34. Heparin Anticoagulants I – Moorman
35. Heparin Anticoagulants II – Moorman
36. Antiplatelet Drugs – Fareed
37. Thrombolytics – Fareed
38. Drugs to Treat Hyperlipidemia I – Clipstone
39. Drugs to Treat Hyperlipidemia II – Clipstone
40. Pharmacology of Nitric Oxide – Fareed
41. Pharmacology of Vasoactive Peptides – Fareed
42. Diuretics – Byron
43. Antihypertensive Drugs I – Scrogin (To be Posted Later)
44. Antihypertensive Drugs II – Scrogin (To be Posted Later)
45. Antianginal Drugs – Samarel
46. Drugs to Treat Congestive Heart Failure – Samarel
47. Antiarrhythmic Drugs I – Majetschak
48. Antiarrhythmic Drugs II - Majetschak
I. **ANTICOAGULANT DRUGS**

A. **Introduction.**
Drugs used to anticoagulate blood for the treatment of thrombosis and for surgical indications.

B. **Heparin:**

1. Naturally occurring anticoagulant found in the granules of mast cells along with histamine and serotonin.

2. **Chemistry:**

Heparin is a strongly acidic (highly ionized) mucopolysaccharide composed of repeating units of sulfated glucuronic acid and sulfated glucosamine.

**MOLECULAR HETEROGENEITY IN HEPARIN**

(Heparin is composed of high molecular weight and low molecular weight components)

a. Heparin's composition varies in molecular weight constituents (2,000 - 40,000 DA)

CHEMICAL STRUCTURE OF A HEPARIN OLIGOSACCHARIDE UNIT

Refer to Figure 34-4 in Katzung, 10th Edition, pg. 547.

3. Source:
   a. Extracted from tissues rich in mast cells (beef lung and porcine intestine).

4. Standardization:
   a. Because of variability in its molecular composition heparin is assayed and compared to a USP reference standard using an anti-Xa and anti-IIa method.
   b. 1 mg of heparin should be equivalent to at least 120 USP units (12 μg = 1 unit).

5. Actions of heparin:
   a. Inhibits the action of activated factor Xa and factor IIa (Thrombin).
   b. Inhibits the action of several other serine protease enzymes (XIIa, XIa).
   c. Inhibits the aggregation of platelets (at high concentration).
   d. Plasma clearing effect: turbid plasma is rapidly cleared of fat
chylomicrons by a release of lipase from the blood vessels.

e. Binds to vascular lining and neutralizes the positive charge.

f. Causes a release of tissue factor pathway inhibitor (TFPI).

6. Heparin preparations:

a. Mucosal heparin
   - sheep (rarely used)
   - porcine (derived from pig intestine)

B. Different salts of heparin (Na\(^+\), Ca\(^{2+}\))

7. Route of administration:

a. Intravenous and Subcutaneous

b. Not absorbed via oral or rectal route. Heparin is highly charged at all pH's.

8. Therapeutic monitoring

a. There is a poor correlation between the dose of heparin and weight of the patient. The anticoagulant effect is carefully monitored using the APTT method to determine the dose.

b. The therapeutic range is achieved when the APTT falls between 2.0-2.5 times the patient's baseline. Therefore a therapeutic APTT is in the range of 56-70 seconds.

9. Metabolism:

a. 20-25% of heparin is excreted in urine

b. Some heparin is picked up by mast cells

c. Endothelium is able to bind heparin

d. Metabolized in liver by heparinase into small components

10. Duration of action:

a. Biologic T\(\frac{1}{2}\) of intravenous heparin is 1-3 hours, depending on the dose.
Onset of action is 5-10 minutes (as measured by APTT method).

