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Principles of Pharmacology

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Pharmacokinetics (Study of How the Body Processes Drugs)

- Absorption
  1. Movement of drug from site of entry into the systemic circulation
  2. Bioavailability—percentage of active drug that is absorbed and available at the target tissue
  3. Affected by cell membranes, blood flow, drug solubility, pH of drug, variables related to the gastrointestinal tract, drug concentration, dosage form, route of administration
- Distribution
  1. Movement of drug into body fluids and body tissues
  2. Affected by permeability of capillaries and tissues, systemic circulation, size of drug molecule, affinity for lipid and aqueous tissues, protein binding, and pH
  3. Plasma protein binding—drugs may attach to proteins (mainly albumin) in the blood; only unbound drug is active; as free drug is excreted, more of drug is released from binding to replace what is lost; competition for binding sites by different drugs and hypoalbuminemia can affect amount of free drug that is available
  4. Blood–brain barrier affects drug distribution—endothelial cells of capillaries surrounding brain are packed tightly together, which limits passive transport from blood into cerebral tissue; drug must be highly lipophilic to pass into brain
  5. Placental barrier affects drug distribution
     a. Several layers of placental tissue separate maternal and fetal circulation, so the placenta is not an absolute barrier to drugs; almost all drugs taken by mother pass through placenta to fetus to some degree, and they reach steady state levels in fetus between 50% to 100% of maternal concentration
     b. General determinants of drug transfer across placenta include lipid solubility, extent of plasma protein binding, and degree of ionization of weak acids and bases
     c. Placenta has enzyme systems that metabolize some drugs, and P-glycoprotein that actively transports some drug substrates away from fetal circulation
  6. Steady state—when rate of drug elimination equals rate of drug availability (absorption)
  7. Half-life—time it takes for plasma concentration of a drug to be reduced by 50%; used to determine time required to reach steady state and dosage interval
  8. Volume of distribution—apparent volume in which drug is dissolved; relates to concentration of drug in plasma and the amount in the body; may be used to calculate loading dose need to achieve a desired steady state drug level immediately
- Metabolism
  1. Chemical inactivation of drug by conversion to a more water-soluble compound (metabolite) that can be excreted from the body
  2. Chemical alterations are produced by microsomal enzymes mainly in the liver
  3. Hepatic first-pass effect—orally administered drug goes from GI tract through portal system to liver before going to the general circulation; some metabolism of drug may occur as it is taken up by hepatic microsomal enzymes
  4. Drug interactions can affect metabolism by enzyme induction or inhibition
  5. Variation in drug metabolism may be affected by genetics, age, pregnancy, liver disease, diet, alcohol, circadian rhythm
  6. Prodrugs—drugs that must be metabolized to become effective (active metabolites); developed to improve stability, increase absorption, or prolong duration of drug activity; that is, valacyclovir is not effective, but its active metabolite, acyclovir, is
- Excretion
  1. Removal of drug from body via the kidneys, intestines, sweat and salivary glands, lungs, or mammary glands
  2. Urinary excretion—net effect of glomerular filtration, active tubular secretion, and partial reabsorption
  3. Enterohepatic recirculation—some fat-soluble drugs may be reabsorbed into the bloodstream from the intestines and returned to the liver

- Pharmacokinetic changes during pregnancy
  1. Absorption—not significantly affected
  2. Distribution
     a. Increase in plasma volume may result in lower serum levels of drug
     b. Reduction in plasma proteins (albumin) may result in higher levels of free (unbound) drug
  3. Metabolism
     a. Hepatic enzyme systems (e.g., CYP3A4, CYP1A2) are affected by rising levels of estrogen and progesterone and may result in either faster or slower metabolism of some drugs
     b. Blood flow through the liver is not changed significantly so there is no change in first-pass effects
  4. Excretion—increase in glomerular filtration rate (GFR) may result in faster elimination of drugs excreted primarily through the kidneys

Pharmacodynamics (Study of Mechanism of Drug Action on Living Tissue)

