

# **Knowledge objectives for Cardiovascular Pharmacology, Fall 2006**

## **DIURETICS**

Focus on the following points:

- Definition of diuretics and the purposes of diuretic therapy.
- Please remember the table of different types of diuretics: types, examples, sites and mechanisms of action.
- Several diuretics are sulfonamide derivatives.
- Major clinical indications of each types of diuretics, particularly those explained by their mechanism of action.
- Side effects of each types of diuretics related to their mechanisms of action. Particularly pay attention to the distortion of water and electrolyte balance.
  - Carbonic anhydrase inhibitors inhibit carbonate reabsorption and proton excretion.
  - Osmotic diuretics inhibit reabsorption of water by osmotic force. It also expand volume of extracellular compartment and may increase heart burden.
  - Loop diuretics inhibit the  $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$  symport in thick ascending limb of loop of Henle.
    - There are two types of loop diuretics (example: furosemide and ethacrynic acid).
    - Loop diuretics inhibit reabsorption of most ions in the tubular fluid.
  - The difference between loop diuretics and thiazide diuretics.
    - Thiazide use and mechanism of action.
- Difference between potassium-sparing diuretics and other diuretics.
- Different types of potassium-sparing diuretics and their use.
- Drug interaction between diuretics and between diuretics and other drugs.

## **CALCIUM ANTAGONISTS.**

Review mechanisms for regulation of intracellular calcium concentration (import, compartmentalization, sequestering, etc.)

Know the major types of voltage-dependent  $\text{Ca}^{2+}$  channels: L-type, long lasting, T-type, transient, and N-P-type.

Ca antagonists selectively interact with L-type channels in vessels and heart.

As a result of vascular selectivity, Ca antagonists increase coronary perfusion that leads to improved oxygen supply. They also decrease peripheral vessel resistance that leads to decrease in blood pressure. Together, these effects result in improved heart performance.

Know the major cardiovascular pathologies treated by Ca antagonists. Know that verapamil and diltiazem have selectivity to sino-atrial node and can be used in treatment of supraventricular dysrhythmia. New calcium antagonists have selectivity toward T-type calcium channels. They do not have negative inotropism; they do not have sympathetic activation. They can reduce heart rate, they are highly selective towards coronary vessels, they have minimal side effects.

## DRUG TREATMENT OF HEART FAILURE

Understand the two major therapeutic issues in CHF: Volume control and cardiac contractility

### *volume control*

(diuretics, ace inhibitors, natriuretic peptide)

Know the key role of angiotensin

Why is control of volume and afterload one key to controlling symptoms of CHF?

### *Positive Inotropic agents*

- used in conjunction with diuretic agents, ACE inhibitors, vasodilators
- increase cardiac output (at constant preload and heart rate)
- increase intrinsic contractility of heart

Why is enhancement of cardiac contractility one key to controlling symptoms of CHF?

### *Cardiac glycosides*

- increase cardiac contractility by direct action on cardiomyocyte
- (Na,K)-ionic pump is receptor for cardiac glycoside
- *digoxin* and *digitoxin* are commonly used glycosides
- antiarrhythmic action against supraventricular arrhythmia: slowing of A-V conduction (negative dromotropic effect)
- negative chronotropic action: due to reflex bradycardia (vagal effect)
- *indications*: for use in low output heart failure particularly when atrial arrhythmias are present
- digitalis toxicity: ventricular tachyarrhythmias; gastrointestinal upset; CNS symptoms such as dizziness, convulsion

### *Other inotropic agents*

dobutamine

### *PDE (phosphodiesterase) inhibitors*

amrinone

milrinone

### *Secondary drugs:*

vasodilators

beta blockers

What is the rationale for these?

## ANTIARRHYTHMIC AGENTS

Know the four classes of antiarrhythmic drugs. Note that side effects of overdoses of these drugs is often arrhythmia.

- Group I: Na channel blockers. Useful for treatment of ventricular tachyarrhythmia and occasionally atrial tachyarrhythmia
- Group II: Beta-adrenoceptor blockers. Useful against supraventricular tachyarrhythmias.
- Group III: Action potential prolonging agents. Used against ventricular arrhythmias due to reentry circuits. *Bretyllium* is a 'chemical defibrillator'.
- Group IV: Calcium channel blockers. Highly effective in treatment of supraventricular tachyarrhythmias.

## ANTIANGINAL AGENTS

These substances are for symptomatic treatment of angina.

Know the three basic mechanisms of anti-anginal drugs:

- *Nitrates and nitrites.*: Nitroglycerin and related substances restore oxygen supply-demand balance through redistribution of coronary flow, reductions in preload, afterload, and total peripheral resistance.
- *Beta-adrenoceptor blockers* reduce cardiac contractility and heart rate by antagonizing beta-effects of endogenous catecholamines, thus resulting in diminished myocardial oxygen consumption.
- *Calcium channel blockers* reduce afterload and thereby decrease oxygen demand of the heart.

## ANTIHYPERTENSIVE DRUGS

Know classification of antihypertensive drugs (AHDs) based on their mechanisms.

