MDSC3311 CARDIOVASCULAR & RENAL

Objectives

Diuretic Agents
1. Review the physiology of sodium and water reabsorption in the renal tubule.
2. Identify the physiological targets for diuretic agents and relate this to their diuretic potency.
3. List the major classes of diuretic agents (including carbonic anhydrase inhibitors, loop diuretics, thiazides, potassium-sparing diuretics and osmotic diuretics) and describe their mechanisms of action. Identify at least two (2) diuretic agents from each class.
4. Identify edematous and non-edematous indications for the use of diuretics.
5. Identify contraindications for diuretic use.
6. Identify adverse drug effects for commonly used diuretic agents.
7. Understand the use of diuretics in the therapeutic management of hypertension.

Management of Acute and Chronic Heart Failure

Introduction to cardiac inotropism
1. Describe the acute inotropic, dromotropic and chronotropic, effects of catecholamines (e.g. epinephrine, norepinephrine, dopamine, isoproterenol).
2. Compare and contrast the management of acute and chronic heart failure.

Drugs and Drug Classes to Consider:
ACE INHIBITORS (e.g. ENALAPRIL), ANGIOTENSIN RECEPTOR ANTAGONISTS (e.g. LOSARTAN), Amrinone, β-ADRENOCEPTOR ANTAGONISTS (e.g. CARVEDILOL, METOPROLOL), β-ADRENOCEPTOR AGONISTS (e.g. DOBUTAMINE), CARDIAC GLYCOSIDES (e.g. DIGOXIN), DIURETICS (e.g. furosemide), PHOSPHODIESTERASE INHIBITORS (e.g. MILRINONE), NESIRITIDE, VASODILATORS (e.g. HYDRALAZINE)
3. Principles and knowledge objectives.

a) Mechanism of action
1. Describe the basic pathophysiology of heart failure and the cardiac and extracardiac compensatory mechanisms that are activated.
2. Describe the effects of cardiac glycosides on myocardial contractility.
3. Explain the ionic basis for the mechanism of action of the cardiac glycosides – Na+, K+-ATPase inhibition; Na+/Ca2+ exchanger.
4. Describe the electrophysiologic effects of cardiac glycosides on atrial and ventricular muscle and specialized conducting tissue.
1. Explain the significance of direct and indirect (autonomic) actions of the cardiac glycosides.
2. Describe the positive inotropic effects of the β-adrenoceptor-agonists and phosphodiesterase inhibitors.
3. Explain the effects of β-adrenoceptor antagonists and ACE-inhibitors on cardiac function and ventricular remodeling in the setting of heart failure

**b) Actions on organ systems. Describe the hemodynamic actions of cardiac glycosides in the failing heart.**
1. Describe the extracardiac actions of cardiac glycosides.
2. Explain the effects of the vasodilators on pre-and afterload.
3. Describe the extracardiac actions of the β-adrenoceptor agonists, β-adrenoceptor antagonists, phosphodiesterase inhibitors and ACE-inhibitors.

**c) Pharmacokinetics**
1. Describe the routes of administration, the extent of oral absorption and bioavailability, the routes of elimination and extent of biotransformation of the cardiac glycosides and other drugs used in heart failure.
2. Know the differences in the pharmacokinetics of cardiac glycosides in young and old patients.
3. Describe the time-course of the cardiac actions of cardiac glycosides (onset and duration of action) with reference to differences between digoxin and digitoxin. Explain the concept of digitalization (loading dose) and maintenance therapy. Review the "plateau principle" with regard to maintenance therapy without a loading dose.

**d) Therapeutic indications**
1. Describe the use of cardiac glycosides in congestive heart failure.
2. Describe the role of β-adrenoceptor agonists, β-adrenoceptor antagonists, vasodilators, diuretics and ACE-inhibitors in the treatment of acute and chronic heart failure.

**e) Adverse effects, drug interactions and contraindications.**
3. Describe the cardiac (delayed after depolarizations and arrhythmias) and extracardiac manifestations of digitalis toxicity.
4. Describe the significance of changes in serum electrolyte levels (potassium, sodium, calcium, magnesium) with regard to digitalis toxicity.
5. Discuss the potential adverse effects with concomitant use of diuretics in the elderly or in patients with congestive heart failure, hypothyroidism and renal disease.
6. Describe the interactions of digitalis glycosides and quinidine, verapamil, and other relevant drugs.
7. Describe the cardiac and extracardiac side effects and limitations of the antagonist agents, vasodilators, phosphodiesterase inhibitors, and ACE-inhibitors.