- Drug effects produced by
  1. Drug-receptor interaction
  2. Drug-enzyme interaction
  3. Nonspecific drug interaction
- Drug receptors—cellular protein, enzyme, or membrane that, when bound to a drug, initiates a physiologic response or blocks a response that receptor normally stimulates
  1. Agonist—drug combines with receptor to stimulate a response
  2. Antagonist—drug interferes with receptor action or with other drug agonists present
- Drug–response relationship—study of relationship between concentration of drug in circulation and response obtained
  1. Affinity—propensity of a drug to bind itself to a given receptor site
  2. Efficacy—ability to initiate biologic activity as a result of such binding
- Therapeutic effect
  1. All pharmacologic responses have a maximum effect at which no further response is achieved, regardless of drug concentration
  2. Therapeutic range (window)—plasma concentration of drug that produces desired action without toxic effects
  3. Therapeutic index (TI)—ratio of lethal doses in 50% of population over the median minimum effective dose in 50% of the population; higher TI = safer drug

Adverse Reactions—Unintended, Undesired Effects of Drug

- Predictable—may occur related to
  1. Age
  2. Body mass
  3. Gender
  4. Pathologic state
  5. Circadian rhythm
  6. Genetic factors
  7. Psychologic factors
- Unpredictable types include:
  1. Drug allergy
  2. Idiosyncrasy
  3. Tolerance
  4. Drug dependence
- Iatrogenic responses include:
  1. Blood dyscrasias
  2. Hepatic toxicity
  3. Renal damage
  4. Teratogenic effects
  5. Dermatologic effects

Drug Interactions

- Modification of an expected drug response due to exposure to another drug or substance at approximately the same time; may be pharmacokinetic or pharmacodynamic
- Pharmacokinetic—inhibition of absorption, enzyme inhibition, or induction that increases risk for drug toxicity or results in reduced drug effect, altered renal elimination
- Pharmacodynamic—additive if two drugs have similar pharmacodynamic effects, antagonistic if two drugs have opposing pharmacodynamics effects
- Drug–food interactions may decrease bioavailability by interfering with absorption; they may increase bioavailability via inhibition of enzymatic activity in intestinal wall
- Drug–herb interactions may decrease or increase bioavailability of drug

Drug Contraindications

- Allergies, medical conditions, concurrent use of another drug, age, pregnancy, lactation may be drug contraindications
- FDA Pregnancy and Lactation Labeling Rule (PLLR) (Food and Drug Administration, 2014)
  1. Assists in assessing benefits versus risks of a drug for pregnant women and nursing mothers
  2. Includes subsections for pregnancy, lactation, and females and males of reproductive potential in the Use in Special Populations section.
  3. Pregnancy letter categories (A, B, C, D, X) have been removed
  4. Pregnancy subsection—contact information for pregnancy exposure registry for drug if available, risk summary, clinical considerations, available human and animal data
  5. Lactation subsection—risk summary, applicable clinical considerations, available human and animal data

6. Females and males of reproductive potential subsection—included if human or animal study data show potential drug-associated effects on fertility and/or implantation loss

- Lactation and drugs
  1. Properties of drug that determine how much of drug will be in breastmilk include pH, protein binding, liposolubility, and molecular weight
  2. Infant pharmacokinetics have influence—drug metabolism variables such as gastric acid production, liver function, amount of body fat, renal excretion

Pharmacotherapy (Applying Knowledge of Benefits and Risks of Drug Therapy to Individual Care)

- Effects of age
- Gender differences in drug metabolism
- Health status
- Family history and genetic factors
- Lifestyle behaviors
- Polypharmacy
- Drug regimen adherence

Client Education

- Purpose of drug, mechanism of action, effectiveness
- Benefits and risks
- Dosage and administration
- Major side effects/adverse reactions
- Plan for follow-up