<table>
<thead>
<tr>
<th>Dose</th>
<th>Half Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 U/kg</td>
<td>56 minutes</td>
</tr>
<tr>
<td>200 U/kg</td>
<td>96 minutes</td>
</tr>
<tr>
<td>400 U/kg</td>
<td>152 minutes</td>
</tr>
</tbody>
</table>

11. Endogenous modulators of heparin action:
   a. AT (main heparin co-factor)
   b. Heparin cofactor II (second cofactor)
   c. Tissue factor pathway inhibitor (TFPI)
   d. Platelet factor 4 (heparin neutralizing protein)

12. Side effects of heparin:
   a. Hemorrhagic complications
      Adrenal, gut, etc.
   b. Heparin induced thrombocytopenia and heparin induced thrombosis
      - Generation of antiheparin platelet factor 4 antibodies. These antibodies
        activate platelets and endothelial cells.
   c. Osteoporotic manifestation with spontaneous fracture following chronic
      administration and large doses
   d. Alopecia (loss of hair)
      Long-term usage

13. Clinical use of heparin:
   a. Therapeutic anticoagulation
   b. Surgical anticoagulation
   c. Prophylactic anticoagulation
   d. Unstable angina and related coronary syndromes
   e. Adjunct therapy with thrombolytic drugs
   f. Thrombotic and ischemic stroke
14. Protamine sulfate and heparin neutralization:

a. Protamine is a powerful heparin antagonist. It has a low molecular weight and is a highly basic protein found in the sperm of certain fish.

b. It combines with strongly acidic heparin to form a stable salt with loss of anticoagulant activity.

c. Available as a 1% solution and generally used on a weight basis.

d. One USP unit of heparin is neutralized by 10 μg of protamine (2500 units of heparin is neutralized by 25 mg of protamine).

e. Intravenous injection of protamine may cause the following:

Fall in blood pressure
Bradycardia

f. Question related to protamine neutralization.

A patient was initially administered with 25,000 units of heparin for a surgical procedure. Forty minutes after the surgical procedure, he was administered with an additional 10,000 units of heparin. The surgical procedure was completed in 100 minutes and the patient was found to have 8700 units of heparin in his circulation. How much protamine is needed to neutralize this circulating heparin?

A. 87 mg  
B. 807 mg  
C. 870 mg  
D. 8700 mg  
E. 0.87 mg
II. LOW MOLECULAR WEIGHT HEPARINS & SYNTHETIC HEPARIN PENTASACCHARIDE

1. Prepared by fractionation or depolymerization of native heparin:

**PRODUCTION OF LOW MOLECULAR WEIGHT HEPARIN**

2. Bioavailability of low molecular weight heparins in % bioavailability after subcutaneous administration.
- Low molecular weight heparins are bioavailable at 100% whereas heparin has a limited bioavailability (<30%)


3. Clinical advantages of low molecular weight heparins:
   a. Better bioavailability
   b. Longer duration of action
   c. Less bleeding
   d. Lesser thrombocytopenia

4. Clinical use:
a. Prophylaxis of DVT
b. Treatment of DVT
c. Management of acute coronary syndromes
d. Other uses such as anticoagulation for surgical and interventional cardiovascular procedures

III. GENERIC ENOXAPARIN

1. Sandoz Enoxaparin
2. Amphastar Enoxaparin

IV. ANTITHROMBIN – CONCENTRATES (AT):

Antithrombin-concentrate is prepared by using heparin-sepharose affinity chromatography. This concentrate is used to treat patients with acquired or congenital antithrombin-deficiency. AT is also useful in sepsis and disseminated intravascular coagulation.

V. DIRECT ANTITHROMBIN AGENTS:

Hirudin is a protein from the saliva of the medicinal leech (*Hirudo medicinalis*) which contains several pharmacologically active substances. Using recombinant technology recombinant forms of this drug are produced. Currently r-hirudin is used in the anticoagulant management of heparin induced thrombocytopenic patients. A commercial preparation, namely, refludan (Pharmion) is available for clinical use.

Argatroban is a synthetic antithrombin agent which is currently used as an anticoagulant in patients who can not be treated with heparin, special usage in the management of heparin induced thrombocytopenia.

Bivalirudin (Angiomax®) is a synthetic antithrombin agent. This agent is a hybrid molecule between a component of hirudin and a tripeptide. This drug is approved for PTCA anticoagulation.
HEPARIN ANTICOAGULANTS I

**Date:** September 25, 2013-8:30 am

**KEY CONCEPTS & LEARNING OBJECTIVES**

1. Describe the major classes of anticoagulant drugs with reference to their mechanism of action.
2. Describe the mechanism of the anticoagulant action of heparin with particular reference to its interaction with antithrombin.
3. Explain the mechanism of protamine neutralization of heparin and calculate the amount of protamine needed for the neutralization of the action of a given amount of heparin.
4. Discuss the differences between heparin and low molecular weight heparins.
5. Identify the currently approved indications for low molecular weight heparins.
6. Explain the laboratory tests needed for monitoring the actions of heparin.
7. Discuss the mechanism of anticoagulant action of the antithrombin agents and how it differs from heparin and low molecular weight heparin.
8. Explain why direct thrombin inhibitors can be used in the management of heparin induced thrombocytopenia.
9. Explain the mechanism of heparin-induced thrombocytopenia and discuss why heparin is contraindicated.

