Cardiovascular and Respiratory Pharmacology

Subcommittee:

Taylor, David, Chair, taylorda@mail.ecu.edu
Caldwell, R. William wcaldwel@georgiahealth.edu
Karpa, Kelly kelly.karpa@verizon.net
Kass, Robert S. rsk20@columbia.edu
Kerecsen, Laszlo lkerec@midwestern.edu
Marcus, Philip

In memoriam

We dedicate this edition of the Cardiovascular and Respiratory Pharmacology section of the Knowledge Objectives to Dr. Philip Marcus who died unexpectedly on April 9, 2012. Dr. Marcus made valuable contributions to several editions of the Knowledge Objectives and his valuable input will be missed.

CARDIOVASCULAR AND RESPIRATORY PHARMACOLOGY
Recommended Total Curriculum Equivalent: 15 hrs.
Learning Objectives for Introduction to Cardiovascular Drugs
Physiology and Pathophysiology: Review of Cardiovascular Physiology (2 hrs equivalent)
Review the properties of the heart including contractility (e.g. excitation-contraction coupling) and electrical activity (e.g. the action potential, automaticity, excitability, refractory period, conduction and the relationship to the electrocardiogram). Review the concepts of inotropism, chronotropism, dromotropism and lusitropism as they pertain to mechanism of action of commonly used drugs. Discuss the mechanisms by which the autonomic nervous system regulates heart rate and contractility.
Review the neuroendocrine properties of the heart (both response and output).
Discuss mechanisms of myocardial growth, hypertrophy and signal transduction.
Review the intrinsic and extrinsic regulation of the cardiovascular system.
Describe cardiac and vascular smooth muscle cellular pathobiology including mechanisms of apoptosis and responses to hypoxia, reperfusion, ischemia and mechanical and oxidative stress.

Antiarrhythmic Agents			
Recommended Curriculum Equivalent: 3.0 hr			
Drug Classes and Drugs to Consider (Major or Prototype Drugs Capitalized)			
CLASS I			**CLASS II**
Class IA	**Class IB**	**Class IC**	**β-ADRENOCEPTOR ANTAGONISTS**
QUINIDINE PROCAINAMIDE disopyramide	LIDOCAINE mexiletine	flecainide propafenone	ESMOLOL METOPROLOL PROPRANOLOL atenolol
CLASS III	**CLASS IV**		**Others**
Prolongation of Action Potential Duration	**Calcium Channel Blockers**		
AMIODARONE dronedarone sotalol dofetilide ibutilide	DILTIAZEM VERAPAMIL		ADENOSINE atropine digoxin

Learning Objectives for Management of Cardiac Arrhythmias

Physiology and pathophysiology: Introduction to Cardiac Electrophysiology and Pathophysiology

Describe the ionic basis of the cardiac action potential.

Discuss the role of specific ions and ionic conductances in the production and propagation of the cardiac action potential with emphasis on fast (sodium dependent) and slow (calcium dependent) responses and their relevance to specific cardiac tissue types.

Review the electrophysiological differences between normal atrial and ventricular cardiac muscle cells and between specialized and normal cardiac cells.

Describe how cardiac electrical activity is altered in the production of cardiac arrhythmias.

Discuss the relationship between cellular cardiac electrical activity and the electrocardiogram.

Describe the pathophysiologic mechanisms of cardiac arrhythmias (abnormal automaticity, triggered rhythms, reentrant rhythms and abnormal impulse conduction).

Discuss the pharmacogenomics of long QT syndrome and the relationship of genetics to drug selection.

Describe the two forms of this disorder (i.e. drug-induced [or acquired LQT] and congenital) and which ion channels are responsible for each.

Mechanism of action

Classify antiarrhythmic drugs according to the Vaughn-Williams classification into classes I, II, III and IV including miscellaneous agents not otherwise classified, though recognizing the limitations of this classification system.

Explain the molecular mechanism of action of each drug in each drug class.

Describe the electrophysiologic actions of antiarrhythmic drugs in normal and abnormal myocardial and conduction tissue, and their effect on the phases of the cardiac action potential.

Describe the alteration of slow (calcium-dependent) and fast (sodium-dependent) responses by antiarrhythmic drugs and how that relates to the use of specific agents in arrhythmias of different origins (ventricular vs. supraventricular).

Describe the indirect autonomic actions of these drugs.

Describe the effect of age on fast and slow channels and on the agents affecting these channels.

Actions on organ systems

Describe the relevant extracardiac actions of antiarrhythmic drugs with special reference to the actions of amiodarone.

Describe the indirect autonomic actions of these drugs.

Pharmacokinetics

Describe the routes of administration, biotransformation and excretion of selected antiarrhythmic drugs.

Describe the pharmacokinetics and time-course of the cardiac actions of antiarrhythmic drugs (onset and duration of action).

Discuss the impact of reduced cardiac output due to myocardial infarction and cardiomyopathy on pharmacokinetics (including half-life) and pharmacodynamics.

Describe the influence of age on pharmacokinetic parameters, i.e., liver metabolism (lidocaine, procainamide, and propranolol) and elimination through kidney (digoxin and sotalol).

Describe the pharmacogenetic confounding effect of NAT2 pharmacogenetics on the choice of procainamide as an antiarrhythmic drug, especially in patients with renal impairment.

Adverse effects, drug interactions and contraindications

Describe the cardiac and extracardiac manifestations of toxicity from antiarrhythmic drugs.

Describe the beneficial and adverse interactions among antiarrhythmic drugs and between antiarrhythmic drugs and digoxin.

Describe the significance of electrolyte and acid-base imbalance in arrhythmia generation and their influence on antiarrhythmic drug action.