Selected Drug Review

- Metronidazole
  1. Class: nitroimidazole
  2. Indications for use include but are not limited to treatment of:
     a. Trichomonas vaginalis
     b. Bacterial vaginosis
     c. Pelvic inflammatory disease (PID), in combination with other antibiotics
     d. Pseudomembranous colitis caused by clostridium difficile
     e. Gastric or peptic ulcer associated with Helicobacter pylori
  3. Pharmacokinetics
     a. Absorption and distribution
        (1) Oral route—excellent, bioavailability at least 90%
        (2) Intravaginal route—absorbed systemically; peak serum concentrations are < 2% of levels achieved with oral doses
        (3) Widely distributed throughout body tissues and fluids
        (4) Crosses placenta and enters breastmilk
        (5) Mean elimination half-life is 8 hours
     b. Metabolism—mostly in liver
     c. Excretion—mostly through urine, some fecal excretion
  4. Pharmacodynamics
     a. Disrupts DNA and protein synthesis of susceptible organisms
     b. Amebicidal, bactericidal, antiprotozoal
     c. Selectivity for anaerobic bacteria
  5. Adverse reactions
     a. More common with oral than vaginal route
     b. GI—nausea, vomiting, dry mouth, metallic taste, anorexia, abdominal cramping
     c. Headache
     d. Hypersensitivity
     e. Mild leukopenia or neutropenia—not persistent after treatment
     f. Peripheral neuropathy—high doses, prolonged use
     g. Seizures—high doses, prolonged use
  6. Drug interactions
     a. Disulfiram—acute psychosis and confusion if metronidazole taken within 2 weeks of taking disulfiram
     b. Alcohol (including medications with significant alcohol content)—may cause nausea/vomiting, headache, flushing, abdominal cramps
     c. Warfarin—metronidazole can potentiate action
     d. Cimetidine—can decrease hepatic metabolism of metronidazole and increase serum levels
     e. Phenobarbital/phenytoin—can increase hepatic metabolism of metronidazole, clinical significance uncertain
  7. Contraindications/precautions
     a. Hypersensitivity
     b. History of drug-induced hematological dyscrasias
     c. Hematological disease
     d. Severe hepatic disease/impairment
     e. Renal impairment/renal failure
     f. Preexisting seizure disorder
  8. Use in pregnancy and lactation is considered safe in all trimesters of pregnancy; interrupt nursing for 12–24 hours after drug dose to allow excretion of drug
  9. Client education
     a. Take with food to decrease GI irritation
     b. Avoid alcohol and alcohol-containing substances during and for 48 hours after last dose
     c. Chew gum or suck on ice or hard candy to help reduce dry mouth and metallic taste
     d. May cause darkening of urine
     e. Report any central nervous system (CNS) symptoms
     f. If taking for trichomoniasis, refrain from sex until self and partner treatment is complete
- Fluconazole
  1. Class: triazole
  2. Indications for use include but are not limited to treatment of:
     a. Candidiasis—oropharyngeal, esophageal, vulvovaginal
     b. Fungal meningitis—cryptococcosis, candida species, histoplasmosis

3. Pharmacokinetics
   a. Absorption and distribution
      (1) Rapidly absorbed in GI tract, bioavailability over 90%
      (2) Widely distributed in body tissues and fluids
      (3) Vaginal secretion, saliva, and sputum concentrations about 10 times that of plasma concentrations
      (4) Distribution in breastmilk and across placenta unknown
      (5) Mean elimination half-life is 30 hours
   b. Metabolism—liver via interaction with CYP450 enzyme system, no first-pass metabolism
   c. Excretion—majority through urine (60–80%) as unchanged drug
4. Pharmacodynamics
   a. Highly selective inhibitor of fungal CYP450 enzymes
   b. Alters fungal cell membrane function and cell wall synthesis
   c. Broad spectrum of antifungal activity
   d. Emerging resistance of non–candida albican species
5. Adverse reactions
   a. Headache
   b. GI effects—nausea, abdominal pain
6. Drug interactions
   a. Cisapride (Propulsid)—prolonged QT interval
   b. Cyclosporin—nephrotoxicity
   c. Carbamazepine (Tegretol)—increased carbamazepine levels, decreased fluconazole levels
   d. Phenytoin (Dilantin)—nystagmus, ataxia
   e. Sulfanylureas—hypoglycemic reactions
   f. Theophylline—increased theophylline levels
   g. Warfarin—increased warfarin levels
7. Contraindications/precautions
   a. History of heart arrhythmia
   b. Hepatic disease
   c. Renal impairment/renal failure
   d. Hypersensitivity
   e. Multiple drug interactions
8. Use in pregnancy and lactation
   a. Available human data do not suggest increased risk of congenital anomalies following a single maternal dose of 150 mg
   b. Recommended treatment for vulvovaginal candidiasis in pregnancy is topical azole for 7 days
   c. Distributed in breastmilk at concentrations similar to those in plasma
   d. Considered compatible with breastfeeding
9. Client education
   a. Symptoms should start to go away about 24 hours after taking medication
   b. It may take several days for symptoms to go away completely
   c. Notify provider of all medications because several drug interactions are possible
   d. Avoid overuse/unnecessary use of antibiotics