**LIST OF DRUGS COVERED IN LECTURE**

A. Heparin (systemic anticoagulant)
B. Low molecular weight heparin (enoxaparin, dalteparin, tinzaparin)
C. Generic Enoxaparin
D. Pentasaccharide (Arixtra®)
E. Protamine sulfate
F. Antithrombin-III
G. Hirudin (Refludan®)
H. Argatroban (Novastan®, Acova)
I. Bivalirudin (Angiomax®)

**ALTERNATIVE THERAPIES**

A. Compression devices
B. TED (Thromboembolic Deterrent) stockings
C. Foot Pump
D. Exercise
HEPARIN ANTICOAGULANTS II: ORAL ANTICOAGULANTS

I. Warfarin and the coumarin anticoagulants:

1. Only the coumarin derivatives are used in the U.S. The warfarin, (Coumadin®), brand of oral anticoagulant is most widely prescribed.

2. Prophylactic use: Prevention of thrombotic disorders

3. Therapeutic use: Treatment of established thrombus

Integrated Coagulation Cascade and Its Modulation by Anticoagulant Drugs.

Refer to Katzung 10th Edition, Figure 34-2, page 544.
Chemical structure of oral anticoagulants structurally similar to vitamin K (analogues).

[Diagram of chemical structures]

Refer to Katzung 10th Edition, Figure 34-5, pg. 550.

**Mechanism of action**

All agents depress the formation of functional forms of factors II (prothrombin), VII, IX and X by inhibiting the carboxylation of glutamic acid in these proteins which is essential for Ca\(^{2+}\) binding.

[Diagram of mechanism]

Refer to Katzung, 10th Edition, Figure 34-6, pg. 550.
Refer to Katzung, 8th Edition, Figure 34-7, pg. 571.

II. Dose:

1st day: 5 - 10 mg/d (Initial dosing).

2nd day: 5 - 7 mg/d (maintenance).

III. Route of administration:

All are well absorbed orally

IV. Fate:

Long T½ of the oral anticoagulants, due to binding to plasma albumin (warfarin is about 97% bound).

V. Metabolism:

1. Dicumarol and warfarin are hydroxylated to inactive compounds by the hepatic endoplasmic reticulum.

2. Metabolism varies greatly in patients.
VI. Therapeutic monitoring of oral anticoagulant drugs:

1. Warfarin depresses the functionality of vitamin K dependent factors (II, VII, IX and X). Thus, it impairs the blood coagulation in the extrinsic pathway. Prothrombin time (PT) is used to monitor the anticoagulant effects of warfarin.

2. A 1.5 time prolongation of the PT from the baseline is considered to be therapeutic. For example, if a patient's baseline PT is 12 seconds, he is considered in the therapeutic range around 18 seconds.

3. A patient with a lesser prolongation than 1.5 times the baseline is subtherapeutic and a dose increase may be necessary.

4. Reagent based variations have been noted in the prothrombin time. To obtain uniform degrees of anticoagulation, the concept of international normalized ratio (INR) has been introduced.

\[
\text{INR} = \frac{\text{PT (sec) patient}}{\text{PT (sec) mean normal control}}^{\text{ISI}}
\]

The INR can be used universally to adjust the level of anticoagulant in a given patient. Thus it helps in the optimization of dosage.

VII. Control of dose:

Many factors affect the dose of the oral anticoagulants.

1. Nutrition
2. Anemia
3. Liver disease
4. Biliary obstruction
5. Drugs

VIII. Drug interactions with warfarin:

1. Drugs cause warfarin potentiation:
   a. by causing vitamin K deficiency.
   b. by displacing warfarin from protein binding sites.
   c. by decreasing clotting-factor synthesis.
d. by suppressing or competing for microsomal enzymes.

e. by having antiplatelet aggregating properties.