Describe the possible contraindications of antiarrhythmic drugs in the presence of heart block or congestive heart failure, and the precautions and contraindications in other conditions.

Know the classes of drugs (both antiarrhythmic and non antiarrhythmic) that can produce acquired Long QT Syndrome (LQTS).

Therapeutic uses

Describe the use of antiarrhythmic drugs in supraventricular arrhythmias (atrial flutter, atrial fibrillation, paroxysmal atrial tachycardia, junctional arrhythmias).

Describe the use of antiarrhythmic drugs in ventricular arrhythmias (ventricular premature beats, ventricular tachycardia, and ventricular fibrillation).

Discuss the utility of antiarrhythmic drugs in combination with electrical cardioversion or implantable cardioverter-defibrillators and ablation procedures.

Recognize that the therapeutic management of congenital Long QT Syndrome depends on the genotype, despite a uniform phenotype.

Notes

Objectives for Calcium-Channel Blockers are covered under Management of Hypertension.

Objectives for β-Adrenoceptor Antagonist Agents are covered under Autonomic Nervous System.

Clinical Pharmacology

The CAST study has changed our understanding of the risk of using sodium channel blockers post myocardial infarction in the management of cardiac arrhythmias. The use of antiarrhythmic drugs is being impacted considerably by data arising from studies of the pharmacogenomics of inherited channelopathies of ion transporters. As well as the long QT syndrome, there is now an appreciation of the existence of a short QT syndrome that is associated with atrial fibrillation and sudden death. Both phenotypes predispose an affected individual to cardiac arrhythmias, and can be induced by drug therapy for other disease states. Quinidine has provided benefit in lengthening the QT interval in the short QT syndrome. Disopyramide may also be effective in this pathological state. Currently, beta-adrenoreceptor blocking drugs are perceived to be the treatment of choice for long QT syndrome.

Relevance

USMLE topic Cardiovascular System-Abnormal Processes- Metabolic and Regulatory Disorders (dysarrhythmias, ischemic heart disease, myocardial infarction)	**Principles of therapeutics** Antiarrhythmic Drugs
AAMC Medical School Objectives Project Report X Patient Safety-Table 1	**Topic C:** Drug treatment of common conditions

<table>
<tr><th colspan="4">Management of Acute and Chronic Heart Failure</th></tr>
<tr><td colspan="4">Recommended Curriculum Equivalent: 2.0 hr</td></tr>
<tr><td colspan="4">Drug Classes and Drugs to Consider (Major or Prototype Drugs Capitalized)</td></tr>
<tr><td colspan="3">Renin-Angiotensin Aldosterone System</td><td>Other Peptide Systems</td></tr>
<tr><td>ACE Inhibitors</td><td>Angiotensin Receptor Blockers</td><td>Aldosterone Antagonists</td><td>ANP Agents</td></tr>
<tr><td>CAPTOPRIL
ENALAPRIL
LISINOPRIL</td><td>LOSARTAN
valsartan
candesartan</td><td>SPIRONOLACTONE
EPLERENONE</td><td>nesiritide</td></tr>
<tr><td colspan="2">C. Sympathetic Agents</td><td rowspan="2">D. PDE Inhibitors</td><td rowspan="2">E. Vasodilators</td></tr>
<tr><td>Antagonists</td><td>Agonists</td></tr>
<tr><td>CARVEDILOL
METOPROLOL
bisoprolol</td><td>DOBUTAMINE
dopamine</td><td>inamrinone
milrinone</td><td>HYDRALAZINE
ISOSORBIDE DINITRATE
NITROGLYCERIN
Combination of hydralazine and isosorbide dinitrate (BiDil) used in African Americans
nitroprusside</td></tr>
<tr><td colspan="2">F. Diuretics</td><td colspan="2">G. Cardiac Glycosides</td></tr>
<tr><td colspan="2">FUROSEMIDE
Thiazides</td><td colspan="2">DIGOXIN</td></tr>
<tr><td colspan="4">Principles and Learning Objectives for Management of Heart Failure</td></tr>
<tr><td colspan="4">Physiology and pathophysiology: Introduction to cardiac inotropism
Describe the acute inotropic, dromotropic, and chronotropic effects of catecholamines (e.g. epinephrine, norepinephrine, dopamine, isoproterenol).
Discuss the lusitropic actions of the catecholamines as they relate to normal and abnormal cardiac function.
Compare and contrast the management of acute and chronic heart failure.
Discuss preventing cardiac remodeling at the onset of heart failure.
Describe the basic pathophysiology of heart failure and the cardiac and extracardiac compensatory mechanisms that are activated.
Discuss the role of genetics and ethnicity in the pathophysiology of heart failure and in the regulation of responsiveness to agents used in heart failure.</td></tr>
<tr><td colspan="4">Mechanism of action
Describe the effects of digoxin on myocardial contractility.
Explain the ionic basis for the mechanism of action of digoxin: discuss the roles of Na^+, K^+-ATPase inhibition and the $Na^+/Ca2^+$ exchanger.
Describe the electrophysiologic effects of digoxin on atrial and ventricular muscle and specialized conducting tissue.
Explain the significance of direct and indirect (autonomic) actions of digoxin.
Describe the positive inotropic effects of the β-adrenoceptor-agonists and phosphodiesterase inhibitors.
Explain the effects of adrenoceptor antagonists and ACE-inhibitors on cardiac function and ventricular remodeling in the setting of heart failure.</td></tr>
</table>

Actions on organ systems

Describe the hemodynamic actions of digoxin in the failing and the normal heart.
Describe the extracardiac actions of digoxin.
Explain the effects of vasodilators, loop diuretics and β-blockers on preload and afterload.
Explain the effects of vasodilators on renal and coronary perfusion.
Describe the extracardiac actions of the adrenoceptor agonists, adrenoceptor antagonists, phosphodiesterase inhibitors and ACE-inhibitors.

