.

10. If bleeding is noted while a patient is receiving a thrombolytic drug, the patient may receive:
A) Heparin;
B) whole blood or fresh, frozen plasma;
C) a diuretic;
D) protamine sulfate.

Lesson 3

CLINICAL PHARMACOLOGY OF ANTIHYPERTENSIVE DRUGS

QUESTIONS FOR IN-CLASS WORK

1. General principles of the treatment of arterial hypertention.
2. Alfa-adrenergic blocking drugs: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
3. Beta-adrenergic blocking drugs: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
4. Calcium antagonists: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
5. Diuretics: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
6. Angiotensin-Converting Enzyme Inhibitors: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
7. Angiotensin II receptor agonists: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.

THEORETICAL ISSUES

The types of drugs used for the treatment of hypertension include:

1. Vasodilating drugs (hydralazine, minoxidil);
2. Beta-adrenergic blocking drugs (atenolol, metoprolol, and propranolol);
3. Antiadrenergic drugs (centrally acting) (guanabenz, guanfacine);
4. Antiadrenergic drugs (peripherally acting) (guanadrel);
5. Alpha-adrenergic blocking drugs (doxazosin, prazosin);
6. Calcium channel blocking drugs (amlodipine, diltiazem);
7. Angiotensin-converting enzyme inhibitors (captopril, enalapril, lisinopril);
8. Angiotensin II receptor antagonists (irbesartan, losartan, and valsartan);
9. Diuretics (furosemide, hydrochlorothiazide).

1. ACTIONS

Many antihypertensive drugs lower the blood pressure by dilating or increasing the size of the arterial blood vessels. Vasodilatation creates an increase in the lumen (the space or opening within an artery) of the arterial blood vessels, which in turn increases the amount of space available for the blood to circulate. Because blood volume (the amount of blood) remains relatively constant, an

increase in the space in which the blood circulates (ie, the blood vessels) lowers the pressure of the fluid (measured as blood pressure) in the blood vessels. Although the method by which antihypertensive drugs dilate blood vessels varies, the result remains basically the same. Antihypertensive drugs that have vasodilating activity include adrenergic blocking drugs, antiadrenergic blocking drugs, calcium channel blocking drugs, vasodilating drugs.

Another type of antihypertensive drug is the diuretic. The mechanism by which the diuretics reduce elevated blood pressure is unknown, but it is thought to be based, in part, on their ability to increase the excretion of sodium from the body. The actions and uses of diuretics are discussed in lesson 6.

The mechanism of action of the ACE inhibitors is not fully understood. It is believed that these drugs may inhibit the activity of angiotensin-converting enzyme, which converts angiotensin I to angiotensin II, a powerful vasoconstrictor. Both angiotensin I and ACE normally are manufactured by the body and are called endogenous substances. The vasoconstricting activity of angiotensin II stimulates the secretion of the endogenous hormone aldosterone by the adrenal cortex. Aldosterone promotes the retention of sodium and water, which may contribute to a rise in blood pressure. By preventing the conversion of angiotensin I to angiotensin II, this chain of events is interrupted, sodium and water are not retained, and the blood pressure decreases. The angiotensin II receptor antagonists act to block the vasoconstrictor and aldosterone effects of angiotensin II at various receptor sites, resulting in a lowering of the blood pressure.

2. USES

Antihypertensives are used in the treatment of hypertension.

Although many antihypertensive drugs are available, not all drugs may work equally well in a given patient. In some instances, the doctor may find it necessary to prescribe a different antihypertensive drug when the patient experiences no response to therapy. Some antihypertensive drugs are used only in severe cases of hypertension and when other less potent drugs have failed to lower the blood pressure. At times, two antihypertensive drugs may be given together to achieve a better response. Nitroprusside is example of intravenous drugs that may be used to treat hypertensive emergencies. A hypertensive emergency is a case of extremely high blood pressure that does not respond to conventional antihypertensive drug therapy.

3. ADVERSE REACTIONS

When any antihypertensive drug is given, postural or orthostatic hypotension may be seen in some patients, especially early in therapy. Postural hypotension is the occurrence of dizziness and light-headedness when the individual rises suddenly from a lying or sitting position. Orthostatic hypotension occurs when the individual has been standing in one place for a long time. These reactions can be avoided or minimized by having the patient rise slowly from a lying or sitting position and by avoiding standing in one place for a prolonged period.

4. CONTRAINDICATIONS

Antihypertensive drugs are contraindicated in patients with known hypersensitivity to the individual drugs. When an antihypertensive is administered by a transdermal system (eg, clonidine), the system is contraindicated if the patient is allergic to any component of the adhesive layer of the transdermal system. Use of the angiotensin II receptor antagonists during the second and third trimester of pregnancy is contraindicated because use may cause fetal and neonatal injury or death.

5. PRECAUTIONS

Antihypertensive drugs are used cautiously in patients with renal or hepatic impairment or electrolyte imbalances, during lactation and pregnancy, and in older patients. ACE inhibitors are used cautiously in patients with sodium depletion, hypovolemia, or coronary or cerebrovascular insufficiency and those receiving diuretic therapy or dialysis. The angiotensin II receptor agonists are used cautiously in patients with renal or hepatic dysfunction, hypovolemia, or volume or salt depletion, and patients receiving high doses of diuretics.

6. INTERACTIONS

The hypotensive effects of most antihypertensive drugs are increased when administered with diuretics and other antihypertensives. Many drugs can interact with the antihypertensive drugs and decrease their effectiveness (eg, antidepressants, monoamine oxidase inhibitors, antihistamines, and sympathomimetic bronchodilators). When the ACE inhibitors are administered with the NSAIDs, their antihypertensive effect may be decreased. Absorption of the ACE inhibitors may be decreased when administered with the antacids. Administration of potassium-sparing diuretics or potassium supplements concurrently with the ACE inhibitors may cause hyperkalemia. When the angiotensin II receptor agonists are administered with NSAIDs or phenobarbital, their antihypertensive effects may be decreased.

EXERCISES FOR OUT-CLASS WORK

Exercise 1. Administrate beta-adrenergic blocking drugs for the patient with hypertension.

Exercise 2. Explain interactions of beta-adrenergic blockers with:

1) verapamil;
2) indomethacin, ibuprofen, sulindac, or barbiturates;
3) diuretics;
4) clonidine;
5) lidocaine and cimetidine.

Exercise 3. Using the table 1, administrate alfa-adrenergic blocking drugs for the patient with:

6) hypertension;
7) benign prostatic hypertrophy (BPH).

Table 1. Uses, adverse reactions and dosage ranges of alfa-adrenergic blocking drugs.

Drugs	Uses	Adverse reactions	Dosage ranges
Doxazosin mesylate (Cardura)	Hypertension, benign prostatic hypertrophy (BPH)	Headache, fatigue, dizziness, postural hypotension, dizziness, lethargy, vertigo, nausea, dyspepsia, diarrhea, tachycardia, palpitations, edema, sexual dysfunction	Hypertension: 1—16 mg/d PO once a day; BPH: 1—8 mg/d PO
Prazosin	Hypertension	Dizziness, headache, drowsiness, lethargy, weakness, nausea, palpitations	1—20 mg/d PO in divided doses
Terazosin (Kornam)	BPH, Hypertension	Dizziness, headache, drowsiness, lack of energy, weakness, somnolence, nausea, palpitations, edema, dyspnea, nasal congestion, sinusitis	1—20 mg/d PO at HS

Exercise 4. Using the table 2, administrate Angiotensin II Receptor Antagonists for the patient with hypertension.

Table 2. Uses, adverse reactions and dosage ranges of Angiotensin II Receptor Antagonists.

Drugs	Uses	Adverse reactions	Dosage ranges
Candesartan	Hypertension	Diarrhea, abdominal pain, nausea, headache, dizziness, upper respiratory infection (URI) symptoms, hypotension, rash	16–32 mg/d PO in divided doses
Eprosartan (Teveten)	Hypertension	Abdominal pain, fatigue, depression, URI symptoms, hypotension	400–800 mg/d PO in divided doses BID
Irbesartan	Hypertension	Headache, dizziness, diarrhea, abdominal pain, nausea, hypotension, URI symptoms, cough, fatigue	75–300 mg/d PO as one dose
Losartan (Cozaar)	Hypertension	Diarrhea, abdominal pain, nausea, headache, dizziness, hypotension, URI symptoms, cough	25–100 mg/d PO in one or two doses
Telmisartan (Micardis)	Hypertension	Diarrhea, abdominal pain, nausea, headache, dizziness, light-headedness, URI symptoms, hypotension	40–80 mg/d PO
Valsartan (Diovan)	Hypertension	Headache, dizziness, diarrhea, abdominal pain, nausea, URL symptoms, cough	80–320 mg/d PO

Exercise 5. Using the table 3, explain interactions of angiotensin II receptor agonists.

Table 3. Interactions and dosage ranges of angiotensin II receptor agonists.

Interacted drugs		Pharmacological effect
Angiotensin II receptor agonists	NSAIDs, phenobarbital	Antihypertensive effect may be decreased

Exercise 6. Using the table 4, administrate angiotensin-converting enzyme inhibitors for the patient with:

1) hypertension;
2) HF;
3) left ventricular dysfunction (LVD) after MI;
4) acute IM;
5) diabetic nephropathy;
6) coronary artery disease (CAD).

Table 4. Uses, adverse reactions and dosage ranges of angiotensin-converting enzyme inhibitors.

Drugs	Uses	Adverse reactions	Dosage ranges
Captopril (Capoten)	Hypertension, HF, left ventricular dysfunction after MI, diabetic nephropathy	Tachycardia, gastric irritation, peptic ulcer, proteinuria, rash, pruritus, cough	Hypertension: 50—450 mg/d PO in divided doses; CHF: 25–450 mg/d in divided doses; LVD: 6.25—150 mg/d PO TID; diabetic nephropathy: 25 mg PO TID
Enalapril	Hypertension, asymptomatic left ventricular dysfunction, HF	Headache, dizziness, fatigue, nausea, diarrhea, decreased hematocrit and hemoglobin, cough	Hypertension: 5—40 mg/d PO as a single dose or in two divided doses; 0.625—1.25 mg q6h IV; HF: 2.5—40 mg/d in two divided doses PO
Fosinopril sodium (Monopril)	Hypertension, HF	Nausea, cough, abdominal pain, vomiting, orthostatic hypotension, palpitation, rash	10—40 mg/d PO in a single or two divided doses
Lisinopril	Hypertension, HF, acute MI	Headache, dizziness, insomnia, fatigue, gastric irritation, nausea, diarrhea, orthostatic hypotension, proteinuria, cough	Hypertension: 10—40 mg/d PO as a single dose; CHF: 5—20 mg/d PO; acute MI: 5—10 mg PO
Moexipril HCl	Hypertension	Tachycardia, gastric irritation, peptic ulcers, diarrhea, diarrhea, proteinuria, rash, pruritus, flushing, flu-like syndrome, dizziness, cough	7.5—30 mg PO in one or two divided doses
Perindopril	Essential hypertension	Orthostatic hypotension, headache, dizziness, insomnia, fatigue, proteinuria, nausea, gastric irritation, cough	4–16 mg/d PO
Quinapril HCl	Hypertension, HF	Nausea, cough, abdominal pain, vomiting, orthostatic hypotension, palpitation, rash	Hypertension: 10–80 mg/d PO as a single dose or two divided doses; CHF: 5–20 mg PO BID
Ramipril	Hypertension, HF, coronary artery disease	Nausea, cough, abdominal pain, vomiting, orthostatic hypotension, palpitation	Hypertension: 2.5–20 mg/d PO as a single dose or PO BID; CHF: 2.5–5 mg PO BID

Exercise 7. Using the table 5, explain interactions of angiotensin-converting enzyme inhibitors.

Table 5. Interactions and dosage ranges of angiotensin-converting enzyme inhibitors.

Interacted drugs		**Pharmacological effect**
ACE inhibitors	NSAIDs	Antihypertensive effect may be decreased
	Potassium-sparing diuretics or potassium supplements	Hyperkalemia

Exercise 8. Using the table 6, administrate treatment for the patient with malignant hypertension.

Table 6. Therapeutic agents used to treat malignant hypertension.

Drug	**Route**	**Starting dose**	**Time Course of Action**			**Oral preparation available**
			Onset	**Peak**	**Duration**	
IMMEDIATE ONSET						
Nitroprusside	Continuous IV	0.25 μg/kg per min	<1 min	1–2 min	2–5 min	No
Nitroglycerin (Perlinganit)	Continuous IV	5 μg/min	1–5 min	2–6 min	3–10 min	No
Diazoxide	IV bolus	50 mg q5–10min up to 600 mg	1–5 min	2–4 min	4–12 h	No
Fenoldopan	Continuous IV	0.1–0.3 μg/kg per min	<5 min	5–10 min	30 min	No
Esmolol	Continuous IV	250–500 μg/min × 1 min; then 50–100 μg/kg per min × 4 min	1–2 min	2–3 min	10–20 min	No
DELAYED ONSET						
Enalaprilat	IV	1.25 mg q6h	10–15 min	3–4 h	6–24 h	Yes
Hydralazine	IV, IM	5–10 mg q20min × 3	10–20 min	20–40 min	4–12 h	Yes
Labetalol	IV	20–80 mg q10min up to 300 mg	5 min	20–30 min	3–6 h	Yes
Nicardipine	IV	5–15 mg/h	5–10 min	20–40 min	1–4 h	Yes

Exercise 9. Using the table 7, explain indications and contraindications of antihypertensives.

Table 7. Guidelines for selecting initial drug treatment of hypertension.

Class of drug	Compelling indications	Possible indications	Compelling contraindications	Possible contraindications
Diuretics	Heart failure Elderly patients Systolic hypertension	Diabetes	Gout	Dyslipidemia Sexually active males
β-Blockers	Angina After myocardial infarct Tachyarrhythmias	Heart failure Pregnancy Diabetes	Asthma and COPD Heart block	Dyslipidemia Athletes and physically active patients Peripheral vascular disease
ACE inhibitors	Heart failure Left ventricular dysfunction After myocardial infarct Diabetic nephropathy		Pregnancy Hyperkalemia Bilateral renal artery stenosis	
Calcium antagonists	Angina Elderly patients Systolic hypertension	Peripheral vascular disease	Heart block	Congestive heart failure
Angiotensin II antagonists	ACE inhibitor cough	Heart failure	Pregnancy Bilateral renal artery stenosis Hyperkalemia	

Exercise 10. Using results of randomized clinical trials (table 8), explain which drugs should be used to initiate therapy of arterial hypertension.

Table 8. Clinical trials of arterial hypertension.

Trial Reference	Patient Number and Characteristics / Trial Arms	Conclusion
SYST-EUR, JA Staessen et al, Lancet 350:757, 1997	4695, >60 years old 2 years' follow-up / Nitrendipine/ enalapril or HTZ Placebo	Among elderly patients with isolated systolic hypertension, nitrendipine reduced cardiovascular complications; treatment of 1000 patients for 5 years with this regimen may prevent 29 strokes and/or 53 major cardiovascular endpoints

Trial Reference	Patient Number and Characteristics / Trial Arms	Conclusion
SYST-EUR,J Tuomilehto et al, N Engl J Med 341:372, 1999	4695 (diabetic = 492) >60 years old 2 years' follow-up / Nitrendipine/enalapril or HTZ Placebo	Calcium channel antagonist significantly reduces cardiovascular morbidity and mortality in elder hypertensive patients; the effect is greater in diabetic than nondiabetic subjects
CAPPP Trial, L Hansson et al, Lancet 353:611, 1999	10,985, age 25–66, diastolic BP ≥ 100 mmHg 2–3 years' follow-up / Captopril Diuretics/beta blocker	Captopril and conventional treatment did not differ in preventing cardiovascular morbidity and mortality
HOT Study, Hansson et al, Lancet 351:1755, 1998	18,790, 50–80 years with diastolic BP 100–115 mmHg 3–4 years' follow-up / Felodipine plus four other agents to reduce diastolic BP to 90 mmHg or 85 mmHg or 80 mmHg	Intensive lowering of BP was associated with a low rate of cardiovascular events down to a diastolic BP of 82.6 mmHg
FG Messerli et al, JAMA 279:1903, 1998	Meta-analysis of efficacy of beta blockers vs. diuretics as first-line therapy for elderly patients (>60 years) with hypertension Diuretics, 8 trials Beta blockers, 2 trials	In elderly patients with hypertension, first-line diuretics reduced morbidity and mortality better than beta blockers
HOPE,S Yusuf et al, 2000	9297 high-risk patients (≥55 years old) with vascular disease or diabetes plus one other cardiovascular risk factor / Ramipril vs. placebo for 5 years	Ramipril significantly reduced the rates of death, MI, and stroke in high-risk patients not known to have a low ejection fraction or heart failure.
LIFE,B Dahlof et al, Lancet 359:995, 2002	9193, age 55–80, with essential hypertension and LVH by ECG / Once daily losartan-based or atenolol-based antihypertensive treatment for 4 years and until 1040 patients had primary cardiovascular event	Losartan prevented more cardiovascular morbidity and death than atenolol for similar reduction in BP
ALLHAT, ALLHAT Collaborative Research Group, 2002	42,419 high-risk hypertensives ≥ 55 years / Chlorthalidone vs. lisinopril vs. amlodipine vs. doxazosin	No difference in primary endpoints or in all-cause mortality between ACE inhibition, calcium channel blockade, and diuretics

CLINICAL EXERCISES FOR OUT-CLASS WORK

1. Discuss important preadministration assessments that should be performed on a patient prescribed captopril for hypertension.
2. While working in the medical clinic of a hospital associated health care satellite, the doctor asks you to explain to a patient what can be done to avoid dizziness and light-headedness when rising from a sitting or lying down

position. When talking to the patient, you discover that he understands little English. Discuss how you might communicate to this patient what he can do to decrease the symptoms of postural and orthostatic hypotension.

3. Mr. Bates, who has been treated for hypertension, is admitted for treatment of a kidney stone. On admission, he had severe pain and his blood pressure was 160/96 mm Hg. For the past 2 days, his blood pressure has been between 140/92 and 148/92 mm Hg. When taking his blood pressure before giving him an oral antihypertensive drug, you find that it now is 118/82 mm Hg. Analyze the situation and discuss what actions you would take.
4. Develop a teaching plan for a patient prescribed verapamil for hypertension. Discuss what information you would need from the patient before developing this plan. Identify important points to include in the plan.
5. Ms. Jones is admitted to the emergency department in hypertensive crisis. Nitroprusside therapy is begun, and you are asked to monitor this patient. Discuss important points that the nurse should keep in mind when administering this drug. Identify methods you would use to monitor the patient and prevent complications.

REVIEW QUESTIONS

1. The nurse instructs the patient using the transdermal system:
   A) to place the patch on the torso and keep it in place for 24 hours;
   B) to change placement of the patch every day after bathing;
   C) to place the patch on the upper arm or torso and keep it in place for 7 days;
   D) avoid getting the patch wet because it might detach from the skin.

2. To avoid symptoms associated with orthostatic hypotension, the nurse advises the patient to:
   A) sleep in a slide-lying position;
   B) avoid sitting for prolong periods;
   C) change position slowly;
   D) get up from a sitting position quickly.

3. After the first dose of an ACE inhibitor, the doctor monitors .
   A) the patient for a hypotensive crisis;
   B) the vital signs every 4 hours or more often if the patient reports being dizzy;
   C) the blood pressure every hour until it is stable;
   D) the blood pressure every 15 to 30 minutes for at least 2 hours.

4. When discontinuing use of an antihypertensive drug, the doctor:
   A) monitors the blood pressure every hour for 8 hours after the drug therapy is discontinued;

B) expects the primary care provider to order that the drug dosage be gradually decreased during a period of 2 to 4 days to avoid rebound hypertension;
C) checks the blood pressure and pulse every 30 minutes after discontinuing the drug therapy;
D) expects to taper the dosage of the drug during a period of 2 weeks to avoid a return of hypertension.

5. When administering an antihypertensive drug for a hypertensive emergency, the doctor:
A) weighs the patient before administering the drug;
B) places the patient in a supine position;
C) darkens the room to decrease stimuli;
D) places the patient in a high Fowler's position.

6. What are the pharmacokinetic processes?
A) Effect of the drug on the body
B) Dynamic processes in the liver
C) Effect of the drugs on the liver
D) Dynamic changes of drugs
E) Effect of the body on the drug
F) Effect of the drug on the nutrition
G) Effect of food on the drug

7. What are the important biological processes in the evaluation of the pharmacokinetics of drugs?
A) Absorption
B) Adsorption
C) Distribution
D) Metabolism
E) Interactions between the drugs and endogenous compounds
F) Excretion
G) a, c, d, f

8. What is the most common transport of therapeutic agents?
A) Carrier-mediated transcellular diffusion
B) Transcellular diffusion subject to P-glycoprotein efflux
C) Active transport
D) Passive diffusion
E) Pinocytosis
F) Solvent drag
G) Ion-pair absorption

9. What is the P-glycoprotein?
A) Blood pronein
B) Intracellular protein
C) Lipophilic carrier
D) bilayer of glicoproteins

E) Efflux membrane transporter
F) Isozyme
G) Membrane receptor

10. What is the bioavailability?
A) Relation of the pKa of a drug and pH of the stomach.
B) Elimination rate constant
C) Relationship between the rate of metabolism and the elimination rate constant
D) Fraction of the administered dose that reaches the systemic circulation
E) Relationship between the rate of metabolism and the steady state concentration
F) Relation of the pKa of a drug and pH of the stomach.
G) Relationship between the rate of metabolism and the elimination rate constant

11. What is the clearance?
A) Rate of elimination
B) Rate of metabolism
C) Fraction of the eliminated dose
D) Relation of the pKa of a drug and pH of the stomach.
E) Elimination rate constant
F) Volume of blood which is completely cleared of the drug in a given period
G) Relationship between the rate of metabolism and the elimination rate constant

Lesson 4

CLINICAL PHARMACOLOGY OF ANTIARRHYTHMIC DRUGS

QUESTIONS FOR IN-CLASS WORK

1. General principles of antiarrhythmic therapy.
2. Class I antiarrhythmics: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
3. Class II antiarrhythmics: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
4. Class III antiarrhythmics: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
5. Class IV antiarrhythmics: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
6. Clinical features and treatment of common arrhythmias (atrial flutter; atrial fibrillation; atrial premature beats; atrial tachycardia with block; multiple atrial tachycardia; paroxysmal SVT; preexcitation syndrome; sinus tachycardia; supraventricular tachycardias with aberrant ventricular conduction; Torsades de pointes; ventricular fibrillation; ventricular premature beats; ventricular tachycardia).

THEORETICAL ISSUES

The antiarrhythmic drugs are primarily used to treat cardiac arrhythmias. A cardiac arrhythmia is a disturbance or irregularity in the heart rate, rhythm, or both, which requires administration of one of the antiarrhythmic drugs.

The goal of antiarrhythmic drug therapy is to restore normal cardiac function and to prevent life-threatening arrhythmias.

1. ACTIONS

The myocardium has attributes of both nerve and muscle and therefore has the properties of both. Some cardiac arrhythmias are caused by the generation of an abnormal number of electrical impulses. These abnormal impulses may come from the sinoatrial node or may be generated in other areas of the myocardium. The antiarrhythmic drugs are classified according to their effects on the action potential of cardiac cells and their presumed mechanism of action. As understanding of the pathophysiology of cardiac arrhythmias and the drugs used to treat these arrhythmias has increased, a method of classification has been developed that includes four basic classifications and several subclasses.

Drugs in each class have certain similarities, yet each drug has subtle differences that make it unique.

Class I Antiarrhythmic Drugs

Class I antiarrhythmic drugs, such as moricizine, have a membrane-stabilizing or anesthetic effect on the cells of the myocardium, making them valuable in treating cardiac arrhythmias. Class I antiarrhythmic drugs contain the largest number of drugs of the four classifications.

Because the actions differ slightly, they are subdivided into classes I-A, I-B, and I-C.

Class I-A Antiarrhythmic Drugs

The drugs disopyramide, procainamide, and quinidine are examples of class I-A drugs. Quinidine depresses myocardial excitability or the ability of the myocardium to respond to an electrical stimulus. By depressing the myocardium and its ability to respond to some, but not all, electrical stimuli, the pulse rate decreases and the arrhythmia is corrected. Quinidine also prolongs or lengthens the refractory period and decreases the height and rate of the action potential of the impulses traveling through the myocardium.

All cells are electrically polarized, with the inside of the cell more negatively charged than the outside. The difference in electrical charge is called the resting membrane potential. Nerve and muscle cells are excitable and can change the resting membrane potential in response to electrochemical stimuli. The action potential is an electrical impulse that passes from cell to cell in the myocardium, stimulating the fibers to shorten, causing systole. After the action potential passes, the fibers relax and return to diastole. An action potential generated in one part of the myocardium passes almost simultaneously through all of the fibers, causing rapid contraction.

Only one impulse can pass along a nerve fiber at any given time. After the passage of an impulse, there is a brief pause, or interval, before the next impulse can pass along the nerve fiber. This pause is called the refractory period, which is the period between the transmission of nerve impulses along a nerve fiber. By lengthening the refractory period, the number of impulses traveling along a nerve fiber within a given time is decreased. For example, a patient has a pulse rate of 120 bpm. By lengthening the refractory period between each impulse and decreasing the height and rate of the rise of action potential, fewer impulses would be generated each minute, and the pulse rate would decrease. Procainamide is thought to act by decreasing the rate of diastolic depolarization in the ventricles, decreasing the rate and height of the action potential and increasing the fibrillation threshold.

Disopyramide decreases the rate of depolarization of myocardial fibers during the diastolic phase of the cardiac cycle, prolongs the refractory period, and decreases the rate of rise of the action potential.

Nerve cells have positive ions on the outside and negative ions on the inside of the cell membrane when they are at rest. This is called polarization.

When a stimulus passes along the nerve, the positive ions move from outside the cell into the cell, and the negative ions move from inside the cell to outside the cell. This movement of ions is called depolarization.

Unless positive ions move into and negative ions move out of a nerve cell, a stimulus (or impulse) cannot pass along the nerve fiber. Once the stimulus has passed along the nerve fiber, the positive and negative ions move back to their original place, that is, the positive ions on the outside and the negative ions on the inside of the nerve cell. This movement back to the original place is called repolarization. By decreasing the rate of depolarization, the stimulus must literally wait for this process before it can pass along the nerve fiber. Thus, decreasing the rate of depolarization decreases the number of impulses that can pass along a nerve fiber during a specific time period.

Class I-B Antiarrhythmic Drugs

Lidocaine, the representative class I-B drug, raises the threshold of the ventricular myocardium. Threshold is a term applied to any stimulus of the lowest intensity that will give rise to a response in a nerve fiber. A stimulus must be of a specific intensity (strength, amplitude) to pass along a given nerve fiber.

To further illustrate the threshold phenomenon using plain figures instead of precise electrical values, a certain nerve fiber has a threshold of 10. If a stimulus rated as 9 reaches the fiber, it will not pass along the fiber because its intensity is lower than the fiber's threshold of 10. If another stimulus reaches the fiber and is rated 14, it will pass along the fiber because its intensity is greater than the fiber's threshold of 10. If the threshold of a fiber is raised from 10 to 15, only the stimuli greater than 15 can pass along the nerve fiber.

Some cardiac arrhythmias result from many stimuli present in the myocardium. Some of these are weak or of low intensity but are still able to excite myocardial tissue.

Lidocaine, by raising the threshold of myocardial fibers, reduces the number of stimuli that will pass along these fibers and therefore decreases the pulse rate and corrects the arrhythmia. Mexiletine and tocainide are also antiarrhythmic drugs with actions similar to those of lidocaine.

Class I-C Antiarrhythmic Drugs

Flecainide and propafenone are examples of class I-C drugs. These drugs have a direct stabilizing action on the myocardium, decreasing the height and rate of rise of cardiac action potentials, thus slowing conduction in all parts of the heart.

Class II Antiarrhythmic Drugs

Class II antiarrhythmic drugs include beta-adrenergic blocking drugs, such as acebutolol, esmolol, and propranolol. These drugs also decrease myocardial response to epinephrine and norepinephrine because of their ability to block stimulation of beta- receptors of the heart. Adrenergic neurohormones stimulate the

receptors of the myocardium and therefore increase the heart rate. Blocking the effect of these neurohormones decreases the heart rate.

Class III Antiarrhythmic Drugs

Bretylium prolongs repolarization, prolongs refractory period, and increases the ventricular fibrillation threshold. Amiodarone appears to act directly on the cardiac cell membrane, prolonging the refractory period and repolarization and increasing the ventricular fibrillation threshold. Newer class III antiarrhythmic drugs include ibutilide and dofetilide. These two drugs are used to convert atrial fibrillation or flutter to a normal sinus rhythm. Ibutilide acts by prolonging the action potential, producing a mild slowing of the sinus rate and atrioventricular conduction. Dofetilide selectively blocks potassium channels, widens the QRS complex, and prolongs the action potential. The drug has no effect on calcium channels or cardiac contraction.

Class IV Antiarrhythmic Drugs

Class IV antiarrhythmic drugs include verapamil and the other calcium channel blockers. Calcium channel blockers produce their antiarrhythmic action by inhibiting the movement of calcium through channels across the myocardial cell membranes and vascular smooth muscle. Contraction of cardiac and vascular smooth muscle depends on the movement of calcium ions into these cells through specific ion channels. By reducing the calcium flow, conduction through the sinoatrial and atrioventricular nodes is slowed and the refractory period is prolonged, resulting in suppression of the arrhythmia. The calcium channel blockers are also called slow channel blockers or calcium antagonists. Two calcium channel blockers that have been approved as antiarrhythmics are verapamil and diltiazem.