- Acyclovir
  1. Class: nucleoside analog
  2. Indications for use include treatment of:
     a. Herpes simplex
     b. Herpes genitalia
     c. Herpes zoster
     d. Varicella
  3. Pharmacokinetics (oral)
     a. Absorption and distribution
        (1) Poorly absorbed, 15–20% bioavailability; however, therapeutic levels achieved
        (2) Widely distributed
        (3) Crosses placenta and enters breastmilk
        (4) Mean elimination half-life—3–4 hours
     b. Metabolism—mostly in liver
     c. Excretion—90% in urine as unchanged drug
  4. Pharmacodynamics
     a. Selectively activated in infected cells
     b. Inhibits viral DNA synthesis
     c. Only effective against rapidly replicating herpes virus
     d. Does not eliminate latent herpes virus
  5. Adverse reactions
     a. GI effects—nausea/vomiting, diarrhea
     b. Headache
     c. Skin rash
     d. Acute renal failure—rare with oral route
  6. Drug interactions—increased risk for renal toxicity with nephrotoxic drugs
  7. Contraindications/precautions—renal or hepatic function impairment
  8. Use in pregnancy and lactation
     a. Acyclovir registry has not found any increase in birth defects in pregnant women who use this drug
     b. May use to treat first episode of genital herpes or severe recurrent herpes
     c. May consider treatment in late pregnancy to reduce frequency of recurrences at term
     d. Lactation—use if indicated; some excretion in breastmilk
  9. Client education
     a. Take with full glass of water
     b. Space doses evenly
     c. Start at first sign of recurrent episode
     d. Additional education for suppressive regimens
  10. Other nucleoside analogs—same indications, mechanism of action, adverse reactions, contraindications/precautions
      a. Famcyclovir—converted to active form via first-pass metabolism, better bioavailability
      b. Valacycolvir—prodrug converted to acyclovir, better bioavailability, less frequent dosing

- Alendronate
  1. Class: bisphosphonate
  2. Indications for use include:
     a. Prevention of osteoporosis in postmenopausal women
     b. Treatment of osteoporosis postmenopausal women
     c. Treatment of osteoporosis in men
     d. Treatment of glucocorticoid-induced osteoporosis
     e. Treatment of Paget's disease of the bone