**Heart Failure - Vasodilators and Afterload Reducers in the Treatment of CHF**
By the end of this session, you should be able to:
1. Define the concepts of preload, myocardial contractility and afterload as determinants of left ventricular performance.
2. Explain the difference between systolic dysfunction and diastolic dysfunction in congestive heart failure.
3. Explain the beneficial actions of diuretics, inotropic agents, vasodilators, ACE inhibitors and beta-adrenergic blockers in congestive heart failure.

**DRUG LIST**: hydrochlorothiazide, furosemide, dopamine, dobutamine, digoxin, nitroglycerin, isosorbide dinitrate, hydralazine, captopril, enalapril, carvedilol, propranolol, metoprolol, diltiazem, verapamil, spironolactone

**Digoxin**

By the end of this session, you should be able to:
1. Explain how congestive heart failure results in the activation of 3 different compensatory mechanisms.
2. Explain how digoxin produces a positive inotropic effect by inhibiting the Na/K pump.
3. Describe the effect of CHF on the slope and position of the Frank-Starling relationship, and how digoxin alters this relationship.
4. Discuss digoxin's use for controlling the ventricular rate in patients with atrial tachyarrhythmias.
5. Describe the cellular mechanisms by which digoxin can produce serious cardiac arrhythmias (3rd degree AV block, bigeminy, ventricular tachycardia).
6. Explain how digoxin toxicity can be enhanced by hypokalemia, hypercalcemia and drug interactions with antiarrhythmics and diuretics.
7. List some of the more common "non cardiac" signs and symptoms of digoxin toxicity (that serve as a "warning sign").
8. Describe the steps that should be taken to diagnose and treat digoxin toxicity.

**DRUG LIST**: digoxin, digoxin immune Fab (Digibind ®)

**Antihypertensive Drugs**

1. State the treatment goals for uncomplicated and complicated hypertension.
2. Understand the rationale underlying the decision to treat hypertension.
3. Understand the regulation of blood pressure by the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) and the physiological targets for blood pressure control.
4. List the major classes of antihypertensive drugs that act on the sympathetic nervous system, including beta-antagonists, alpha-1 antagonists, mixed alpha-beta antagonists, central alpha-2 agonists and peripheral adrenergic antagonists, and describe their mechanisms of action. Identify at least two (2) antihypertensive drugs belonging to each class.
5. List the major classes of antihypertensive drugs that act on the renin-angiotensin-aldosterone system, including ACE inhibitors, diuretic and angiotensin-receptor II antagonists, and describe their mechanisms of action. Identify at least two (2) antihypertensive drugs belonging to each class.
6. Identify antihypertensive agents that cause direct vasodilation (including Ca$^{2+}$ channel blockers) and describe their mechanism of action.
7. Identify other indications for the use of the major classes of antihypertensive drugs.
8. Identify contraindications for the use of antihypertensive drugs.
9. Identify commonly occurring adverse drug effects for the major classes of antihypertensive drugs.
10. Discuss the therapeutic management of hypertensive emergencies and urgencies.
11. Understand the therapeutic approach to the management of hypertension as outlined in the current Joint National Committee (JNC) guidelines for the prevention, detection, evaluation, and treatment of high blood pressure.

Anemia
1. Identify the types of anemia resulting from the deficiency of iron, erythropoietin, vitamin B₁₂, and folic acid.
2. List indications for the treatment of anemia by erythropoietin, iron, folic acid, and vitamin B₁₂.
3. Discuss the rationale for the use of hydroxyurea in thalassaemia intermedia.
4. Discuss the rationale for chelation therapy in this patient.

Anti-arrhythmic Drugs
1. Review the electrophysiology of the cardiac conducting system.
2. Understand the flow of Na⁺, K⁺, and Ca²⁺ ions across the myocardial membrane in the different phases of the cardiac action potential.
3. Understand disturbances of impulse conduction leading to arrhythmias, including abnormal automaticity and re-entrant conduction.
4. List the major classes of anti-arrhythmic agents, including Na⁺-channel blockers, beta-blockers, K⁺-channel blockers, and Ca²⁺-channel blockers. Identify at least two (2) agents from each class.
5. Understand the primary mechanisms of action for each drug class.
6. Understand how blockade of these channels (and receptors) affects the cardiac action potential and modulates disturbances in impulse conduction.
7. Identify the classes of anti-arrhythmic drugs efficacious in ventricular and supraventricular arrhythmias.
8. Identify important adverse effects associated with anti-arrhythmic drugs.