2. USES

In general antiarrhythmic drugs are used to prevent and treat cardiac arrhythmias, such as premature ventricular contractions (PVCs), ventricular tachycardia (VT), premature atrial contractions (PACs), paroxysmal atrial tachycardia (PAT), atrial fibrillation, and atrial flutter.

Some of the antiarrhythmic drugs are used for other conditions. For example, propranolol, in addition to its use as an antiarrhythmic, may also be used for patients with myocardial infarction. This drug has reduced the risk of death and repeated myocardial infarctions in those surviving the acute phase of a myocardial infarction. Additional uses include control of tachycardia in those with pheochromocytoma, migraine headaches, angina pectoris caused by atherosclerosis, and hypertrophic subaortic stenosis.

3. ADVERSE REACTIONS

General adverse reactions common to most antiarrhythmic drugs include light-headedness, weakness, hypotension, bradycardia, and drowsiness.

All antiarrhythmic drugs may cause new arrhythmias or worsen existing arrhythmias, even though they are administered to resolve an existing arrhythmia. This phenomenon is called the proarrhythmic effect. This effect ranges from an increase in frequency of premature ventricular contractions (PVCs), to the development of more severe ventricular tachycardia, to ventricular fibrillation, and may lead to death. Proarrhythmic effects may occur at any time but occur more often when excessive dosages are given, when the preexisting arrhythmia is life-threatening, or if the drug is given IV.

4. CONTRAINDICATIONS

The antiarrhythmic drugs are reserved for emergency situations and are contraindicated in patients with known hypersensitivity to the antiarrhythmic drugs and during pregnancy and lactation. Safe use of antiarrhythmic drugs during pregnancy, lactation, or in children has not been established.

Fetal harm can occur if amiodarone is administered to a pregnant woman. It is used only if the potential benefits outweigh the potential hazards to the fetus.

Antiarrhythmic drugs are contraindicated in patients with second- or third-degree AV block, severe congestive heart failure, aortic stenosis, hypotension, and cardiogenic shock. Quinidine and procainamide are contraindicated in patients with myasthenia gravis.

5. PRECAUTIONS

All antiarrhythmic drugs are used cautiously in patients with renal or hepatic disease. When renal or hepatic dysfunction is present, a dosage reduction may be necessary. All patients should be observed for renal and hepatic dysfunction. Quinidine and procainamide are used cautiously in patients with CHF. Disopyramide is used cautiously in patients with CHF, myasthenia gravis, or glaucoma, and in men with prostate enlargement.

Bretylium is used cautiously in patients with digitalis toxicity because the initial release of norepinephrine with digitalis toxicity may exacerbate arrhythmias and symptoms of toxicity. Verapamil is used cautiously in patients with a history of serious ventricular arrhythmias or CHF. Electrolyte disturbances such as hypokalemia, hyperkalemia, or hypomagnesemia may alter the effects of the antiarrhythmic drugs.

6. INTERACTIONS

When two antiarrhythmic drugs are administered concurrently the patient may experience additive effects and is at increased risk for drug toxicity. When quinidine and procainamide are administered with digitalis, the risk of digitalis toxicity is increased. Pharmacologic effects of procainamide may be increased when procainamide is administered with quinidine. When quinidine is administered with the barbiturates or cimetidine, quinidine serum levels may be increased. When quinidine is administered with verapamil, there is an increased risk of hypotensive effects. When quinidine is administered with disopyramide,

there is an increased risk of increased disopyramide blood levels and/or decreased serum quinidine levels.

Propranolol may increase procainamide plasma levels. Additive cholinergic effects may occur when procainamide is administered with other drugs with anticholinergic effects. There is the potential of additive cardiodepressant effects when procainamide is administered with lidocaine. When a beta blocker is administered with lidocaine, there is an increased risk of lidocaine toxicity.

Propranolol may alter the effectiveness of insulin or oral hypoglycemic drugs. Dosage adjustments may be necessary.

Verapamil may cause an additive hypotensive effect when administered with other antihypertensives, alcohol, or the nitrates. Verapamil increases plasma digoxin levels and may cause bradycardia or CHF.

EXERCISES FOR OUT-CLASS WORK

Exercise 1. It is known, that Class I (Na+ channel block) antiarrhythmic drugs reduce maximal velocity of phase of depolarization (Vmax) due to block of inward Na+ current in tissue with fast response action potentials. Using the table 1, administrate class I antiarrhythmic drugs for the patient with life-threatening ventricular arrhythmias.

Table 1. Uses, adverse reactions and dosage ranges of class I antiarrhythmics.

Drugs	Uses	Adverse reactions	Dosage ranges
Class IA ↓ V_{max} at all heart rates and ↑ action potential duration			
Procainamide HCl (Novocainamidum)	Life-threatening ventricular arrhythmias	Hypotension, disturbances of cardiac rhythm, urticaria, fever, chills, nausea, vomiting, rash, confusion, dizziness, weakness, anorexia	Oral: 50 mg/kg/d PO in divided doses q3h; IM: 0.5—1.0 g q4—8h; IV: 500–600 mg over 25–30 min then 2–6 mg/min
Class IB Little effect at slow rates on Vmax in normal tissue; ↓ Vmax in partially depolarized cells with fast response action potentials No change or ↓ in action potential duration,			
Lidocaine HCl	Ventricular arrhythmias	Light-headedness, nervousness, bradycardia, hypotension, drowsiness, apprehension	50—100 mg IV bolus; 1—4 mg/min IV infusion 20-50 mcg/kg/min; 300 mg IM
Phenytoin (Dipheninum)	Ventricular arrhythmias	Light-headedness, nervousness	100-300 mg/day PO
Mexiletine HCl	Ventricular arrhythmias	Palpitations, nausea, vomiting, chest pain, heartburn, dizziness, light-headedness, rash	Initial dose: 200 mg PO q8h; maximum dosage, 1200 mg/d PO
Class IC ↓ V_{max} at normal rates in normal tissue			
propafenone HCl (Rytmonorm)	Ventricular arrhythmias	Dizziness, nausea, vomiting, constipation, unusual taste, first-degree AV block	Initial dose: 150 mg PO q8h; may be increased to 300 mg PO q8h

Exercise 2. It is known, class II antiarrhythmic drugs (β-adrenergic blockers) ↓ SA nodal automaticity, ↑ AV nodal refractoriness, and ↓ AV nodal conduction velocity. Using the table 2, administrate class II antiarrhythmic drugs for the patient with:

1) ventricular rate in superventricular arrhythmia;
2) migraine headache;
3) angina pectoris;
4) sinus tachycardia
5) hypertension;
6) essential tremor;
7) myocardial infarction;
8) migraine headache.

Table 2. Uses, adverse reactions and dosage ranges of class II antiarrhythmics.

Drugs	Uses	Adverse reactions	Dosage ranges
Esmolol HCl (Brevibloc)	Rapid, short-term treatment of ventricular rate in superventricular arrhythmia, sinus tachycardia	Dizziness, headache, hypotension, nausea, cold extremities, bradycardia	Loading dose: 500 _g/kg/min IV for 1 minute, followed by infusion of 50 mcg/kg/min IV for 4 min; maintenance dose, 25 mcg/kg/min IV
Propranolol HCl	Cardiac arrhythmias, angina pectoris, hypertension, essential tremor, myocardial infarction, migraine headache	Fatigue, weakness, depression, bradycardia, dizziness, vertigo, rash, decreased libido, hypotension, hyperglycemia	Cardiac arrhythmias: 10—30 mg PO 3—4 times daily; life-threatening arrhythmias: 1—3 mg IV, may repeat once in 2 min; angina pectoris: 80— 320 mg/d PO in 2—4 divided doses; hypertension: initially, 40 mg PO BID or 80 mg sustained released once daily; maintenance dose: up to 640 mg/d PO in divided doses

Exercise 3. It is known, class III antiarrhythmic drugs prolong action potential duration in tissue with fast-response action potentials, e.g., bretylium, amiodarone, sotalol, ibutilide, dofetilide. Using the table 3, administrate class III antiarrhythmic drugs for the patient with life-threatening ventricular arrhythmias.

Exercise 4. It is known, class IV antiarrhythmic drugs (Calcium channel blocking agents) reduce conduction velocity and increase refractoriness in tissue with slow-response action potentials, e.g., verapamil, diltiazem. Using the table 4, administrate class IV antiarrhythmic drugs for the patient with life-threatening ventricular arrhythmias.

Table 3. Uses, adverse reactions and dosage ranges of class III antiarrhythmics.

Drugs	Uses	Adverse reactions	Dosage ranges
Amiodarone HCl (Cordarone)	Life-threatening ventricular arrhythmias	Malaise, fatigue, tremor, proarrhythmias, nausea, vomiting, constipation, ataxia, anorexia, bradycardia, photosensitivity	Loading dose: 800–1600 mg/d PO in divided doses; maintenance dose: 400 mg/d PO; up to 1000 mg/d over 24 h IV
Sotalol	Treatment of life-threatening ventricular arrhythmias, reduction and delay of atrial fibrillation and flutter for ventricular arrhythmias (Betapace AF)	Drowsiness, difficulty sleeping, unusual tiredness or weakness, depression, decreased sexual libido, bradycardia, CHF, cold hands and feet, nausea, vomiting, nasal congestion, anxiety, life-threatening arrhythmias (proarrhythmias)	Initially: 80 mg BID PO; may increase up to 240–320 mg/d (Betapace); up to 120 mg BID (Betapace AF)

Table 4. Uses, adverse reactions and dosage ranges of class IV antiarrhythmics.

Drugs	Uses	Adverse reactions	Dosage ranges
Verapamil (Isoptin)	Superventricular tachyarrhythmias, temporary control of rapid ventricular rate in atrial flutter/fibrillation, angina, unstable angina, hypertension	Constipation, dizziness, light-headedness, headache, asthenia, nausea, peripheral edema, hypotension, proarrhythmias, CHF	Adults: Oral—initial dose 80–120 mg TID; maintenance 320–480 mg/d Hypertension: 240 mg PO daily; sustained release in AM 80 mg TID; ER capsules, 100–300 mg HS PO Parenteral: IV use only; initial dose 5–10 mg over 2 min; may repeat 10 mg 30 min later.

Exercise 5. Using the table 5, administrate antiarrhythmics for the patient with:

1) atrial flutter;
2) atrial fibrillation;
3) atrial premature beats;
4) atrial tachycardia with block;
5) multiple atrial tachycardia;
6) paroxysmal SVT (reentrant);
7) preexcitation syndrome (WPW);
8) sinus tachycardia;
9) supraventricular tachycardias with aberrant ventricular conduction;
10) Torsades de pointes;
11) ventricular fibrillation;
12) ventricular premature beats;
13) ventricular tachycardia.

Table 5. Clinical features and treatment of common arrhythmias.

Rhythm	Precipitating conditions	Initial treatment
Atrial premature beats	Can be normal; or due to anxiety, CHF, hypoxia, caffeine, abnormal electrolytes	Remove precipitating cause; if symptomatic: beta blockers
Sinus tachycardia	Fever, dehydration, pain, CHF, hyperthyroidism, COPD	Remove precipitating cause; if symptomatic: beta blockers
Paroxysmal SVT (reentrant)	Healthy individuals; preexcitation syndromes	Vagal maneuvers; if unsuccessful: adenosine, verapamil, beta blockers, cardioversion
Atrial tachycardia with block	Digitalis toxicity	Hold digitoxin, correct [K+]
Atrial flutter, atrial fibrillation	Mitral valve disease, hypertension, pulmonary embolism, pericaditis, postcardiac surgery, hyperthyroidism, COPD	1. Slow the ventricular rate: beta blockers, verapamil, diltiazem, or digoxin. 2. Convert to NSR (after anticoagulation if chronic) with IV ibutilide or orally with group IC, III, IA agent; may require cardioversion; radio frequency ablation highly effective to prevent recurrences
Multiple atrial tachycardia	Severe respiratory insufficiency	Treat underlying lung disease; verapamil may be used to slow ventricular rate
Ventricular premature beats	Coronary artery disease, myocardial infurction. CHF, hypoxia, hypokalemia, digitalis toxicity, prolonged QT interval (congenital or drugs: quinidine and other antiarrhythmics, tricyclics, phenothiazines)	May not require therapy; use beta blockers or same drugs as ventricular tachycardia
Ventricular tachycardia	Same as ventricular premature beats	Acute management: procainamide, amiodarone, lidocaine; chronic management: group I, III, drugs
Ventricular fibrillation	Same as ventricular premature beats	Immediate defibrillation
Torsades de pointes	Prolonged QT (congenital or drugs: quinidine and other antiarrhythmics, tricyclics, phenothiazines)	IV magnesium (1-2 g bolus); lidocaine; isoproterenol (unless CAD present)
Supraventricular tachycardias with aberrant ventricular conduction	Etiologies of the respective supraventricular rhythms listed above; atrial fibrillation with rapid, wide QRS may be due to preexcitation (WPW)	Same as treatment of respective supraventricular rhythm; if ventricular rate rapid (>200), treat as WPW
Preexcitation syndrome (WPW)	Accessory pathway between atria and ventricles	Narrow QRS complex tachycardia: IV adenosine or beta blockers. Wide QRS complex tachycardia: IV procainamide, not digoxine, beta blocker, or verapamil.

Exercise 6. Explain interactions of antiarrhythmic drugs:

1) procainamide with digitalis, quinidine;
2) quinidine with the barbiturates or cimetidine;
3) quinidine with verapamil, disopyramide;
4) Propranolol with procainamide;
5) procainamide with anticholinergic effects;
6) procainamide with lidocaine;
7) beta blockers with lidocaine;
8) propranolol with insulin or oral hypoglycemic drugs.

CLINICAL EXERCISES FOR OUT-CLASS WORK

1. Mr. Parker is at an outpatient clinic for a follow-up visit. He has been taking quinidine for several months for a cardiac arrhythmia. Analyze what assessments you would make on Mr. Parker to determine the effectiveness of quinidine therapy. Discuss what questions you would ask to determine the presence of any adverse reactions.
2. Ms. Grady, age 48 years, will be discharged in 2 days. The primary health care provider has prescribed propranolol to treat her arrhythmia. Develop a patient educational handout for Ms. Grady to take home with her explaining the most important points for her to know when taking propranolol.
3. Mr. Summers has a ventricular arrhythmia and is placed on a cardiac monitor. The primary health care provider prescribes IV lidocaine. Discuss preadministration assessments you would perform on Mr. Summers. Analyze which adverse reactions would be most important to monitor for during the ongoing assessment. Determine what reactions should be reported immediately.
4. Ms. Walters is receiving bretylium for a ventricular arrhythmia. Discuss the ongoing assessments you would make when caring for Ms. Walters.

REVIEW QUESTIONS

1. Which of the following adverse reactions of lidocaine should be reported immediately to the doctor?
   A) Sudden change in mental status
   B) Dry mouth
   C) Occipital headache
   D) Light-headedness
2. Which of the following drugs, when given with quinidine, would increase the risk for hypotension?
   A) Verapamil
   B) Propranolol

C) Encainide
D) Disopyramide

3. Common adverse reactions of the antiarrhythmic drugs include:
   A) light-headedness, hypotension, and weakness
   B) headache, hypertension, and lethargy
   C) weakness, lethargy, and hyperglycemia
   D) anorexia, gastrointestinal upset, and hypertension

4. When administering lidocaine, the nurse reports a blood level greater than:
   A) 2 mcg/mL
   B) 3 mcg/mL
   C) 4 mcg/mL
   D) 6 mcg/mL

5. Which of the following statements would the doctor include in a teaching plan for the patient taking an antiarrhythmic drug on an outpatient basis?
   A) Take the drug without regard to meals.
   B) Limit fluid intake during the evening hours.
   C) Avoid drinking alcoholic beverages unless their consumption has been approved by the primary care provider.
   D) Eat a diet high in potassium.

6. What are the disadvantages of intramuscular administration?
   A) Trained personnel required for injections
   B) There is loss of drug by first pass effect
   C) Solvent may be absorbed faster than the drug causing precipitation of the drug at the site of injection.
   D) Necessity for cooperation on the part of the patient
   E) a, c
   F) a, b, c
   G) a, b, c, d

7. What drugs absorbed from the rectum are subject to the first-pass metabolism?
   A) Weak acidic drugs
   B) Weak basic drugs
   C) Absorbed from the upper part of the rectum
   D) Absorbed from the middle part of the rectum
   E) Absorbed from the lower part of the rectum
   F) Lipid soluble drugs
   G) Water soluble drugs

8. What are the common factors that modify transdermal absorption?
   A) Integrity of skin and whether it is normal or diseased
   B) Skin biotransformation
   C) Partition coefficient of drug
   D) Particle and molecular size
   E) Viscosity of dosage forms

F) Temperature, humidity, air current
G) a, b, c, d, e, f

9. What substances may be administrated by intradermal route?
   A) Lipid soluble drugs
   B) Allergens for allergy testing
   C) Vaccines
   D) Water soluble drugs
   E) Weak acidic drugs
   F) a, b, c, d, e
   G) b, c

10. What is the bioequivalence of drugs?
   A) Rate of elimination
   B) Absence of a significant difference in the rate and extent to absorption when administered at the same molar dose under similar conditions
   C) Rate of metabolism
   D) Relation of the pKa of a drug and pH of the stomach
   E) Volume of blood which is completely cleared of a drug in a given period
   F) a, b, d
   G) a, b, c, d, e

11. What are the pharmacodynamic processes?
   A) Effect of the drug on the body
   B) Dynamic processes in the liver
   C) Effect of the drugs on the liver
   D) Dynamic changes of drugs
   E) Effect of the body on the drug
   F) Effect of the drug on the nutrition
   G) Effect of food on the drug

Lesson 5

CLINICAL PHARMACOLOGY OF INOTROPIC DRUGS

QUESTIONS FOR IN-CLASS WORK

1. Cardiotonics: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
2. Miscellaneous inotropic drugs: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
3. Adrenergic drugs: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.

THEORETICAL ISSUES

The cardiotonics are drugs used to increase the efficiency and improve the contraction of the heart muscle, which leads to improved blood flow to all tissues of the body. The drugs have long been used to treat congestive heart failure.

Digoxin is the most commonly used cardiotonic drug. Other terms used to identify the cardiotonics are cardiac glycosides or digitalis glycosides.

The digitalis or cardiac glycosides are obtained from the leaves of the purple foxglove plant or the Digitalis purpurea and the Digitalis lanata.

Miscellaneous drugs with positive inotropic action such as inamrinone and milrinone are nonglycosides used in the short-term management of HF.

Although in the past the cardiotonics were the mainstay in the treatment of HF, currently they are used as the fourth line of treatment for patients who continue to experience symptoms after using the ACE inhibitors, diuretics, and beta blockers.

1. ACTIONS

Digitalis acts in two ways: increases cardiac output through positive inotropic activity and decreases the conduction velocity through the atrioventricular (AV) and sinoatrial (SA) nodes in the heart

1.1. Increased Cardiac Output

Cardiotonic drugs increase the force of the contraction of the myocardium of the heart. This is called a positive inotropic action. When the force of contraction of the myocardium is increased, the amount of blood leaving the left ventricle at the time of each contraction is increased. When the amount of blood leaving the left ventricle is increased, cardiac output is increased.

When cardiac output is increased, the blood supply to the kidneys and other vital organs is increased. Water, electrolytes, and waste products are removed in adequate amounts, and the symptoms of inadequate heart action or HF are relieved. In most instances, the heart rate also decreases.

This occurs because vital organs are now receiving an adequate blood supply because of the increased force of myocardial contraction.

1.2. Depression of the Sinoatrial and Atrioventricular Nodes

The cardiotonics affect the transmission of electrical impulses along the pathway of the conduction system of the heart.

Cardiotonic drugs depress the SA node and slow conduction of the electrical impulse to and through the AV node. Slowing this part of the transmission of nerve impulses decreases the number of impulses and the number of ventricular contractions per minute, thereby decreasing the heart rate and allowing the heart to function more normally. The therapeutic effects of digoxin on atrial arrhythmias are thought to be related to the depressive action on the SA and AV nodes and baroreceptor sensitization.

2. ADVERSE REACTIONS

Adverse reactions are dose dependent. Because some patients are more sensitive to side effects with digoxin, the dosage is selected carefully and adjusted as the clinical condition indicates. Adverse reactions were more common and severe in past years before careful attention to weight, renal function, and the concurrent administration of certain medications was given. The incidence and severity of digoxin toxicity has decreased significantly in recent years.

There is a narrow margin of safety between the full therapeutic effects and the toxic effects of cardiotonic drugs. Even normal doses of a cardiotonic drug can cause toxic drug effects. Because substantial individual variations may occur, it is important to individualize the dosage. The term digitalis toxicity (digitalis intoxication) is used when toxic drug effects occur when digoxin is administered. The signs of digitalis toxicity include:

- Gastrointestinal signs – anorexia (usually the first sign), nausea, vomiting, diarrhea;
- muscular signs – weakness;
- central nervous system signs – headache, apathy, drowsiness, visual disturbances (blurred vision, disturbance in yellow/green vision, halo effect around dark objects), mental depression, confusion, disorientation, delirium;
- cardiac signs – changes in pulse rate or rhythm; electrocardiographic changes, such as bradycardia, tachycardia, premature ventricular contractions, bigeminal (two beats followed by a pause), or trigeminal (three beats followed by a pause) pulse. Other arrhythmias (abnormal heart rhythms) also may be seen.

Digoxin has a rapid onset and a short duration of action. Once the drug is withheld, the toxic effects of digoxin will disappear rapidly.

3. CONTRAINDICATIONS

The cardiotonics are contraindicated in patients with known hypersensitivity, ventricular failure, ventricular tachycardia, or AV block and in the presence of digitalis toxicity.

4. PRECAUTIONS

The cardiotonics are given cautiously in patients with electrolyte imbalance (especially hypokalemia, hypocalcemia, and hypomagnesemia), severe carditis, heart block, myocardial infarction, severe pulmonary disease, acute glomerulonephritis, and impaired renal or hepatic function. Fetal toxicity and neonatal death have been reported from maternal digoxin overdosage.

These drugs are used only when the potential benefit outweighs the potential harm to the fetus.

EXERCISES FOR OUT-CLASS WORK

Exercise 1. Using the table 1, administrate cardiotonics for treatment of:

6) heart failure;
7) atrial fibrillation;
8) atrial flutter;
9) paroxysmal atrial tachycardia

Table 1. Uses, adverse reactions and dosage ranges of cardiotonics.

Drugs	Uses	Adverse reactions	Dosage ranges
Digoxin	Heart failure, atrial fibrillation, atrial flutter, paroxysmal atrial tachycardia	Headache, weakness, drowsiness, visual disturbances, nausea, vomiting, anorexia, arrhythmias	Loading dose: 0.75–1.25 mg or 0.125–0.25 mg IV; maintenance: 0.125–0.25 mg/d PO

Exercise 2. Using the table 2, explain interactions of cardiotonics.

Table 2. Interactions and dosage ranges of cardiotonics.

Interacted drugs		Pharmacological effect
Digoxin	Amiodarone, benzodiazepines, cyclosporine, diphenoxylate, indomethacin, itraconazole, macrolides (erythromycin, clarithromycin), propafenone, quinidine, quinine, spironolactone, tetracyclines, and verapamil	The level of plasma digitalis may be increased leading to toxicity
	Oral aminoglycosides, antacids, antineoplastics (bleomycin, carmustine, cyclophosphamide, methotrexate, and vincristine), activated charcoal, cholestyramine, colestipol, kaolin/pectin, neomycin, penicillamine, rifampin, St. John's wort, and sulfasalazine	The level of plasma digitalis may be decreased
	Thyroid hormones	The effectiveness of digitalis may be decreased
	Thiazide and loop diuretics	The electrolyte disturbances may be induced, predisposing the patient to digitalis-induced arrhythmias

Exercise 3. Using the table 3, administrate miscellaneous inotropic drugs for treatment of:

1) heart failure;
2) short-term management of HF in patients with no response to digitalis;
3) short-term management of HF in patients with no response to diuretics;
4) hort-term management of HF in patients with no response to vasodilators.

Table 3. Uses, adverse reactions and dosage ranges of miscellaneous inotropic drugs.

Drugs	Uses	Adverse reactions	Dosage ranges
Inamrinone lactate	Short-term management of HF in patients with no response to digitalis, diuretics, or vasodilators	Arrhythmia, hypotension, nausea, vomiting, abdominal pain, anorexia, hepatotoxicity	IV: 0.75 mg/kg bolus, may repeat in 30 min; maintenance: IV 5—10 mcg/kg/min, not to exceed 10 mg/kg/d
Milrinone lactate	HF	Ventricular arrhythmias, hypotension, angina/chest pain, headaches, hypokalemia	IV: up tp 1.13 mg/kg/d

Exercise 4. Using the table 4, administrate adrenergic drugs for treatment of:

1) heart failure;
2) cardiac decompensation due to depressed contractility caused by organic heart disease;
3) cardiac decompensation due to depressed contractility caused by cardiac surgical procedures trauma;
4) open-heart surgery;
5) renal failure.
6) ventricular standstill;
7) treatment and prophylaxis of cardiac arrest
8) heart block;
9) rhinitis, and acute sinusitis;
10) relief of bronchial asthmatic paroxysms;
11) simple open-angle glaucoma;
12) shock;
13) hypotension;
14) cardiac arrest.

Table 4. Uses, adverse reactions and dosage ranges of adrenergic drugs.

Drugs	Uses	Adverse reactions	Dosage ranges
Dobutamine	Cardiac decompensation due to depressed contractility caused by organic heart disease or cardiac surgical procedures	Headache, nausea, increased heart rate, increase in systolic blood pressure, palpitations, anginal and nonspecific chest pain	2.5—15 mcg/kg/min IV (up to 40 mcg/kg/min); titrate to patient's hemodynamic and renal status
Dopamine	Shock due to MI, trauma, open-heart surgery, renal failure, and chronic cardiac decompensation in CHF	Nausea, vomiting, ectopic beats, tachycardia, anginal pain, palpitations, hypotension, dyspnea	2—50 mcg/kg/min IV (infusion rate determined by patient's response)
Epinephrine (Adrenalin chloride)	Ventricular standstill; treatment and prophylaxis of cardiac arrest, heart block; muscosal congestion of hay fever, rhinitis, and acute sinusitis; relief of bronchial asthmatic paroxysms; simple open-angle glaucoma	Anxiety, insomnia, tenseness, restlessness, headache, light-headedness, dizziness, nausea, dysuria, pallor	Cardiac arrest: 0.5—1.0 mg IV; respiratory distress (eg, asthma, anaphylaxis): 0.3—0.5 mL of 1:1000 solution, SC or IM q20 min for 4h or 0.1—0.3 mL/SC of 1:200 suspension; 1 inhalation q3h; 1—3 deep inhalation by nebulizer 4—6 times/day; ophthalmic, 1—2 gtts times daily
Norepinephrine	Shock, hypotension, cardiac arrest	Restlessness, headache, dizziness, bradycardia, hypertension	1 mg/mL in 1000 mL 5% dextrose solution, 2—3 mL/min IV, rate adjusted to maintain desired blood pressure; average dose, 2—4 mcg/min

Exercise 5. Using the table 5, explain interactions of adrenergic drugs.

Table 5. Interactions and dosage ranges of adrenergic drugs.

Interacted drugs		Pharmacological effect
Dobutamine	Beta-adrenergic blocking drugs	The risk of hypertension is increased
Dopamine	Monoamine oxidase inhibitors tricyclic antidepressants	The effects of dopamine are increased
	Phenytoin	The risk of seizures, hypotension, and bradycardia is increased
Epinephrine	Tricyclic antidepressants	The risk of sympathomimetic effects is increased
	Propranolol	Excessive hypertension
	Beta-adrenergic drugs	A decreased bronchodilating effect

CLINICAL EXERCISES FOR OUT-CLASS WORK

1. Mr. Taylor has been taking digoxin for 3 weeks and has come to the clinic for a follow-up visit. Analyze the situation to determine what questions you would ask Mr. Taylor during the interview to evaluate his knowledge of the drug regimen and to find out if he is experiencing any adverse reactions.
2. You are to participate in a team conference on the cardiac glycosides. Your topic to discuss is discharge teaching for the patient receiving a cardiac glycoside. Determine what points would be most important for you to include.
3. Mr. Cole is receiving dopamine for the treatment of severe hypotension. In planning the care for Mr. Cole, determine what would be the most important aspects of management. Explain your answers.
4. Plan a teaching program to explain the nervous system to a group of doctor at a staff education meeting. Discuss the preadministration assessment for a patient requiring an adrenergic drug for hypotension.
5. Describe what information is important to include in an education session for a patient taking an adrenergic drug for nasal congestion.

REVIEW QUESTIONS

1. Which of the following is commonly associated with left ventricular systolic dysfunction?
   A) Ejection fraction of 60% or more
   B) Ejection fraction below 40%
   C) Increased cardiac output
   D) Normal cardiac output
2. Which of the following serum digoxin levels would be most indicative that a patient taking digoxin may be experiencing toxicity?
   A) A. 0.5 ng/mL
   B) 0.8 ng/mL
   C) 1.0 ng/mL
   D) 2.0 ng/mL
3. In which of the following situations would the doctor withhold a dosage of digoxin and notify the primary care provider?
   A) A pulse rate greater than 100 bpm
   B) A pulse rate less than 100 bpm
   C) A pulse rate of 60 bpm
   D) A pulse rate of 72 bpm
4. Which drug would the doctor expect to be prescribed for a patient with digoxin toxicity?