Pharmacokinetics

Describe the routes of administration, the extent of oral absorption and bioavailability, the routes of elimination and extent of biotransformation of digoxin and other drugs used in heart failure.
Contrast the pharmacokinetics of digoxin in young and old patients.
Describe the time-course of the cardiac actions of digoxin (onset and duration of action).
Explain the concept of digitalization (loading dose) and maintenance therapy.
Review the "plateau principle" with regard to maintenance therapy without a loading dose.

Adverse effects, drug interactions and contraindications

Describe the cardiac (delayed depolarizations and arrhythmias) and extracardiac manifestations of digoxin toxicity (digoxin levels > 2.0 ng/mL are associated with toxicity).
Discuss the potential for low levels (0.4-0.8 ng/mL) to reduce mortality in acute decompensated heart failure.
Describe the significance of changes in serum electrolyte levels (potassium, sodium, calcium, magnesium) with regard to digoxin toxicity.
Discuss the potential adverse effects with concomitant use of diuretics (both potassium-sparing and potassium depleting) in the elderly or in patients with congestive heart failure, hypothyroidism and renal disease.
Describe the interactions of digoxin and quinidine, verapamil, and other relevant drugs.
Describe the cardiac and extracardiac side effects and limitations of the antagonist agents, vasodilators, phosphodiesterase inhibitors, and ACE-inhibitors.

Therapeutic uses

Describe the use of digoxin in congestive heart failure and in atrial arrhythmias.
Describe the role of adrenoceptor agonists, adrenoceptor antagonists, vasodilators, diuretics and ACE-inhibitors in the treatment of acute and chronic heart failure.
Discuss the use of atrial natriuretic peptide agonists in the management of acute severe heart failure unresponsive to other agents.

Notes

Objectives for Renin-angiotensin aldosterone agents are covered under vasoactive peptides.
Objectives for Sympathetic nervous system drugs are covered under Autonomic Nervous System.

Clinical Pharmacology

The latest Cochrane Review indicates that ACE inhibitors and ARB drugs do not reduce total morbidity and mortality in patients with heart failure. With the increased likelihood of impaired renal perfusion in association with heart failure, a loop diuretic (furosemide) is likely to be a prudent choice to relieve congestion. There is a reasonable consensus that beta-receptor adrenergic blocking drugs are becoming the pharmacological treatment of choice for this pathological state.

Relevance

USMLE topic Cardiovascular System; Renal/Urinary System- Abnormal Processes- Metabolic and Regulatory Disorders (Systolic and diastolic dysfunction, low-and high output heart failure, systemic hypertension)	**Principles of therapeutics** Mechanisms of action, use, adverse effects of drugs for treatment of disorder of cardiovascular system-Inotropic agents and treatment of heart failure
AAMC Medical School Objectives Project Report X Patient Safety-Table 1	**Topic C:** Drug treatment of common conditions

Management of Hypertension						
Recommended Curriculum Equivalent: 4.0 hr						
Drug Classes and Drugs to consider (Major or Prototype Drugs Capitalized)						
Renin-Angiotensin Aldosterone System				**Endothelin Antagonists**		
Angiotensin Converting Enzyme Inhibitors	**Angiotensin Receptor Blockers**	**Aldosterone Antagonists**	**Renin Inhibitor**			
ENALAPRIL CAPTOPRIL LISINOPRIL fosinopril	LOSARTAN VALSARTAN candesartan olmesartan	SPIRONOLACTONE eplerenone	aliskiren	ambrisentan bosentan		
Sympathetic Antagonist Agents						
Alpha		**Beta**		**Mixed α and β**		
Non-selective	α_1 Selective	Nonselective	β_1 Selective			
phenoxybenzamine phentolamine	PRAZOSIN doxazosin	PROPRANOLOL nadolol pindolol timolol	METOPROLOL atenolol nebivolol	CARVEDILOL LABETALOL		
Diuretics	**Vasodilators**					
amiloride CHLORTHALIDONE eplerenone furosemide HYDROCHLOROTHIAZIDE spironolactone triamterene	**Venous**	**Arterial**	**Both**			
	ISOSORBIDE DINITRATE nitroglycerin	CALCIUM BLOCKERS (DIHYDROPYRIDINES, DILTIAZEM, VERAPAMIL) HYDRALAZINE diazoxide minoxidil	NITROPRUSSIDE ANGIOTENSIN CONVERTING ENZYME INHIBITORS ANGIOTENSIN RECEPTOR BLOCKERS alpha blockers Combination of hydralazine and isosorbide dinitrate (BiDil)			
Centrally Acting Agents	**Pulmonary Hypertension**			**Hypertensive Emergency and Urgency**		
CLONIDINE methyldopa	**Endothelin Antagonists**	**PDE 5 Inhibitors**	**Prostaglandins (Prostacyclin)**	NITROPRUSSIDE clevidipine esmolol fenoldopam nicardipine trimethaphan (Historical)		
	ambrisentan bosentan	sildenafil tadalafil	epoprostenol iloprost treprostinil			

Principles and Learning Objectives for Management of Hypertension

Introduction to the Vascular System and its Regulation

Review the determinants of systemic arterial blood pressure including the role of the autonomic nervous system, the regulation of fluid volume and the renin-angiotensin aldosterone system.
Describe the role of the central nervous system in the regulation of blood pressure.
Discuss the role of vascular endothelium and locally released regulators of vascular tone in the maintenance of blood pressure.
List the types of hypertension and the relative prevalence of each.
Describe the current views for the etiology of essential hypertension.