3. Pharmacokinetics
   a. Absorption and distribution
      (1) Reaches maximum concentration in bone at 3 to 6 months
      (2) Systemic bioavailability is low with little exposure to tissues other than bone
      (3) Bioavailability reduced by 40% when taken with food and 60% when taken with coffee or orange juice
      (4) Approximately 50% of oral dose binds to exposed bone surface
      (5) Estimated elimination half-life from bone—greater than 10 years
   b. Metabolism—high affinity for bone; no evidence of metabolism in liver
   c. Excretion—50% of dose that remains after it binds to bone is excreted unchanged in urine
4. Pharmacodynamics
   a. Reduces bone resorption by inhibiting activity of osteoclasts
   b. No direct effect on bone formation
5. Adverse reactions
   a. Local irritation of the upper gastrointestinal mucosa
   b. Esophagitis, esophageal ulcers, and esophageal erosions
   c. Hypocalcemia
   d. Severe and occasionally incapacitating bone, joint, and/or muscle pain
   e. Osteonecrosis of the jaw—more likely with intravenous administered bisphosphonate and generally associated with dental work
   f. Low impact fractures of femoral shaft—rare, more common in long-term users
   g. Hypersensitivity reactions
6. Drug interactions—Calcium and magnesium- or aluminum-containing antacids likely to reduce absorption of alendronate if taken at same time
7. Contraindications/precautions
   a. Abnormalities of esophagus that delay esophageal emptying
   b. Inability to stand or sit upright for at least 30 minutes after taking alendronate
   c. Hypocalcemia
   d. Renal impairment
   e. Hypersensitivity
8. Use in pregnancy and lactation
   a. No well-designed studies of use during pregnancy in humans; small studies and case reports have shown no increase in rate of birth defects or long-term health concerns
   b. Limited evidence indicates that breastfeeding after cessation of long-term bisphosphonate treatment appears to have no adverse effects on infant
   c. No data available on use during breastfeeding; poorly absorbed by mother so amount in breastmilk likely small
9. Client education
   a. Take in the morning with 8 ounces of plain water
   b. Do not eat food, drink fluids, or take other medications for at least 30 to 60 minutes
   c. Remain upright for at least 30 to 60 minutes
   d. Take at least 2 hours before any calcium supplement or antacids

- Oxybutynin
  1. Class: antimuscarinic anticholinergic
  2. Indications for use—treatment of women with overactive bladder
  3. Pharmacokinetics
     a. Absorption and distribution
        (1) Rapid; reaches maximum concentration within an hour
        (2) Bioavailability about 6%
        (3) Widely distributed in body tissues
        (4) Mean elimination half-life is 2–3 hours
     b. Metabolism—liver via interaction with CYP3A4 enzyme
     c. Excretion—extensively metabolized in liver with less than 0.1% of dose excreted unchanged in urine
  4. Pharmacodynamics
     a. Targets M_1 and M_3 receptors to reduce muscarinic action of acetylcholine on smooth muscle
     b. Mild antispasmodic—increases bladder capacity, diminishes frequency of uninhibited contractions of detrusor muscle
  5. Adverse reactions
     a. Systemic anticholinergic side effects, for example, dry mouth, blurred vision, constipation, tachycardia, urinary retention, drowsiness, impaired sweating, confusion, are common reasons for discontinuation
     b. Transdermal patch may decrease serum levels of active metabolite and reduce anticholinergic side effects
     c. Heatstroke in hot climates if sweating is impaired
  6. Drug interactions
     a. Inhibitors of CYP3A4 enzyme may cause increased plasma concentrations of oxybutynin
     b. May enhance effects of other anticholinergic drugs
     c. May enhance sedative effects of opioids or other sedation-causing agents
  7. Contraindications/precautions
     a. Hypersensitivity
     b. Uncontrolled narrow-angle glaucoma
     c. Gastric retention
     d. Urinary retention
     e. Concomitant use of other anticholinergic drugs
     f. Esophageal disease
     g. Hepatic or renal impairment
     h. Myasthenia gravis
     i. Cardiac disease
     j. Hypertension
  8. Use in pregnancy and lactation
     a. No evidence of impaired fertility or harm to animal fetus; safety in pregnant women has not been established
     b. It is not known if oxybutynin is excreted in breastmilk
  9. Client education
     a. Take with full glass of water at same time each day
     b. May take with or without food
     c. Avoid becoming overheated or dehydrated during exercise or in hot weather