A) Digoxin immune fab
B) Milrinone
C) Inamrinone lactate
D) Any inotropic drug

5. During rapid digitalization the doctor expects the first dose to be:
   A) the smallest dose in case the patient is allergic to digoxin
   B) given orally, with succeeding doses given intravenously
   C) approximately half of the total digitalization dose
   D) approximately three quarters of the total digitalization dose

6. The physician prescribes norepinephrine, a potent vasopressor, to be administered to a patient in shock. The rate of the administration of the IV fluid containing the norepinephrine is:
   A) maintained at a set rate of infusion
   B) adjusted accordingly to maintain the patient's blood pressure
   C) given at a rate not to exceed 5 mg/min
   D) discontinued when the blood pressure is 100 mm Hg systolic

7. At what intervals would the nurse monitor the blood pressure of a patient taking norepinephrine?
   A) Every 5 to 15 minutes
   B) Every 30 minute
   C) Every hour
   D) Every 4 hours

8. Which of the following are the common adverse reactions the doctor would expect with the administration of the adrenergic drugs?
   A) Bradycardia, lethargy, bronchial constriction
   B) Increase in appetite, nervousness, drowsiness
   C) Nausea, vomiting, hypotension
   D) Insomnia, nervousness, anorexia

9. When dobutamine is administered with the beta-adrenergic blocking drugs the doctor is aware of an increased risk for:
   A) seizures
   B) arrhythmias
   C) hypotension
   D) hypertension

10. Epinephrine is administered cautiously in patients with Parkinson's disease because the drug may:
   A) precipitate congestive heart failure
   B) temporarily increase rigidity and tremor
   C) decrease the response to antiparkinsonism drugs
   D) cause confusion

Lesson 6

CLINICAL PHARMACOLOGY OF DIURETICS

QUESTIONS FOR IN-CLASS WORK

1. General principles of the treatment of myocardial ischemia.
2. Carbonic Anhydrase Inhibitors: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
3. Loop Diuretics: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
4. Osmotic Diuretics: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
5. Potassium-Sparing Diuretics: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
6. Thiazides and Related Diuretics: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.

THEORETICAL ISSUES

A diuretic is a drug that increases the secretion of urine (ie, water, electrolytes, and waste products) by the kidneys. Many conditions or diseases, such as heart failure, endocrine disturbances, and kidney and liver diseases can cause retention of excess fluid.

The different types of diuretic drugs are:

- Carbonic anhydrase inhibitors
- Loop diuretics
- Osmotic diuretics
- Potassium-sparing diuretics
- Thiazides and related diuretics

1.ACTION

1.1. Carbonic Anhydrase Inhibitors

Carbonic anhydrase is an enzyme that produces free hydrogen ions, which are then exchanged for sodium ions in the kidney tubules. Carbonic anhydrase inhibitors inhibit the action of the enzyme carbonic anhydrase. This effect results in the excretion of sodium, potassium, bicarbonate, and water. Carbonic anhydrase inhibitors also decrease the production of aqueous humor in the eye, which in turn decreases intraocular pressure (IOP) (ie, the pressure within the eye).

1.2. Loop Diuretics

The loop diuretics, furosemide (Lasix) and ethacrynic acid, increase the excretion of sodium and chloride by inhibiting reabsorption of these ions in the distal and proximal tubules and in the loop of Henle.

This mechanism of action at these three sites appears to increase their effectiveness as diuretics. Torsemide also increases urinary excretion of sodium, chloride, and water but acts primarily in the ascending portion of the loop of Henle. Bumetanide primarily increases the excretion of chloride but also has some sodium-excreting ability. This drug acts primarily on the proximal tubule of the nephron.

1.3. Osmotic Diuretics

Osmotic diuretics increase the density of the filtrate in the glomerulus. This prevents selective reabsorption of water, which allows the water to be excreted. Sodium and chloride excretion is also increased.

1.4. Potassium-Sparing Diuretics

Potassium-sparing diuretics work in either of two ways. Triamterene and amiloride depress the reabsorption of sodium in the kidney tubules, therefore increasing sodium and water excretion. Both drugs additionally depress the excretion of potassium and therefore are called potassium-sparing (or potassiumsaving) diuretics. Spironolactone, also a potassium-sparing diuretic, antagonizes the action of aldosterone. Aldosterone, a hormone produced by the adrenal cortex, enhances the reabsorption of sodium in the distal convoluted tubules of the kidney. When this activity of aldosterone is blocked, sodium (but not potassium) and water are excreted.

1.5. Thiazides and Related Diuretics

Thiazides and related diuretics inhibit the reabsorption of sodium and chloride ions in the ascending portion of the loop of Henle and the early distal tubule of the nephron. This action results in the excretion of sodium, chloride, and water.

2. CONTRAINDICATIONS, PRECAUTIONS, AND INTERACTIONS

2.1. Carbonic Anhydrase Inhibitors

The carbonic anhydrase inhibitors are contraindicated in patients with known hypersensitivity to the drugs, electrolyte imbalances, severe kidney or liver dysfunction, or anuria, and for long-term use in chronic noncongestive angle-closure glaucoma (may mask worsening glaucoma).

The safety of these drugs for use during pregnancy and lactation has not been established, so they should be used only when the drug is clearly needed and when the potential benefits to the patient outweigh the potential hazards to the fetus.

There is an increased risk of cyclosporine toxicity when the drug is administered with acetazolamide.

Decreased serum and urine concentrations of primidone occur when the drug is administered with acetazolamide.

2.2. Loop Diuretics

Loop diuretics are contraindicated in patients with known hypersensitivity to the loop diuretics or to the sulfonamides, severe electrolyte imbalances, hepatic coma, or anuria, and in infants (ethacrynic acid).

Loop diuretics must be used cautiously during pregnancy and lactation. Furosemide is used in children but should be used cautiously. The loop diuretics are used cautiously in patients with liver disease, diabetes, lupus erythematosus (may exacerbate or activate the disease), or diarrhea. Patients with sensitivity to the sulfonamides may show allergic reactions to furosemide, torsemide, or bumetanide.

Additive hypotensive effects occur when the loop diuretics are given with alcohol, other antihypertensive drugs, or nitrates. Loop diuretics may increase the effectiveness of the anticoagulants or the thrombolytics.

There is an increased risk of glycoside toxicity and digitalis-induced arrhythmias if the patient experiences hypokalemia while taking the loop diuretics.

Ototoxicity is more likely to occur if loop diuretics are given with the aminoglycosides. Plasma levels of propranolol may increase when the drug is administered with furosemide. There is an increased risk of lithium toxicity when lithium is administered with a loop diuretic. Phenytoin may reduce the diuretic effects of furosemide. The effects of the loop diuretics may be decreased when they are administered with the NSAIDs.

2.4. Osmotic Diuretics

The osmotic diuretics are contraindicated in patients with known hypersensitivity to the drugs, electrolyte imbalances, severe dehydration, or anuria and those who experience progressive renal damage after instituting therapy (mannitol). Mannitol is contraindicated in patients with active intracranial bleeding (except during craniotomy).

Osmotic diuretics are used cautiously in patients with renal or kidney impairment or electrolyte imbalances.

Additive hypotensive effects occur when the osmotic diuretics are given with other antihypertensive drugs or nitrates.

2.5. Potassium-Sparing Diuretics

The potassium-sparing diuretics are contraindicated in patients with known hypersensitivity to the drugs, serious electrolyte imbalances, significant renal impairment, or anuria, and those receiving another potassium-sparing diuretic. The potassium-sparing diuretics are contraindicated in patients with hyperkalemia and are not recommended for children. The potassium-sparing diuretics are used cautiously in patients with renal or kidney impairment.

Additive hypotensive effects occur when the potassium-sparing diuretics are given with alcohol, other antihypertensive drugs, or nitrates. When the potassium-sparing diuretics are administered to patients taking angiotensin-converting enzyme (ACE) inhibitors, there is an increased risk for hyperkalemia.

When the potassium-sparing diuretics are administered with potassium preparations, severe hyperkalemia may occur, possibly with cardiac arrhythmias or cardiac arrest. When spironolactone is administered with anticoagulant drugs or the NSAIDs, there is a decreased effectiveness of the anticoagulant or NSAID. When

spironolactone or triamterene is administered with the ACE inhibitors, significant hyperkalemia may occur.

2.6. Thiazides and Related Diuretics

The thiazide diuretics are contraindicated in patients with known hypersensitivity to the thiazides or related diuretics, electrolyte imbalances, renal decompensation, hepatic coma, or anuria. A cross-sensitivity reaction may occur with the thiazides and sulfonamides. Some of the thiazide diuretics contain tartrazine, which may cause allergic-type reactions or bronchial asthma in individuals sensitive to tartrazine.

The thiazide diuretics are used cautiously in patients with liver or kidney disease, lupus erythematosus (may exacerbate or activate the disease), or diabetes. Additive hypotensive effects occur when the thiazides are given with alcohol, other antihypertensive drugs, or nitrates.

Concurrent use of the thiazides with allopurinol may increase the incidence of hypersensitivity to allopurinol. The effects of anesthetics may be increased by thiazide administration. The effects of anticoagulants may be diminished when they are administered with a thiazide diuretic. Because thiazide diuretics may raise blood uric acid levels, dosage adjustments of antigout drugs may be necessary.

Thiazide diuretics may prolong antineoplasticinduced leukopenia. Hyperglycemia may occur when the thiazides area administered with the antidiabetic drugs. Synergistic effects may occur when the thiazide diuretics are administered concurrently with the loop diuretics, causing profound diuresis and serious electrolyte abnormalities. There is an increased risk of glycoside toxicity if the patient experiences hypokalemia while taking the thiazide diuretics.

EXERCISES FOR OUT-CLASS WORK

Exercise 1. Using the table 1, administrate Carbonic Anhydrase Inhibitors for:

- open-angle glaucoma;
- secondary glaucoma;
- preoperatively to lower intraocular pressure;
- edema due to CHF;
- drug-induced edema;
- centrencephalic epilepsy.

Table 1. Uses, adverse reactions of Carbonic Anhydrase Inhibitors.

Drugs	Uses	Adverse reactions	Dosage ranges
Acetazolamide	Open-angle glaucoma, secondary glaucoma, preoperatively to lower intraocular pressure (IOP), edema due to CHF, drug-induced edema, centrencephalic epilepsy	Fever, rash, paresthesias, photosensitivity, crystalluria, acidosis, urticaria, pruritus, hematuria, weakness, malaise, anorexia, hematologic changes, convulsions	Glaucoma: up to 1 g/d PO in divided doses; acute glaucoma: 500 mg initially then 125–250 mg PO q4h; epilepsy: 8–30 mg kg/d in divided doses; CHF and edema; 250–375 mg/d PO

Exercise 2. Using the table 2, explain interactions of Carbonic Anhydrase Inhibitors.

Table 2. Interactions and dosage ranges of Carbonic Anhydrase Inhibitors.

Interacted drugs		Pharmacological effect
Acetazolamide	Cyclosporine	Increased risk of cyclosporine toxicity
	Primidone	Decreased serum and urine concentrations of primidone

Exercise 3. Using the table 3, administrate Loop Diuretics for:

1) Edema due to CHF;
2) cirrhosis of the liver;
3) renal disease;
4) acute pulmonary edema (IV);
5) hypertension.

Table 3. Uses, adverse reactions and dosage ranges of Loop Diuretics.

Drugs	Uses	Adverse reactions	Dosage ranges
Furosemide Lasix	Edema due to CHF, cirrhosis of the liver, renal disease, acute pulmonary edema (IV), hypertension	Electrolyte imbalances, anorexia, nausea, vomiting, dizziness, rash, photosensitivity reactions, postural or orthostatic hypotension, glycosuria	0.5–10 mg/d PO, IV, IM
Torsemide	Same as furosemide	Headache, dizziness, diarrhea, electrolyte imbalances, ECG abnormalities, nausea, anorexia, drowsiness	CHF: 10–20 mg/d PO, IV; renal failure: 20 mg/d PO, IV; cirrhosis, hypertension: 5–10 mg/d PO, IV

Exercise 4. Using the table 4, explain interactions of Loop Diuretics.

Table 4. Interactions and dosage ranges of Loop Diuretics.

Interacted drugs		Pharmacological effect
Loop Diuretics	Alcohol, nitrates, or other antihypertensive drugs	Additive hypotensive effects
	Anticoagulants or the thrombolytics	Increasing the effectiveness of the anticoagulants or the thrombolytics
	Digitalis-induced arrhythmias	Increased risk of glycoside toxicity
	Aminoglycosides	Increased risk of Ototoxicity
	NSAIDs	The effects of the loop diuretics may be decreased
Furosemide	Propranolol	Plasma levels of propranolol may increase
	Lithium	Increased risk of lithium toxicity
	Hydantoins (phenytoin	reducing the diuretic effects of furosemide

Exercise 5. Using the table 5, administrate osmotic diuretics for:

1) Reduction of IOP
2) reduction of intracranial pressure.

Table 5. Uses, adverse reactions and dosage ranges of osmotic diuretics.

Drugs	Uses	Adverse reactions	Dosage ranges
Mannitol	To promote diuresis in acute renal failure, reduction of IOP, treatment of cerebral edema	Edema, fluid and electrolyte imbalance, headache, blurred vision, nausea, vomiting, diarrhea, urinary retention	50–200 g/24 h IV; IOP: 1.5–2 g/kg IV
Urea	Reduction of IOP, reduction of intracranial pressure	Headache, nausea, vomiting, fluid and electrolyte imbalance, syncope	Up to 120 g/d IV

Exercise 6. Using the table 6, explain interactions of osmotic diuretics.

Table 6. Interactions and dosage ranges of osmotic diuretics.

Interacted drugs		Pharmacological effect
Osmotic diuretics	Antihypertensive drugs or nitrates	Additive hypotensive effects

Exercise 7. Using the table 7, administrate potassium-sparing diuretics for:

1) CHF;
2) hypertension;
3) hypokalemia from other diuretics;
4) prevention of hypokalemia in at-risk patients;
5) cirrhosis;
6) renal disease;
7) hyperaldosteronism.

Table 7. Uses, adverse reactions and dosage ranges of potassium-sparing diuretics.

Drugs	Uses	Adverse reactions	Dosage ranges
Amiloride hydrochloride	CHF, hypertension, hypokalemia from other diuretics, prevention of hypokalemia in at-risk patients	Headache, nausea, anorexia, diarrhea, vomiting, weakness, hyperkalemia, dizziness, rash, hypotension	5–20 mg/d PO
Spironolactone	Hypertension, edema due to CHF, cirrhosis, renal disease; hypokalemia, prophylaxis of hypokalemia in those taking digitalis, hyperaldosteronism	Cramping, diarrhea, drowsiness, lethargy, rash, drug fever, hyperkalemia, gastritis, headache, inability to achieve an erection, gynecomastia	Up to 400 mg/d PO in single dose or divided doses
Triamterene	Prevention of hypokalemia, edema due to CHF, cirrhosis, renal disease	Diarrhea, nausea, vomiting, hyperkalemia, photosensitivity reactions, azotemia, thrombocytopenia	Up to 300 mg/d PO in divided doses

Exercise 8. Using the table 8, explain interactions of potassium-sparing diuretics.

Table 8. Interactions and dosage ranges of potassium-sparing diuretics.

Interacted drugs		Pharmacological effect
Potassium-sparing diuretics	Alcohol, antihypertensive drugs, or nitrates.	Additive hypotensive effects
	Angiotensin-converting enzyme (ACE) inhibitors	Increased risk for hyperkalemia
	Potassium preparations	Severe hyperkalemia, possibly with cardiac arrhythmias or cardiac arrest
Spironolactone	Anticoagulant drugs or the NSAIDs	Decreased effectiveness of the anticoagulant or NSAID

Exercise 9. Using the table 9, administrate thiazides or related diuretics for:

1) hypertension;
2) edema due to CHF;
3) cirrhosis.

Table 9. Uses, adverse reactions and dosage ranges of thiazides and related diuretics.

Drugs	Uses	Adverse reactions	Dosage ranges
Hydrochlorothiazide (Hypothiazid)	Hypertension, edema due to CHF, cirrhosis, corticosteroid and estrogen therapy	Hypotension, dizziness, vertigo, light-headedness, anorexia, gastric distress, nausea, hematologic changes, photosensitivity reactions, weakness, hyperglycemia, fluid and electrolyte imbalances, diarrhea, constipation, rash	Hypertension: 25–50 mg/d PO; edema: 25–200 mg/d PO
Indapamide (Arifon retard)	Hypertension, edema due to CHF	Same as Hydrochlorothiazide	Hypertension: 2.5–5 mg/d PO; edema: 2.5–5 mg/d PO

Exercise 10. Using the table 10, explain interactions of thiazides and related diuretics.

Table 10. Interactions and dosage ranges of thiazides and related diuretics.

Interacted drugs		Pharmacological effect
Thiazides	Alcohol, nitrates, or other antihypertensive drugs	Additive hypotensive effects
	Allopurinol	Increase the incidence of hypersensitivity to allopurinol
	Anesthetics	The effects of anesthetics may be increased
	Anticoagulants	The effects of anticoagulants may be diminished
	Antidiabetic drugs	Hyperglycemia
	Loop diuretics	Synergistic effects, causing profound diuresis and serious electrolyte abnormalities

CLINICAL EXERCISES FOR OUT-CLASS WORK

1. Mr. Walsh, age 46 years, sees his doctor and is prescribed a thiazide diuretic for hypertension. He tells you that it will be inconvenient for him to take his drug in the morning and he would prefer to take it at night. Other than asking him why taking the drug in the evening is more convenient, discuss what other questions you would ask Mr. Walsh. Analyze the situation to determine what explanation regarding present and future actions of this diuretic you would tell this patient.
2. Mr. Rodriguez, age 68 years, is taking amiloride for hypertension. He and his wife stopped by the clinic for a routine blood pressure check. Mrs. Rodriguez states that her husband has been confused and very irritable for the last 2 days. He complains of nausea and has had several "loose" stools. Discuss what actions you would take, giving a rationale for each action.
3. Ms. Palmer, age 88 years, is a resident in a nursing home. Her doctor prescribes a thiazide diuretic for CHF. The nurse in charge advises you to evaluate Ms. Palmer for signs and symptoms of dehydration and hyponatremia. Discuss the assessment you would make. Identify which of these signs and symptoms might be difficult to evaluate considering the patient's age.

REVIEW QUESTIONS

1. When evaluating the effectiveness of acetazolamide (Diamox) given for acute glaucoma, the nurse questions the patient about:
   A) the amount of urine each time the patient voids;
   B) the relief of eye pain;
   C) the amount of fluid being taken
   D) occipital headaches
2. When a patient taking mannitol for increased intracranial pressure is being assessed, which of the following findings would be most important for the doctor to report?
   A) A serum potassium of 3.5 mEq/mL
   B) Urine output of 20 mL for the last 2 hours
   C) A blood pressure of 140/80 mm Hg
   D) A heart rate of 72 bpm
3. When administering spironolactone (Aldactone), the doctor monitors the patient closely for which of the following electrolyte imbalances?
   A) Hypernatremia
   B) Hyponatremia
   C) Hyperkalemia
   D) Hypokalemia

4. When a diuretic is being administered for heart failure, which of the following would be most indicative of an effective response of diuretic therapy?
    A) Output of 30 mL/h
    B) Daily weight loss of 2 lb
    C) An increase in blood pressure
    D) Increasing edema of the lower extremities

5. Which electrolyte imbalance would the patient receiving a loop or thiazide diuretic most likely develop?
    A) Hypernatremia
    B) Hyponatremia
    C) Hyperkalemia
    D) Hypokalemia

6. Which of the following foods would the doctor most likely recommend the patient include in the daily diet to prevent hypokalemia?
    A) Green beans
    B) Apples
    C) Bananas
    D) Corn

7. What are the common factors that modify absorption?
    A) The drug solubility
    B) Binding of drugs to proteins
    C) Local conditions at the site of absorption
    D) Concentration of a drug
    E) Area of the absorbing surface
    F) a, c, d, e
    G) a, b, c, d, e
    H) Effect of food on the drug

8. What are the advantages of oral administration?
    A) Incapability to absorb some drugs because of their physical characteristics
    B) Safest, most convenient, most economical route of administration
    C) Destruction of some drugs by digestive enzymes or low gastric pH
    D) Irregularities in the absorption or propulsion in the presence of food or other drugs
    E) Necessity for cooperation on the part of the patient
    F) Drugs in the gastrointestinal tract may be metabolized by the enzymes of the mucosa, the intestinal flora, or the liver before they gain access to the general circulation
    G) a, b, c, d, e, f

9. What are the advantages of gastrointestinal absorption?

A) Various regional pH of gastrointestinal tract and pKa of the drug
B) Gastric emptying process and intestinal motility
C) First-pass extraction
D) Formulation of different dosage forms of the drug
E) Food
F) Disease states
G) a, b, c, d, e, f

10. What are the advantages of buccal/sublingual administration?
A) There is no loss of drug by first pass effect
B) Relation of the pKa of a drug and pH of the stomach.
C) Rate of absorption is usually quite rapid
D) First-pass extraction
E) Improved by massage or heat
F) a, c
G) a, b, c, d, e

11. What are the advantages of subcutaneous administration?
A) Can be given by patient
B) Absorption slow but usually complete
C) Improved by massage or heat
D) Vasoconstrictor may be added to reduce the absorption of a local anesthetic agent
E) a, b
F) a, b, c
G) a, b, c, d

Lesson 7

CLINICAL PHARMACOLOGY OF BRONCHODILATORS

QUESTIONS FOR IN-CLASS WORK

1. Sympathomimetics: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
2. Anticholinergic: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
3. Xanthine derivatives: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
4. Drugs used in asthma and other allergic diseases: corticosteroids, leukotriene receptor antagonists, mast cell stabilizers, mucolytic, antihistamines.

THEORETICAL ISSUES

Within the past few years a number of new drugs have been introduced to treat respiratory disorders, such as bronchial asthma and disorders that produce chronic airway obstruction.

A bronchodilator is a drug used to relieve bronchospasm associated with respiratory disorders, such as bronchial asthma, chronic bronchitis, and emphysema.

These conditions are progressive disorders characterized by a decrease in the inspiratory and expiratory capacity of the lung. Collectively, they are often referred to as COPD.

The patient with COPD experiences dyspnea (difficulty breathing) with physical exertion, has difficulty inhaling and exhaling, and may exhibit a chronic cough.

The two major types of bronchodilators are the sympathomimetics and the xanthine derivatives. The anticholinergic drug ipratropium bromide (Atrovent) is used for bronchospasm associated with COPD, chronic bronchitis, and emphysema.

1 .BRONCHODILATORS

1. Beta-2 receptor agonists.

Actions. Many of the sympathomimetics used as bronchodilators have the subclassification of beta-2 receptor agonists.

When bronchospasm occurs, there is a decrease in the inside diameter of the bronchi, which decreases the amount of air taken into the lungs with each breath. A decrease in the amount of air taken into the lungs results in respiratory distress. Use of a bronchodilating drug opens the bronchi and allows more air to enter the lungs, which in turn, completely or partially relieves respiratory distress.

Contraindications, precautions, and interactions. The sympathomimetic bronchodilators are contraindicated in patients with known hypersensitivity to the drug, cardiac arrhythmias associated with tachycardia, organic brain damage,

cerebral arteriosclerosis, and narrow angle glaucoma. Salmeterol is contraindicated during acute bronchospasm. The sympathomimetics are used cautiously in patients with hypertension, cardiac dysfunction, hyperthyroidism, glaucoma, diabetes, prostatic hypertrophy, or a history of seizures. The sympathomimetic drugs are used cautiously during pregnancy, and lactation.

When the sympathomimetics are used concurrently with other sympathomimetic drugs, additive adrenergic effects can occur. When used with the monoamine oxidase inhibitors, the patient is at increased risk for a hypertensive crisis.

When the sympathomimetics are administered with a beta-adrenergic blocker, the drugs may inhibit the cardiac, bronchodilating, and vasodilating effects of the sympathomimetic.

When a beta-blocker such as propranolol is administered with a sympathomimetic such as epinephrine, an initial hypertensive episode may occur followed by bradycardia. Concurrent use of the sympathomimetics with oxytocic drugs may result in severe hypotension.

When the sympathomimetics are administered with theophylline there is an increased risk for cardiotoxicity.

When epinephrine is administered with insulin or oral hypoglycemic drugs, the patient may require an increased dose of the hypoglycemic drug.

The xanthine derivatives are contraindicated in those with known hypersensitivity, peptic ulcers, seizure disorders (unless well controlled with appropriate anticonvulsant medication), serious uncontrolled arrhythmias, and hyperthyroidism.

The xanthine derivatives are used cautiously in patients older than 60 years, those with cardiac disease, hypoxemia, hypertension, congestive heart failure, or liver disease.

When xanthine bronchodilators are administered with sympathomimetic drugs, additive CNS and cardiovascular effects may occur. If a patient eats large amounts of charcoal-broiled foods while taking the xanthines, a decrease in the therapeutic effect of the xanthines may occur. Certain foods contain xanthine (eg, coffee, colas, or chocolate) and may increase the risk of cardiac and CNS adverse reactions.

Cigarettes, nicotine gum and patches, barbiturates, phenytoin, loop diuretics, isoniazid, and rifampin may decrease the effectiveness of the xanthines. There is an increased risk of xanthine toxicity when the drugs are administered with influenza vaccination, oral contraceptives, glucocorticoids, beta-adrenergic blockers, cimetidine, macrolides, thyroid hormones, or allopurinol.

2. Xanthine derivatives

Actions. The xanthine derivatives, although a different class of drugs, also have bronchodilating activity by means of their direct relaxation of the smooth muscles of the bronchi.

Contraindications, precautions, and interactions. The xanthine derivatives are contraindicated in those with known hypersensitivity, peptic ulcers, seizure

disorders (unless well controlled with appropriate anticonvulsant medication), serious uncontrolled arrhythmias, and hyperthyroidism.

The xanthine derivatives are used cautiously in patients older than 60 years, those with cardiac disease, hypoxemia, hypertension, congestive heart failure, or liver disease.

When xanthine bronchodilators are administered with sympathomimetic drugs, additive CNS and cardiovascular effects may occur. If a patient eats large amounts of charcoal-broiled foods while taking the xanthines, a decrease in the therapeutic effect of the xanthines may occur. Certain foods contain xanthine (eg, coffee, colas, or chocolate) and may increase the risk of cardiac and CNS adverse reactions.

Cigarettes, nicotine gum and patches, barbiturates, phenytoin, loop diuretics, isoniazid, and rifampin may decrease the effectiveness of the xanthines. There is an increased risk of xanthine toxicity when the drugs are administered with influenza vaccination, oral contraceptives, glucocorticoids, beta-adrenergic blockers, cimetidine, macrolides, thyroid hormones, or allopurinol.

2. ANTIASTHMA DRUGS

Along with the bronchodilators, several types of drugs are effective in the treatment of asthma. These include corticosteroids, leukotriene formation inhibitors, leukotriene receptor agonists, and mast cell stabilizers.

Antiasthma drugs are used in various combinations to treat and manage asthma. Using several drugs may be more beneficial than using a single drug. A multidrug regimen allows smaller dosages of each drug, decreasing the number and severity of adverse reactions. Various combinations of these drugs are used depending on the patient's response.

2.1. Corticosteroids

Actions. Corticosteroids, such as beclomethasone (Beclovent), flunisolide (AeroBid), and triamcinolone, are given by inhalation and act to decrease the inflammatory process in the airways of the patient with asthma. In addition, the corticosteroids increase the sensitivity of the beta2- receptors. With increased sensitivity of the beta2-receptors, the beta2-receptor agonist drugs are more effective.

Contraindications, precautions, and interactions. The corticosteroids are contraindicated in patients with hypersensitivity to the corticosteroids, acute bronchospasm, status asthmaticus, or other acute episodes of asthma. Vanceril is contraindicated for the relief of symptoms that can be controlled by a bronchodilator and other nonsteroidal medications and in the treatment of nonasthmatic bronchitis. The corticosteroids are used cautiously in patients with compromised immune systems, glaucoma, kidney or liver disease, convulsive disorders, or diabetes, those taking systemic corticosteroids, and during pregnancy and lactation. Ketoconazole may increase plasma levels of budesonide and fluticasone.

2.2.Leukotriene Receptor Antagonists and Leukotriene Formation Inhibitors

Leukotriene receptor antagonists include montelukast sodium (Singulair) and zafirlukast (Accolate). Zileuton (Zyflo) is classified as a leukotriene formation inhibitor.

Actions. Leukotrienes are bronchoconstrictive substances released by the body during the inflammatory process. When leukotriene production is inhibited, bronchodilation is facilitated. Zileuton acts by decreasing the formation of leukotrienes. Although the result is the same, montelukast and zafirlukast work in a manner slightly differently from that of zileuton. Montelukast and zafirlukast are considered leukotriene receptor antagonists because they inhibit leukotriene receptor sites in the respiratory tract, preventing airway edema and facilitating bronchodilation.

Contraindications, precautions, and interactions. These drugs are contraindicated in patients with a known hypersensitivity to the drugs. Montelukast, zafirlukast, and zileuton are not used in the reversal of bronchospasm in acute asthma attacks. Zileuton is contraindicated in active liver disease. The drugs are used cautiously in patients with hepatic dysfunction and during pregnancy and lactation.

Administration of zafirlukast and aspirin increases plasma levels of zafirlukast, When zafirlukast is administered with warfarin, there is an increased effect of the anticoagulant. Administration of zafirlukast and theophylline or erythromycin may result in a decreased level of zafirlukast. Administration of montelukast with other drugs has not revealed any adverse responses.

Administration of montelukast with aspirin and NSAIDs is avoided in patients with known aspirin sensitivity.

Administration of zileuton with propranolol increases the activity or the propranolol; with theophylline increases serum theophylline levels; and with warfarin may increase prothrombin time (PT). A prothrombin blood test should be done regularly in the event dosages of warfarin need to be decreased.

2.3. Mast cell stabilizers include cromolyn sodium and nedocromil sodium

Actions. These drugs inhibit the release of substances that cause bronchoconstriction and inflammation from the mast cells in the respiratory tract.