Mechanism of action

Discuss the mechanism of action of each of the several classes of agents used to manage hypertension according to the site of action within the pathogenesis of hypertension.
Describe the mechanism by which each antihypertensive drug or drug class exerts its therapeutic function.

Actions on organ systems

Review the end organ effects of untreated hypertension and the beneficial effects achieved by therapeutic management of the disease.
Describe the actions of antihypertensive drugs on the heart, renal blood flow and renal function.
Describe the relevant actions of antihypertensive drugs in other organ systems (CNS, other).

Pharmacokinetics

Describe the time-course of their antihypertensive activity (onset and duration of action) for each class of agents.

Adverse effects, drug interactions and contraindications

Describe the cardiac and extracardiac side effects of antihypertensive drugs, including reflex effects.
Describe the beneficial and adverse interactions between antihypertensive drugs and between antihypertensive drugs and other therapeutic agents.

Therapeutic uses

Discuss the role of non-pharmacological treatment modalities in the management of hypertension.
Describe the use of antihypertensive drugs in mild, moderate and severe essential hypertension.
Describe the use of antihypertensive drugs in hypertensive emergencies and in pregnancy (e.g. eclampsia).
Describe the use of antihypertensive drugs in pheochromocytoma.
Discuss the pathophysiology of pulmonary hypertension and describe the use of prostacyclin agonists, phosphodiesterase 5 inhibitors and endothelin receptor antagonists in the management of this form of hypertension.
Discuss population subgroups with special antihypertensive drug considerations (e.g. African-Americans, diabetics, isolated systolic hypertension esp. in elderly patients, renal failure patients).

Notes

Objectives for Renin-angiotensin aldosterone agents are covered under vasoactive peptides
Objectives for Sympathetic nervous system drugs are covered under Autonomic Nervous System

Clinical Pharmacology

ACE inhibitors are becoming a first line drug choice, especially in patients with diabetes. Usually a low dose of diuretic is added to inhibit the upregulation of aldosterone when ACE inhbitiors are used alone. In diabetic patients, a target diastolic blood pressure of 80 mm Hg is chosen rather that the conventional target of 90 mm Hg. ARB's are a consideration when cough occurs in patients prescribed ACE inhibitor drugs. There is no evidence for improved efficacy of using ACE inhibitors and ARB drugs concurrently. No beta-adrenergic receptor blocking drug is sufficiently selective to prevent bronchoconstriction in patients with a history of reversible airways constriction. When cardiac perfusion is a concurrent pathological issue, beta-adrenoreceptor blockers and long-acting calcium channel blocking drugs are reasonable choices for the management of hypertension.

Relevance

USMLE topic Cardiovascular System-Abnormal Processes-Metabolic and Regulatory Disorders (Systemic hypertension)	**Principles of therapeutics** Mechanisms of action, use, adverse effects of drugs for treatment of disorder of cardiovascular system-Antihypertensive drugs
AAMC Medical School Objectives **Project Report X Patient Safety-**Table 1	**Topic C:** Drug treatment of common conditions

Drugs for the Treatment of Angina and Coronary Artery Disease			
Recommended Curriculum Equivalent: 1.0 hr			
Drug Classes and Drugs to consider (Major or Prototype Drugs Capitalized)			
Beta Adrenoceptor Antagonists	**Calcium Channel Blockers**	**Organic Nitrates**	**Metabolic Modulators**
ATENOLOL METOPROLOL PROPRANOLOL	AMLODIPINE NICARDIPINE NIFEDIPINE diltiazem verapamil	ISOSORBIDE MONONITRATE NITROGLYCERIN isosorbide dinitrate	ranolazine
Principles and Learning Objectives for Management of Angina and Coronary Artery Disease			
Introduction to Coronary Blood Flow and its Regulation Describe the normal regulation of coronary blood flow and the relationship to the events of the cardiac cycle Describe the normal determinants of cardiac oxygen consumption and supply. Describe the basic pathophysiology of myocardial ischemia. Explain the significance of atherosclerotic coronary artery disease and coronary artery spasm (Prinzmetal's) in the production of myocardial ischemia and angina pectoris.			
Mechanism of action Describe the hemodynamic actions of antianginal drugs, including their coronary and peripheral vasodilator actions. Describe the effects of each antianginal drug or drug class on the determinants of myocardial oxygen consumption (heart rate, myocardial wall tension, etc.) and/or oxygen supply (coronary blood flow). Describe the effects of the antianginal drugs at the cellular level.			
Actions on organ systems Describe the cardiac actions of antianginal drugs (electrophysiologic, coronary vasodilator, inotropic actions). Describe the actions of antianginal drugs on the peripheral circulation (arterial, venous) and their effects on ventricular preload and afterload.			
Pharmacokinetics Describe the routes of administration, biotransformation and excretion of antianginal drugs. Describe the significance of a "first-pass effect" for orally administered antianginal drugs and the rationale underlying sublingual and transdermal administration of nitrates. Describe the time-course of antianginal activity (onset and duration of action). Describe the problem of dose intervals and tolerance development with the nitrates.			
Adverse effects, drug interactions and contraindications Describe the cardiac and extra-cardiac side effects of antianginal drugs with special reference to the interaction with drugs used to treat erectile dysfunction (PDE 5 inhibitors). Describe the beneficial and adverse interactions between antianginal drugs and between antianginal drugs and other cardiovascular drugs.			