- Atorvastatin
  1. Class: HMG CoA Reductase Inhibitor—statin

2. Indications for use—first-line treatment in reducing low density lipoprotein (LDL) levels
3. Pharmacokinetics
   a. Absorption and distribution
      (1) Rapid, maximum plasma concentrations within 1–2 hours
      (2) Low systemic bioavailability of about 14% due to extensive first-pass metabolism, a benefit as liver is target organ for drug
      (3) Animal studies show drug crosses placenta and is present in breastmilk
      (4) Mean elimination half-life is 14 hours
   b. Metabolism—liver via interaction with CYP3A4 enzyme
   c. Excretion—eliminated primarily in bile; does not appear to undergo enterohepatic recirculation; less than 2% eliminated via urine
4. Pharmacodynamics
   a. Reduces cholesterol production in liver through inhibition of HMG CoA, an enzyme involved in cholesterol synthesis
   b. Stimulates up-regulation of LDL receptors in liver, which bind the LDL and increase extraction from plasma
   c. Some statins cause decrease in triglycerides and increase in HDL secondary to LDL reduction
   d. Improves plaque stability while reducing endothelial inflammation
5. Adverse reactions
   a. Muscle pain and soreness or muscle cramps—may be resolved with switch to different statin
   b. Rhabdomyolysis—rare, skeletal muscle breakdown that may cause renal dysfunction; check creatine kinase level if significant muscle pain or weakness or dark-colored urine
   c. GI effects—abdominal pain, constipation, diarrhea, nausea
   d. Asymptomatic elevations in hepatic aminotransferase activity
6. Drug interactions
   a. Concurrent use of drugs that increase serum levels of statins increases the risk for myopathy and rhabdomyolysis
   b. CYP3A4 enzyme inhibitors—for example, macrolide antibiotics, selective serotonin reuptake inhibitors, ketoconazole, protease inhibitors, rifampin, calcium channel blockers, cimetidine, and grapefruit juice (large quantities) increase statin serum levels
   c. Concurrent use with other antilipid drugs such as gemfibrozil and niacin increases risk for myopathy and rhabdomyolysis
   d. Warfarin—increased anticoagulant effect
   e. Digoxin—slight increase in digoxin levels
7. Contraindications/precautions
   a. Do not use in pregnancy
   b. Active liver disease with elevated liver enzymes
8. Use in pregnancy and lactation
   a. Contraindicated in pregnancy—can cause adverse fetal outcomes; CNS and limb abnormalities found in animal studies
   b. Contraindicated for women who are breastfeeding
9. Client education
   a. Follow a heart-healthy diet and regular exercise regime along with taking statin
   b. Report promptly any unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever
   c. Report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice

- Tamoxifen
  1. Class: selective estrogen receptor modulator (SERM)
  2. Indications for use include:
     a. Treatment of estrogen receptor (ER) positive breast cancer
     b. Prevention of ER positive breast cancer for high-risk individuals
  3. Pharmacokinetics
     a. Absorption and distribution
        (1) Peak plasma concentrations within 5 hours
        (2) Mean elimination half-life is 5–7 days
     b. Metabolism—tamoxifen is a prodrug metabolized to more active forms by various CYP450 enzymes in liver
     c. Excretion—primarily in feces
  4. Pharmacodynamics
     a. Estrogen-antagonist effects—binds to ERs; prevents estrogen from binding, thus blocking its action at selected target sites, for example, breast tissue
     b. Partial estrogen agonist—acts like an estrogen in other sites, for example, uterus, bone
  5. Adverse reactions
     a. Venous thromboembolism
     b. Endometrial cancer
     c. Hot flashes
     d. Nausea
     e. Menstrual irregularities
     f. Vaginal dryness
     g. Weight gain
     h. Bone loss in premenopausal women
  6. Drug interactions
     a. May cause significant increase in effect of coumarin-type anticoagulants
     b. Increased risk for thromboembolic events when cytotoxic agents used in combination with tamoxifen
     c. Anastrozole decreases levels of oral tamoxifen oral by unspecified interaction mechanism
     d. Strong inhibitors of CYP2D6 may cause lower blood levels of active metabolite
  7. Contraindications/precautions
     a. Hypersensitivity to drug
     b. History of thromboembolic event
     c. Pregnancy
  8. Use in pregnancy and lactation
     a. No adequate and well-controlled studies of use in pregnant women
     b. Small number of reports of vaginal bleeding, spontaneous abortions, birth defects, fetal deaths in pregnant women
     c. Has been reported to inhibit lactation
     d. Unknown if drug is excreted in breastmilk
  9. Client education
     a. Take with or without food
     b. Report any signs or symptoms that may indicate blood clot formation
     c. Report any unusual vaginal bleeding

Questions

Select the best answer.