2. Drugs reported to cause inhibition of the anticoagulant action of warfarin:

a. by decreasing warfarin absorption.

b. by enhancing warfarin metabolism.

Refer to Katzung 10th Edition, Table 34-2, pg. 551

Table 34-2. Pharmacokinetic and pharmacodynamic drug and body interactions with oral anticoagulants.

<table>
<thead>
<tr>
<th>Pharmacokinetic</th>
<th>Pharmacodynamic</th>
<th>Pharmacokinetic</th>
<th>Pharmacodynamic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased Prothrombin Time</td>
<td></td>
<td>Decreased Prothrombin Time</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Drugs</td>
<td>Barbiturates</td>
<td>Drugs</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Aspirin (high doses)</td>
<td>Cholestyramine</td>
<td>Diuretics</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>Cephalosporins, third-generation</td>
<td>Rifampin</td>
<td>Vitamin K</td>
</tr>
<tr>
<td>Metronidazole&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Heparin</td>
<td></td>
<td>Body factors</td>
</tr>
<tr>
<td>Metronidazole&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Body factors</td>
<td></td>
<td>Hereditary resistance</td>
</tr>
<tr>
<td>Metronidazole&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Heptic disease</td>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Phenylbutazone&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Hyperthyroidism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfipyrazole&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sulfoximethoxazole</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

<sup>1</sup>Stereoselectively inhibits the oxidative metabolism of the (S)-warfarin enantiomorph of racemic warfarin.

Refer to Katzung 10th Edition, Table 34-2, pg. 551

IX. Toxicity of Warfarin:

1. Principal toxicity is a marked hypoprothrombinemia resulting in ecchymosis, purpura, hematuria, hemorrhage.

2. All oral anticoagulants pass the placental barrier and may cause fetal malformation.

3. Warfarin also produces necrosis (Coumadin® induced necrosis). This is basically due to the impairment of the functionality of protein C. This protein also requires γ-carboxylation of glutamic acid for functionality.


a. Replacement of 4 factors. Infusion of whole fresh blood or frozen plasma.

b. Recombinant factor VIIa

c. Vitamin K
X. Vitamin K:

1. Naturally occurring fat-soluble vitamin found in green vegetables and synthesized by gut flora. These agents are structurally similar to the oral anticoagulants.

2. Function of vitamin K:
   a. Essential to the attachment of a calcium binding functional group to prothrombin protein (presence of $\gamma$-carboxyglutamic acid).
   b. Required for the synthesis of coagulation factors (II, VII, IX and X).

3. Therapeutic use:
   a. Drug induced hypoprothrombinemia - antidote.
   b. Intestinal disorders and surgery (gastrectomy).
   c. Hypoprothrombinemias of newborn.

4. Toxicity - remarkably non-toxic:
   High doses sometimes cause hemolysis in infants (mainly water soluble vitamin K).

XI. New Oral Anticoagulants*

1. Anti-Xa agents
   a. Rivaroxaban (Xarelto)
      - Approved for prophylaxis and treatment of DVT
      - Also approved for stroke prevention in Atrial fibrillation
      - Renal clearance 65%
   b. Apixaban
      - Also approved for stroke prevention in Atrial fibrillation
      - Renal clearance 25%

2. Antithrombin agents
   a. Dabigatran
      - Also approved for stroke prevention in Atrial fibrillation
      - Renal clearance 100%
Heparin Anticoagulants II: ORAL ANTICOAGULANTS

Date: September 25, 2011-9:30 am

KEY CONCEPTS & LEARNING OBJECTIVES

1. Define the mechanism of action of warfarin with particular reference to the role of $\gamma$-carboxylation of glutamic acid.

2. Describe major drug interactions with oral anticoagulant drugs.

3. Identify the role of vitamin K in the synthesis of coagulation factors II, VII, IX and X.

4. Describe the laboratory tests needed for monitoring the actions of oral anticoagulants.

5. Explain the concept of International Normalized Ratio (INR). Apply the concept of INR in the management of anticoagulation.