Therapeutic uses

Describe the use of antianginal drugs in classic (effort-related) angina pectoris and vasospastic angina pectoris.

Describe the concept of "myocardial preservation" and discuss the use of antianginal drugs in the context of acute myocardial infarction with particular emphasis on adrenoceptor antagonists.

Notes

Objectives for Sympathetic nervous system drugs are covered under Autonomic Nervous System.

Clinical Pharmacology

Nitroglycerin remains the initial treatment of choice for acute anginal attacks. Patients must be reminded that exposure to moisture will destroy a sublingual tablet formulation and potentially be misinterpreted as worsening of the disease. For chronic angina, long-acting nitrates are a reasonable next step, but tolerance is a problem when the drug is used at evenly spaced time intervals over 24 hours. For chronic stable angina, beta-adrenergic receptor blocking drugs remain a reasonable choice with calcium channel blocking drugs as a secondary choice. Calcium channel-blocking drugs are preferred for vasospasm-induced angina, but the long-acting formulations are indicated as an appropriate treatment.

Relevance

USMLE topic	**Principles of therapeutics**
Cardiovascular System- Abnormal Processes- Metabolic and Regulatory Disorders (Ischemic heart disease, Myocardial infarction)	Mechanisms of action, use, adverse effects of drugs for treatment of disorder of cardiovascular system-coronary and peripheral vasodilators, drugs to treat peripheral arterial diseases
AAMC Medical School Objectives Project Report X Patient Safety-Table 1	**Topic C:** Drug treatment of common conditions

Drugs for the Treatment of Hyperlipidemias

Recommended Curriculum Equivalent: 1.0 hr

Drug Classes and Drugs to consider (Major or Prototype Drugs Capitalized)

BILE ACID SEQUESTRANTS	FIBRIC ACID DERIVATIVES	HMG CoA REDUCTASE INHIBITORS	OTHERS
CHOLESTYRAMINE colesevelam colestipol	GEMFIBROZIL fenofibrate	ATORVASTATIN FLUVASTATIN LOVASTATIN PRAVASTATIN ROSUVASTATIN SIMVASTATIN	EZETIMIBE nicotinic acid omega-3 fatty acids

Principles and Learning Objectives for the Management of Hyperlipidemias

Physiology and Pathophysiology: Lipid Interactions with the Cardiovascular System

Discuss cholesterol synthesis, transport, export, excretion, and receptor mediated cellular uptake.

Review "normal" values for lipid levels.

Discuss the relevant hypotheses regarding the etiology of hyperlipidemias (e.g. intrinsic versus extrinsic elevations in plasma lipids).

Describe the basic pathophysiology of atherosclerotic vascular disease and its relationship to the hyperlipidemias ("cholesterol" or "infectious agent").

Describe the types of hyperlipidemias (I, II, III, IV, and V) and the alterations in serum lipids in each type (triglycerides, cholesterol, LDL, HDL, LDL, lipoproteins).

Discuss the lipid profile characteristic of insulin-resistant diabetics.

Discuss genetic conditions leading to hyperlipidemia.

Describe the concept of "plaque stability".

Mechanisms of action

Describe the actions of each drug class on serum lipids, and compare and contrast the mechanism of each of these actions.

Characterize these agents according to their action to reduce lipid synthesis or enhance removal.

Discuss the advantages of combinations of agents in the management of hyperlipidemia.

Identify the putative role of antioxidants in the management of hyperlipidemia.

Actions on organ systems

Describe the relevant actions of these drugs, other than on lipid metabolism (e.g. pleiotropic effects).

Discuss drug-induced alterations in plasma lipids (e.g. protease inhibitor-induced hyperlipidemia; estrogen-induced hypolipidemia).

Review the role of thyroid hormone in affecting serum lipids and the findings in hyper- and hypothyroidism.

Discuss the role of the HMG CoA reductase inhibitors in preventing acute coronary events and stroke and as possible adjuncts in the management of dementia and other pathological disorders. Consider the potential anti-inflammatory effects of "statins" on other disease states.

Pharmacokinetics

Describe the absorption, distribution, metabolism and excretion of drugs used for hyperlipidemias.

Compare and contrast the pharmacokinetics of nicotinic acid (niacin) and fibric acids.

Adverse effects, drug interactions and contraindications

Describe the cardiovascular and other systemic side effects of these drugs with special reference to the muscle and liver toxicities.

Describe the beneficial and adverse interactions between these drugs, and their interactions with digoxin, oral anticoagulants, and other relevant drugs.

Therapeutic uses:

Describe the non-pharmacological management of hyperlipidemia (i.e. life style modifications and natural remedies that may benefit patients).

Describe the use of these agents in familial and acquired hyperlipidemias, and their efficacy in atherosclerotic vascular disease.

Discuss important multicenter clinical trial data documenting efficacy in multiple patient groups.

Discuss new National Cholesterol Education Program (NCEP) guidelines for lowering LDL.

Discuss the apparent lack of a threshold effect (lower is always better, even in the normal range of LDL).

Notes

Objectives for nicotinic acid (niacin) are also found under Vitamins.

Clinical Pharmacology

The statin class of drugs has become the de facto primary choice for treatment of hyperlipidemias. Choice of agent is often based on potential drug interactions, since their bioavailability is very low. Accumulation may be problematic with inhibition of first-pass elimination mechanisms. It is still controversial as to whether or not use of this drug class in elderly patients has an acceptable risk:benefit ratio.