1. Which of the following pharmacokinetic changes could decrease the effect of a medication?
   a. Decrease in plasma protein binding
   b. Increase in hepatic first-pass effect
   c. Increase in enterohepatic recirculation
   d. Increase in bioavailability
2. The 2015 FDA Pregnancy and Lactation Labeling Rule requires inclusion of:
   a. alternative medication choices when a particular drug is contraindicated during pregnancy.
   b. any available data on potential drug-associated effects on female and male fertility.
   c. expanded pregnancy letter category (A, B, C, D, X) information.
   d. information on a centralized pregnancy exposure registry for all drugs.
3. Plasma protein binding most significantly affects drug:
   a. absorption.
   b. distribution.
   c. metabolism.
   d. excretion.
4. The half-life of a drug is used to:
   a. calculate the loading dose needed to achieve immediately the desired steady state.
   b. determine the time required to reach steady state and dosage interval.
   c. estimate the therapeutic index.
   d. predict the likelihood of an adverse reaction.
5. Acyclovir is not effective in eliminating latent herpes virus because it:
   a. has a short elimination half-life of three to four hours.
   b. has only a 15–20% bioavailability.
   c. is a prodrug that is converted to active form by first-pass metabolism.
   d. is effective only against rapidly replicating herpes virus.
6. A patient taking metronidazole and cimetidine at the same time is at increased risk for:
   a. bothersome side effects from the metronidazole.
   b. decreased effectiveness of cimetidine.
   c. renal impairment.
   d. severe disulfiram type reaction.
7. The term used to describe a drug that initiates a physiologic response when it is bound to a drug receptor is:
   a. agonist.
   b. antagonist.
   c. metabolite.
   d. prodrug.
8. The term used to describe the propensity of a drug to bind with a specific receptor is:
   a. affinity.
   b. bioavailability.
   c. efficacy.
   d. potency.
9. Fluconazole is effective in a one-time dose because it:
   a. is rapidly absorbed in the GI tract.
   b. has a bioavailability over 90%.
   c. is widely distributed into body tissues and fluids.
   d. has a mean elimination half-life of 30 hours.
10. Which of the following statements in regard to pharmacokinetic changes during pregnancy is correct?
    a. First-pass metabolism of drugs is increased during pregnancy because of increased blood flow through the liver.
    b. Drug elimination may be faster because of an increase in glomerular filtration rate.
    c. Higher levels of drug protein binding may occur with decreased albumin levels.
    d. Drug absorption may be decreased because of increased plasma volume.
11. Instructions for a patient for whom you are prescribing an oral bisphosphonate should include:
    a. take in the evening at bedtime.
    b. take with an antacid to avoid gastrointestinal irritation.
    c. take with eight ounces of plain water.
    d. take with orange juice to enhance absorption.
12. A common side effect of oral oxybutynin is:
    a. dry mouth.
    b. nausea.
    c. increased sweating.
    d. muscle pain.
13. Which of the following medications is considered a prodrug metabolized to a more active form by enzymes in the liver?
    a. Alendronate
    b. Atorvastatin
    c. Oxybutynin
    d. Tamoxifen
14. Rhabdomyolysis, a rare skeletal muscle breakdown that may cause renal dysfunction, may occur as an adverse reaction to:
    a. atorvastatin.
    b. fluconazole.
    c. metronidazole.
    d. tamoxifen.
15. Which of the following statements is correct?
    a. A narrow therapeutic range is desired for reducing possible toxic effects of a drug.
    b. Drug–drug interactions may increase or decrease bioavailability of a drug.
    c. Drugs that are highly lipophilic are not likely to pass through the blood-brain barrier.
    d. Unpredictable adverse reactions to a drug may occur because of age, body mass, or gender.
16. The partial estrogen agonist effect of tamoxifen may result in:
    a. increased occurrence of hot flashes.
    b. increased risk for endometrial cancer.
    c. prevention of estrogen ability to bind to receptors in breast tissue.
    d. vaginal dryness.
17. The low serum bioavailability of atorvastatin is attributed to:
    a. extensive hepatic first-pass metabolism.
    b. high level of protein binding.
    c. minimal enterohepatic recirculation.
    d. short elimination half-life of two to three hours.