Contraindications, precautions, and interactions. The mast cell stabilizers are contraindicated in patients with known hypersensitivity to the drugs. The mast cell stabilizers are contraindicated in patients during attacks of acute asthma because they may worsen bronchospasm during the acute asthma attack.

It is important to use the mast cell stabilizers cautiously in patients with impaired renal or hepatic function and during pregnancy and lactation. No significant drug interactions have been reported.

EXERCISES FOR OUT-CLASS WORK

Exercise 1. Using the table 1, administrate sympathomimetics for:

1) maintenance treatment of asthma;

2) prevention of exercise-induced bronchospasm;
3) maintenance treatment of COPD.

Table 1. Uses and dosage ranges of sympathomimetics.

Drugs	Uses	Adverse reactions	Dosage ranges
Non-selective β-agonists			
Orciprenalinum metaproterenol (Astmopent)	Bronchospasm	Palpitations, tachycardia, headache, flushing, cardiac arrhythmias	Aerosol 2—3 inhalations q3—4h; do not exceed 12 inhalations
Selective β2-agonists			
Salbutamol albuterol (Ventolin)	Maintenance treatment of asthma, prevention of exercise-induced bronchospasm (EIB)	Palpitations, tachycardia, hypertension, tremor, dizziness, shakiness, nervousness, nausea, vomiting	2—4 mg TID, QID PO; 1—2 inhalations q4—6h; 2 inhalations before exercise; by nebulization: 4-32 mg q12h PO
Fenoterol (Berotec)	Treatment of asthma, prevention of EIB	Palpitations, tachycardia, dizziness, nervousness	Asthma/bronchospasm: aerosol, 2 inhalations 3 times a day
Terbutaline	Asthma, bronchospasm	Palpitations, tremor, dizziness, vertigo, nervousness, drowsiness, headache, nausea	2.5—5 mg q6h PO TID during waking hours; 0.25 mg SC (may repeat one time if needed)
Formoterol (Foradil)	Maintenance treatment of asthma, prevention of EIB	Palpitations, tachycardia, dizziness, nervousness	12-mcg capsule q12h using Aerolizer Inhaler; EIB 1 12-mcg capsule 15 min before exercise
Salmeterol (Serevent)	Asthma, bronchospasm	Palpitations, tachycardia, tremor, nervousness, headache, nausea, cough, heartburn, diarrhea	Aerosol, 2 inhalations BID; inhalation powder, 1 (50 mcg) inhalation BID

Exercise 2. Explain interactions of sympathomimetics with:
1) monoamine oxidase inhibitors;
2) theophylline.

Exercise 3. Using the table 2, administrate anticholinergics for:
1) maintenance treatment of asthma;
2) maintenance treatment of chronic obstructive pulmonary disease.

Table 2. Uses and dosage ranges of anticholinergics.

Drugs	Uses	Adverse reactions	Dosage ranges
Ipratropium bromide (Atrovent)	Bronchospasm associated with chronic obstructive pulmonary disease, chronic bronchitis and emphysema, rhinorrhea	Dryness of the oropharynx, nervousness, irritation from aerosol, dizziness, headache, GI distress, dry mouth, exacerbation of symptoms, nausea, palpitations	Aerosol: 2-12 inhalations (36-216 mcg) QID; solution: 500 mcg TID, QID by oral nebulization; nasal spray: 2 sprays per nostril BID, TID of 0.03% or 2 sprays per nostril TID, QID of 0.06%
Tiotropium (Spiiriva)	Same as ipratropium	Same as ipratropium	Aerosol: 2 inhalations (36 mcg) BID

Exercise 4. Using the table 3, administrate xanthine derivatives for:

1) prevention of bronchospasm in patient with bronchial asthma;
2) prevention reversible bronchospasm of COPD.

Exercise 5. Explain interactions of xanthine derivatives with:

1) sympathomimetic drugs;
2) charcoal-broiled foods;
3) cigarettes, nicotine gum and patches, barbiturates, phenytoin, loop diuretics, isoniazid, rifampin;
4) influenza vaccination, oral contraceptives, glucocorticoids, beta-adrenergic blockers, cimetidine, macrolides, thyroid hormones, allopurinol.

Table 3. Uses and dosage ranges of xanthine derivatives.

Drugs	Uses	Adverse reactions	Dosage ranges
Aminophylline (Euphyllinum)	Symptomatic relief or prevention of bronchial asthma and reversible bronchospasm of chronic bronchitis and emphysema	Nausea, vomiting, diarrhea, headache, insomnia, irritability, hyperglycemia, hypotension, cardiac arrhythmias, tachycardia, tachypnea, seizures	Individualize dosage: base adjustments on clinical responses, monitor serum theophylline levels, maintain therapeutic range of 10–20 mcg/mL; base dosage on lean body mass
Theophylline	Same as aminophylline	Same as aminophylline	Long-term therapy: 16 mg/kg/24h or 400 mg/24h in divided doses. Monitor serum theophylline levels.

Exercise 6. Using the table 4, administrate leukotriene receptor antagonists for:

1) prevention of bronchospasm in patient with bronchial asthma;
2) prevention reversible bronchospasm of COPD.

Exercise 7. Explain interactions of:

1) zafirlukast with aspirin, warfarin, theophylline, erythromycin;
2) montelukast with aspirin and NSAIDs.

Table 4. Uses and dosage ranges of leukotriene receptor antagonists.

Drugs	Uses	Adverse reactions	Dosage ranges
Montelukast sodium (Singulair)	Prophylaxis and treatment of chronic asthma in adults and children older than 2 years	Headache, dizziness, dyspepsia, gastroenteritis, influenza symptoms, cough, abdominal pain, fatigue	Adults and children older than 15 years: 10 mg PO in the evening; children 2-14 years: 1 5-mg chew-able tablet daily, in the evening
Zafirlukast (Accolate)	Prophylaxis and treatment of chronic asthma in adults and children 12 years or older	Headache, dizziness, nausea, diarrhea, abdominal pain, vomiting, infection, pain, asthenia, accidental injury, myalgia, fever, ALT elevation	20 mg BID PO

Exercise 8. Using the table 5, administrate leukotriene formation inhibitors for:

1) prevention of bronchospasm in patient with bronchial asthma;
2) prevention reversible bronchospasm of COPD.

Table 5. Uses and dosage ranges of leukotriene formation inhibitors.

Drugs	Uses	Adverse reactions	Dosage ranges
Zileuton (Zyflo)	Prophylaxis and treatment of chronic asthma in adults and children 12 years or older	Dyspepsia, nausea, headache, pain, abdominal pain, asthenia, myalgia, accidental injury, ALT elevation	600 mg QID PO

Exercise 9. Explain interactions of: zileuton with propranolol, theophylline, warfarin.

Exercise 10. Using the table 6, administrate corticosteroids for:

1) prevention of bronchospasm in patient with bronchial asthma;
2) prevention reversible bronchospasm of COPD.

Table 6. Uses and dosage ranges of corticosteroids.

Drugs	Uses	Adverse reactions	Dosage ranges
Beclomethasone dipropionate (Becloforte, Beconase)	Respiratory inhalant use: asthma Intranasal use: allergic rhinitis, prevention of recurrence of nasal polyps after surgical removal	Oral, laryngeal, pharyngeal irritation, fungal infections, suppression of hypothalamic-pituitary-adrenal (HPA) function	Respiratory inhalation use: 2-20 inhalations (84–840 mcg) TID, QID. Intranasal therapy: 1 inhalation (42–84 mcg) in each nostril BID, QID
Budesonide	Allergic rhinitis Management of asthma in adults and children over age 6; respules: maintenance treatment of asthma in children 12 months to 8 years;	Oral, laryngeal, pharyngeal irritation, fungal infections, suppression of HPA function	Adults: 200-800 mcg BID; children 6 years and older: 200-400 mcg BID; children 12 months to 8 years: 0.5-1 mcg total daily dose
Flunisolide (AeroBid)	Chronic asthma Respiratory inhalant: asthma Intranasal: rhinitis	Oral, laryngeal, pharyngeal irritation, fungal infections, suppression of HPA function	Adults: 2 inhalations BID; maximum dose, 4 inhalations BID; Intranasal: 2-4 sprays each nostril BID
Fluticasone propionate (Flixonase, flixotide)	Prophylactic maintenance and treatment of asthma	Oral, laryngeal, pharyngeal irritation, fungal infections, suppression of HPA function	Aerosol: 88—880 mcg BID; powder: adults and adolescents 100—1000 mcg BID; children 4–11 years, 500–600 mcg BID
Triamcinolone acetonide (Azmacort)	Maintenance and prophylactic treatment of asthma	Oral, laryngeal, pharyngeal irritation, fungal infections	Adults: 2-4 inhalations TID, QID; children 6-12 years: 1-2 inhalations TID, QID

Exercise 11. Explain interactions of budesonide and fluticasone with ketoconazole.

Exercise 12. Using the table 7, administrate mast cell stabilizers for prevention of bronchospasm in patient with:

1) bronchial asthma;
2) allergic conjunctivitis.

Exercise 13**.** Using the table 8, administrate mucolytics for reduction of viscosity of mucus in:

1) bronchial asthma;
2) COPD.

Table 7. Uses and dosage ranges of mast cell stabilizers.

Drugs	Uses	Adverse reactions	Dosage ranges
Cromolyn (Intal)	Prophylaxis of bronchial asthma; prevention of exercise- induced asthma (EIA) Nasal preparations: prevention and treatment of allergic rhinitis	Dizziness, headache, nausea, dry and irritated throat, rash, joint swelling and pain	Nebulizer solution: 20 mg (1 capsule) inhaled QID Aerosol: adults and children 5 years and older, 2 metered sprays QID. Nasal solution: 1 spray each nostril 3–6 times/d. Oral: adults and children 13 years and older: 2 ampules QID 30 min before meals and at bedtime; children 2—12 years, 1 ampule QID before meals and at bedtime; do not exceed 40 mg/kg/d
Nedocromil (Tilade)	Maintenance therapyin mild bronchial asthma Treatment of itching caused by allergic conjunctivitis	Cough, nausea, pharyngitis, rhinitis, vomiting, dyspepsia, chest pain, headache, bronchospasm	2 inhalations QID. Eyedrops 1–2 g HS each eye BID

Table 8. Uses and dosage ranges of mucolytics.

Drugs	Uses	Adverse reactions	Dosage ranges
Acetylcysteine	Reduction of viscosity of mucus in acute and chronic bronchopulmonary disease, tracheostomy care, atelectasis due to mucus obstruction	Stomatitis, nausea, vomiting, fever, drowsiness, bronchospasm, irritation of the trachea and bronchi	10 mL of 20% solution or 2–20 mL of 10% solution q2–6h
Ambroxolum (Lasolvan)	Chronic bronchopulmonary disease, tracheostomy care, atelectasis	Nausea, vomiting, rash	30 mg q8-12h PO
Bromhexinum	Same as ambroxolum	Nausea, vomiting,	8 mg q6-8h PO

Exercise 14. Using the table 9, administrate antihistamines for:

1) allergic rhinitis;

2) urticaria;
3) pruritus;
4) sedation;
5) adjunctive therapy for analgesia;
6) nausea and vomiting associated with anesthesia and surgery;
7) sedation and apprehension;
8) preoperative and postoperative sedation.

Table 9. Uses and dosage ranges of antihistamines.

Drugs	Uses	Adverse reactions	Dosage ranges
First-generation agents			
Clemastine fumarate (Tavegyl)	Allergic rhinitis, urticaria	Drowsiness, sedation, hypotension, palpitations, blurred vision, dry mouth, urinary hesitancy	1.34 mg PO BID to 8.04 mg/d
Diphenhydramine hydrochloride (Dimedrol)	Allergic symptoms, hypersensitivity	Drowsiness, dry mouth, anorexia, blurred vision, urinary frequency	25–50 mg PO q4–6h; 10–400 mg IM, IV
Hydroxyzine (Atarax)	Pruritus, sedation (oral only), adjunctive therapy for analgesia (parenteral only), antiemetic (parenteral)	Drowsiness, dry mouth, dizziness, wheezing, chest tightness	25 mg 3—4 times a day PO; 25—100 mg IM; sedation, 50—100 mg PO
Promethazine HCl (Pipolphen)	Allergic symptoms, motion sickness, nausea and vomiting associated with anesthesia and surgery, preoperative and postoperative sedation	Excessive sedation, confusion, disorientation, dizziness, fatigue, blurred vision, dry mouth	Allergy: 12.5—25 mg PO, 25 mg IM, IV; nausea, vomiting: 12.5—25 mg PO, IM, IV; preoperative: 50 mg IM or PO the night before surgery
Second-generation agents			
Acrivastine (Semprex)	Seasonal rhinitis, chronic urticaria	Sedation, diarrhea, somnolence	8 mg 3 times a day
Azelastine (Allergodil)	Allergic rhinitis, allergic conjunctivitis	Sedation, diarrhea, somnolence	2 sprays per nosdril 2 times a day
Cetirizine HCl (Zyrtec)	Seasonal rhinitis, chronic urticaria	Sedation, diarrhea, somnolence	5–10 mg daily PO; maximum dosage, 20 mg/d
Loratadine (Claritin)	Allergic rhinitis	Dizziness, migraine, headache, tremors, conjunctivitis, blurred vision, altered salivation	PO 10 mg/d
Desloratadine (Aerius)	Seasonal or perennial allergic rhinitis	Headache, fatigue, drowsiness, dry mouth, nose, and throat	Adults and children 12 years and older: 5 mg once daily PO
Fexofenadine (Telfast)	Seasonal rhinitis, urticaria	Drowsiness, nausea, headache, back pain, upper respiratory infection	30–60 mg PO BID; maximum dosage, 180 mg/d

CLINICAL EXERCISES FOR OUT-CLASS WORK

1. Mr. Potter, age 57 years, is admitted to the pulmonary unit in acute respiratory distress. The doctor orders IV aminophylline. In developing a care plan for Mr. Potter, you select the ineffective airway clearance. Suggest interventions that would be most important in managing this problem.
2. Ms. Smith, age 68 years, returned to the clinic for a follow-up visit after receiving a diagnosis of COPD. She is taking theophylline daily and using a metered-dose inhaler 4 times a day. Determine what assessments would be most important for you to make at this time.
3. Discuss what to include in a teaching plan for a patient taking montelukast for asthma.
4. Your neighbor, Mr. Peterson, tells you that he has had a chronic cough for the past several months and asks you what the best "cough medicine" to buy is. Describe the advice you would give to Mr. Peterson.
5. Ms. Moore, a patient in a nursing home, has had a cough for the past 3 weeks. Ms. Moore's physician is aware of her problem and has ordered an expectorant but told her that he wants her to cough and raise sputum. Ms. Moore's family asks you if something can be given to their mother to stop her from coughing. Explain how you would discuss this problem and explain the prescribed therapy with Ms. Moore's family.
6. Discuss any precautions the nurse would consider when the expectorants are administered. Give a rationale for your answer.
7. A number of the antihistamines have anticholinergic effects. Discuss this term and identify interactions important when caring for a patient experiencing anticholinergic effects while taking an antihistamine.
8. Discuss important teaching points that should be included in developing a teaching plan for a patient taking a nasal decongestant. Determine what teaching points would be the most important. Provide a rationale for your answer.

REVIEW QUESTIONS

1. Which of the following is a common adverse reaction seen when administering an antihistamine?

A) Sedation
B) Blurred vision
C) Headache
D) Hypertension

2. Antihistamines are not routinely given to patient with lower respiratory disorders because:

A) the depressant effects may cause a hypotensive crisis;
B) stimulation of the central nervous system may occur, resulting in paradoxical excitement;
C) the effects of these drugs on the respiratory tract may cause secretions to thicken;
D) antihistamines may irritate the bronchi, causing bronchospasm.

3. When antihistamines are administered to patients receiving central nervous system depressants, the doctor monitors the patient for:
A) an increase in anticholinergic effects;
B) excessive sedation;
C) seizure activity;
D) loss of hearing.

4. A patient receives a prescription for phenylephrine. The doctor explains that overuse of this drug may:
A) result in hypotensive episodes;
B) decrease sinus drainage;
C) cause rebound nasal congestion;
D) dilate capillaries in the nasal mucosa.

5. Which of the following laboratory exams would the nurse expect to be ordered for a patient taking aminophylline?
A) Thyroid levels.
B) Alanine aminotransferase.
C) Electrolytes.
D) Serum aminophylline levels.

6. When the sympathomimetics are administered to older adults there is an increased risk of:
A) gastrointestinal effects;
B) nephrotoxic effects;
C) ;neurotoxic effects;
D) ;cardiovascular effects.

7. When zileuton is prescribed, the doctor expects which laboratory test to be checked periodically?
A) Urine for culture and sensitivity (C&S).
B) Complete blood count (CBC).
C) Prothrombin test (PT).
D) Alanine aminotransferase (ALT).

8. When administering aminophylline, a xanthine derivative bronchodilating drug, the nurse monitors the patient for adverse reactions, which include:
A) restlessness, nervousness;
B) hypoglycemia, hypothyroidism;
C) bradycardia, bronchospasm;
D) somnolence, lethargy.

9. The doctor correctly administers montelukast (Singulair):
    A) once daily in the evening;
    B) twice daily in the morning and evening;
    C) three times a day with meals;
    D) once daily in the morning.

10. Antitussives are given with caution to patients with:
    A) an unproductive cough;
    B) a chronic cough;
    C) hypertension;
    D) hypotension.

11. Which of these drugs is classified as an expectorant?
    A) Guaifenesin
    B) Codeine
    C) Dextromethorphan
    D) Diphenhydramine

12. Which of the following statements is appropriate for the doctor to include in discharge instructions for a patient taking an antitussive?
    A) Increase the dosage if the drug does not relieve the cough.
    B) Limit fluids to less than 1000 mL each day.
    C) Expect the cough to worsen during the first few days of treatment.
    D) Frequent sips of water and sugarless hard candy may diminish coughing.

Lesson 8

CLINICAL PHARMACOLOGY OF ANTI-INFLAMMATORY DRUGS

QUESTIONS FOR IN-CLASS WORK

1. Nonsteroidal anti-inflammatory drugs: mechanism of action, antibacterial spectrum, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
2. Glucocorticoids: mechanism of action, antibacterial spectrum, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.

THEORETICAL ISSUES

1. NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

The nonsteroidal anti-inflammatory drug (NSAID) group contains a large number of drugs. There are more than 70 drugs in this category, with new drugs continually becoming available. Some texts include the salicylates in the NSAID group, whereas others do not.

The NSAIDs are another type of nonnarcotic analgesic. This chapter covers general information on the NSAID group and discusses four of the more commonly used NSAIDs specifically. Like the salicylates, the NSAIDs have antiinflammatory, antipyretic, and analgesic effects.

1.1. Actions

The NSAIDs are so named because they do not belong to the steroid group of drugs and thus do not possess the adverse reactions associated with the steroids, and yet they have anti-inflammatory effects.

In addition, NSAIDs have analgesic and antipyretic properties. Although the exact mechanisms of actions are not known, the NSAIDs are thought to act by inhibiting prostaglandin (a group of naturally occurring fatty acids that act within the body to regulate acid secretion of the stomach, regulate body temperature and

platelet aggregation, and control inflammation) synthesis by inhibiting the action of the enzyme cyclooxygenase, the enzyme responsible for prostaglandin synthesis.

The NSAIDs act to inhibit the activity of two related enzymes:

1) cycloo1xygenase-1 (COX-1), the enzyme that helps to maintain the stomach lining;
2) cyclooxygenase-2 (COX-2), the enzyme that triggers pain and inflammation.

The anti-inflammatory effects of the NSAIDs are carried out by inhibition of COX-2. The gastrointestinal adverse reactions are caused by inhibition of COX-1. The newer NSAIDs (celecoxib and rofecoxib) appear to work by specifically inhibiting the COX-2 enzyme, without inhibiting the COX-1 enzyme.

Celecoxib and rofecoxib relieve pain and inflammation with less potential for gastrointestinal adverse reactions. The traditional NSAIDs, such as ibuprofen and

naproxen, are thought to regulate the pain and inflammation by blocking COX-2. Unlike celecoxib and rofecoxib, these drugs also inhibit COX-1, the enzyme that helps maintain the lining of the stomach.

This inhibition of COX-1 causes the unwanted gastrointestinal reactions, such as stomach irritation and ulcers.

1.2. Contraindications, precautions, and interactions

The NSAIDs are contraindicated in patients with known hypersensitivity. There is a cross-sensitivity to other NSAIDs. If a patient is allergic to one NSAID, there is an increased risk of an allergic reaction with any other NSAID. Hypersensitivity to aspirin is a contraindication for all NSAIDs. In general, the NSAIDs are contraindicated during the third trimester of pregnancy and during lactation.

The NSAIDs are used cautiously in patients with bleeding disorders, renal disease, cardiovascular disease, or hepatic impairment and in the elderly. There is an increased risk of ulcer formation in patients older than 65 years. In general, the NSAIDs are used with extreme caution during pregnancy, especially in large doses or during the third trimester.

The NSAIDs prolong bleeding time and increase the effects of anticoagulants, lithium, cyclosporine, and the hydantoins. These drugs may decrease the effects of diuretics or antihypertensive drugs. Long-term use of the NSAIDs with acetaminophen may increase the risk of renal impairment.

Celecoxib

Celecoxib is contraindicated in patients who are allergic to the drug itself, the sulfonamides, other NSAIDs, or aspirin; it also is contraindicated during pregnancy and lactation.

The drug is used cautiously in patients with a history of peptic ulcer, individuals older than 60 years, and those taking an anticoagulant or steroids. In rare instances, serious stomach problems such as bleeding can occur without warning. When celecoxib is given with the anticoagulants, there is an increased risk for bleeding.

Ibuprofen

Ibuprofen is contraindicated in individuals who are allergic to the drug or other NSAIDs; those who have hypertension, peptic ulceration, or gastrointestinal bleeding; and during pregnancy and lactation.

The drug is used cautiously in patients with renal or liver dysfunction. When ibuprofen is used with lithium, there is an increased risk of lithium toxicity. A decreased effect of the diuretic may occur when administered with ibuprofen. When ibuprofen is administered with the beta-adrenergic blocking drugs there is a risk for a decrease in the antihypertensive effect of the beta-adrenergic blocking drug.

Naproxen

Naproxen is contraindicated in patients who are allergic to the drug or other NSAIDs and during pregnancy and lactation. The drug is used cautiously in patients with asthma, hypertension, cardiac problems, peptic ulcer disease, and

impaired liver or kidney function. Like ibuprofen, naproxen increases the risk of lithium toxicity when the drug is administered with naproxen. When naproxen is administered with the anticoagulants there is an increased risk for bleeding.

When naproxen is administered with the antihypertensives, there is a decrease in the antihypertensive effect.

Coadministration of naproxen with the diuretics decreases the diuretic effect.

1.3. Common adverse reactions of select NSAIDS

Celecoxib

The most common adverse reactions seen with celecoxib include dyspepsia, abdominal pain, diarrhea, nausea, and headache. Like other NSAIDs, celecoxib may compromise renal function. Elevation of aminotransferase levels also occurs.

Ibuprofen

This drug is available to individuals as an over-thecounter drug and may be purchased without a prescription. The drug is used in children with juvenile arthritis and for fever reduction in children 6 months to 12 years.

Common adverse reactions seen with ibuprofen include headache, dizziness, somnolence, nausea, dyspepsia, gastrointestinal pain, and rash.

Naproxen

Common adverse reactions seen with naproxen include headache, dizziness, somnolence, insomnia, nausea, dyspepsia, gastrointestinal pain, and rash.

2. GLUCOCORTICOIDS

The adrenal gland lies on the superior surface of each kidney. It is a double organ composed of an outer cortex and an inner medulla. In response to ACTH secreted by the anterior pituitary, the adrenal cortex secretes several hormones (the glucocorticoids, the mineralocorticoids, and small amounts of sex hormones).

These hormones are essential to life and influence many organs and structures of the body. The glucocorticoids and mineralocorticoids are collectively called corticosteroids. The glucocorticoids influence or regulate functions such as the immune response system, the regulation of glucose, fat and protein metabolism, and control of the anti-inflammatory response.

2.1. Actions and uses

The glucocorticoids enter target cells and bind to receptors, initiating many complex reactions in the body. Some of these actions are considered undesirable, depending on the indication for which these drugs are being used.

Examples of the glucocorticoids include cortisone, hydrocortisone, prednisone, prednisolone, and triamcinolone.

The glucocorticoids are used as replacement therapy for adrenocortical insufficiency, to treat allergic reactions, collagen diseases (eg, systemic lupus

erythematosus), dermatologic conditions, rheumatic disorders, shock, and other conditions. The anti-inflammatory activity of these hormones make them valuable as anti-inflammatories and as immunosuppressants to suppress inflammation and modify the immune response.

2.2. Contraindications, precautions, and interactions

The glucocorticoids are contraindicated in patients with serious infections, such as tuberculosis and fungal and antibiotic-resistant infections.

The glucocorticoids are administered with caution to patients with renal or hepatic disease, hypothyroidism, ulcerative colitis, diverticulitis, peptic ulcer disease, inflammatory bowel disease, hypertension, osteoporosis, convulsive disorders, or diabetes. The glucocorticoids should be used with caution during pregnancy and lactation.

Multiple drug interactions may occur with the glucocorticoids.

EXERCISES FOR OUT-CLASS WORK

Exercise 1. Using the table 1, administrate NSAIDs for:

3) relief of signs and symptoms of osteoarthritis;
4) rheumatoid arthritis, and other musculoskeletal disorders;
5) Mild to moderate pain relief;
6) primary dysmenorrheal;
7) fever reduction.

Exercise 2. Explain interactions of nonsteroidal anti-inflammatory drugs with:

1) anticoagulants;
2) lithium;
3) cyclosporine;
4) hydantoins;
5) diuretics;
6) antihypertensive drugs;
7) acetaminophen.

Exercise 3. Using the table 2, administrate glucocorticoids for:

1) adrenocortical insufficiencyl
2) allergic reactions;
3) collagen diseases;
4) dermatologic conditions;
5) rheumatic disorders
6) shock.

Exercise 4. Explain interactions of glucocorticoids with:

1) anticoagulants;
2) lithium;
3) cyclosporine;
4) diuretics;
5) antihypertensive drugs;
6) acetaminophen.

Table 1. Uses and dosage ranges of nonsteroidal anti-inflammatory drugs.

Drugs	Uses	Adverse reactions	Dosage ranges
Salicylates			
Acetylsalicylic acid (Aspirin)	Analgesic, antipyretic, antiinflammatory	Nausea, vomiting, epigastric distress, GI bleeding, tinnitus, anaphylactic reactions	325—650 mg PO with up to 8 g/d PO in divided doses; 325-650 mg rectally
Choline salicylate (Faringin)	Same as aspirin	Same as aspirin	150 mg q3-4h
Para-aminophenol derivative			
Acetaminophen (paracetamol)	Analgesic, antipyretic	Urticaria, hemolytic anemia, pancytopenia, jaundice, hepatotoxicity	325-650 mg/d PO q4-6h or 1 g PO 3—4 times daily; maximum 4 g/d
Acetic acid derivatives			
Indomethacin	Rheumatoid arthritis, ankylosing spondylitis	Nausea, constipation, gastric or duodenal ulcer formation, GI bleeding, hematologic changes	25–50 mg PO BID–TID not to exceed 200 mg/d
Ketorolac (Ketanov)	Management of pain; rheumatoid arthritis, osteoarthritis	Dyspepsia, nausea, GI pain, pain at injection site, drowsiness	30–60 mg IM initially, followed by half the initial dose q6h; maximum dose, 40 mg/d
Diclofenac potassium	Pain, rheumatoid arthritis, osteoarthritis	Nausea, gastric or duodenal ulcer formation, gastrointestinal (GI) bleeding	25-50 mg PO BID–TID
Proprionic acid derivatives			
Ibuprofen	Pain, rheumatoid disorders, painful dysmenorrhea	Nausea, dizziness, somnolence, dyspepsia, gastric or duodenal ulcer formation, GI bleeding, headache	Arthritis disorders: 1.2–3.2 g/d PO in divided doses; pain: 400 mg PO q4–6h; dysmenorrhea: 400 mg PO q4h
Naproxen	Pain, rheumatoid arthritis, osteoarthritis, dysmenorrhea	Dizziness, visual disturbances, headache, nausea, vomiting, ulcer formation, GI bleeding	250-500 mg initially then 250 mg q6–8h;
Ketoprofen (Ketonal, Fastum Gel)	Pain, rheumatoid disorders, painful dysmenorrhea	Dizziness, nausea, vomiting, visual disturbances, diarrhea, constipation, ulcer formation, GI bleeding	Arthritis: 150–300 mg/d in divided doses; Primary dysmenorrhea: 25–50 mg q6–8h PRN
Enolic acid derivatives			
Piroxicam	Pain, rheumatoid arthritis, osteoarthritis	Nausea, vomiting, diarrhea, drowsiness, gastric or duodenal ulcer, GI bleeding	20 mg/d PO as a single dose or 10 mg PO BID
Meloxicam (Movalis)	Osteoarthritis	Nausea, dyspepsia, GI pain, headache, insomnia, rash	7.5–15 mg PO QD
COX-2 selective inhibitors			
Valdecoxib (Bextra)	Osteoarthritis, rheumatoid arthritis	Headache, nausea, dyspepsia, abdominal pain, anemia	Arthritis 10 mg/d PO; primary dysmenorrhea, 20 mg BID PRN

Table 2. Uses and dosage ranges of glucocorticoids.