Respiratory Pharmacology
1. Know the disease process of asthma involving airway inflammation, bronchial smooth muscle constriction and mast cell degranulation.
2. Mediators (histamine, acetylcholine, proteases, leukotrienes C4, D4; prostaglandins; cytokines)
3. Describe the mechanisms of action, adverse effects of each antiasthmatic drug.
4. Know the routes and limitations of drug administration, systemic and inhalant.
5. Describe the types of therapy available: short term relief and long-term control.
6. Describe the mechanisms of action, use, and adverse effects of drugs used in the treatment of disorders of the respiratory system (Know briefly the applications and rational for use of expectorants, mucolytics, decongestants, cough suppressants, bronchodilators, anti-inflammatory drugs).
7. List the three major subtypes of drugs used in the treatment of asthma.
8. Discuss the types of drugs used for the treatment of acute asthmatic bronchoconstriction.
9. Discuss the types of drugs used for the treatment of chronic asthma.
10. Describe the target sites for pharmacologic intervention in asthmatic patients.
11. Explain the beneficial aspects of aerosol drug formulations vs. oral drug formulations.
12. Describe the role of cyclic AMP, cyclic GMP, and leukotrienes in the regulation of bronchiolar smooth muscle and pulmonary vasculature.
13. Describe the side effects and toxicity of theophylline.

Management of Asthma and Chronic Obstructive Pulmonary Disease


Leukotriene Antagonists: receptor blocker: montelukast, 5-lipoxygenase inhibitor: zileuton

Mechanism of action
1. Describe the mechanism of action of each of the major classes of agents relative to the component of the pathogenesis that is involved.

Actions on organ systems
1. Describe the relevant actions of these drugs on other physiological systems.

Pharmacokinetics
1. Identify the factors that influence the plasma levels of theophylline?
2. Know the appropriate route of administration of the various bronchodilators relative to the physico-chemical characteristics and the pharmacological action of the drug.

Therapeutic indications
1. Compare and contrast the management of acute and chronic asthma and obstructive pulmonary disease.
2. Discuss the developing approaches to the management (e.g. monoclonal antibodies).
3. Adverse effects, drug interactions and contraindications. Discuss the adverse effects and contraindications for each of the six classes of agents.
Anticoagulants, antiplatelets & thrombolytic agents

1. Review the coagulation cascade to appreciate the action of anticoagulants.
2. List the major classes of anticoagulants, including unfractionated heparin (UFH), low molecular weight heparins (LMWHs), direct thrombin inhibitors and warfarin.
3. Describe the mechanisms of action of the major classes of anticoagulants and identify at least two (2) LMWHs and direct thrombin inhibitors.
4. Understand the importance of laboratory monitoring with UFH use.
5. Identify indications and contraindications for heparin use.
6. List the clinical advantages of LMWHs over UFH.
7. Appreciate the initiation and adjustment of warfarin therapy.
8. List indications for direct thrombin inhibitors.
9. Identify common adverse effects of anticoagulants.
10. Identify at least two (2) important drug interactions with warfarin associated with increased anticoagulant effect, decreased anticoagulant effect and increased bleeding time.
11. List important pharmacokinetic properties of anticoagulants.
12. List the major classes of antiplatelet agents, including COX inhibitors and ADP and GPIIa/IIIb platelet receptor inhibitors, and describe their mechanisms of action. Give at least one (1) example in each class.
13. List the common adverse effects of antiplatelet drugs.
15. List indications and contraindications for the use of thrombolytic agents.

Antibacterial Drugs
Principles of Antimicrobial Action
By the end of this session, in conjunction with learning in MD1002 you should be able to:

1. Define the terms: antibiotics, selective toxicity, therapeutic index, bacteriostatic and bactericidal.
2. Explain the host determinants in relation to selection of an antimicrobial drug for therapy.
3. Define MIC and MBC values.
4. Describe the methodology for sensitivity assays.
5. Define bacterial resistance and list the mechanisms involved in acquiring bacterial resistance.
6. Explain the mechanisms involved in transfer of drug resistance to bacterial cells.
7. Describe the basic principles of combination therapy with antimicrobial drugs.
8. Describe the terms of synergism and antagonism by giving examples.
9. Discuss the classification of antimicrobial drugs based upon the mechanism of action.
10. Explain the modes of action of various antimicrobial drugs.

Penicillins
By the end of this session, you should be able to:
1. Describe the structural relationship of the penicillin molecule with antimicrobial activity.
2. Explain the mechanism of action of b-lactam antibiotics.
3. Describe the pharmacokinetic properties of penicillins.
4. Discuss primary therapeutic indications for penicillin G.
5. Describe the repository penicillins.
6. Explain the major side effects of penicillins.
7. Describe the indications for broad-spectrum penicillins.
8. List the penicillinase-resistant penicillins.
9. List the combinations of inhibitors of b-lactamase with penicillins.
10. Describe the antimicrobial activity of monobactams and carbapenems.
11. Explain the pharmacological basis for combining imipenem with cilastatin.