Relevance

USMLE topic Cardiovascular System-Abnormal Processes-Metabolic and Regulatory Disorders & Vascular Disorders	**Principles of therapeutics** Drug affecting cholesterol and lipid metabolism
AAMC Medical School Objectives **Project Report X Patient Safety-**Table 1	**Topic C** Drug treatment of common conditions and diseases

Thrombolytic and Anticoagulant Agents in the Management of ST-Elevation Myocardial Infarction (STEMI)/Myocardial Infarction/Acute Coronary Syndrome and Chronic Treatment of Cardiovascular Diseases including Atrial Fibrillation

Recommended Curriculum Equivalent: 1 hr

Drug Classes and Drugs to consider (Major or Prototype Drugs Capitalized)

ANTIPLATELET AGENTS

ADP Receptor Antagonists	Glycoprotein IIb/IIIA Receptor Antagonists	Others
CLOPIDOGREL PRASUGREL Ticlopidine Ticagrelor	ABCIXIMAB Eptifibatide Tirofiban	ASPIRIN Dipyridamole Cilostazol

ANTICOAGULANTS

Heparins	Oral Anticoagulants	Thrombin Inhibitors	Factor Xa Inhibitors
HEPARIN ENOXAPARIN dalteparin tinzaparin	WARFARIN	DABIGATRAN (oral) argatroban bivalirudin lepirudin desirudin	fondaparinux rivaroxaban (oral)

FIBRINOLYTICS

ALTEPLASE
UROKINASE
Anistreplase
Reteplase
Streptokinase (Historical)
Tenecteplase

Mechanisms of action

Understand the mechanisms involved in coagulation.
Describe the mechanisms of platelet activation and aggregation
Know the mechanism of action of antiplatelet agents, their major routes of administration and elimination and adverse effects.
Know the mechanism of action of anticoagulant agents.
Understand the differences in the mechanisms and actions of heparin, warfarin and thrombin and factor Xa inhibitors, respectively.
Describe the use of thrombolytic agents as first-line in the therapy of acute myocardial infarction and stroke. Discuss the role of acute catheter-mediated intervention as an alternative or complementary strategy.
Consider the spectrum of agents available for cardioprotection and plaque stabilization in the setting of acute coronary syndrome.

Actions on organ systems

Discuss the long-term use of antiplatelet agents (e.g. ASPIRIN and clopidogrel) in patients with claudication associated with chronic occlusive peripheral arterial disease, stroke and following percutaneous coronary interventions (e.g. angioplasty and stents).

Describe the use of thrombolytic agents as first-line agents in the acute therapy of post-myocardial infarction and as adjuncts in the nonpharmacological management of coronary artery disease (e.g. surgical stent implantation with drug-eluting stents).

Consider the proper use of morphine in the pain of MI, the long-term use of aspirin (antiplatelet activity) as prophylaxis and the use of adrenergic blocking agents for cardiac protection.

Pharmacokinetics

Discuss the appropriate use of parenteral versus oral anticoagulants.

Discuss the route and time of administration of thrombolytic agents.

Adverse effects, drug interactions and contraindications

Discuss the treatment of warfarin overdose and excessive effect of warfarin. Review the role of Vitamin K in such an event.

Discuss the management of heparin-induced thrombocytopenia (HIT) and the potential for heparin-induced thrombocytopenic thrombosis (HITT).

Therapeutic uses

Describe the use of thrombolytic and anticoagulant agents in the acute management of myocardial infarction.

Discuss the use of anticoagulant agents in the management of DVT and in total hip and knee replacement surgery.

Discuss the use of antiplatelet drugs, anticoagulant drugs, nitroglycerin, adrenergic blocking agents and angiotensin converting enzyme inhibitors as adjunctive agents in the management of myocardial infarctions.

Notes

See Section I Drugs Acting on the Blood and Blood-forming Organs for Objectives on Thrombolytics, Anticoagulants and Antithrombotic Drugs.

Clinical Pharmacology

Many new agents are rapidly reaching the market to treat STEMI. Therapy with low dose aspirin plus clopidogrel appears to have reasonable evidence for efficacy. Alternately, low molecular weight heparin therapy with addition of a glycoprotein IIb/IIIa receptor antagonist is also considered acceptable. There is increasing evidence that low molecular weight heparins are more effective and safer than the previously used standard intervention with unfractionated heparin. Use of combination endpoints to assess safety and efficacy of alternative drug treatments has clouded the ability to compare alternative strategies. In the management of atrial fibrillation, warfarin still appears to be the drug treatment of choice, in spite of difficulties with control of INR. The hope that pharmacogenetic diagnostic tools would resolve this problem has provided only a modest incremental improvement in the safety and efficacy of using warfarin as a drug intervention.

Relevance

USMLE topic	**Principles of therapeutics**
Hematopoietic and Lymphoreticular Systems-Abnormal Processes-Hemorrhagic and Hemostatic Disorders Cardiovascular System-Abnormal Processes-Traumatic and Mechanical Disorders & Vascular Disorders	Drug affecting blood coagulation, thrombolytic agents, and antiplatelet agents

AAMC Medical School Objectives **Project Report X Patient Safety-**Table 1	**Topic C:** Drug treatment of common conditions **Topic D:** Management of less common but severe medical conditions and emergencies

Drugs Used for the Management of Asthma and COPD

Recommended Curriculum Equivalent: 1 hr

Drug Classes and Drugs to consider (Major or Prototype Drugs Capitalized)

Antiinflammatory Drugs			Leukotriene Modifiers	
Inhaled Steroids	**Modulators of Mast Cell Degranulation**		**Leukotriene Receptor Antagonists**	**5-LO Inhibitor**
	Mast Cell Stabilizer	**Anti-IgE**		
BUDESONIDE BECLOMETHASONE FLUTICASONE MOMETASONE ciclesonide	CROMOLYN	OMALIZUMAB	zafirlukast MONTELUKAST	ZILEUTON

Bronchodilators

β_2 Agonists		Methylxanthines	Muscarinic Receptor Antagonists	Phosphodiesterase 4 Inhibitors
Short-Acting	**Long-Acting**	THEOPHYLLINE aminophylline	IPRATROPIUM TIOTROPIUM	roflumilast
ALBUTEROL levalbuterol pirbuterol	SALMETEROL FORMOTEROL INDACATEROL			

Principles and Learning Objectives for the Management of Respiratory Diseases

Physiology and Pathophysiology: Introduction to Respiratory Physiology

Describe the endogenous chemical mediators and their receptors that function to regulate bronchial smooth muscle tone.