Drugs	Uses	Dosage ranges
Methylprednisolone (Medrol)	Adrenocortical insufficiency, allergic reactions, collagen diseases dermatologic conditions, rheumatic disorders, shock	Initial dose: 4–48 mg/d PO; Dosepak 21 day therapy: follow manufacturer's directions; alternate day therapy: twice the usual dose is administered every other morning
Dexamethasone	Acute self-limited allergic disorder or acute exacerbations of chronic allergic disorders	Individualize dosage based on severity of condition and response; give daily dose before 9 AM to minimize adrenal suppression; after long-term therapy, reduce slowly to avoid adrenal insufficiency
Betamethasone (Diprospan)	Same as methylprednisolone	Up to 9 mg/d IM, IV
Hydrocortisone	Same as methylprednisolone	20–240 mg PO in single or divided doses
Prednisolone	Same as methylprednisolone	5–60 mg/d PO; acute exacerbations in MS: 200 mg/d for 1 wk, followed by 80 mg every other day for 1 month PO
Triamcinolone	Same as methylprednisolone	4–48 mg/d PO

Exercise 3. Using the table 3, explain side effects of glucocorticoids.
Exercise 4. Using the table 4, explain interactions of glucocorticoids with other drugs.

Table 3. Activity of glucocorticoids in the body.

Function within the body	Description of bodily activity
Anti-inflammatory	Stabilizes lysosomal membrane and prevents the release of proteolytic enzymes released during the inflammatory process
Regulation of blood pressure	Potentiates vasoconstrictor action of norepinephrine. Without glucocorticoids the vasoconstricting action is decreased, and blood pressure falls.
Metabolism of carbohydrates and protein	Facilitates the breakdown of protein in the muscle, leading to increased plasma amino acid levels. Increases activity of enzymes necessary for glucogenesis producing hyperglycemia, which can aggravate diabetes, and cause insulin resistance
Metabolism of fat	A complex phenomena that promotes the use of fat for energy (a positive effect) and permits fat stores to accumulate in the body, causing buffalo hump and moon- or round-shaped face (a negative effect).
Interference with the immune response	Decreases the production of lymphocytes and eosinophils in the blood by causing atrophy of the thymus gland; blocks the release of cytokines, resulting in a decreased performance of T and B monocytes in the immune response.
Stress	As a protective mechanism, the corticosteroids are released during stress. The release of epinephrine or norepinephrine by the adrenal medulla has a synergistic effect along with the corticosteroids.
Central nervous system disturbances	Affects mood and possibly causes neuronal or brain excitability, causing euphoria, anxiety, depression, psychosis, and an increase in motor activity in some individuals

Table 3. Select drug interactions of glucocorticoids.

Precipitant drug	Object drug	Description
Barbiturates	Corticosteroids	Decreased pharmacologic effects of the corticosteroid may be observed.
Cholestyramine	Hydrocortisone	The effects of hydrocortisone may be decreased.
Contraceptives, oral	Corticosteroids	Corticosteroid concentration may be increased and clearance decreased.
Estrogens	Corticosteroids	Corticosteroid clearance may be decreased.
Hydantoins	Corticosteroids	Corticosteroid clearance may be increased, resulting in reduced therapeutic effects.
Ketoconazole	Corticosteroids	Corticosteroid clearance may be decreased.
Rifampin	Corticosteroids	Corticosteroid clearance may be increased, resulting in decreased therapeutic effects.
Corticosteroids	Anticholinesterases	Anticholinesterase effects may be antagonized in myasthenia gravis.
Corticosteroids	Anticoagulants, oral	Anticoagulant dose requirements may be reduced. Corticosteroids may decrease the anticoagulant action.
Corticosteroids	Digitalis glycosides	Co-administration may enhance the possibility of digitalis toxicity associated with hypokalemia.
Corticosteroids	Isoniazid	Isoniazid serum concentrations may be decreased.
Corticosteroids	Potassium-depleting diuretics	Hypokalemia may occur.
Corticosteroids	Salicylates	Corticosteroids will reduce serum salicylate levels and may decrease their effectiveness.
Corticosteroids	Theophyllines	Alterations in the pharmacologic activity of either agent may occur.

CLINICAL EXERCISES FOR OUT-CLASS WORK

1. On a visit to an outpatient clinic, Ms. Cain tells you that she takes aspirin daily for the minor aches and pains she experiences. Determine what you might want to discuss with Ms. Cain to explore her use of this drug. Discuss what you might incorporate into the teaching plan to increase her knowledge of the drug and to prevent any complications.
2. Jim, a 49-year-old man, is at the outpatient clinic with complaints of muscular aches and pain. He is currently taking an over-the-counter aspirin product but states he is experiencing some gastric upset. He tells you that he plans to begin taking Tylenol because he has heard that it does not cause an upset stomach. What assessments would be important for the doctor to make? What information would you give Jim concerning the Tylenol?

REVIEW QUESTIONS

1. Which of these drugs would be prescribed for a patient with an acetaminophen overdosage?

A) Acetylcysteine

B) Guaifenesin
C) Benzonatate
D) Dextromethorphan

2. At a team conference the doctor explains that the anti-inflammatory actions of the salicylates is most likely due to:
A) a decrease in the prothrombin time;
B) a decrease in the productions of endorphins;
C) the inhibition of prostaglandins;
D) vasodilation of the blood vessels.

3. Which of the following symptoms would the doctor expect in a patient experiencing salicylism?
A) dizziness, tinnitus, mental confusion;
B) diarrhea, nausea, weight loss;
C) constipation, anorexia, rash;
D) weight gain, hyperglycemia, urinary frequency.

4. When administering a salicylate the doctor most correctly administers the drug:
A) between meals;
B) with a carbonated beverage;
C) with food or milk;
D) dissolved in juice.

5. A doctor instructs the patient taking aspirin to avoid foods containing salicylates because this increases the risk of adverse reactions. Which foods should the patient avoid?
A) Salt, soft drinks
B) Broccoli, milk
C) Prunes, tea
D) Liver, pepper

6. The nurse monitors the alcoholic patient taking acetaminophen for symptoms of toxicity, which include:
A) Hypertension;
B) visual disturbances;
C) liver tenderness;
D) skin lesions.

7. Which of the following drugs would the nurse most likely administer to a child with an elevated temperature?
A) Baby aspirin
B) Acetaminophen
C) Fenoprofen
D) Diflunisal

Lesson 9

CLINICAL PHARMACOLOGY OF ANTIMICROBIAL AGENTS

QUESTIONS FOR IN-CLASS WORK

1. General principles of antimicrobial therapy.
2. Sulfonamides: mechanism of action, antibacterial spectrum, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
3. Quinolones: mechanism of action, antibacterial spectrum, pharmacokinetic profiles, therapeutic uses, adverse effects, contraindications, interactions.
4. Penicillins: mechanism of action, antibacterial spectrum, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
5. Cephalosporins: mechanism of action, antibacterial spectrum, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
6. The aminoglycosides: mechanism of action, antibacterial spectrum, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
7. Tetracyclines: mechanism of action, antibacterial spectrum, pharmacokinetic profiles, therapeutic uses, adverse effects, contraindications, interactions.
8. Macrolides: mechanism of action, antibacterial spectrum, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
9. Lincosamides: mechanism of action, antibacterial spectrum, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
10. Glicopeptides: mechanism of action, antibacterial spectrum, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
11. Drugs used in the chemotherapy of tuberculosis: mechanism of action, antibacterial spectrum, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
12. Antifungal agents: mechanism of action, antifungal activity, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
13. Antiviral and antiretroviral agents: mechanism of action, antiviral activity, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.

THEORETICAL ISSUES

1. SULFONAMIDES

The sulfonamides (sulfa) drugs were the first antibiotic drugs developed that effectively treated infections. Although the use of sulfonamides began to decline after the introduction of more effective anti-infectives, such as the penicillins and other antibiotics, these drugs still remain important for the treatment of certain types of infections. Sulfadiazine, sulfisoxazole, and sulfamethizole are examples of sulfonamide preparations.

1.1. Actions

The sulfonamides are primarily bacteriostatic, which means they slow or retard the multiplication of bacteria. This bacteriostatic activity is due to sulfonamide antagonism to para-aminobenzoic acid, a substance that some, but not all, bacteria need to multiply. Once the rate of bacterial multiplication is slowed, the body's own defense mechanisms are able to rid the body of the invading microorganisms and therefore control the infection.

1.2. Contraindications

The sulfonamides are contraindicated in patients with hypersensitivity to the sulfonamides, during lactation, and in children less than 2 years old. The sulfonamides are not used near the end of pregnancy. If the sulfonamides are given near the end of pregnancy, significant blood levels of the drug may occur, causing jaundice or hemolytic anemia in the neonate. Additionally, the sulfonamides are not used for infections caused by group A beta-hemolytic streptococci because the sulfonamides have *not* been shown to be effective in preventing the complications of rheumatic fever or glomerulonephritis.

1.3. Precautions

The sulfonamides are used with caution in patients with renal or hepatic impairment and bronchial asthma.

These drugs are given with caution to patients with allergies. Safety for use during pregnancy has not been established.

1.4. Interactions

When a sulfonamide is administered with an oral anticoagulant, the action of the anticoagulant may be enhanced. The risk of bone marrow suppression may be increased when a sulfonamide is administered with methotrexate. When a sulfonamide is administered with a hydantoin, the serum hydantoin level may be increased.

Sulfonamides may inhibit the hepatic metabolism of the oral hypoglycemic drugs tolbutamide and chlorpropamide. This would increase the possibility of a hypoglycemic reaction.

2. PENICILLINS

The antibacterial properties of natural penicillins were discovered in 1928 by Sir Arthur Fleming while he was performing research on influenza. Ten years later, British scientists studied the effects of natural penicillins on disease-causing microorganisms. However, it was not until 1941 that natural penicillins were used clinically for the treatment of infections. Although used for more than 60 years, the penicillins are still an important and effective group of antibiotics for the treatment of susceptible pathogens.

There are four groups of penicillins: natural penicillins, penicillinase-resistant penicillins, aminopenicillins, and the extended-spectrum penicillins.

2.1. Drug resistance

Because the natural penicillins have been used for many years, drug-resistant strains of microorganisms have developed, making the natural penicillins less effective than some of the newer antibiotics in treating a broad range of infections. Bacterial resistance has occurred within the penicillins. Bacterial resistance is the ability of bacteria to produce substances that inactivate or destroy the penicillin. One example of bacterial resistance is the ability of certain bacteria to produce penicillinase, an enzyme that inactivates penicillin. The penicillinase-resistant penicillins were developed to combat this problem.

The natural penicillins also have a fairly narrow spectrum of activity, which means that they are effective against only a few strains of bacteria. Newer penicillins have been developed to combat this problem.

These penicillins are a result of chemical treatment of a biologic precursor to penicillin. Because of their chemical modifications, they are more slowly excreted by the kidneys and, thus, have a somewhat wider spectrum of antibacterial activity. Penicillin beta-lactamase inhibitor combinations are a type of penicillin that have a wider spectrum of antibacterial activity. Certain bacteria have developed the ability to produce enzymes called beta-lactamases, which are able to destroy a component of the penicillin called the beta-lactam ring.

Fortunately, chemicals were discovered that inhibit the activity of these enzymes. Three examples of these beta-lactamase inhibitors are clavulanic acid, sulbactam, and tazobactam. When these chemicals are used alone, they have little antimicrobial activity. However, when combined with certain penicillins, they extend the spectrum of penicillin's antibacterial activity. The beta-lactamase inhibitors bind with the penicillin and protect the penicillin from destruction.

2.2. Actions

Penicillins prevent bacteria from using a substance that is necessary for the maintenance of the bacteria's outer cell wall. Unable to use this substance for cell wall maintenance, the bacteria swell, rupture, assume unusual shapes, and finally die.

The penicillins may be bactericidal or bacteriostatic. They are bactericidal against sensitive microorganisms provided there is an adequate concentration of penicillin in the body. An inadequate concentration of penicillin may produce bacteriostatic activity, which may or may not control the infection.

To determine if a specific type of bacteria is sensitive to penicillin, culture and sensitivity tests are performed.

2.3. Contraindications

Penicillins are contraindicated in patients with a history of hypersensitivity to penicillin or the cephalosporins.

2.4. Precautions

Penicillins should be used cautiously in patients with renal disease, pregnancy, lactation, and in those with a history of allergies. Any indication of

sensitivity is reason for caution. The drug is also used with caution in patients with asthma, renal disease, bleeding disorders, and gastrointestinal disease.

2.5. Interactions

Some penicillins (ampicillin, penicillin V) may interfere with the effectiveness of birth control pills that contain estrogen. There is a decreased effectiveness of the penicillin when it is administered with the tetracyclines. Large doses of penicillin can increase bleeding risks of patients taking anticoagulant agents.

Some reports indicate that when oral penicillins are administered with beta-adrenergic blocking drugs, the patient may be at increased risk for an anaphylactic reaction. Absorption of most penicillins is affected by food. In general, penicillins should be given 1 hour before or 2 hours after meals.

3. CEPHALOSPORINS

The cephalosporins are a valuable group of drugs that are effective in the treatment of almost all of the strains of bacteria affected by the penicillins, as well as some strains of bacteria that have become resistant to penicillin. The cephalosporins are structurally and chemically related to penicillin.

The cephalosporins are divided into first-, second-, third- and fourth generation drugs. Particular cephalosporins also may be differentiated within each group according to the microorganisms that are sensitive to them. Generally, progression from the first-generation to the second-generation and then to the third- and fourth generation drugs shows an increase in the sensitivity of gram-negative microorganisms and a decrease in the sensitivity of gram-positive microorganisms.

3.1. Actions

Cephalosporins affect the bacterial cell wall, making it defective and unstable. This action is similar to the action of penicillin. The cephalosporins are usually bactericidal.

3.2. Contraindications

The doctor should not administer cephalosporins if the patient has a history of allergies to cephalosporins or penicillins.

3.3. Precautions

The doctor should use cephalosporins cautiously in patients with renal or hepatic impairment and in patients with bleeding disorders. Safety of cephalosporin administration has not been established in pregnancy or lactation.

3.4. Interactions

The risk of nephrotoxicity increases when the cephalosporins are administered with the aminoglycosides. The risk for bleeding increases when the cephalosporins are taken with oral anticoagulants.

A disulfiram-like reaction may occur if alcohol is consumed within 72 hours after cephalosporin administration.

Symptoms of a disulfiram-like reactions include flushing, throbbing in the head and neck, respiratory difficulty, vomiting, sweating, chest pain, and hypotension. Severe reactions may cause arrhythmias and unconsciousness. When the cephalosporins are administered with the aminoglycosides, the risk for nephrotoxicity increases.

4. TETRACYCLINES

The tetracyclines are a group of anti-infectives composed of natural and semisynthetic compounds. They are useful in select infections when the organism shows sensitivityto the tetracyclines, such as in cholera, Rocky Mountain spotted fever, and typhus.

4.1. Actions

The tetracyclines exert their effect by inhibiting bacterial protein synthesis, which is a process necessary for reproduction of the microorganism. The ultimate effect of this action is that the bacteria are either destroyed or their multiplication rate is slowed. The tetracyclines are bacteriostatic.

4.2. Contraindications

The tetracyclines are contraindicated if the patient is known to be hypersensitive to any of the tetracyclines.

Tetracyclines also are contraindicated during pregnancy because of the possibility of toxic effects to the developing fetus. These drugs also are contraindicated during lactation and in children younger than 9 years (may cause permanent discoloration of the teeth).

4.3. Precautions

It is important to use the tetracyclines cautiously in patients with renal function impairment. In addition, doses greater that 2 g/d can be extremely damaging to the liver. The doctor should carefully check the expiration dates of the tetracyclines before administration because degradation of the tetracyclines can occur; after degradation, the agents are highly toxic to the kidneys.

4.4. Interactions

Antacids containing aluminum, zinc, magnesium, or bismuth salts, or foods high in calcium impair absorption of the tetracyclines. When the tetracyclines are administered with oral anticoagulants, an increase in the effects of the anticoagulant may occur. When tetracyclines are administered to women using oral contraceptives, a decrease in the effect of the oral contraceptive may be seen. This may result in breakthrough bleeding or pregnancy. When digoxin is administered with the tetracyclines there is an increased risk for digitalis toxicity. The effects of this could last for months after tetracycline administration is discontinued.

Tetracyclines may reduce insulin requirements. Blood glucose levels should be monitored frequently during tetracycline therapy.

5. MACROLIDES

The macrolides are effective against a wide variety of pathogenic organisms, particularly infections of the respiratory and genital tract.

5.1. Actions

The macrolides are bacteriostatic or bactericidal in susceptible bacteria. The drugs act by binding to cell membranes and causing changes in protein function.

5.2. Contraindications

These drugs are contraindicated in patients with a hypersensitivity to the macrolides and patients with pre-existing liver disease.

5.3. Precautions

It is important to use these drugs cautiously during pregnancy and lactation. Because azithromycin, erythromycin, and troleandomycin are primarily eliminated from the body by the liver, these drugs should be used with great caution in patients with liver dysfunction. There is a decreased gastrointestinal absorption of the macrolides when administered with kaolin, aluminum salts, or magaldrate.

5.4. Interactions

Use of the macrolides increases serum levels of digoxin and increases the effects of anticoagulants. Use of antacids decreases the absorption of most macrolides.

The macrolides should not be administered with clindamycin, lincomycin, or chloramphenicol; a decrease in the therapeutic activity of the macrolides can occur.

Concurrent administration of the macrolides with theophylline may increase serum theophylline levels.

6. LINCOSAMIDES

The lincosamides are effective against many gram-positive organisms, such as streptococci and staphylococci. However, because of their high potential for toxicity, the lincosamides are usually used only for the treatment of serious infections in which penicillin or macrolide is not effective.

6.1. Actions

The lincosamides act by inhibiting protein synthesis in susceptible bacteria, causing death.

6.2. Contraindications

The lincosamides are contraindicated in patients with hypersensitivity to the lincosamides, those with minor bacterial or viral infections, and during lactation and infancy.

6.3. Precautions

It is important to use these drugs with caution in patients with a history of gastrointestinal disorders, renal disease, or liver impairment. The neuromuscular blocking action of the lincosamides poses a danger to patients with myasthenia gravis.

6.4. Interactions

When kaolin or aluminum is administered with the lincosamides, the absorption of the lincosamide is decreased. When the lincosamides are administered with the neuromuscular blocking drugs the action of the neuromuscular blocking drug is enhanced, possibly leading to severe and profound respiratory depression.

7. FLUOROQUINOLONES

The fluoroquinolones include ciprofloxacin, enoxacin, gatifloxacin, lomefloxacin, moxifloxacin, ofloxacin, and sparfloxacin.

7.1. Actions

The fluoroquinolones exert their bactericidal effect by interfering with an enzyme (DNA gyrase) needed by bacteria for the synthesis of DNA.

This interference prevents cell reproduction, leading to death of the bacteria.

7.2. Contraindications

The fluoroquinolones are contraindicated in patients with a history of hypersensitivity to the fluoroquinolones, in children younger than 18 years, and in pregnant women. These drugs also are contraindicated in patients whose life-styles do not allow for adherence to the precautions regarding photosensitivity.

7.3. Precautions

The fluoroquinolones are used cautiously in patients with renal impairment or a history of seizures, in geriatric patients, and in patients on dialysis.

7.4. Interactions

Concurrent use of the fluoroquinolones with theophylline causes an increase in serum theophylline levels.

When used concurrently with cimetidine, the cimetidine may interfere with the elimination of the fluoroquinolones.

Use of the fluoroquinolones with an oral anticoagulant may cause an increase in the effects of the oral coagulant. Administration of the fluoroquinolones with antacids, iron salts, or zinc will decrease absorption of the fluoroquinolones. There is a risk of seizures if fluoroquinolones are given with the NSAIDs. There is a risk

of severe cardiac arrhythmias when the fluoroquinolones gatifloxacin and moxifloxacin are administered with drugs that increase the QT interval (eg, quinidine, procainamide, amiodarone, and sotalol).

8. AMINOGLYCOSIDES

The aminoglycosides include amikacin, gentamicin, kanamycin, neomycin, netilmicin, streptomycin, and tobramycin.

8.1. Actions

The aminoglycosides exert their bactericidal effect by blocking a step in protein synthesis necessary for bacterial multiplication. They disrupt the functional ability of the bacterial cell membrane causing cell death.

8.2. Contraindications

The aminoglycosides are contraindicated in patients with hypersensitivity to aminoglycosides. The aminoglycosides should not be given to patients requiring long-term therapy because of the potential for ototoxicity and nephrotoxicity. One exception is the use of streptomycin for long-term management of tuberculosis.

These drugs are contraindicated in patients with preexisting hearing loss, myasthenia gravis, parkinsonism, and during lactation or pregnancy.

8.3.Precautions

The aminoglycosides are used cautiously in patients with renal failure, in the elderly, and in patients with neuromuscular disorders.

8.4. Interactions

Administration of the aminoglycosides with the cephalosporins may increase the risks of nephrotoxicity.

When the aminoglycosides are administered with loop diuretics there is an increased risk of ototoxicity. There is an increased risk of neuromuscular blockage (paralysis of the respiratory muscles) if the aminoglycosides are given shortly after general anesthetics.

9. CHLORAMPHENICOL

9.1. Actions

Chloramphenicol interferes with or inhibits protein synthesis, a process necessary for the growth and multiplication of microorganisms. This is a potentially dangerous drug (see below), and therefore its use is limited to serious infections when less potentially dangerous drugs are ineffective or contraindicated.

9.2. Contraindications, precautions, and interactions

Chloramphenicol is contraindicated in patients with known hypersensitivity to the drug. This drug is used cautiously in patients with severe liver or kidney disease, in geriatric patients, in individuals with glucose-6-phosphate dehydrogenase deficiency, and during pregnancy or lactation. Newborns are at

increased risk for experiencing adverse reactions due to their inability to metabolize and excrete chloramphenicol.

The effects of oral hypoglycemic drugs, oral anticoagulants, and phenytoin may be increased when administered with chloramphenicol. Phenobarbital or rifampin may decrease chloramphenicol blood levels.

10. MEROPENEM

10.1. Actions

Meropenem inhibits synthesis of the bacterial cell wall and causes the death of susceptible cells. This drug is used for intra-abdominal infections caused by Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, and other susceptible organisms. Meropenem also is effective against bacterial meningitis caused by Neisseria meningitidis, Streptococcus pneumoniae, and Hemophilus influenzae.

10.2. Contraindications, precautions, and interactions

Meropenem is contraindicated in patients who are allergic to cephalosporins and penicillins and in patients with renal failure. This drug is not recommended in children younger than 3 months or for women during pregnancy or lactation. Meropenem is used cautiously in patients with central nervous system disorders, seizure disorders, and in patients with renal or hepatic failure. When administered with probenecid, the excretion of meropenem is inhibited.

11. METRONIDAZOLE

11.1. Actions

The mode of action of metronidazole is not well understood, but it is thought to disrupt DNA and protein synthesis in susceptible organisms. This drug may be used in the treatment of serious infections, such as intraabdominal, bone, soft tissue, lower respiratory, gynecologic, and CNS infections caused by susceptible anaerobic microorganisms.

11.2. Contraindications, precautions, and interactions

This drug is contraindicated in patients with known hypersensitivity to the drug and during the first trimester of pregnancy. This drug is used cautiously in patients with blood dyscrasias, seizure disorders, and hepatic dysfunction. Safety in children has not been established.

The metabolism of metronidazole may decrease when administered with cimetidine. When administered with phenobarbital, the effectiveness of metronidazole may decrease. When metronidazole is administered with warfarin, the effectiveness of the warfarin is increased.

12. VANCOMYCIN

12.1. Actions

Vancomycin acts against susceptible gram-positive bacteria by inhibiting bacterial cell wall synthesis and increasing cell wall permeability. This drug is used

in the treatment of serious gram-positive infections that do not respond to treatment with other anti-infectives. It also may be used in treating anti-infective–associated pseudomembranous colitis caused by Clostridium difficile.

12.2. Contraindications, precautions, and interactions

This drug is contraindicated in patients with known hypersensitivity to vancomycin. Vancomycin is used cautiously in patients with renal or hearing impairment and during pregnancy and lactation.

When administered with other ototoxic and nephrotoxic drugs, additive effects may be seen.

13. ANTITUBERCULAR DRUGS

Tuberculosis is a major health problem throughout the world, infecting more than 8 million individuals each year. It is the world's leading cause of death from infectious disease.

Tuberculosis responds well to long-term treatment with a combination of three or more antitubercular drugs. Antitubercular drugs are used to treat active cases of tuberculosis and as a prophylactic to prevent the spread of tuberculosis. The drugs used to treat tuberculosis do not "cure" the disease, but they render the patient noninfectious to others.

Antitubercular drugs are classified as primary and second-line drugs. First-line drugs provide the foundation for treatment. Second-line or secondary drugs are less effective and more toxic than primary drugs. These drugs are used in various combinations to treat tuberculosis.

13.1. Actions

Most antitubercular drugs are bacteriostatic against the M. tuberculosis bacillus. These drugs usually act to inhibit bacterial cell wall synthesis, which slows the multiplication rate of the bacteria. Only isoniazid is bactericidal, with rifampin and streptomycin having some bactericidal activity.

13.2. Resistance to the antitubercular drugs

Of increasing concern is the development of mutant strains of tuberculosis that are resistant to many of the antitubercular drugs currently in use. Bacterial resistance develops, sometimes rapidly, with the use of antitubercular drugs. To slow the development of bacterial resistance, it was recommended the use of three or more drugs with initial therapy, as well as in retreatment.

Using a combination of drugs slows the development of bacterial resistance.

Tuberculosis caused by drug-resistant organisms should be considered in patients who have no response to therapy and in patients who have been treated in the past.

13.3. Standard treatment

Standard treatment for tuberculosis is divided into two phases: the initial phase followed by a continuing phase.

During the initial phase, drugs are used to kill the rapidly multiplying M. tuberculosis and to prevent drug resistance. The initial phase lasts approximately 2 months and the continuing phase approximately 4 months, with the total treatment regimen lasting for 6 to 9 months, depending on the patient's response to therapy.

The initial phase must contain three or more of the following drugs: isoniazid, rifampin, and pyrazinamide, along with either ethambutol or streptomycin.

It was recommended to begin the treatment as soon as possible after the diagnosis of tuberculosis. The treatment recommendation regimen is for the administration of rifampin, isoniazid, and pyrazinamide for a minimum of 2 months, followed by rifampin and isoniazid for 4 months in areas with a low incidence of tuberculosis. In areas of high incidence of tuberculosis, it was recommended the addition of streptomycin or ethambutol for the first 2 months.

13.4. Retreatment

At times treatment fails due to noncompliance with the drug regimen or to inadequate initial drug treatment.

When treatment fails, retreatment is necessary. Retreatment generally includes the use of four or more antitubercular drugs. Retreatment drug regimens most often consist of the secondary drugs ethionamide, aminosalicylic acid, cycloserine, and capreomycin.

Ofloxacin and ciprofloxacin may also be used in retreatment.

14.ANTIVIRAL DRUGS

14.1. Actions

Most antiviral drugs act by inhibiting viral DNA or RNA replication in the virus, causing viral death.

14.2. Contraindications, precautions, and interactions

All antiviral drugs are contraindicated in patients with previous hypersensitivity to the individual antiviral drug. The antiviral drugs are also contraindicated in patients with congestive heart failure, seizures, renal disease, and during lactation.

The antiviral drugs are given with caution in patients with renal impairment and require dosage adjustments. Antivirals are used with caution in children, during pregnancy (except ribavirin), and during lactation.

Other contraindications and precautions are listed below, according to the specific drug. Numerous interactions are possible with the antiviral drugs.

15.ANTIFUNGAL DRUGS

15.1. Actions

Antifungal drugs may be fungicidal or fungistatic. Amphotericin B, miconazole, nystatin, and ketoconazole are thought to have an effect on the cell

membrane of the fungus, resulting in a fungicidal or fungistatic effect. The fungicidal or fungistatic effect of these drugs appears to be related to their concentration in body tissues. Fluconazole has fungistatic activity that appears to result from the depletion of sterols in the fungus cells.

Griseofulvin exerts its effect by being deposited in keratin precursor cells, which are then gradually lost, and replaced by new, noninfected cells.

Clotrimazole binds with phospholipids in the fungal cell membrane, increasing permeability of the cell and resulting in loss of intracellular components.

15.2. Contraindications, precautions, and interactions

Amphotericin B is contraindicated in patients with a history of allergy to the drug and during lactation. It is used cautiously in patients with renal dysfunction, electrolyte imbalances, and in combination with antineoplastic drugs (because it can cause severe bone marrow suppression).

This drug is used during pregnancy only when the situation is life threatening. When given with the corticosteroids, severe hypokalemia may occur. There may be an increased risk of digitalis toxicity if digoxin is administered concurrently with amphotericin B.

Administration with nephrotoxic drugs (eg, aminoglycosides or cyclosporine) may increase the risk of nephrotoxicity in patients also taking amphotericin B. Amphotericin B decreases the effects of miconazole. Amphotericin B is given only under close supervision in the hospital setting.

Fluconazole is contraindicated in patients with known hypersensitivity to the drug. The drug is used cautiously in patients with renal impairment and during pregnancy and lactation. The drug is given during pregnancy only if the benefit of the drug clearly outweighs any possible risk to the infant. When fluconazole is administered with oral hypoglycemics, there is an increased effect of the oral hypoglycemics.

Fluconazole may decrease the metabolism of phenytoin and warfarin.

Griseofulvin is contraindicated in patients with known hypersensitivity to the drug and in those with severe liver disease. This drug is used cautiously during pregnancy and lactation. It is important to use caution when administering concurrently with penicillin because there is a possibility of crosssensitivity.

When griseofulvin is administered with warfarin, the anticoagulant effect may be decreased. When administered with the barbiturates the effect of griseofulvin may be decreased. A decrease in the effects of oral contraceptives may occur with griseofulvin therapy, causing breakthrough bleeding, pregnancy, or amenorrhea. Blood salicylate concentrations may be decreased when the salicylates are administered with griseofulvin.