**DRUG LIST:** penicillin G, penicillin V, methicillin, oxacillin, cloxacillin, nafcillin, ampicillin, amoxicillin, carbenicillin, indanyl carbenicillin, ticarcillin, piperacillin, mezlocillin, meropenem, imipenem, aztreonam. Beta-lactamase inhibitors: clavulanic acid, sulbactam & tazobactam.

**Cephalosporins & Vancomycin**
By the end of this session, you should be able to:
1. Know the structural differences between penicillins and cephalosporins with relevance to the pharmacological activity.
2. Explain the mechanism of action of cephalosporins.
3. Describe the four generations of cephalosporins with specific examples and the differences in their antimicrobial spectrum and pharmacokinetic properties.
4. Describe the adverse effects due to cephalosporins.
5. Explain the terms superinfection and cross-hypersensitivity.
6. Discuss the mechanism of action of vancomycin.
7. Describe the pharmacokinetic properties of vancomycin.
8. Describe the main therapeutic indications and toxicities of vancomycin.

**DRUG LIST:** cephalexin, cefazolin, cefoxitin, cefaclor, cefprozil (Cefzil ®), cefotaxime, ceftriaxone, ceftazidime, cefepime, vancomycin

**Chloramphenicol/Tetracyclines/Fluoroquinolones**
By the end of this session, you should be able to:
1. Explain the mechanism of action and the mode of bacterial resistance of each class of antibiotics.
2. Discuss the pharmacokinetics of the prototype drugs
3. Describe the therapeutic indications for each class of antibiotics.
4. List the various toxicities associated with each class of antibiotics.
5. Explain the drug interaction of tetracyclines and antacid, and tetracyclines and penicillins.
6. List the advantages of newer fluoroquinolones over older fluoroquinolones.
7. Describe the adverse effects of ciprofloxacin, including contraindications in children and pregnant women.
**DRUG LIST**: chloramphenicol, tetracyclines (tetracycline, doxycycline, minocycline), fluoroquinolones (ciprofloxacin, levofloxacin).

**Sulfonamides**

By the end of this session, you should be able to:

1. Discuss the mechanism of action of sulfonamides and explain the synergistic inhibition due to sequential blockade with cotrimoxazole.
2. Classify sulfonamides giving an example for each group.
3. Describe the pharmacokinetic properties of sulfonamides and discuss the principles for use of combination of sulfonamides to avoid crystalluria.
4. Describe the major therapeutic indications of sulfonamides alone, and in combination with trimethoprim (cotrimoxazole).
5. Describe the major adverse effects associated with the use of sulfonamides.

**DRUG LIST**: sulfamethoxazole, trimethoprim (Bactrim®, Septra®, cotrimoxazole).

**Metronidazole & Miscellaneous Agents**

By the end of this session, you should be able to:

1. Explain the mechanism of action of metronidazole, mupirocin and nitrofurantoin.
2. Describe the pharmacokinetic properties of metronidazole, mupirocin and nitrofurantoin.
3. Describe the major therapeutic indications for use of these 3 drugs against anaerobic bacterial infections and their use as an antiparasitic agents.
4. Describe the major toxicities of these drugs (including the disulfiram-like reaction with metronidazole due to alcohol).

**DRUG LIST**: metronidazole, mupirocin, nitrofurantoin

**Aminoglycosides**

By the end of this session, you should be able to:

1. Discuss the mechanism of action of aminoglycosides.
2. Describe the pharmacokinetic properties of aminoglycosides. Explain the importance of peak and trough levels of aminoglycosides.
3. Discuss the need of and the method of dose adjustment for aminoglycosides in patients with compromised renal function.
4. Explain the mechanism of acquired drug resistance due to aminoglycosides and compare the relative ease development of resistance to streptomycin, gentamicin, tobramycin and amikacin.
5. Describe the therapeutic indications of aminoglycosides.
6. Explain the rational basis for combination therapy with an aminoglycoside and a penicillin, cephalosporin, or vancomycin.
7. Discuss the main three toxicities of aminoglycosides and precautions taken to limit them.

**DRUG LIST**: streptomycin, neomycin, gentamicin, tobramycin, amikacin, netilmicin.
Macrolides, Clindamycin and Streptogramins

By the end of this session, you should be able to:
1. Describe the mechanism of action of macrolides, clindamycin and streptogramins.
2. Explain the pharmacokinetic properties of erythromycin and compare with clarithromycin, azithromycin and clindamycin.
3. Describe the primary therapeutic indications for each class of antibiotics.
4. Describe the major drug interactions of macrolides due to inhibition of cytochrome P450 enzymes.
5. Discuss the major side effects of each class of antibiotics.

**DRUG LIST:** erythromycin, clarithromycin (Biaxin ®), azithromycin (Zithromax ®), clindamycin, Streptogramins (quinupristin/dalfopristin)