Describe the role of cyclic AMP, cyclic GMP, leukotrienes and nitric oxide in regulation of bronchiolar smooth muscle and pulmonary vasculature.

Describe the role of phosphodiesterases and the various isoenzymes of PDE (i.e. PDE4) in the function of bronchiolar smooth muscle and in the inflammatory process.

Identify the relationship of bronchial smooth muscle reactivity to the pathogenesis of asthma.

Characterize the role of inflammation in the pathogenesis of asthma and chronic obstructive pulmonary disease (COPD).

Describe the similarities and differences between asthma and chronic obstructive pulmonary disease and the treatments of each disorder.

Recognize the allergic basis of asthma and its association with other atopic disorders (e.g. allergic rhinitis).

Mechanisms of action

Describe the mechanism of action of each of the major classes of agents relative to the component of pathogenesis to distinguish between agents that modify the disease process versus those that relieve symptoms.

Describe the putative mechanism of action of theophylline.

Discuss the use of combinations of agents (e.g. fluticasone and salmeterol) in the chronic management of asthma.

Describe the use of agents to treat acute episodes of asthma and in the treatment of exercise-induced asthma.

Describe the use of various agents in the treatment of COPD.

Discuss the role of agents in reducing COPD exacerbations and improving outcomes.

Actions on organ systems

Describe the actions of agents used to treat asthma on smooth muscle versus inflammatory processes.

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

Pharmacokinetics

Identify the factors that influence the plasma levels of theophylline.

Know the appropriate route of administration of the various bronchodilators relative to the physico-chemical characteristics and the pharmacological action of the drug.

Discuss the relative merits of inhalant administration versus oral or parenteral administration for the management of both episodic and chronic asthma as well as COPD.

Identify the potential role of single-isomers in the management of airway diseases (e.g. levalbuterol and arformoterol).

Adverse effects, drug interactions and contraindications

Discuss the adverse effects and potential contraindications for each class of agents.

Therapeutic uses

Compare and contrast the management of acute and chronic asthma and chronic obstructive pulmonary disease.

Discuss the management of asthma in special patient populations (e.g. pediatric and pregnant and/or lactating females).

Discuss the emerging therapies for the management of asthma and chronic obstructive pulmonary disease (e.g. monoclonal antibodies).

Discuss the non-pharmacologic approaches to the management of asthma and COPD (e.g. smoking cessation and oxygen).

Discuss recently introduced guidelines for management of asthma (National Heart, Lung and Blood Institute) and COPD (Global Initiative for Obstructive Lung Disease [GOLD]).

Notes

For additional information and objectives see Management of Asthma and COPD in Autocoids Section.

Clinical Pharmacology

The availability of inhaled short-acting beta-2 receptor agonists has transformed the management of mild to moderate asthma. Inhaled corticosteroids have become the cornerstone of management of inflammation of the bronchioles in patients with chronic disease. An inhaled steroid with extensive first-pass elimination is preferred to limit the systemic effects of that portion of the administered dose that is swallowed. The addition of long-acting beta-2 receptor drug formulations has not solved the issue of management of chronic bronchoconstriction. Due to down regulation of beta-2 receptors with the long-acting formulations, they should be used only concurrently with an inhaled steroid in patients with chronic moderate to severe reversible bronchoconstriction. Theophylline remains an effective and economical oral therapy for persons with mild to moderate disease, especially in countries where cost limits availability of alternative drug treatments. The drug management of obstructive lung disease remains controversial. Outside of North America, a prodrug of terbutaline [bambuterol] offers an alternative and effective oral therapy for patients with reversible bronchoconstriction who have difficulty in inhaling their prescribed bronchodilators. Other drugs for management of bronchiolar obstruction remain for the most part second-line alternative choices.

Relevance

USMLE topic	**Principles of therapeutics**
Respiratory system	Bronchodilator drugs

AAMC Medical School Objectives **Project Report X Patient Safety –** Table 1	**Topic C** Drug treatment of common conditions and diseases

Summary of Classes and Specific Cardiovascular and Respiratory Drugs for Consideration				
Primary Agents to be considered in each class are indicated by CAPITALIZATION. Drugs only used outside the US are identified by boldface print and brackets. Important drugs of historical significance are identified as (historical).				
1. Adenosine Diphosphate Receptor Antagonists				
CLOPIDOGREL PRASUGREL ticlopidine				
2. Adrenoceptor Agonists				
β-Adrenoceptor Agonists		**β_2-Adrenoceptor Selective Agonists**		
DOBUTAMINE dopamine EPINEPHRINE isoproterenol		ALBUTEROL (salbutamol) bitolterol FORMOTEROL indacaterol levalbuterol pirbuterol SALMETEROL terbutaline [**bambuterol**]		
3. Adrenoceptor Antagonists				
Alpha-Adrenoceptor Antagonists		**Beta-Adrenoceptor Antagonists**		
Nonselective	**α_1-selective**	**Mixed**	**Nonselective**	**β_1-selective**
phentolamine phenoxybenzamine	doxazosin PRAZOSIN terazosin	CARVEDILOL LABETALOL	nadolol penbutolol pindolol PROPRANOLOL sotalol timolol	acebutolol ATENOLOL betaxolol bisoprolol ESMOLOL METOPROLOL nebivolol
4. Aldosterone Antagonists				
SPIRONOLACTONE eplerenone				
5. Direct Renin Inhibitors				
aliskiren				