Itraconazole is contraindicated in patients with known hypersensitivity to the drug. The drug is used cautiously in patients with hepatitis, those with human immunodeficiency virus, impaired liver function, and in pregnant women. In patients with hypochlorhydria, the absorption of itraconazole is decreased. Multiple drug interactions occur with itraconazole.

Itraconazole elevates blood concentrations of digoxin and cyclosporine. Phenytoin decreases blood levels of itraconazole and alters the metabolism of phenytoin. Histamine antagonists, isoniazid, and rifampin decrease plasma levels of itraconazole. There is an increased anticoagulant effect when warfarin is administered concurrently with itraconazole.

Ketoconazole is contraindicated in patients with known hypersensitivity to the drug. Ketoconazole is used cautiously in patients with hepatic impairment, those who are pregnant, and during lactation. The absorption of ketoconazole is impaired when the drug is taken with histamine antagonists and antacids.

Ketoconazole enhances the anticoagulant effect of warfarin and causes an additive hepatotoxicity when given with other hepatotoxic drugs and alcohol.

Administration of ketoconazole with rifampin or isoniazid may decrease the blood levels of ketoconazole.

Miconazole is contraindicated in patients with known hypersensitivity to the drug. The drug is given cautiously in cases of chronic or recurrent candidiasis.

The drug is used cautiously during pregnancy. If used during pregnancy, a vaginal applicator may be contraindicated.

Manual insertion of the vaginal tablets may be preferred. Because small amounts of these drugs may be absorbed from the vagina, the drug is used during the first trimester only when essential.

EXERCISES FOR OUT-CLASS WORK

Exercise 1. Using the table 1, administrate sulfonamides for the patient with:

1) urinary tract infections;
2) ulcerative colitis;
3) ophthalmic infections;
4) malaria;
5) burns.

Exercise 2. Describe clinical features and treatment of Stevens-Johnson syndrome.

Exercise 3. Explain interactions of sulfonamides with:

1) oral anticoagulant;
2) methotrexate;
3) oral hypoglycemic drugs (tolbutamide, chlorpropamide).

Exercise 4. Using the table 2, administrate quinolones for the patient with:

1) pyelonephritis;
2) urethritis;
3) cystitis;
4) prostatitis;
5) pneumonia.

Table 1. Uses, adverse reactions and dosage ranges of sulfonamides.

Drugs	Uses	Adverse reactions	Dosage ranges
1. Agents, that are absorbed and excreted rapidly			
Sulfadiazine (Dermazin)	Urinary tract infections, chancroid, acute otitis media, Hemophilus *influenzae* and meningococcal meningitis, rheumatic fever	Hematologic changes, Stevens-Johnson syndrome, nausea, vomiting, headache, diarrhea, chills, fever, anorexia, crystalluria, stomatitis, urticaria, pruritus	Loading dose: 2–4 g PO; maintenance dose: 2–4 g/d PO in 4–6 divided doses
Sulfisoxazole	Same as sulfadiazine	Same as sulfadiazine	Loading dose: 2–4 g PO; maintenance dose: 4–8 g/d PO in 4–6 divided doses
2. Agents, that are absorbed very poorly when administrated orally			
Sulfasalazine (Salazopyrin-en-tabs)	Ulcerative colitis, rheumatoid arthritis	Same as sulfadiazine; may cause skin and urine to turn orange-yellow	Initial therapy: 1–4 g/d PO in divided doses; maintenance dose: 2 g/d in evenly spaced doses 500 mg qid
3. Agents, that are used mainly topically			
Sulfacetamide (Sulfacylum natrium)	Ophthalmic infections	Sensitization	
Mafenide	Second- and third-degree burns	Pain or burning sensation, rash, itching, facial edema	Apply to burned area 1–2 times/d
4. Long-acting sulfonamides			
Sulfadoxine	Malaria caused by mefloquine-resistant strains	Stevens-Johnson syndrome	
5. Multiple preparations			
Trimethoprim (TMP) and sulfamethoxazole (SMZ)	Urinary tract infections due to susceptible microorganisms, acute otitis media, traveler's diarrhea due to *Escherichia coli*	Gastrointestinal disturbances, allergic skin reactions, hematologic changes, Stevens-Johnson syndrome, headache	160 mg TMP/800 mg SMZ PO q12h; 8–10 mg/kg/d (based on TMP) IV in 2–4 divided doses

Exercise 5. Explain interactions of quinolones with:

1) theophylline;
2) cimetidine;
3) oral anticoagulant;
4) antacids;
5) iron salts;
6) NSAIDs;
7) drugs that increase the QT interval (eg, quinidine, procainamide, amiodarone, and sotalol).

Table 2. Uses, adverse reactions and dosage ranges of quinolones.

Drugs	Uses	Adverse reactions	Dosage ranges
Ciprofloxacin (Ciprobay)	Treatment of infections due to susceptible microorganisms	Nausea, diarrhea, headache, abdominal discomfort, photosensitivity, superinfections, hypersensitivity reactions	250–750 mg PO q12h; 200–400 mg IV q12h
Gatifloxacin (Tabris)	Same as ciprofloxacin	Same as ciprofloxacin	200–400 mg qd PO or IV
Levofloxacin (Tavanik)	Same as ciprofloxacin	Same as ciprofloxacin	250–500 mg/d PO, IV
Lomefloxacin (Okacin)	Same as ciprofloxacin	Same as ciprofloxacin	400 mg PO once daily
Moxifloxacin (Avelox)	Same as ciprofloxacin	Same as ciprofloxacin	400 mg qd PO
Norfloxacin	Same as ciprofloxacin	Same as ciprofloxacin	400 mg PO q12h
Ofloxacin (Tarivid)	Same as ciprofloxacin	Same as ciprofloxacin	200–400 mg PO, IV q12h
Pefloxacin (Abaktal)	Same as ciprofloxacin	Same as ciprofloxacin	400 mg PO or IV q12h
Sparfloxacin	Same as ciprofloxacin	Same as ciprofloxacin	400 mg PO once daily

Exercise 6. Using the table 3, administrate tetracyclines for the patient with:

1) intestinal amebiasis;
2) typhus fever;
3) acne.

Exercise 7. Explain interactions of tetracylines with:

1) antacids containing aluminum, zinc, magnesium, or bismuth salts;
2) foods high in calcium;
3) contraceptives;
4) digoxin.

Table 3. Uses, adverse reactions and dosage ranges of tetracyclines.

Drugs	Uses	Adverse reactions	Dosage ranges
Doxycycline (Vibramycin)	Rocky Mountain spotted fever, typhus fever, tick fevers, intestinal amebiasis, infections caused by *Chlamydia trachomatis, Helicobacter pylori*, acne	Nausea, vomiting, diarrhea, hypersensitivity reactions, photosensitivity reactions, pseudomembranous colitis, hematologic changes, discoloration of teeth in fetus and young children	150 mg PO QID or 300 mg PO BID; gonorrhea: 600 mg PO initially then 300 mg PO q12h for 4 d
Tetracycline	Same as doxycycline	Same as doxycycline	1–2 g/d PO in 2–4 divided doses

Exercise 8. Using the table 4, administrate macrolides for the patient with:

1) respiratory infections;
2) skin infections.

Exercise 9. Explain interactions of macrolides with:

1) digoxin;
2) anticoagulants;
3) antacids;
4) clindamycin, lincomycin, chloramphenicol;
5) theophylline levels.

Table 4. Uses, adverse reactions and dosage ranges of macrolides.

Drugs	Uses	Adverse reactions	Dosage ranges
Azithromycin (Sumamed)	Treatment of infections due to susceptible microorganisms	Nausea, vomiting, diarrhea, abdominal pains, hypersensitivity reactions, pseudo-membranous colitis	500 mg PO first day then 250 mg/d PO for 4 d
Clarithromycin (Klacid)	Same as azithromycin	Same as azithromycin	250–500 mg PO BID
Erythromycin base	Same as azithromycin	Same as azithromycin	250 mg PO q6h or 333 mg q8h 400 mg PO q6h

Exercise 10. Using the table 5, administrate penicillins for the patient with:

1) meningitis;
2) gonorrhea;
3) syphilis;
4) respiratory infections.

Exercise 11. Explain interactions of penicillins with:

1) birth control pills that contain estrogen;
2) tetracyclines;
3) anticoagulant agents;
4) food.

Exercise 12. Using the table 6, administrate cephalosporins for the patient with:

1) lower respiratory infections;
2) urinary tract infections;
3) septicemia;
4) gonorrhea.

Exercise 13. Explain interactions of cephalosporins with:

1) aminoglycosides;
2) oral anticoagulants;
3) alcohol.

Table 5. Uses, adverse reactions and dosage ranges of penicillins.

Drugs	Uses	Adverse reactions	Dosage ranges
1. Natural penicillins			
Penicillin G (Benzylpenicillinum)	Infections due to susceptible microorganisms; syphilis, gonorrhea	Glossitis, stomatitis, gastritis, furry tongue, nausea, vomiting, diarrhea, rash, hypersensitivity reactions, fever	Up to 20—30 million U/d IV or IM; dosage may also be based on weight
Penicillin G benzathine (Retarpen)	Infections due to susceptible microorganisms, syphilis; prophylaxis of rheumatic fever	Same as penicillin G	Up to 2.4 million U/d IM
Penicillin V (Phenoxymethyl-penicillinum)	Infections due to susceptible organisms	Same as penicillin G	125-500 mg PO q6h or q8h
2. Penicillinase-resistant penicillins			
Oxacillin sodium	Same as penicillin G	Same as penicillin G	500 mg—1 g PO q4—6h; 250 mg—1 g q 4—6h IM, IV
3. Aminopenicillins			
Amoxicillin	Same as penicillin G	Same as penicillin G	250-500 mg PO q8h or 875 mg PO BID
Amoxicillin and clavulanate acid (Amoksiklav)	Same as penicillin G	Same as penicillin G	250-500 mg PO q8h or 875 mg q12h
Ampicillin	Same as penicillin G	Same as penicillin G	250-500 mg PO q6h 1-12 g/d IM, IV in divided doses of q6h
Ampillicin/sulbactam (Unazyn)	Same as penicillin G	Same as penicillin G	0.5-1 g Sulbactam with 1-2 g ampicillin IM or IV q6–8h
4. Extended-Spectrum Penicillins			
Ticarcillin andclavulanate potassium (Timentin)	Same as penicillin G	Same as penicillin G	3.1 g IV q4-6h or 200-300 mg/kg/d IV in divided doses q6h
Piperacillin sodium and tazobactam sodium (Zopercin)	Same as penicillin G	Same as penicillin G	12 mg/1.5 g IV given as 3.375 g q6h

Exercise 14. Explain interactions of aminoglycosides with:

1) cephalosporins;
2) loop diuretics;
3) general anesthetics (neuromuscular junction blockers).

Table 6. Uses, adverse reactions and dosage ranges of cephalosporins.

Drugs	Uses	Adverse reactions	Dosage ranges
First-Generation Cephalosporins			
Cefadroxil (Duracef)	Infections due to susceptible microorganisms	Nausea, vomiting, diarrhea, hypersensitivity reactions, superinfection, nephrotoxicity, headache, Stevens-Johnson syndrome, pseudomembranous colitis	1–2 g/d PO in divided doses
Cefazolin sodium (Totacef)	Infections due to susceptible microorganisms; perioperative prophylaxis	Same as cefadroxil	250 mg–1 g IM, IV 6–12h; perioperative, 0.5–1g IM, IV
Cephalexin (Ospexin)	Same as cefadroxil	Same as cefadroxil	1–4 g/d PO in divided doses
Second-Generation Cephalosporins			
Cefamandole	Treatment of infections due to susceptible organisms	Nausea, vomiting, diarrhea, hypersensitivity reactions, nephrotoxicity, headache	500 mg to 1 g IM, IV q4–6h
Cefuroxime (Zinacef)	Treatment of infections due to susceptible organisms	Same as cefamandole	250 mg PO BID; 750 mg–1.5 g IM or IV8h;
Third-Generation Cephalosporins			
Cefoperazone (Cefobid)	Treatment of infections due to susceptible organisms, periope-rative prophylaxis	Nausea, vomiting, diarrhea, hypersensitivity reactions, nephrotoxicity, headache	2–4 g/d IM, IV in equally divided doses q8-12h
Cefotaxime (Claforan)	Same as cefoperazone	Same as cefoperazone	2–12 g/d IM or IV q6–8h
Ceftazidime (Fortum)	Same as cefoperazone	Same as cefoperazone	250 mg–2 g IV, IM q8-12h
Ceftibuten hydrochloride	Same as cefoperazone	Same as cefoperazone	400 mg/d for 10 days
Ceftriaxone (Rocephin)	Same as cefoperazone, gonorrhea	Same as cefoperazone	1–4 g/d IM, IV QID, BID
Fourth-Generation Cephalosporins			
Cefepime (Maxipime)	Same as cefoperazone	Same as cefoperazone	0.5 mg–2 g IV, IM q12h

Exercise 15. Using the table 7, administrate aminoglycosides for the patient:

1) with urinary tract infections;
2) after surgery on the bowel;
3) with hepatic coma.

Exercise 16. Using the table 8, administrate lincosamides for the patient with:

1) respiratory infections;
2) skin infections.

Table 7. Uses, adverse reactions and dosage ranges of aminoglycosides.

Drugs	Uses	Adverse reactions	Dosage ranges
Amikacin (Amikin)	Treatment of serious infections caused by susceptible strains of microorganisms	Nausea, vomiting, diarrhea, rash, ototoxicity, nephrotoxicity, neurotoxicity, hypersensitivity reactions, neuromuscular blockade	15 mg/kg IM, IV, in divided doses, not to exceed 1.5 g/d
Gentamicin	Same as amikacin	Same as amikacin	3-5 mg/kg/d q8h IM, IV in divided doses
Kanamycin	Same as amikacin oral, use for suppression of intestinal bacteria	Same as amikacin	7.5–15 mg/kg/d in divided doses IM and IV; suppression of intestinal bacteria 1 g qh for 4h then 1 g q6h for 36—72 h PO
Netilmicin (Netromycin)	Same as amikacin	Same as amikacin	Up to 6.5 mg/kg/d IV in divided doses
Streptomycin	Same as amikacin, fourth drug in the treatment of TB	Same as amikacin	15 mg/kg/d IM or 25–30 mg/kg IM 2–3 times per week
Tobramycin	Same as amikacin	Same as amikacin	3–5 mg/kg/d IM, IV q8h

Exercise 17. Explain interactions of lincosamides with:

1) antacids containing aluminum salts;
2) neuromuscular blocking drugs.

Table 8. Uses, adverse reactions and dosage ranges of lincosamides.

Drugs	Uses	Adverse reactions	Dosage ranges
Clindamycin (Dalacin)	Treatment of infections due to susceptible microorganisms	Abdominal pain, esophagitis, nausea, vomiting, diarrhea, skin rash, hypersensitivity reactions, pseudo-membranous colitis	150–450 mg PO q6h; 600–2700 mg/d in 2–4 equal doses; up to 4.8 g/d IV, IM
Lincomycin (Lincocin)	Same as clindamycin	Same as clindamycin	500 mg PO q6–8h; 600 mg IM q12–24h; up to 8 g/d IV

Exercise 18. Using the table 9, administrate glicopeptides for the patient with:

1) gram-positive infections that do not respond to treatment with other antibiotics;
2) pseudomembranous colitis caused by Clostridium difficile.

Exercise 19. Explain interactions of glicopeptides with:

1) aminoglycosides;
2) antacids.

Table 9. Uses, adverse reactions and dosage ranges of glicopeptides.

Drugs	Uses	Adverse reactions	Dosage ranges
Vancomycin (Edicin)	Serious susceptible gram-positive infections not responding to treatment with other antibiotics	Nephrotoxicity, ototoxicity, nausea, chills, fever, urticaria, sudden fall in blood pressure, redness on face, neck, arms, and back	500 mg to 2 g/d PO in divided doses; 500 mg IV q6h or 1 g IV q8—12h

Exercise 20. Using the table 10, administrate antitubercular drugs for the patient:

1) with primary tuberculosis;
2) in preventive therapy (prophylaxis).

Table 10. Uses, adverse reactions and dosage ranges of antitubercular drugs.

Drugs	Uses	Adverse reactions	Dosage ranges
First-line therapy			
Isoniazid	Active TB; prophylaxis for TB	Peripheral neuropathy, nausea, vomiting, epigastric distress, jaundice, hepatitis, pyridoxine deficiency, skin eruptions	Active TB: up to 300 mg/d PO or up to 300 mg/d IM, to 900 mg IM 2—3 times/wk; TB prophylaxis: 30 mg/d PO
Rifampin	Active TB	Heartburn, drowsiness, fatigue, dizziness, epigastric distress, renal insufficiency, hematologic changes	600 mg PO, IV
Pyrazinamide	Active TB	Hepatotoxicity, nausea, vomiting, diarrhea, myalgia, rashes	15—30 mg/kg/d, maximum 3 g/d PO;
Ethambutol	Pulmonary tuberculosis (TB)	Optic neuritis, fever, pruritis, headache, nausea, anorexia, dermatitis, psychic disturbances	15–25 mg/kg/d PO
Streptomycin	TB	Nephrotoxicity, ototoxicity, numbness, tingling, nausea, dizziness	Up to 1 g/d IM
Alternative agents			
Gatifloxacin (Tabris)	TB	Nausea, diarrhea, headache, abdominal discomfort, photosensitivity, superinfections	200–400 mg qd PO or IV
Moxifloxacin	TB	Same as gatifloxacin	400 mg qd PO
Cycloserine	TB	Convulsions, somnolence, renal impairment, congestive heart failure, psychoses	500 mg to 1 g PO in divided doses
Capreomycin sulfate	TB	Hypersensitivity reactions, ototoxicity, nephrotoxicity, hepatic impairment, induration at injection site	I g/d (maximum, 20 mg/kg/d) IM
Amikacin (Amikin)	TB	Nausea, vomiting, neuromuscular blockade, nephrotoxicity, ototoxicity, neurotoxicity, diarrhea,	15 mg/kg IM, IV, in divided doses, not to exceed 1.5 g/d
Kanamycin	TB	Same as amikacin	7.5–15 mg/kg/d in divided doses IM, IV
p-Amino-salicylic acid	TB	Nausea, vomiting, diarrhea, abdominal pain	4 g (1 packet) PO TID

Exercise 21. Explain interactions of:

1) isoniazid with alcohol, antacids containing aluminum salts, anticoagulants, phenytoin, foods containing tyramine (aged cheese and meats, bananas, yeast products);

2) rifampin with digoxin, isoniazid, oral anticoagulants, oral hypoglycemics, oral contraceptives, chloramphenicol, phenytoin, verapamil.

3) streptomycin with ethacrynic acid, furosemide, and mannitol.

Exercise 22. Using the table 11, administrate antifungal agents for the patient with:

1) esophageal candidiasis;
2) ringworm infections of the skin;
3) systemic fungal infections.

Table 11. Uses, adverse reactions and dosage ranges of antifungal agents.

Drugs	Uses	Adverse reactions	Dosage ranges
Amphotericin B	Systemic fungal infections	Headache, hypotension, fever, shaking, chills, malaise, nausea, vomiting, diarrhea, abnormal renal function, joint and muscle pain	0.25 mg/kg/d IV
Fluconazole (Diflucan)	Oropharyngeal and esophageal candidiasis, vaginal candidiasis, cryptococcal meningitis	Headache, nausea, vomiting, diarrhea, skin rash	50–400 mg/d PO, IV
Griseofulvin	Ringworm infections of the skin, hair, nails	Nausea, vomiting, diarrhea, oral thrush, headache, rash, urticaria	125–500 mg/d PO
Itraconazole	Fungal infections; especially candidiasis	Nausea, vomiting, diarrhea, rash, abdominal pain, edema	200–400 mg/d PO, IV as a single or divided dose
Ketoconazole (Nizoral)	Treatment of fungal infections	Nausea, vomiting, abdominal pain, headache, pruritus	200 mg/d PO; may increase to 400 mg/d PO
Nystatin	Nonesophageal membrane GI candidiasis	Rash, diarrhea, nausea, vomiting	500,000–1,000,000 U TID

Exercise 23. Explain interactions of:

1) amphotericin B with antineoplastic drugs, corticosteroids, digoxin, nephrotoxic drugs (aminoglycosides, cyclosporine), miconazole;

2) fluconazole with oral hypoglycemics, phenitoin, warfarin;

3) griseofulvin with warfarin, barbiturates, oral contraceptives, salicylates;

4) intraconazole with digoxin, cyclosporine, phenytoin, histamine antagonists, isoniazid, rifampin, warfarin;

5) ketoconazole with histamine antagonists, antacids, warfarin, alcogol, isoniazid, rifampin.

Exercise 24. Using the table 12, administrate antiviral agents for the patient with:

1) Herpes simplex;
2) influenza A;
3) Hepatitis C;
4) CMV retinitis.

Table 12. Uses, adverse reactions and dosage ranges of antiviral agents (nonretroviral).

Drugs	Uses	Adverse reactions	Dosage ranges
1. Antiherpevirus agents			
Acyclovir (Zovirax)	Herpes simplex, herpes zoster	Nausea, vomiting, diarrhea, headache, dizziness, lethargy, confusion, rashes, crystalluria, phlebitis	Oral, 200 mg q4h; IV, 5–10 mg/kg q8h; topical, apply to lesions q3h
Famciclovir (Famvir)	Acute herpes zoster, HSV type 2	Fatigue, fever, nausea, vomiting, diarrhea, sinusitis, constipation, headache	Herpes zoster: 500 mg PO q8h for 7 d; HSV-2: 125 mg PO BID for 5 d
Ganciclovir (Cymevene)	CMV retinitis	Hematologic changes, fever, rash, anemia	5 mg/kg IV q12h for 14–21 d, then QD
Valacyclovir (Valtrex)	HSV type 2; herpes zoster	Nausea, dizziness, headache, vomiting, anorexia, diarrhea	HSV type 2: 500 mg PO BID for 5 d; herpes zoster: 1 g PO TID
2. Antiinfluenza agents			
Amantadine	Prevention and treatment of influenza A	Nausea, vomiting, diarrhea, dizziness, hypotension, blurred vision, psychosis, urinary retention	200 mg/d PO or 100 mg PO BID; up to 400 mg/d
Oseltamivir (Tamiflu)	Treatment of influenza A and B	Nausea, vomiting, diarrhea, abdominal pain, dizziness, headache, cough	75–150 mg/d PO
Rimantadine HCL	Influenza A virus	Light-headedness, dizziness, insomnia, nausea, anorexia	100 mg/d PO BID
3. Antihepatitis agents			
Interferon-alfa (Intron-A)	Hepatitis C	Headache, asthenia, myalgia	5000000-10000000 ME SC 3 times per week
Lamivudine (Zeffix)	Hepatitis C, HIV infection (combined with zidovudine)	Headache, asthenia, nausea, diarrhea, agranulocytopenia, nasal congestion, cough, fever, rash, pancreatitis, hepatomegaly	150 mg PO BID
Peginterferon alfa-2A (Pegasys)	Hepatitis C	Headache, asthenia, nausea, diarrhea, dermatitis	180 mkg SC 1 time per week
Peginterferon alfa-2B (Pegintron)	Hepatitis C	Headache, asthenia, nausea, diarrhea	180 mkg SC 1 time per week
4. Other antiviral agents			
Ribavirin (Virazole)	Respiratory tract infections	Worsening of pulmonary status, bacterial pneumonia, hypotension	Administered by aerosol with special aerosol generator

Exercise 25. Explain interactions of:

1) acyclovir with zidovudine, nephrotoxic drugs;

2) amantadine with antihistamines, phenothiazines, tricyclic antidepressants.

Exercise 26. Using the table 13, administrate antiretroviral agents for the patient with HIV infection.

Table 13. Uses, adverse reactions and dosage ranges of antiretroviral agents.

Drugs	Uses	Adverse reactions	Dosage ranges
1. Nucleoside reverse transcriptase inhibitors			
Zidovudine (Retrovir)	HIV infection	Asthenia, malaise, weakness, headache, anorexia, diarrhea, nausea, abdominal pain, dizziness, insomnia, anemia, agranulocytosis	100 mg q4h PO; 1–2 mg/kg IV q4h
Didanosine (Videx)	HIV infection	Headache, rhinitis, cough, nausea, rash, vomiting, anorexia, hepatotoxicity, pancreatitis, peripheral neuropathy	For patients with creatinine clearance (Ccr) > 60 mL/min and weighing 60 kg, 400 mg/d
Stavudine (Zerit)	HIV infection	Headache, nausea, diarrhea, fever, agranulocytopenia	40 mg PO q12h
Lamivudine (Zeffix)	HIV infection (combined with zidovudine), Hepatitis C	Headache, asthenia, nausea, diarrhea, agranulocytopenia, nasal congestion, cough, fever, rash, pancreatitis, hepatomegaly	150 mg PO BID
Abacavir sulfate (Ziagen)	HIV infection	Nausea, vomiting, diarrhea, anorexia, liver dysfunction	300 mg BID
2. Nonnucleoside reverse transcriptase inhibitors			
Nevirapine (Viramune)	HIV infection, in combination with other antivirals	Rash, fever, headache, nausea, stomatitis, liver dysfunction, paresthesia	200 mg PO QD or BID
Efavirenz	HIV infection	Erythema, pruritus, dizziness, fatigue, nausea, vomiting	200–600 mg/d PO
3. Protease inhibitors			
Indinavir (Crixivan)	HIV infection	Headache, nausea, vomiting, diarrhea, hyperbilirubinemia, cough, dysuria, acne	800 mg PO q8h
Ritonavir (Norvir)	HIV infection	Peripheral and circumoral paresthesias, nausea, vomiting, diarrhea, anorexia, dysuria	600 mg PO BID
Nelfinavir (Viracept)	HIV infection, in combination with other antivirals	Diarrhea, nausea, GI pain, rash, dermatitis	750–1250 mg PO BID
4. Fusion inhibitor			
Enfuviride	HIV infection	Diarrhea, nausea, GI pain, rash	600 mg PO BID

Exercise 28. Explain interactions of zidovudine with antineoplastic drugs, acyclovir, clarithromycin.

CLINICAL EXERCISES FOR OUT-CLASS WORK

1. Ms. Bartlett, age 80, has been prescribed a sulfonamide for a urinary tract infection and is to take the drug for 10 days. You note that Ms. Bartlett seems forgetful and at times confused. Determine what problems might be associated with Ms. Bartlett's mental state and her possible noncompliance to her prescribed treatment regimen.
2. Mr. Garcia is receiving sulfisoxazole for a recurrent bladder infection. When keeping an outpatient clinic appointment, he tells you that he developed a fever and sore throat yesterday. Analyze the steps you would take to investigate his recent problem. Give a reason for your answers.
3. Ms. Watson has diabetes and is taking tolbutamide. You prescribe the combination drug sulfamethoxazole and trimethoprim for a bladder infection. Discuss any instructions/information you would give to Ms. Watson in the patient education session.
4. Ms. Barker had a bowel resection 4 days ago. After a culture and sensitivity test of her draining surgical wound, you order penicillin G aqueous IV as a continuous drip. Determine what questions you would ask Ms. Barker before the penicillin is added to the IV solution.
5. After administering penicillin to a patient in an outpatient setting, you request that the patient wait about 30 minutes before leaving. The patient is reluctant to stay, saying that she has a busy schedule. Discuss how you would handle this situation.
6. A 28-year-old married woman with three children is prescribed ampicillin for an upper respiratory infection caused by Streptococcus pneumoniae. What information would be important for you to obtain from this woman? What special instructions would you give her because of her gender and age?
7. Mr. Jonas is receiving a cephalosporin IM. He tells you that he has had to get out of bed several times this morning because he has diarrhea. Determine what questions you would ask Mr. Jonas. Analyze what steps you would take to resolve this problem.
8. Analyze what assessments you would make if you suspect that a patient receiving a cephalosporin is experiencing Stevens-Johnson syndrome.
9. Ms. Jones has been prescribed tetracycline. She works nights and is home sleeping during the day. To decrease the possibility of noncompliance with the treatment regimen, discuss how and what you would teach Ms. Jones about her drug regimen.
10. Mr. Park, a patient in a nursing home, has been receiving clarithromycin for an upper respiratory infection for 9 days. The nurse assistant reports that he has been incontinent of feces for the past 2 days. Analyze whether this matter should be investigated.

11. When taking the drug history of Mr. Woods, a patient in the outpatient clinic, you note that he has been taking 0.25 mg digoxin, one baby aspirin, and the tetracycline. Based on your knowledge of the tetracyclines, determine whether there is any reason to be concerned about the drug regimen that Mr. Woods is on. Explain your answer.

12. Ms. Evans, age 75 years, is to be dismissed on a regimen of doxycycline. You note that she is alert and has good communication skills. Because she lives alone, she will be responsible for administering her own drug. Devise a teaching plan for Ms. Evans.

13. Mr. Baker is receiving amikacin IV as treatment for a bacterial septicemia. When checking a drug reference you note that this drug is an aminoglycoside. Considering the most serious toxic effects associated with this group of drugs, determine what daily assessments you would perform to detect early signs and symptoms of these adverse drug effects.

14. Ms. Carson is seen in the outpatient clinic for a severe respiratory infection and is prescribed ciprofloxacin. Discuss what you would include in the teaching plan for this patient.

15. A patient is prescribed ciprofloxacin for a severe respiratory infection. What serious adverse reaction(s) should the nurse warn the patient to be especially observant for? What common adverse reactions should the patient be aware of? What important information should the nurse include in the teaching plan concerning adverse reactions?

16. Mr. Stone is receiving vancomycin. One adverse reaction that may be seen with the administration of this drug is ototoxicity. Rather than ask Mr. Stone directly whether he is having any problem with his hearing, discuss how you might determine if ototoxicity might be occurring.

17. Mr. Reeves has a severe infection and is receiving chloramphenicol IV. The nurse notes several bruises on Mr.Reeves arm after 2 days of therapy. What action should the nurse take. Give a rationale for your answer.