6. Identify the clinical use of oral anticoagulant drugs.

7. Describe the role of vitamin K in the synthesis of functional coagulation factors II, VII, IX and X.

8. Describe the mechanism of action of the new oral anticoagulants (dabigatran, apixaban and rivaroxaban).

ALTERNATIVE THERAPIES

None at this time.
Anti-Xa and Anti-IIa agents (under development)

LIST OF DRUGS COVERED IN LECTURE

A. Warfarin (oral anticoagulant).

B. Vitamin K

C. Fresh frozen plasma

D. Recombinant factor VIIa

E. Anti-Xa agents- Rivaroxaban, Apixaban

F. Anti-IIa agents- Dabigatran
KEY CONCEPTS & LEARNING OBJECTIVES

1. Identify the major antiplatelet drugs and their site of actions.
2. Describe the mechanism of action of aspirin and related inhibitors of cyclooxygenase.
3. Explain the mechanism of action of ADP receptor inhibitors (P2Y12), clopidogrel (Plavix®), Prasugrel (Effient) and Ticagrelor (Brilinta).
4. Discuss the use of antiplatelet drugs for the treatment of arterial thrombosis.
5. Discuss the mechanisms of action of the glycoprotein IIb/IIIa inhibitors (GPIIb/IIIa inhibitors).
6. Describe the mechanism of the antiplatelet action of omega-3 fatty acids.
7. Discuss the rationale of antiplatelet therapy used in the management of acute coronary syndromes.
8. Describe the laboratory tests useful in the monitoring of antiplatelet drugs.
9. Describe the drug interactions between antiplatelet agents and other anticoagulant drugs.
LIST OF DRUGS COVERED IN LECTURE:

1. Aspirin
2. Ticlopidine (Ticlid®)
3. Clopidogrel (Plavix®)
4. Prasugrel (Effient)
5. Ticagrelor (Brilinta)
6. Dipyridamole (Persantine®)
7. Cilostazol (Pletal®)
8. Abciximab (ReoPro®)
9. Tirofiban (Aggrastat®)
10. Eptifibatide (Integrilin®)
11. Celebrex® (COX-2 inhibitor)
12. Vioxx® (COX-2 inhibitor)
13. Bextra® (COX-2 inhibitor)
14. Propionic acid derivatives (Ibuprofen)
15. Cangrelor (in development for IV use)

ALTERNATIVE THERAPIES

1. Fish oil emulsions
2. Gingko products
3. Garlic extracts
4. Soy products
ANTIPLATELET DRUGS

I. Pharmacology of platelet aggregation:

During platelet release reactions many pharmacologically active substances are secreted from the dense (Beta) and light (alpha) granules. In addition, many of the prostaglandin derivatives such as thromboxanes are formed. All of these substances exert a profound action on the overall function of platelets.

1. Light (alpha) granule release products:
   a. Platelet factor 4
   b. Beta-thromboglobulin
   c. Platelet-derived growth factor (PDGF)

2. Dark (Beta) granule release products:
   a. Ca\(^{+2}\)
   b. Serotonin (5-Hydroxytryptamine)
   c. ATP/ADP


II. Antiplatelet agents:

Antiplatelet agents - decrease platelet aggregation primarily in the arterial system.

1. Aspirin - antipyretic analgesic, decreased platelet aggregation, prolongs bleeding.
2. ADP Receptor inhibitors-Ticlopidine (Ticlid), Clopidogrel (Plavix), Prasugrel (Effient) and Ticagrelor (Brilinta).
3. Propionic acid derivatives (NSAIDs)- Analgesic agents (also exhibit antiplatelet effects).
4. Dipyridamole (Persantine®)-a coronary vasodilator
5. Cilostazol (Pletal®) - a new drug for the management of intermittent claudication
6. GPIIb/IIIa Inhibitors (ReoPro®, Aggrastat® and Integrilin®)
7. Prostacyclin analogue (Iloprost®) and thromboxane receptor antagonists

8. Cyclooxygenase (COX) inhibitors (COX 1 and COX 2 inhibitors), Celebrex®, Vioxx® and Bextra

9. Anti-platelet drug combinations
   a. Aspirin/clopidogrel, aspirin/prasugrel, aspirin/ticagrelor
   b. Aspirin/GP IIb/IIIa inhibitor
   c. Anticoagulant/antiplatelet drugs
   d. Antiplatelet/thrombolytic drugs
   e. Dipyridamole/aspirin

III. Clinical applications of antiplatelet drugs:
   1. Cerebrovascular disease:
      a. Transient ischemic attack (TIA)
b. Complete stroke
c. Carotid endarterectomy
d. Geriatric patients (institutionalized)