6. Angiotensin Converting Enzyme Inhibitors (ACEIs)
BENAZEPRIL
CAPTOPRIL
ENALAPRIL
FOSINOPRIL
LISINOPRIL
QUINAPRIL
RAMIPRIL
enalaprilat
moexipril
perindopril
trandolapril
7. Angiotensin Receptor Antagonists (ARBs)
IRBESARTAN
LOSARTAN
VALSARTAN
azilsartan
candesartan
eprosartan
olmesartan
telmisartan
8. Antiarrhythmic Agents (Miscellaneous Mechanisms)
ADENOSINE
AMIODARONE
DRONEDARONE
LIDOCAINE
PROCAINAMIDE
QUINIDINE
disopyramide
dofetilide
flecainide
ibutilide
mexiletine
propafenone

9. Antiasthmatic Agents (Miscellaneous Mechanisms)	
Mast Cell Stabilizers	**Anti-IgE Agents**
CROMOLYN	omalizumab

10. Anticholesterolemic Agents			
Bile Acid Sequestrants	**HMG CoA Reductase Inhibitors**	**Fibric Acid Derivatives**	**Miscellaneous Mechanisms**
CHOLESTYRAMINE colestipol colesevelam	ATORVASTATIN FLUVASTATIN LOVASTATIN PRAVASTATIN ROSUVASTATIN SIMVASTATIN	GEMFIBROZIL fenofibrate	EZETIMIBE niacin nicotinic acid omega-3 ethyl esters

11. Anticholinergic Agents	
Nicotinic Receptor Antagonists (Ganglionic Blockers)	**Muscarinic Receptor Antagonists**
trimethaphan (historical) hexamethonium (historical)	**ATROPINE** **IPRATROPIUM** tiotropium

12. Anticoagulant Agents			
Oral Anticoagulants	**Heparins**	**Thrombin Inhibitors**	**Factor Xa Inhibitor**
WARFARIN	ENOXAPARIN HEPARIN dalteparin tinzaparin	argatroban bivalirudin DABIGATRAN (oral) LEPIRUDIN	fondaparinux rivaroxaban (oral)

13. Antiplatelet Agents			
Miscellaneous Mechanisms	**Phosphodiesterase Inhibitors**	**Glycoprotein IIb/IIIA Inhibitors**	**ADP Receptor Antagonists**
ASPIRIN dipyridamole	cilostazol	ABCIXIMAB eptifibatide tirofiban	CLOPIDOGREL PRASUGREL ticlopidine ticagrelor

14. Atrial Natriuretic Peptide Agonists
nesiritide

15. Calcium Channel Blockers (Calcium Entry Blockers)			
Dihydropyridines	**Phenylalkylamine**	**Benzothiazepines**	**Others**
AMLODIPINE FELODIPINE NIFEDIPINE clevidipine isradipine nicardipine nimodipine nisoldipine	VERAPAMIL	DILTIAZEM	bepridil flunarizine

16. Cardiac Glycosides
DIGOXIN digitoxin (historical)

17. Centrally Acting Antihypertensive Drugs
CLONIDINE Guanfacine Guanabenz methyldopa reserpine (historical)

18. Corticosteroids (Inhaled)
BECLOMETHASONE BUDESONIDE FLUTICASONE ciclesonide mometasone

19. Diuretics		
Loop Diuretics	**Thiazide Diuretics**	**Potassium-Sparing Diuretics**
ETHACRYNIC ACID FUROSEMIDE bumetanide torsemide	HYDROCHLOROTHIAZIDE INDAPAMIDE chlorothiazide chlorthalidone metolazone	EPLERENONE SPIRONOLACTONE amiloride triamterene

20. Endothelin Receptor Antagonists
ambrisentan bosentan

21. Fibrates
fenofibrate GEMFIBROZIL

22. Fibrinolytics
ALTEPLASE UROKINASE anistreplase reteplase streptokinase (historical) tenecteplase
23. Glycoprotein IIb/IIIa Receptor Antagonists
ABCIXIMAB eptifibatide tirofiban
24. Leukotriene Modifiers

Leukotriene Receptor Antagonists	**5'-Lipoxygenase Inihibitors**
MONTELUKAST zafirlukast	zileuton

25. Metabolic Modulators
ranolazine
26. Methylxanthines
THEOPHYLLINE aminophylline pentoxyphylline (only for intermittent claudication with peripheral vascular disease)
27. Phosphodiesterase Inhibitors

PDE 3 Inhibitors	**PDE 4 Inhibitors**	**PDE 5 Inhibitors**
cilostazol inamrinone milrinone	roflumilast	sildenafil tadalafil

28. Vasodilators

Organic Nitrates	**Others (Miscellaneous Mechanisms)**
ISOSORBIDE MONONITRATE NITROGLYCERIN amyl nitrite isosorbide dinitrate	HYDRALAZINE NITROPRUSSIDE diazoxide minoxidil combination of isosorbide dinitrate and hydralazine (BiDil) use to treat HF in African Americans