18. Ms. Burns has received a diagnosis of tuberculosis. She is concerned because her doctor has informed her that the treatment regimen consists of three drugs, isoniazid, rifampin, and pyrazinamide, taken for the next 2 months, followed by a 4-month treatment regimen with two of the drugs.

REVIEW QUESTIONS

1. A nurse working in the clinic asks how the sulfonamides control an infection. The most correct answer is that these drugs:
   A) encourage the production of antibodies;
   B) antagonize PABA, which some bacteria need to multiply;
   C) reduce the urine output;
   D) make the urine alkaline, which eliminates bacteria.

2. Patients receiving sulfasalazine for ulcerative colitis are told that the drug:
   A) is not to be taken with food;

B) rarely causes adverse effects;
C) may cause hair loss;
D) may turn the urine orange-yellow in color.

3. When reviewing Ms. Robertson's culture and sensitivity test results, the nurse learns that the bacteria causing Ms. Robertson's infection are sensitive to penicillin. The doctor interprets this result to mean that:
   A) Ms. Robertson is allergic to penicillin;
   B) penicillin will be effective in treating the infection;
   C) penicillin will not be effective in treating the infection;
   D) the test must be repeated to obtain accurate results.

4. Mr. Thomas, who is receiving oral penicillin, reports he has a sore mouth. Upon inspection the doctor notes a black, furry tongue and bright red oral mucous membranes. These symptoms may be caused by:
   A) a vitamin C deficiency;
   B) a superinfection;
   C) dehydration;
   D) poor oral hygiene.

5. The nurse correctly administers penicillin V:
   A) 1 hour before or 2 hours after meals;
   B) without regard to meals;
   C) with meals to prevent gastrointestinal upset;
   D) every 3 hours around the clock.

6. After administering penicillin in an outpatient setting the doctor:
   A) asks the patient to wait 10 to 15 minutes before leaving the clinic;
   B) instructs the patient to report any numbness or tingling of the extremities;
   C) keeps pressure on the injection site for 10 minutes;
   D) asks the patient to wait in the area for at least 30 minutes.

7. The doctor observes a patient taking a cephalosporin for common adverse reactions, which include:
   A) hypotension, dizziness, urticaria;
   B) nausea, vomiting, diarrhea;
   C) skin rash, constipation, headache;
   D) bradycardia, pruritus, insomnia.

8. When giving a cephalosporin IM, the doctor tells the patient that:
   A) a stinging or burning sensation at the site may be experienced;
   B) the injection site will be red for several days;
   C) all injections will be given in the same area;
   D) the injection will not cause any discomfort.

9. A nurse asks why it is so important to determine if the patient is allergic to penicillin before the first dose of the cephalosporin is given. The most correct answer is that persons allergic to penicillin:
   A) are usually allergic to most antibiotics;

B) respond poorly to antibiotic therapy;
C) require higher doses of other antibiotics;
D) have a higher incidence of allergy to the cephalosporins.

10. The doctor observes a patient receiving a cephalosporin for the Stevens-Johnson syndrome. The symptoms that might indicate this syndrome include:
A) swelling of the extremities;
B) increased blood pressure and pulse rate;
C) lesions on the skin and/or mucous membranes;
D) pain in the joints.

11. A patient is receiving erythromycin for an infection. The patient's response to therapy is best evaluated by:
A) monitoring vital signs every 4 hours;
B) comparing initial and current signs and symptoms;
C) monitoring fluid intake and output;
D) asking the patient if he is feeling better.

12. When asked to describe a photosensitivity reaction, the doctor correctly states that this reaction may be described as a(n):
A) tearing of the eyes on exposure to bright light;
B) aversion to bright lights and sunlight;
C) sensitivity to products in the environment;
D) exaggerated sunburn reaction when the skin is exposed to sunlight.

13. When giving one of the macrolide antibiotics, the doctor assesses the patient for the most common adverse reactions, which are:
A) related to the gastrointestinal tract;
B) skin rash and urinary retention;
C) sores in the mouth and hypertension;
D) related to the nervous system.

14. Mr. Allison is taking gentamicin for a severe gramnegative infection. The nurse observes him for signs of neurotoxicity, which include:
A) anorexia and abdominal pain;
B) decreased urinary output and dark, concentrated urine;
C) muscle twitching and numbness;
D) headache and agitation.

15. Patients taking a fluoroquinolone are encouraged to:
A) nap 1 to 2 hours daily while taking the drug;
B) eat a high-protein diet;
C) increase their fluid intake;
D) avoid foods high in carbohydrate.

16. Which of the following complaints by a patient taking tobramycin would be most indicative the patient is experiencing ototoxicity?
A) tingling of the extremities;
B) complaints that he is unable to hear the television;

C) changes in mental status;
D) short periods of dizziness.

17. A patient is prescribed moxifloxacin. The nurse notes that the patient is also taking an antacid. The doctro correctly administers moxifloxacin:
A) once daily PO, 4 hours before the antacid;
B) twice daily PO, immediately following the antacid;
C) once daily IM without regard to the administration of the antacid;
D) every 12 hours IV without regard to the administration of the antacid.

18. The doctor is asked why kanamycin is given as a "bowel prep" before gastrointestinal surgery. The doctor correctly replies:
A) abdominal surgery requires starting antibiotic therapy 4 days before surgery;
B) the bacteria found in the bowel cannot be destroyed after surgery;
C) a reduction of intestinal bacteria lessens the possibility of postoperative infection;
D) anesthesia makes the bowel resistant to an antibiotic after surgery.

19. When educating a patient about the drug linezolid the doctor instructs the patient:
A) to take the drug without food to enhance absorption;
B) to avoid foods high in tyramine such as chocolate, coffee, tea, red wine;
C) to avoid alcohol for at least 10 days after taking the drug;
D) that frequent liver function tests will be necessary while taking the drug.

20. When giving a drug that is potentially neurotoxic, the doctor reports which of the patient's complaints related to neurotoxicity?
A) light-headedness and abdominal pain;
B) severe headache and feeling chilly;
C) numbness of the extremities and dizziness;
D) blurred vision and tinnitus.

Lesson 10

CLINICAL PHARMACOLOGY OF DRUGS AFFECTING GASTROINTESTINAL FUNCTION

QUESTIONS FOR IN-CLASS WORK

1. Proton pump inhibitors: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
2. Miscellaneous gastrointestinal drugs: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
3. Antacids: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
4. Histamine H2 antagonists: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
5. Gastrointestinal stimulants: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
6. Antidiarrheals: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
7. Antiflatulents: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
8. Emetics: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
9. Laxatives: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
10. Drugs used in peptic ulcer disease.
11. Drugs used in nausea and vomiting.
12. Drugs used in ulcerative colitis.
13. Drugs used in Crohn's disease.

THEORETICAL ISSUES

1. ANTACIDS

1.1. Actions

Some of the cells of the stomach secrete hydrochloric acid, a substance that aids in the initial digestive process.

Antacids are drugs that neutralize or reduce the acidity of stomach and duodenal contents by combining with hydrochloric acid and producing salt and water. Examples of antacids include aluminum hydroxide gel, and magnesia or magnesium hydroxide.

1.2. Contraindications, precautions, and interactions

The antacids are contraindicated in patients with severe abdominal pain of unknown cause and during lactation.

Sodium-containing antacids are contraindicated in patients with cardiovascular problems, such as hypertension or congestive heart failure, and those on sodium-restricted diets. Calcium-containing antacids are contraindicated in patients with renal calculi or hypercalcemia.

Aluminum-containing antacids are used cautiously in patients with gastric outlet obstruction. Magnesium- and aluminum-containing antacids are used cautiously in patients with decreased kidney function. The calciumcontaining antacids are used cautiously in patients with respiratory insufficiency, renal impairment, or cardiac disease. Antacids should be used with caution during pregnancy.

Antacids may interfere with other drugs in three ways:

1. Increasing the gastric pH, which causes a decrease in absorption of weakly acidic drugs and results in a decreased drug effect (eg, digoxin, phenytoin, chlorpromazine, and isoniazid).
2. Absorbing or binding drugs to their surface, resulting in decreased bioavailability (eg, tetracycline).
3. Affecting the rate of drug elimination by increasing urinary pH (eg, the excretion of salicylates is increased, whereas excretion of quinidine and amphetamines is decreased).

The following drugs have a decreased pharmacologic effect when administered with an antacid: corticosteroids, digoxin, chlorpromazine, oral iron products, isoniazid, phenothiazines, ranitidine, phenytoin, valproic acid, and the tetracyclines.

2. GASTROINTESTINAL STIMULANTS

2.1. Actions

Metoclopramide and dexpanthenol increase the motility of the upper GI tract. The exact mode of action of these drugs is unclear.

2.2. Contraindications, precautions, and interactions

The GI stimulants are contraindicated in patients with known hypersensitivity to the drugs, GI obstruction, gastric perforation or hemorrhage, or epilepsy. These drugs are secreted in breast milk and should not be used during lactation.

These drugs are used cautiously in patients with diabetes and cardiovascular disease.

The effects of metoclopramide are antagonized by concurrent administration of anticholinergics or narcotic analgesics. Metoclopramide may decrease the absorption of digoxin and cimetidine and increase absorption of acetaminophen, tetracyclines, and levodopa. Metoclopramide may alter the body's insulin requirements.

3. HISTAMINE H2 ANTAGONISTS

3.1. Actions

These drugs inhibit the action of histamine at histamine H2 receptor cells of the stomach, which then reduces the secretion of gastric acid and reduces total pepsin output. The decrease in acid allows the ulcerated areas to heal.

Examples of histamine H2 antagonists include cimetidine, famotidine, nizatidine, ranitidine.

3.2. Contraindications, precautions, and interactions

The histamine H2 antagonists are contraindicated in patients with a known hypersensitivity to the drugs. These drugs are used cautiously in patients with renal or hepatic impairment and in the severely ill or debilitated patient. The histamine H2 antagonists are used cautiously in the older adult (causes confusion). A dosage reduction may be required. Histamine antagonists should be used with caution during pregnancy and lactation.

There are many drug–drug interactions with the histamine H2 antagonists. Antacids and metoclopramide may decrease absorption of the H2 antagonists if administered concurrently.

Concurrent use of cimetidine and digoxin may decrease serum digoxin levels. There may be a decrease in white blood cell count when the H2 antagonists are administered with the alkylating drugs or the antimetabolites. There is an increased risk of toxicity of oral anticoagulants, phenytoin, quinidine, lidocaine, or theophylline when administered with H2 antagonists.

Concurrent use of cimetidine and morphine increases the risk of respiratory depression.

4. ANTIDIARRHEALS

4.1. Actions

Antidiarrheals decrease intestinal peristalsis, which is usually increased when the patient has diarrhea. Examples of these drugs include difenoxin with atropine, diphenoxylate with atropine, and loperamide.

4.2. Contraindications, precautions, and interactions

These drugs are contraindicated in patients whose diarrhea is associated with organisms that can harm the intestinal mucosa (Escherichia coli, Salmonella, Shigella) and in patients with pseudomembranous colitis, abdominal pain of unknown origin, and obstructive jaundice.

The antidiarrheal drugs are contraindicated in children younger than 2 years.

The antidiarrheal drugs are used cautiously in patients with severe hepatic impairment or inflammatory bowel disease.

Antidiarrheals should be used cautiously during pregnancy and lactation.

The antidiarrheal drugs cause an additive CNS depression when administered with alcohol, antihistamines, narcotics, and sedatives or hypnotics. There are additive cholinergic effects when administered with other drugs having anticholinergic activity, such as antidepressants or antihistamines. Concurrent use

of the antidiarrheals with a monoamine oxidase inhibitor increases the risk of a hypertensive crisis.

5. ANTIFLATULENTS

5.1. Actions

Simethicone and charcoal are used as antiflatulents (against flatus or gas in the intestinal tract). Simethicone has a defoaming action that disperses and prevents the formation of mucus-surrounded gas pockets in the intestine. Charcoal is an absorbent that reduces the amount of intestinal gas.

5.2. Contraindications, precautions, and interactions

The antiflatulents are contraindicated in patients with known hypersensitivity to any components of the drug.

There may be a decreased effectiveness of other drugs because of adsorption by charcoal, which can also adsorb other drugs in the GI tract. There are no known interactions with simethicone.

6. EMETICS

6.1. Actions

The emetic (a drug that induces vomiting) ipecac causes vomiting because of its local irritating effect on the stomach and by stimulation of the vomiting center in the medulla.

6.2. Contraindications, precautions, and interactions

Emetics are contraindicated in patients who are unconscious, semiconscious, or convulsing and in poisoning caused by corrosive substances, such as strong acids or petroleum products. Safe use of these drugs in pregnancy has not been established.

Activated charcoal may absorb ipecac, negating its effects.

7. LAXATIVES

7.1. Actions

The action of each laxative is somewhat different, yet they produce the same result—the relief of constipation.

7.2. Contraindications, precautions, and interactions

Laxatives are contraindicated in patients with known hypersensitivity and those with persistent abdominal pain, nausea, or vomiting of unknown cause or signs of acute appendicitis, fecal impaction, intestinal obstruction, or acute hepatitis. These drugs are used only as directed because excessive or prolonged use may cause dependence. Magnesium hydroxide is used cautiously in patients with any degree of renal impairment. Laxatives are used cautiously in patients with rectal bleeding, in pregnant women, and during lactation.

Some laxatives (cascara, sagrada, docusate, glycerin, phenolphthalein, magnesium hydroxide, and senna) are used during pregnancy only when the benefits clearly outweigh the risks to the fetus.

Laxatives may reduce absorption of other drugs present in the GI tract, by combining with them chemically or hastening their passage through the intestinal tract. Milk, antacids, H_2-antagonists, and proton pump inhibitors should not be administered 1 to 2 hours before bisacodyl tablets because the enteric coating may dissolve early, resulting in gastric lining irritation or dyspepsia and decreasing the laxative effect of the drug.

8. PROTON PUMP INHIBITORS

Proton pump inhibitors, such as lansoprazole, omeprazole, pantoprazole and rabeprazole, belong to a group of drugs with antisecretory properties. These drugs suppress gastric acid secretion by inhibition of the hydrogenpotassium adenosine triphosphatase (ATPase) enzyme system at the secretory surface of the gastric parietal cells. They block the last step of acid production.

The proton pump inhibitors are particularly important in the treatment of Helicobacter pylori in patients with active duodenal ulcers.

8.1. Actions

The proton pump inhibitors suppress gastric acid secretion by blocking the final step in the production of gastric acid by the gastric mucosa.

8.2. Contraindications, precautions, and interactions

The proton pump inhibitors are contraindicated in patients who have hypersensitivity to any of the drugs. Omeprazole and lansoprazole, rabeprazole, and pantoprazole are contraindicated during pregnancy and lactation.

The proton pump inhibitors are used cautiously in older adults and in patients with hepatic impairment.

There is a decreased absorption of lansoprazole when it is administered with sucralfate. Lansoprazole may decrease the effects of ketoconazole, iron salts, and digoxin. When lansoprazole is administered with theophylline, there is an increase in theophylline clearance requiring dosage changes of the theophylline.

When omeprazole is administered with clarithromycin, there is a risk for an increase in plasma levels of both drugs. Omeprazole may prolong the elimination of warfarin when the two drugs are administered together. Increased serum levels and the risk for toxicity of benzodiazepines, phenytoin, and warfarin may occur if any of these drugs are used with omeprazole.

9. MISCELLANEOUS DRUGS

The miscellaneous GI drugs include bismuth subsalicylate, mesalamine, misoprostol, olsalazine, sucralfate, and sulfasalazine.

9.1. Actions

Bismuth disrupts the integrity of the bacterial cell wall.

Misoprostol inhibits gastric acid secretion and increases the protective property of the mucosal lining of the GI tract by increasing the production of mucus by the lining of the GI tract.

Sucralfate exerts a local action on the lining of the stomach. The drug forms a complex with the exudate of the stomach lining. This complex forms a protective layer over a duodenal ulcer, thus aiding in healing of the ulcer.

Mesalamine, olsalazine, and sulfasalazine exert a topical anti-inflammatory effect in the bowel. The exact mechanism of action of these drugs is unknown.

9.2. Contraindications, precautions, and interactions

The miscellaneous GI drugs are given with caution to patients with a known hypersensitivity to the drugs. In addition mesalamine, olsalazine, and sulfasalazine are contraindicated in patients who have hypersensitivity to the sulfonamides and salicylates or intestinal obstruction, and in children younger than 2 years.

There is a possible cross-sensitivity of mesalamine, olsalazine, and sulfasalazine with furosemide, sulfonylurea antidiabetic drugs, and carbonic anhydrase inhibitors. Misoprostol is contraindicated in those with an allergy to the prostaglandins and during pregnancy and lactation.

Misoprostol is used cautiously in women of childbearing age. Mesalamine, olsalazine, sucralfate, and sulfasalazine are used with caution during pregnancy (safety has not been established) and lactation.

There is an increased risk of diarrhea in patients taking misoprostol with the magnesium-containing antacids. Sulfasalazine may increase the risk of toxicity of oral hypoglycemic drugs, zidovudine, methotrexate, and phenytoin. There is an increased risk of crystalluria when sulfasalazine is administered with methenamine. A decrease in the absorption of iron and folic acid may occur when these agents are administered with sulfasalazine. When bismuth subsalicylate is administered with aspirin-containing drugs, there is an increased risk of salicylate toxicity. There is an increased risk of toxicity of valproic acid and methotrexate and decreased effectiveness of the corticosteroids when these agents are administered with bismuth subsalicylate.

EXERCISES FOR OUT-CLASS WORK

Exercise 1. Using the table 1, administrate proton pump inhibitors for the patient with:

6) duodenal ulcer;
7) erosive esophagitis
8) gastroesophageal reflux;
9) hypersecretory conditions.

Exercise 2. Explain interactions of omeprazole with:

3) clarithromycin;
4) warfarin;
5) benzodiazepines;
6) phenytoin.

Table 1. Uses and dosage ranges of proton pump inhibitors.

Drugs	Uses	Dosage ranges
Esomeprazole (Nexium)	Erosive esophagitis, gastroesophageal reflux, disease (GERD), long-term treatment of pathologic hypersecretory conditions	20–40 mg/d PO
Lansoprazole	Duodenal ulcer, *H. pylori* eradication in patients with duodenal ulcer, gastric ulcer, erosive esophagitis, GERD, hypersecretory conditions	15–30 mg/d PO
Omeprazole	Duodenal ulcer, *H. pylori* eradication, hypersecretory conditions, gastric ulcer, erosive esophagitis, GERD, hypersecretory conditions	20–40 mg/d PO; 60 mg/d up to 120 mg TID
Pantoprazole	GERD	40 mg PO daily to BID up to 120 mg/d; IV, 80 mg; maximum dosage 240 mg/d
Rabeprazole	Duodenal ulcer, GERD, hypersecretory conditions	2–60 mg/d

Exercise 3. Using the table 2, administrate miscellaneous gastrointestinal drugs for the patient with:

1) duodenal ulcer;
2) Crohn's disease;
3) ulcerative colitis.

Exercise 4. Explain interactions of:

4) sulfasalazine with furosemide, sulfonylurea antidiabetic drugs, zidovudine, methotrexate, iron and folic acid;
5) misoprostol with the magnesium-containing antacids;
6) bismuth subsalicylate with aspirin-containing drugs, valproic acid, methotrexate, corticosteroids.

Table 2. Uses and dosage ranges of miscellaneous gastrointestinal drugs.

Drugs	Uses	Dosage ranges
Bismuth subsalicylate (De-nol)	Nausea, diarrhea, abdominal cramps, *H. pylori* with duodenal ulcer	2 tablets or 30 mL PO q 30 min–1 h up to 8 doses in 24 h
Infliximab (Remicade)	Crohn's disease, rheumatoid arthritis	RA: 3 mg/kg IV; Crohn's: 5 mg/kg IV
Misoprostol	Prevention of gastric ulcers caused by aspirin or NSAID use (unlabeled use)	100–200 _g QID PO
Sucralfate	Active duodenal ulcer	1 g/d PO in divided doses
Sulfasalazine	Ulcerative colitis, rheumatoid arthritis	I g QID PO

Exercise 5. Using the table 3, administrate antacids for the patient with:

1) duodenal ulcer;
2) erosive esophagitis.

Exercise 6. Explain interactions of antacids with:

1) digoxin, phenytoin, chlorpromazine, and isoniazid;
2) tetracycline;
3) salicylates, quinidine, amphetamines.

Table 3. Uses and dosage ranges of antacids.

Drugs	Uses	Dosage ranges
1. Aluminii compounds		
Aluminii phosphas (Phosphalugel)	Erosive esophagitis, duodenal ulcer	suspension: 5–15 mL as needed between meals and HS PO
2. Calcii compounds		
Calcium carbonate (Vitacalcin)	Erosive esophagitis, duodenal ulcer	0.5–12 g PO as needed
3. Multiple preparations		
Maalox	Erosive esophagitis, duodenal ulcer	Suspension:5–15 mL as needed between meals and HS PO

Exercise 7. Using the table 4, administrate histamine H2-antagonists for the patient with:

1) duodenal ulcer;
2) erosive esophagitis.

Exercise 8. Explain interactions of histamine H2-antagonists with:

1) antacids, metoclopramide;
2) alkylating drugs, antimetabolites;
3) oral anticoagulants, phenytoin, quinidine, lidocaine, theophylline.

Table 4. Uses and dosage ranges of antacids histamine H2-antagonists.

Drugs	Uses	Dosage ranges
Ranitidine	Management of gastrointestinal disorders	150 mg PO BID or 300 mg PO HS; 50 mg q6–8h IM, IV (do not exceed 400 mg/d)
Famotidine	Management of gastrointestinal disorders	20–40 mg PO, IV as one dose or BID

Exercise 9. Using the table 5, administrate gastrointestinal stimulants for the patient with nausea, vomiting.

Exercise 10. Explain interactions of metoclopramide with:

1) anticholinergics or narcotic analgesics;
2) digoxin, cimetidine;
3) acetaminophen, tetracyclines, levodopa;
4) insulin.

Table 5. Uses and dosage ranges of gastrointestinal stimulants.

Drugs	Uses	Dosage ranges
Metoclopramide (Cerucal)	Nausea, vomiting	10–15 mg PO 30 min AC and HS
Domperidon (Motilium)	Nausea, vomiting	10 mg PO 30 min AC and HS, q8h.

Exercise 9. Using the table 5, administrate antidiarrheals for the patient with:

3) duodenal ulcer;
4) erosive esophagitis.

Exercise 10. Explain interactions of loperamide with:

1) alcohol, antihistamines, narcotics, sedatives, hypnotics.
2) antidepressants, antihistamines;
3) monoamine oxidase inhibitor.

Table 5. Uses and dosage ranges of antidiarrheals.

Drugs	Uses	Dosage ranges
Loperamide (Imodium A)	Diarrhea	Initial dose 4 mg PO then 2 mg after each loose stool (no more than 16 mg/d)

Exercise 11. Using the table 6, administrate antiflatulents for the patient with:
1) flatus in the intestinal tract;
2) gas in the intestinal tract.

Exercise 12. Explain interactions of charcoal with drug absorbed in the GIT.

Table 6. Uses and dosage ranges of antiflatulents.

Drugs	Uses	Dosage ranges
Charcoal	Flatus or gas in the intestinal tract	520 mg PO after meals or at the first sign of discomfort (up to 4.16 g/d)
Simethicone (Espumisan)	Flatus or gas in the intestinal tract	Capsules: 125 mg PO QID PC and HS; tablets: 40–125 mg PO QID PC and HS; drops: 40–80 mg PO QID PC and HS

Exercise 13. Using the table 7, administrate emetics for the patient with:
1) poison;
2) drug overdose.

Exercise 14. Explain interactions of emetics with:

Table 7. Uses and dosage ranges of emetics.

Drugs	Uses	Dosage ranges
Apomorphine (Juprima)	Poison or drug overdose	2–10 mg SC; do not repeat

Exercise 15. Using the table 8, administrate laxatives for the patient with constipation.

Exercise 16. Explain interactions of:
1) mineral oil with fat-soluble vitamins (A, D, E, and K);
2) bisacodyl tablets with milk, antacids, H2-antagonists, and proton pump inhibitors.

Table 8. Uses and dosage ranges of laxatives.

Drugs	Uses	Dosage ranges
1. Saline Laxatives		
Magnesium preparations (Milk of Magnesia)	Constipation	Follow directions given on the container
2. Irritant or stimulant laxatives		
Bisacodyl	Constipation	Tablets: 10–15 mg daily PO Suppositories: 10 mg once daily
3. Emollients		
Mineral oil (Milkinol)	Constipation	15–45 mL PO at HS
4. Hyperosmotic agents		
Glycerin	Constipation	Suppositories: insert 1 high in the rectum and retain 15 min; rectal liquid: insert all the liquid into rectum toward the navel
Lactulose (Duphalac)	Constipation	10–60 mL/d PO

Exercise 17. Using the table 9, administrate digestive enzymes for the patient with peptic ulcer disease.

Table 9. Drugs used in the treatment of peptic ulcer disease.

Drug Type/Mechanism	***Examples***	***Dose***
1. Acid-suppressing drugs		
Antacids	Mylanta, Maalox, Tums, Gaviscon	100–140 meq/L 1 and 3 h after meals and hs
H_2 receptor antagonists	Ranitidine Famotidine	300 mg hs 40 mg hs
Proton pump inhibitors	Omeprazole Lansoprazole Rabeprazole Pantoprazole Esomeprazole	20 mg/d 30 mg/d 20 mg/d 40 mg/d 20 mg/d
2. Mucosal protective agents		
Sucralfate	Sucralfate	1 g qid
Prostaglandin analogue	Misoprostol	200 μg qid
Bismuth-containing compounds	Bismuth subsalicylate	See anti-*H. pylori* regimens(

Exercise 18. Using the table 10, administrate antihelicobacter treatment for patients with duodenal ulcers.

Table 10. Antihelicobacter treatment in patients with duodenal ulcers.

Drug	***Dose***
Triple therapy	
1. Bismuth subsalicylate *plus* Metronidazole *plus* Tetracycline	2 tablets qid 250 mg qid 500 mg qid
2. Ranitidine bismuth citrate *plus* Tetracycline *plus* Clarithromycin or metronidazole	400 mg bid 500 mg bid 500 mg bid
3. Omeprazole (lansoprazole) *plus* Clarithromycin *plus* Metronidazole *or* Amoxicillin	20 mg bid (30 mg bid) 250 or 500 mg bid 500 mg bid 1 gr bid
Quadruple therapy	
Omeprazole (lansoprazole) Bismuth subsalicylate Metronidazole Tetracycline	20 mg (30 mg) daily 2 tablets qid 250 mg qid 500 mg qid

Exercise 19. Using the table 11, administrate digestive enzymes for the patient with nausea and vomiting.

Table 11.Treatment of nausea and vomiting.

Treatment	Mechanism	Examples	Clinical Indications
Antiemetic agents	Antihistaminergic	Dimenhydrinate, meclizine	Motion sickness, inner ear disease
	Anticholinergic	Scopolamine	Motion sickness, inner ear disease
	Antidopaminergic	Prochlorperazine, droperidol	Medication-, toxin-, or metabolic-induced emesis
	5-HT_3 antagonist	Ondansetron, granisetron	Postoperative, chemotherapy- and radiation-induced emesis
	Tricyclic antidepressant	Amitriptyline, nortriptyline	Functional nausea
Prokinetic agents	5-HT_4 agonist	Cisapride	Gastroparesis, functional dyspepsia, gastroesophageal reflux disease
	5-HT_4 agonist and antidopaminergic	Metoclopramide	Gastroparesis, functional dyspepsia
	Motilin agonist	Erythromycin	Gastroparesis
	Peripheral antidopaminergic	Domperidone	Gastroparesis, functional dyspepsia
	Somatostatin analogue	Octreotide	Intestinal pseudoobstruction
Special settings	Benzodiazepines	Lorazepam	Anticipatory nausea and vomiting with chemotherapy
	Glucocorticoids	Methylprednisolone, dexamethasone	Chemotherapy-induced emesis
	Cannabinoids	Tetrahydrocannabinol	Chemotherapy-induced emesis

Exercise 20. Using the table 12, administrate treatment for patient with ulcerative colitis in active phase.

Table 12. Treatment of ulcerative colitis in active phase.

	Mild	Moderate	Severe	Fulminant
Distal	5-ASA oral and/or enema	5-ASA oral and/or enema Glucocorticoid enema Oral glucocorticoid	5-ASA oral and/or enema Glucocorticoid enema Oral or IV glucocorticoid	Intravenous glucocorticoid Intravenous CSA
Extensive	5-ASA oral and/or enema	5-ASA oral and/or enema Glucocorticoid enema Oral glucocorticoid	5-ASA oral and/or enema Glucocorticoid enema Oral or IV glucocorticoid	Intravenous glucocorticoid Intravenous CSA

Exercise 21. Using the table 13, administrate maintenance treatment for patient with ulcerative colitis.

Table 13. Maintenance treatment of ulcerative colitis in active phase.

	Drugs
Distal colitis	5-ASA oral and/or enema 6-MP or azathioprine
Extensive colitis	5-ASA oral and/or enema 6-MP or azathioprine

Exercise 22. Using the table 14, administrate treatment for patient with Crohn's disease in active phase.

Table 14. Treatment of Crohn's disease in active phase.

Mild–moderate	Severe	Perianal or fistulizing disease
5-ASA oral and/or enema	5-ASA oral and/or enema	Metronidazole and/or ciprofloxacin
Metronidazole and/or ciprofloxacin Oral glucocorticoids Infliximab Budesonide	Metronidazole and/or ciprofloxacin Oral or IV glucocorticoids Infliximab TPN or elemental diet	Azathioprine or 6-MP Infliximab Intravenous CSA

Exercise 23. Using the table 15, administrate maintenance treatment for patient with Crohn's disease.