Answers with Rationales

1. b. Increase in hepatic first-pass effect
   Orally administered drugs go from the gastrointestinal tract through the portal system to the liver before going to the general circulation. Some metabolism (chemical inactivation) of drug may occur as it taken up by hepatic microsomal enzymes.
2. b. any available data on potential drug-associated effects on female and male fertility.
   The 2015 FDA Pregnancy and Lactation Labeling Rule requires inclusion of a female and male of reproductive potential subsection if human or animal study data show potential drug-associated effects on fertility and/or implantation loss.
3. b. distribution.
   Drugs may attach to proteins (mainly albumin) in the blood (plasma protein binding). Only unbound drug is active and able to move out of the blood into body fluids and body tissues (distribution).
4. b. determine the time required to reach steady state and dosage interval.
   Half-life of a drug is the time it takes for plasma concentration of a drug to be reduced by 50%. It can be used to determine the time required to reach steady state and dosage interval.
5. d. is effective only against rapidly replicating herpes virus.
   Acyclovir is selectively activated in infected cells and works by inhibiting viral DNA synthesis. Because it is effective only against rapidly replicating herpes virus, it is not effective in eliminating latent herpes virus.
6. a. bothersome side effects from the metronidazole.
   Cimetidine can decrease hepatic metabolism of metronidazole and increase serum levels.
7. a. agonist.
   One mechanism of drug effect is through drug–receptor interaction. A receptor can be a cellular protein, enzyme, or membrane that when bound to a drug initiates a physiologic response or blocks a response that the receptor normally stimulates. The term *agonist* refers to a drug that, when combined with the receptor, stimulates a physiologic response. The term *antagonist* refers to a drug that, when combined with the receptor, blocks the response.
8. a. affinity.
   Affinity is the propensity of a drug to bind itself to a given receptor site. Efficacy is the ability of the drug to initiate biologic activity as a result of such binding.
9. d. has a mean elimination half-life of 30 hours.
   Half-life is the time it takes for plasma concentration to be reduced by 50% and is used to determine both time required to reach a steady state and dosage interval. Based on a half-life of 30 hours, the recommended dose of fluconazole for uncomplicated vulvovaginal candidiasis is 150 mg oral tablet in a single dose.
10. b. Drug elimination may be faster because of an increase in glomerular filtration rate.
    Glomerular filtration rate (GFR) begins increasing early in pregnancy, peaks at 9 to 16 weeks, and plateaus at a rate about 50% above that of prepregnancy at 34 to 36 weeks. Increased GFR can result in faster elimination of some drugs, resulting in a lower serum concentration during pregnancy.
11. c. take with eight ounces of plain water.
    Instructions for the patient for whom you are prescribing an oral bisphosphonate should include taking it with eight ounces of plain water.
12. a. dry mouth.
    The anticholinergic action of oxybutynin may cause side effects such as dry mouth, constipation, urinary retention, blurred vision, impaired sweating, and drowsiness.
13. d. Tamoxifen
    Tamoxifen is a prodrug metabolized to a more active form by enzymes in the liver.
14. a. atorvastatin.
    Rhabdomylosis, a rare skeletal muscle breakdown that may cause renal dysfunction, may occur as an adverse reaction to atorvastatin. Check creatine kinase level if the patient reports significant muscle pain or weakness or dark-colored urine while on atorvastatin.
15. b. Drug–drug interactions may increase or decrease bioavailability of a drug.
    Drug–drug interactions may induce or inhibit enzyme activity to either increase or decrease hepatic metabolism and thus bioavailability of a drug. These interactions may increase the risk for drug toxicity or reduce the effect of a drug.
16. b. increased risk for endometrial cancer.
    The partial estrogen agonist effect of tamoxifen results in an increased risk for endometrial cancer.
17. a. extensive hepatic first-pass metabolism.
    The low serum bioavailability of atorvastatin is attributed to extensive hepatic first-pass metabolism. This extensive first-pass metabolism is beneficial because the liver is the target organ for the drug to decrease low density lipoprotein levels.

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