2. Coronary artery disease:
a. Acute myocardial infarction
b. Unstable angina

3. Saphenous vein coronary artery bypass grafts:

4. Peripheral vascular disease:
a. Venous thrombosis
b. Peripheral arterial disease (PAOD, intermittent claudication)

5. Small vessel disease:
a. Membrane proliferative glomerulonephritis
b. Thrombotic thrombocytopenic purpura
c. Other syndromes

6. Prevention of thrombus formation on artificial surfaces

IV. Drug interactions with antiplatelet agents:

1. Thrombolytic agents (urokinase, streptokinase and tissue plasminogen activator).
2. Heparin/LMW heparin/oral anticoagulants
3. Warfarin
4. Antithrombin agents (hirudin, bivalirudin and argatroban)
V. Pathways of Arachidonic Acid Release and Metabolism:

Refer to Katzung 11th Edition, Figure 18-1.

Arachidonic acid is metabolized by two major pathways:

1. Cyclooxygenase pathway
2. Lipoxygenase pathway

Both of these pathways and the epoxygenase(s) result in the formation of potent pharmacologic substances that can produce various pathophysiologic and physiologic responses. The products of the cyclooxygenase and lipoxygenase pathways produce different effects on blood vessels and blood cells. These include the following:

a. Vasoconstriction and vasodilation
b. Platelet aggregation and disaggregation
c. Leukocyte activation
d. Target site effects

VI. Cyclooxygenase Pathway:
Refer to Katzung 11th Edition, Figure 18-2.

Aspirin inhibits both COX-1 and COX-2 thereby limiting the production of prostaglandins. In particular thromboxane formation in platelets is inhibited. This is the main mechanism by which aspirin mediates its therapeutic effects.

1. Regulation of prostacyclin and thromboxane synthesis.
   a. Endothelial lining
   b. Lipoproteins and other blood components
   c. Diet
   d. Drugs
e. Hemodynamic factors

**GENERATION OF ARACHIDONIC ACID METABOLITES AND THEIR ROLES IN INFLAMMATION & THROMBOSIS**

![Diagram of arachidonic acid metabolites](image)

*Kumar et al, p.37, Basic Pathology, 199.*

**VII. Pharmacology of Fish Oil**

1. Active ingredients (omega-3 fatty acid).
   a. \(\alpha\)-linolenic acid
   b. eicosapentaenoic acid
   c. docosahexaenoic acid

   a. Membrane effects.
   b. Thromboxane A\(_3\) (inactive) formation
PHARMACOLOGY OF THROMBOLYTIC AGENTS

Date: September 26, 2013-9:30 am

KEY CONCEPTS AND LEARNING OBJECTIVES

1. Describe the different components of the fibrinolytic system in terms of inhibitors, activators and zymogens.
2. Recognize the difference between the plasmin mediated degradation of fibrinogen and fibrin.
3. Identify the role of plasminogen in fibrinolysis.
4. Discuss the physiologic activators of plasminogen with particular reference to the role of endothelial t-PA in physiologic thrombolysis.
5. Identify the site of action of different thrombolytic agents.
6. List the side effects of thrombolytic therapy.
7. Identify the antagonists that can be used for neutralizing the actions of thrombolytic agents.
8. Recognize interactions of thrombolytic agents with aspirin and heparin
9. Describe the laboratory tests that can be used for the monitoring of thrombolytic agents.

LIST OF DRUGS COVERED IN LECTURE:

1. Urokinase
2. Streptokinase
3. Streptokinase Plasminogen Complex (Anistreplase, Eminase)
4. Tissue plasminogen activators (Alteplase, Reteplase, Tenecteplase)
5. Pro-urokinase
6. Epsilon amino caproic acid
7. Tranexamic acid
8. Ancrod
9. Aprotinin

ALTERNATIVE THERAPIES

1. Atherectomy
2. Stents
3. Rotoablation
I. **INTRODUCTION TO FIBRINOLYTIC PROCESSES**

![Diagram of Fibrinolytic Processes](image)

**A. Activation and Inhibition of Blood Fibrinolytic System**

Refer to Katzung 11th Edition Figure 34-3, pg. 590.
The fibrinolytic system is regulated by a variety of activators and inhibitors. A balance between the activators and inhibitors is important.