Table 15. Maintenance treatment of Crohn's disease in active phase.

Inflammatory	Perianal or Fistulizing Disease
5-ASA oral and/or enema	Metronidazole and/or ciprofloxacin
Azathioprine or 6-MP Infliximab	Azathioprine or 6-MP Infliximab

CLINICAL EXERCISES FOR OUT-CLASS WORK

1. Ms. Harris, age 76 years, tells you that she has been using various laxatives for constipation. She states that a laxative did help, but now she is more constipated than she was before she began taking a laxative. Discuss what advice or suggestions you would give this patient.
2. Mr. Gates, your neighbor, has been given a prescription for diphenoxylate with atropine to be taken if he should experience diarrhea while he is traveling in a foreign country. Describe the warnings you would give to your neighbor regarding this drug.
3. The doctor has prescribed cimetidine for the treatment of a duodenal ulcer in Mr. Talley, who is 68 years old. A drug history reveals that Mr. Talley is also taking the following drugs: atropine 0.5 mg orally each day and a daily aspirin tablet. Analyze this situation. Discuss what you would tell Mr. Talley.

4. Ms. Jerkins has four children and wants to keep syrup of ipecac available in case of accidental poisoning. Discuss the information you feel that Ms. Jerkins should know before she administers this drug.

REVIEW QUESTIONS

1. When would the doctor most correctly administer an antacid to a patient taking other oral medications?
   A) With the other drugs;
   B) 30 minutes before or after administration of other drugs.
   C) 2 hours before or after administration of other drugs.
   D) In early morning and at bedtime.

2. The patient asks how fecal softeners relieve constipation. Which of the following would be the best response by the doctor?
   A) Fecal softeners relieve constipation by stimulating.
   B) The walls of the intestine promoting the retention of sodium in the fecal mass.
   C) Promoting water retention in the fecal mass.
   D) Lubricating the intestinal walls.

3. When an anticholinergic drug is prescribed for the treatment of a peptic ulcer, the nurse observes the patient for which of the following adverse effects?
   A) Dry mouth, urinary retention.
   B) Edema, tachycardia.
   C) Weight gain, increased respiratory rate.
   D) Diarrhea, anorexia.

4. The doctor administers antidiarrheal drugs:
   A) hourly until diarrhea ceases;
   B) after each loose bowel movement;
   C) with food;
   D) twice a day, in the morning and at bedtime.

5. When an emetic is administered, the doctor must be alert to the possibility that the patient may:
   A) become violent;
   B) experience severe diarrhea;
   C) retain fluid;
   D) aspirate vomitus.

6. Which of the following drugs is contraindicated in patients with gout?
   A) rifampin;
   B) streptomycin;
   C) isoniazid;
   D) pyrazinamide.

7. Which of the following adverse reactions would the doctor expect in a patient receiving acyclovir by the oral route?

A) nausea and vomiting;
B) constipation and urinary frequency;
C) conjunctivitis and blurred vision;
D) nephrotoxicity.

8. Which of the following would the doctro report immediately in a 3-month-old patient receiving ribavirin?
A) any worsening of the respiratory status;
B) refusal to take foods or fluids;
C) drowsiness;
D) constipation.

9. The nurse is administering didanosine properly when:
A) tablets are crushed and mixed thoroughly with 1 oz of water;
B) the drug is prepared for subcutaneous injection;
C) the drug is given with meals;
D) the drug is given mixed with orange juice or apple juice.

10. Intravenous administration of acyclovir can result in:
A) shock;
B) crystalluria;
C) cardiac arrest;
D) hypertensive crisis.

Lesson 11
CLINICAL PHARMACOLOGY OF DRUGS USED FOR BILIARY AND PANCREATIC DISEASE

QUESTIONS FOR IN-CLASS WORK

1. Digestive enzymes: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
2. Gallstone-solubilizing agents: mechanism of action, pharmacokinetic profiles, therapeutic uses, adverse effects, interactions.
3. Drugs used in cholecystitis.
4. Drugs used in hepatitis.
5. Drugs used in pancreatitis.

THEORETICAL ISSUES

1. DIGESTIVE ENZYMES

1.1. Actions

The enzymes pancreatin and pancrelipase, which are manufactured and secreted by the pancreas, are responsible for the breakdown of fats, starches, and proteins.

These enzymes are necessary for the breakdown and digestion of food. Both enzymes are available as oral supplements.

1.1. Contraindications, precautions, and interactions

The digestive enzymes are contraindicated in patients with a hypersensitivity to hog or cow proteins and in patients with acute pancreatitis. The digestive enzymes are used cautiously in patients with asthma (an acute asthmatic attack can occur), hyperuricemia, and during pregnancy and lactation. Safe use of these drugs in pregnancy has not been established.

Calcium carbonate or magnesium hydroxide antacids may decrease the effectiveness of the digestive enzymes.

When administered concurrently with an iron preparation, the digestive enzymes decrease the absorption of oral iron preparations.

2. GALLSTONE-SOLUBILIZING DRUGS

2.1. Actions

Gallstone-solubilizing (gallstone-dissolving) drugs, such as ursodiol, suppress the manufacture of cholesterol and cholic acid by the liver. The suppression of the manufacture of cholesterol and cholic acid may ultimately result in a decrease in the size of radiolucent gallstones.

2.2. Contraindications, precautions, and interactions

Ursodiol is used cautiously in patients with a hypersensitivity to the drug or bile salts and in patients with liver impairment, calcified stones, radiopaque stones or radiolucent bile pigment stones, severe acute cholecystitis, biliary obstruction, and gallstone pancreatitis. Ursodiol is used cautiously during pregnancy and lactation.

Absorption of ursodiol is decreased if the agent is taken with bile acid sequestering drugs or aluminum-containing antacids. Clofibrate, estrogens, and oral contraceptives increase hepatic cholesterol secretion and encourage cholesterol gallstone formation and may counteract the effectiveness of ursodiol.

EXERCISES FOR OUT-CLASS WORK

Exercise 1. Using the table 1, administrate digestive enzymes for the patient with:
1) cystic fibrosis;
2) chronic pancreatitis.

Exercise 2. Explain interactions of digestive enzymes with:
1) calcium carbonate or magnesium hydroxide antacids;
2) oral iron preparations.

Table 1. Uses and dosage ranges of digestive enzymes.

Drugs	Uses	Dosage ranges
Pancreatin (Creon)	Cystic fibrosis, chronic pancreatitis, cancer of the pancreas, the malabsorption syndrome, surgical removal of all or part of the stomach, and surgical removal of all or part of the pancreas.	1–2 tablets PO with meals or snacks

Exercise 3. Using the table 2, administrate gallstone-solubilizing agent for the patient with radiolucent gallstones.

Exercise 4. Explain interactions of ursodiol with:
1) bile acid sequestering drugs, aluminum-containing antacids;
2) clofibrate, estrogens, and oral contraceptives.

Table 2. Uses and dosage ranges of gallstone-solubilizing agent

Drugs	Uses	Adverse reactions	Dosage ranges
Ursodiol	Radiolucent gallstones	Diarrhea, cramps, nausea, and vomiting, hepatotoxicity	8–10 mg/kg/d PO in 2-3 divided doses

Exercise 5. Using the table 3, administrate treatment for patient with acute and chronic pancreatitis.

Table 3. Medical therapy of pancreatitis.

Goals of pharmacotherapy	Group of drugs	Drugs
Palliation of pain	Nonnarcotic analgesics	acetaminophen
	Narcotics	Morphine sulfate
Decreasing refractory abdominal pain	Somatostatin analogs	Octreotide (Sandostatin)
Prophylactic antibiotics in necrotizing acute pancreatitis	Carbapenems& Monobactam	Imipenem-cilastatin
	Quinolones	Ciprofloxacin (Cipro),
	Antiprotozoal drugs	Metronidazole (Flagyl
Prevention of malabsorption	Enzyme formulations	Pancreatin (Creon)
Replacement therapy for malabsorption	Enzyme formulations	Pancreatin (Creon)
Reducing or prevention of production of stomach acid	H_2 receptor antagonists	Famotidine, ranitidine
	Proton pump inhibitors	Omeprazole
Supplements of the vitamins	Fat-soluble vitamins	Vitamines A, D, E, and K

CLINICAL EXERCISES FOR OUT-CLASS WORK

1. A patient is prescribed 0.7 g of powdered pancrelipase with meals. Discuss the preparation and administration of this drug.
2. A patient is receiving chenodeoxycholic acid. What is the most likely reason for administering this drug?

REVIEW QUESTIONS

1. A doctor is to administer nizatidine once daily. When would the doctor most correctly administer the oncedaily dose of nizatidine?
   A) At bedtime.
   B) With the noon meal.
   C) In the morning before eating.
   D) Any time of the day with 4 ounces of orange juice.
2. A patient has steatorrhea due to pancreatic insufficiency secondary to systic fibrosis. The most reasonable and usually effective drug for managing the symptoms and consequences is which of the following?
   A) Atorvastatin
   B) Famotidine
   C) Bile salts
   D) Metoclopramide
   E) Pancreatin
3. Which of the following is the primary cause of dearth from massive acetaminophen overdoses?
   A) Acute nephropathy
   B) A-V conduction disturbances, heart block
   C) Liver failure

D) Status asthmaticus
E) Status epilepticus

4. The antidote that may be of great benefit in early management of acetraminophen's organ-specific toxicity is which of the following?
   A) N-acetylcysteine
   B) Atropine
   C) Physostigmine
   D) Pralidoxime
   E) Warfarin

5. Which would be administer for adjunctive management of a patient with hepatic porto-systemic encepalopathy?
   A) Diphenoxylate
   B) Lactulose
   C) Loperamide
   D) Omeprazole
   E) Ondansetron

6. When giving spectinomycin to the patient with gonorrhea, the doctor advises him to:
   A) return for a follow-up examination;
   B) limit his fluid intake to 1200 mL per day while taking the drug;
   C) return the next day for a second injection;
   D) avoid drinking alcohol for the next 10 days.

7. When monitoring the IV infusion of vancomycin, the doctor makes sure the drug infuses over a period of 60 minutes because rapid infusion can result in:
   A) a fluid overload and respiratory distress;
   B) a sudden and profound fall in blood pressure;
   C) a fluid deficit and dehydration;
   D) a sudden and severe rise in blood pressure.

8. The nurse explains to the patient that to slow bacterial resistance to an antitubercular drug the primary health care provider may prescribe:
   A) at least three antitubercular drugs;
   B) an antibiotic to be given with the drug;
   C) vitamin B6;
   D) that the drug be given only once a week.

9. The doctor monitors the patient taking isoniazid for toxicity. The most common symptom of toxicity is:
   A) peripheral edema;
   B) circumoral edema;
   C) peripheral neuropathy;
   D) jaundice.

10. Which of the following is a dose-related adverse reaction to ethambutol?
    A) peripheral neuropathy;

B) optic neuritis;
C) hyperglycemia;
D) fatal hepatitis.

Appendix I. PHARMACOKINETIC DATA

Drug	Bioavailability (oral) (%)	Urinary excretion (%)	Bound in plasma (%)	Clearance ($ml \cdot min^{-1} \cdot kg^{-1}$)	Volume of distribution (liters/kg)	Half-life (hours)
Acebutolol	37	40	26	6.8	1.2	2.7
Acetaminophen	88	3	0	5	0.95	2
Acetylsalicylic acid	68	1.4	49	9.3	0.15	0.25
Acyclovir	10-20	75	15	-	0.69	2.4
Alteplase	-	low	-	10	0.10	0.08
Amikacin	-	98	4	1.3	0.27	2.3
Amiodarone	46	0	99.98	1.9	66	25
Amitriptyline	48	<2	94.8	11.5	15	21
Amlodipine	74	10	93	5.9	16	39
Amoxicillin	93	86	18	2.6	0.21	1.7
Ampicillin	62	82	18	1.7	0.28	1.3
Atenolol	56	94	<5	2.0	0.95	6.1
Atropine	50	57	14-22	8	2.0	3.5
Azathioprine	60	<2	-	57	0.81	0.16
Azithromycin	37	12	7-50	9	31	40
Betamethasone	72	4.8	64	2.9	1.4	5.6
Bisoprolol	91	63	35	3.7	3.20	11
Bleomycin	-	68	-	1.1	0.27	3.1
Bretylium	23	77	0-8	10.2	5.9	8.9
Bromocriptine	3-6	2	93	5	2	7
Budesonide	12	0	88	17	2.9	2
Caffeine	100	1.1	3.6	1.4	0.61	4.9
Captopril	65	38	30	12	0.81	2.2
Carbamazepine	>70	<1	74	1.3	1.4	15
Carvedilol	25	<2	95	8.7	1.5	2.2
Cefaclor	50	52	25	6.1	0.36	0.67
Cefadroxil	100	93	20	2.9	0.24	1.2
Cefamandole	96	96	74	2.8	0.16	0.78
Cefazolin	-	80	89	0.95	0.14	1.8
Cefoperazone	-	29	89-93	1.2	0.14	2.2
Cefotaxime	-	55	36	3.7	0.23	1.1
Cefoxitin	-	79	73	-	0.25	0.75
Ceftazidime	90	73	40	3	0.22	1.5
Ceftriaxone	-	49	90-95	0.24	0.16	7.3
Cefuroxime	68	96	33	-	0.20	1.7
Cephalexin	90	91	14	4.3	0.26	0.90
Chloramphenicol	75-90	25	53	2.4	0.94	4.0

Drug	Bioavailability (oral) (%)	Urinary excretion (%)	Bound in plasma (%)	Clearance ($ml \cdot min^{-1} \cdot kg^{-1}$)	Volume of distribution (liters/kg)	Half-life (hours)
Chlorbiazepoxide	100	<1	96.5	0.54	0.30	10.0
Chloroquine	89	61	61	1.8	115	41
Chlorthalidone	64	65	75	0.04	0.10	47
Cimetidine	84	62	19	8.3	1.0	2.0
Cinoxacin	-	60-85	63	2.5	0.33	2.1
Ciprofloxacin	60	65	40	6.0	1.8	4.1
Clarithromycin	55	36	42	7.3	2.6	3.3
Clavulanate	75	43	22	3.6	0.21	0.9
Clemastine	37	<2	-	8.3	13	22
Clindamycin	87	13	93.6	4.7	1.1	2.9
Clofibrate	95	5.7	96.5	0.12	0.11	13
Clonidine	95	62	20	3.1	2.1	12
Cocaine	57	<2	91	32	2.0	0.8
Codeine	50	-	7	11	2.6	2.9
Cyclophosphamide	74	6.5	13	1.3	0.78	7.5
Cyclosporine	27	<1	93	5.3	1.3	5.6
Dapsone	93	15	73	0.60	1.0	28
Dexamethasone	78	2.6	68	3.7	0.82	3.0
Diazepam	100	<1	98.7	0.38	1.1	43
Diclofenac	54	<1	>99.5	4.2	0.17	1.1
Dicloxacillin	50-85	60	95.8	1.6	0.086	0.70
Digitoxin	>90	32	97	0.055	0.54	6.7
Digoxin	70	60	25	-	-	39
Diltiazem	44	<4	78	12	3.1	3.7
Disopyramide	83	55	-	1.2	0.59	6.0
Dobutamine	-	-	-	59	0.20	2.4
Doxorubicin	5	<7	76	17	17	26
Doxycycline	93	41	88	0.53	0.75	16
Enalapril	41	88	<50	4.9	1.7	11
Enoxaparin	-	-	-	0.3	0.12	3.8
Erythromycin	35	12	84	9.1	0.78	1.6
Esmolol	-	<1	55	170	1.9	0.13
Ethambutol	77	79	<5	8.6	1.6	3.1
Ethanol	80	<3	-	-	0.54	0.24
Ethinyl Estradiol	51	1-5	95-98	5.4	3.5	10
Ethosuximide	-	25	0	0.19	0.72	45
Famciclovir	77	74	<20	8.0	0.98	2.3
Famotidine	45	67	17	7.1	1.3	2.6
Felodipine	15	<1	99.6	12	10	14

Drug	Bioavailability (oral) (%)	Urinary excretion (%)	Bound in plasma (%)	Clearance ($ml \cdot min^{-1} \cdot kg^{-1}$)	Volume of distribution (liters/kg)	Half-life (hours)
Fentanyl	-	8	84	13	4.0	3.7
Fluconazole	>90	75	11	0.27	0.60	32
Fluoxetine	>60	<2.5	94	9.6	35	53
Furosemide	61	66	98.8	2.0	0.11	92
Ganciclovir	3	73	1-2	4.6	1.1	4.3
Gemfibrozil	98	<1	97	1.7	0.14	1.1
Haloperidol	60	1	92	11.8	18	18
Hexabarbital	>90	<1	42-52	3.9	1.2	3.7
Hydralazine	16	1-15	87	56	1.5	0.96
Hydrochlorothiazide	71	>95	58	4.98	0.83	2.5
Ibuprofen	>80	<1	>99	0.75	0.15	2
Imipenem	-	69	<20	2.9	0.23	0.9
Imipramine	39	<2	90.1	15	18	12
Indomethacin	98	15	90	1.4	0.29	2.4
Interferon α	-	-	-	2.8	0.40	0.67
Interferon β	-	-	-	13	2.9	4.3
Isoniazid	80-100	29	0	3.7	0.67	1.1
Isosobide dinitate	22	<1	28	45	3.9	1.0
Isosorbide-2-mononitrate	100	-	-	5.8	0.82	1.9
Isradipine	19	0	97	10	4.0	8
Intraconazole	55	<1	99.8	2.3	14	21
Kanamycin	-	90	0	1.4	0.26	2.1
Ketamine	20	4	12	15	1.8	2.3
Ketoconazole	-	<1	99.0	8.4	2.4	3.3
Labetalol	18	<5	50	25	9.4	4.9
Levodopa	41	<1	-	23	1.7	1.4
Levonorgestrel	94	52	37	1.5	1.7	15
Lidocaine	35	2	70	9.2	1.1	1.8
Lincomycin	20-30	14	85	2.1	1.3	5.1
Lisinopril	25-30	88-100	0	4.2	2.4	12
Lithium	100	95	0	0.35	0.66	22
Lomefloxacin	97	65	10	3.3	2.3	8.0
Loratadine	-	-	97	142	120	8
Lorazepam	93	<1	91	1.1	1.3	14
Lovastatin	<5	-	95	4-18	-	1.1-1.7
Mercaptopurine	12	22	19	11	0.56	0.90
Methadone	92	24	89	1.4	3.8	35
Methicillin	-	88	39	6.1	0.43	0.85
Methotrexate	70	81	46	2.1	0.55	7.2

Drug	Bioavailability (oral) (%)	Urinary excretion (%)	Bound in plasma (%)	Clearance ($ml \cdot min^{-1} \cdot kg^{-1}$)	Volume of distribution (liters/kg)	Half-life (hours)
Methyldopa	42	40	1-16	3.7	0.46	1.8
Methylprednisolone	82	4.9	78	6.2	1.2	2.3
Metoclopramide	76	20	40	6.2	3.4	5.0
Metoprolol	38	10	11	15	4.2	3.2
Metronidazole	99	10	11	1.3	0.74	8.5
Midazolam	44	56	95	6.6	1.1	1.9
Milrinone	>80	85	70	6.1	0.32	0.80
Misoprostol	>80	<1	<90	240	14	0.5
Morphine	24	4	35	24	3.3	1.9
Nadolol	34	73	20	2.9	1.9	16
Naloxone	2	-	-	22	2.1	1.1
Neostigmine	-	67	-	8.4	0.7	1.3
Nicardipine	18	<1	98-99.5	10.4	1.1	1.3
Nicotine	30	16.7	4.9	18.5	2.6	2.0
Nifedipine	50	0	96	7.0	0.78	1.8
Nimodipine	10	<1	98	19	1.7	1.1
Nitrazepam	78	<1	87	0.86	1.9	26
Nitrendipine	11	<1	98	21	3.8	4
Nitroglycerin	<1	<1	230	3.3	2.3	2.3
Norfloxacin	30-40	26-32	15-20	7.2	3.2	5.0
Nortriptyline	51	2	92	7.2	18	31
Ofloxacine	100	64	25	3.5	1.8	5.7
Omeprazole	53	-	95	7.5	0.34	0.7
Oxacillin	33	46	92.2	6.1	0.33	0.4-0.7
Oxazepam	97	<1	98.8	1.05	0.60	8.0
Pentazocine	47	15	65	17	7.1	4.6
Pentoxifylline	33	0	0	60	4.2	0.9
Phenobarbital	100	24	5.1	0.062	0.54	99
Phenylbutazone	80-100	1	96.1	0.023	0.097	56
Phenytoin	90	2	89	-	0.64	6-24
Pindolol	75	54	51	8.3	2.3	3.6
Piroxicam	80-100	<5	98.5	0.036	0.15	48
Pravastatin	18	47	43	3.5	0.46	1.8
Prazosin	68	<1	95	3.0	0.60	2.9
Prednisolone	82	26	90-95	8.7	1.5	2.2
Prednisone	80	3	75	3.6	0.97	3.6
Probenecid	100	1.2	-	-	0.17	-
Procainamide	83	67	16	-	1.9	3.0
Propafenone	5-50	<1	85-95	17	3.6	5.5

Drug	Bioavailability (oral) (%)	Urinary excretion (%)	Bound in plasma (%)	Clearance ($ml \cdot min^{-1} \cdot kg^{-1}$)	Volume of distribution (liters/kg)	Half-life (hours)
Propranolol	26	<0.5	87	16	4.3	3.9
Quinapril	-	28	97	2.0	0.4	2.2
Quinidine	71-80	18	87	4.7	2.7	6.2
Quinine	76	12	93	1.9	1.8	11
Ramipril	44	39	56	1.1	-	14
Ranitidine	52	69	15	10.4	1.3	2.1
Ribavirin	45	35	0	5.0	9.3	28
Rifampin	-	7	89	3.5	0.97	3.5
Rimantadine	-	9	40	10	25	30
Salicylic acid	100	2-30	-	0.88	0.17	-
Scopolamine	27	6	-	16	1.4	2.9
Sertraline	-	<1	99	38	76	23
Simvastatin	<1	-	94	7.6	-	1.9
Sotalol	90-100	>75	0	2.6	2.0	12
Spironolactone	25	<1	>90	100	14	1.6
Streptokinase	-	0	-	1.7	0.08	0.61
Streptomycin	-	50-60	48	1.2	0.25	2.6
Sulfamethoxazole	100	14	62	0.32	0.21	10.1
Sulindac	-	-	94	1.5	2	15
Tamoxifen	-	<1	>98	1.4	50-60	4-11
Terbutaline	14	56	20	3.4	1.8	14
Terfenadine	-	25	97	8.8	-	12
Tetracycline	77	58	65	1.67	1.5	10.6
Theophylline	96	18	56	0.65	0.50	9.0
Thiopental	-	<1	85	3.9	2.3	9.0
Timolol	50	15	60	7.3	2.1	4.1
Tobramycin	9	90	<10	-	0.33	2.2
Tolbutamide	93	0	96	0.24	0.10	5.9
Triamcinolone acetonide	23	1.0	40	7.7	1.3	2.0
Triamterene	54	52	61	63	13.4	4.2
Trimethoprim	100	63	37	1.9	1.6	10
Tubocurarine	-	63	50	1.9	0.39	2.0
Valproic acid	100	1.8	93	0.11	0.22	14
Vancomycin	-	79	30	1.4	0.39	5.6
Verapamil	22	<3	90	15	5.0	4.0
Warfarin	93	<2	99	0.045	0.14	37
Zidovudine	63	18	<25	26	1.4	1.1

Appendix II. GLOSSARY OF TERMS AND ABBREVIATIONS

Administration Rate (R_A): The average rate at which a drug is administered to the patient.

Amount of Drug in the Body (Ab): The total amount of active drug that is in the body at any given time.

Average Steady-State Concentration (Css **ave):** The average plasma drug concentration at steady state.

Bioavailability (F): The fraction of an administered dose that reaches the systemic circulation.

Body Surface Area (BSA): The surface area of a patient, as determined by weight and height.

Bolus Dose: A model for rapid input of a dose into the body or an individual dose usually given by intravenous injection.

BSA: *See* Body Surface Area.

Cl: *See* Clearance

Cl_{Cr}: *See* Creatinine Clearance.

Cl_{dial}: Drug clearance by dialysis.

Cl_m: *See* Clearance, metabolic.

Cl_{pat}: Drug clearance of patient, usually associated with decreased renal function.

Cl_r: *See* Clearance, renal.

Clearance (Cl_t or Cl): Total body clearance is a measure of how well a patient can metabolize or eliminate drug. It is used to calculate maintenance doses or average steady-state plasma concentrations.

Clearance, metabolic (Cl_m): A measure of how well the body can metabolize drugs. The major metabolic organ is usually the liver.

Clearance, renal (Cl_r): A measure of how well the kidneys can excrete unchanged or unmetabolized drug. It is usually assumed to be proportional to creatinine clearance.

C: *See* Plasma Concentration.

C_{free}: Unbound or free plasma concentration.

CHF: Congestive heart failure.

CNS: Central nervous system.

Css ave: Average plasma concentration at steady state.

Css max: The maximum or peak concentration at steady state, when a constant dose is administered at a constant dosing interval.

Css min: The minimum or trough concentration at steady state, when a constant dose is administered at a constant dosing interval.

Continuous Renal Replacement Therapy: A type of hemodialysis that is continuous versus intermittent.

Creatinine Clearance (Cl_{cr}): A measure of the kidney's ability to eliminate creatinine from the body. Total renal function is usually assumed to be proportional to creatinine clearance.

Dosing Interval (τ): The time interval between doses when a drug is given intermittently.

Elimination Rate Constant (K): The fractional rate of drug loss from the body or the fraction of the volume of distribution that is cleared of drug during a time interval.

Elimination Rate (R_E): The amount of drug eliminated from the body during a time interval.

Extraction Ratio: Fraction of drug that is removed from the blood or plasma as it passes through the eliminating organ.

F: *See* Bioavailability.

First-Pass: Drug removed from the blood or plasma, following absorption from the gastrointestinal tract, before reaching the systemic circulation.

First-Order Elimination: A process whereby the amount or concentration of drug in the body diminishes logarithmically over time. The rate of elimination is proportional to the drug concentration.

fu: Fraction of total plasma concentration that is free or unbound.

GI: Gastrointestinal

Half-Life *($t_{1/2}$):* Time required for the plasma concentration to be reduced to one-half of the original value.

IBW: *See* Ideal Body Weight.

Ideal Body Weight: Body weight used as an estimate of non-obese weight.

IM: Intramuscular.

Initial Volume of Distribution (Vd_i): Initial volume into which the drug rapidly equilibrates following an intravenous bolus dose injection.

IV: Intravenous.

K: *See* Elimination Rate Constant.

Km (Michaelis-Menten Constant): Plasma concentration at which the rate of metabolism is half the maximum rate.

$K_{metabolic}$ (Km): The elimination rate constant calculated from the metabolic clearance and the volume of distribution (Cl_m/Vd).

K_{renal} (K_r): The elimination rate constant calculated from the renal clearance and the volume of distribution (Cl_r/Vd).

Linear Pharmacokinetics: Assumes the elimination rate constant is not affected by plasma drug concentration and that the rate of drug elimination is directly proportional to the concentration of drug in plasma.

ln: Natural logarithm using the base 2.718 rather than 10, which is used for the common logarithm or log.

Loading Dose: Initial total dose required to rapidly achieve a desired plasma concentration.

Maintenance Dose: The dose required to replace the amount of drug lost from the body so that a desired plasma concentration can be maintained.

One-Compartment Model: Assumes that drug distributes rapidly and equally to all areas of the body. Most drugs can be modeled this way if sampling during the initial distribution phase is avoided.

P_{NL} or P': Plasma protein concentration. P_{NL} refers to the normal plasma protein concentration and P' refers to the plasma protein concentration of the specific patient.

Pharmacokinetics: Study of the absorption, distribution, metabolism, and excretion of a drug and its metabolites in the body.

Plasma Concentration (C): Concentration of drug in plasma. Usually refers to the total drug concentration and includes both the bound and unbound or free drug concentration.

R_A: *See* Administration Rate.

R_E: *See* Elimination Rate.

S: *See* Salt Form.

Salt Form (S): Fraction of administered salt or ester form of the drug that is the active moiety.

SC: Subcutaneous.

Sensitivity Analysis: The practice of examining the relationship between a change in either clearance or volume of distribution and the corresponding change in the calculated plasma concentration.

Steady State: Steady state is achieved when the rate of drug administration is equal to the rate of drug elimination.

$T_{1/2}$: *See* Half-Life.

Tau (T): *See* Dosing Interval.

TBW: *See* Total Body Weight.

Tissue Concentration (C_t): Concentration of drug in the tissue.

Tissue Volume of Distribution (Vd_t): Apparent volume into which the drug appears to distribute following rapid equilibration with the initial volume of distribution.

Total Body Weight: Total weight of a patient usually used for obese patients.

Two-Compartment Model: Comprised of an initial, rapidly equilibrating volume of distribution (Vd_i) and an apparent second, more slowly equilibrating volume of distribution (Vd).

Unbound Vd: Volume of distribution based on the free or unbound plasma concentration.

Vd: *See* Volume of Distribution.

Vd_i: *See* Initial Volume of Distribution.

Vm: Maximum rate at which metabolism can occur.

Vd_t: *See* Tissue Volume of Distribution

Volume of Distribution (Vd): The apparent volume required to account for all the drug in the body if it were present throughout the body in the same concentration as in the sample obtained from the plasma.

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КЛІНІЧНА ФАРМАКОЛОГІЯ
ПОСІБНИК ДЛЯ ПРАКТИЧНИХ ЗАНЯТЬ

Англійською мовою