Think about how blood pressure (BP) is maintained:

$BP = \text{cardiac output (CO)} \times \text{peripheral vascular resistance (PVR)}$ . Therefore, the anatomical sites of action for these drugs are heart, kidney, blood vessels, and part of the brain.

Why diuretics have been used as first-line AHDs? How are they further divided into 3 groups based on mechanisms of action? Know why they are useful when combined with several other AHDs.

$\alpha$ -agonists and blockers:

Know the difference between  $\alpha$ 1 and  $\alpha$ 2 adrenergic receptors. What are the sites of actions?  
Know how centrally acting AHDs work and what are the common adverse effects.

Know the basic mechanism of peripherally-acting AHDs is to block one or more key steps of sympathetic neurotransmission. Examples:

- $\beta$ -blockers: To antagonize  $\beta$ 1 and/or  $\beta$ 2-AR, therefore reduce CO and PVR.
- $\alpha$ 1-blockers: To antagonize  $\alpha$ -AR and reduce PVR.
- Ganglion-blockers: To block both sympathetic and parasympathetic ganglia, and nicotinic cholinergic receptors on postganglionic neurons.
- Blocking adrenergic neurotransmitter synthesis (reserpine) and release (guanethidine): The net effect is depletion of NE and reduced PVR and CO.

For direct vasodilators, know their clinical usage and their action mechanisms. Why these are not commonly used as first-line drugs?

Know how ACE inhibitors and angiotensin-II receptor antagonists work. What is the major difference between these two drugs in their action? What are the major adverse effects?

Know why more than one drug is often given to patients with moderate or high level of hypertension. Give several examples for the benefit of combined use of AHDs.

What kind of medications should be avoided if a patient is to take AHDs (sort out by different categories of AHDs)?

## **ANTI-ANEMIC DRUGS**

Know the different categories of anemia:

Aplastic anemias

Megaloblastic anemias

Hypochromic anemias

**Hypochromic anemias** -What are the causes of iron deficiency: (Dietary insufficiency, Blood loss interference with iron absorption)

What are the treatments:

Oral therapy: Ferrous sulphate; administered when fasting

Parenteral therapy: iron dextran; intramuscular or intravenous injections

**Megaloblastic anemias** - macrocytic rbc; **vitamin B12 or folate** deficiency

Cause of vitamin B12 deficiency: Dietary insufficiency

Deficiency of Intrinsic Factor (Addisonian pernicious anemia)  
Damage to the ileal mucosa

Deficiency of Transcobalamin II (very rare)

Treatments: Oral preparations to supplement deficient diet

Cyanocobalamin injection for problems with absorption

Cause of folate deficiency: Dietary insufficiency; malnutrition and alcoholism

Damage of the small intestine

Treatments: Oral preparations

Folic acid injections

**Aplastic anemias** - disturbed stem cell kinetics

Treated with Erythropoietin, Myeloid Growth Factors:

GM-CSF: granulocyte/macrophage colony-stimulating factor

G-CSF: granulocyte colony-stimulating factor

## **ANTI-THROMBOTIC DRUGS**

Know the three basic approaches to intervention with thrombosis: *anticoagulants, anti-platelet drugs, plasminogen activators*

Anticoagulants and anti-platelet drugs - to prevent the formation of thrombi

Plasminogen activators - to lyse existing thrombi

*Anticoagulants:*

### **Heparin**

Important points: Mechanism of action, Pharmacokinetics (absorption and distribution)

Complications (Hemorrhage, Thrombocytopenia)

### **Coumarins - Warfarin (Oral anticoagulants)**

Important points: Mechanism of action

Pharmacokinetics: Given orally, 99% albumin-bound. Crosses the placenta, cannot be used during pregnancy

Complications: Hemorrhage

*Anti-platelet drugs:*

Know mechanism of action, toxicity/side effects, and major uses of the following drugs:

**Aspirin**

**Dipyridamole**

**clopidogril**

*Plasminogen Activators:*

Main mechanism: plasminogen is converted to plasmin which degrades polymerized fibrin in blood clots.

Drugs used for fibrinolysis:

**Tissue-type plasminogen activator (t-PA)** - serine protease, synthesized by endothelial cells, fibrin specific

**Urokinase (single chain urokinase-type plasminogen activator)** - zymogen, synthesized by kidney cells, fibrin specific

**Streptokinase** - produced by  $\beta$ -hemolytic streptococci, forms a complex with plasminogen and changes its conformation, NOT fibrin specific, leading to degradation of fibrinogen and fibrin

## ANTI-ATHEROSCLEROTIC DRUGS

Review etiology of atherosclerosis and regulation of cholesterol and triglyceride (TG) metabolism:

Therapeutic strategy: identify patients at risk, modify diet and lifestyle, pharmacologic therapy

### Drug Therapy

Know the mechanisms of action of the following drug categories, and major drugs in each category:

**Bile salt sequestrants**

**Niacin (nicotinic acid)**

**Statins (HMG-CoA reductase inhibitors)**

**Fibrates**

**Ezetimibe**

Also know effects of each category on cholesterol synthesis, liver LDL receptor levels, total, LDL and HDL levels and ratio

Know important side effects and toxicity, as discussed in lecture