1. Physiologic Activators:
   a. t-PA I
      Single chain tissue plasminogen activator
   b. t-PA II
      Two chain tissue plasminogen activator
   c. Pro Urokinase (SCUPA: Single chain urinary plasminogen activator)
   d. Urokinase

The physiologic activators of plasminogen are able to convert endogenous plasminogen into plasmin. This action plays a key role in the dissolution of clots which are formed due to coagulation activation.

2. Physiologic Inhibitors:
   a. PA-I
      Rapid-acting plasminogen activator inhibitor.
   b. Thrombin activatable fibrinolytic inhibitor (TAFI)
   c. Alpha 2 - antiplasmin
   d. Alpha 2 - macroglobulin
   e. C1 - esterase inhibitor

B. Physiologic Regulation of Fibrinolysis:

1. Molecular components:
   a. Activators and inhibitors
   b. Plasminogen (Pro-fibrinolysin)

Zymogenic form of the active enzyme plasmin single chain molecule (Mol. Wt. 88,000 Da). Composed of 790 amino acids. Native form is known as Glu-plasminogen. Plasmin cleaves the initial terminal 76 amino acids to form Lys-plasminogen.
c. Plasmin (Fibrinolysin)

Active protease capable of digesting both fibrinogen and fibrin. Formed by the cleavage of the Arg 560-Val bond by plasminogen activators.

C. Degradation of Fibrinogen and Fibrin by Plasmin

1. Fibrinogen can be degraded by plasmin:

   FORMATION OF F.D.P.'S

   Fragments X, Y, D and E are formed by the digestion of fibrinogen.
2. Fibrin:

Fibrin is formed by the action of thrombin on fibrinogen. Formed fibrin strands are stabilized by the action of Factor XIIIa. Plasmin acts on stabilized fibrin to form various products such as the DD/E, YD/DY and YY/E.

![Diagram of fibrin formation and degradation](image)


Fragments DDE, YD/DY and YYDD are formed by the action of plasmin on polymerized fibrin monomers (clots).

D. Physiologic Control of Thrombolysis:

Several factors control physiologic fibrinolysis.

1. Factors that promote fibrinolysis:
   a. Plasminogen incorporation into thrombus via fibrin binding
   b. Clot retraction
   c. Local release of t-PA by endothelial cells
   d. Binding of t-PA to fibrin
   e. Enhanced t-PA or UK activity in the presence of fibrin
   f. Protection of bound plasmin from antiplasmin
2. Factors Which Limit Fibrinolysis:
   a. Fibrin crosslinking by Factor XIIIa
   b. Binding of alpha2-antiplasmin to fibrin
   c. Low ratio of endothelial surface to thrombus volume in large vessels
   d. Efficient inhibition of free plasmin by antiplasmin
   e. Antiplasmin impairs plasmin binding to fibrin.

E. Fibrinolytic Balance: Thrombosis vs. Bleeding

An intricate balance in the fibrinolytic process maintains the blood in the fluid state. Either thrombotic or bleeding complications can result if the balance is not maintained.

II. THROMBOLYTIC THERAPY

A. Introduction:

Comprised mainly of plasminogen activators. Several thrombolytic agents are now clinically used for the dissolution of clots (thrombi). Degradation of clots produce the following effects:

1. Reduction in thrombus size (thrombolytic)
2. Reduction of fibrinogen levels
3. Increase in the fibrinogen and fibrin degradation products
4. Antiplatelet activators

B. Classification of Thrombolytic Agents:

The thrombolytic agents can be classified according to their development and clinical usage.

1. Clinically approved thrombolytic agents
   a. Urokinase-Approved in Canada and Europe
   b. Streptokinase
   c. Recombinant tissue plasminogen activators
- Alteplase (Human t-Pa)
- Reteplase (Mutant form of human t-Pa, more fibrin specific)
- Tenecteplase (Mutant form of human t-Pa with a longer half life)

2. Other thrombolytic agents
   a. Acylated plasminogen: streptokinase activator complex (Anistreplase) (Discontinued in USA)
   b. Single chain pro urokinase (Pro-UK, SCU-PA) (Under development)
   c. Plasmin (Under development)

C. Practical Aspects of Thrombolytic Therapy

Effects of various thrombolytic agents can be depicted in the following figure. Fibrinolytic processes can occur in blood (plasmatic) and on the thrombus.
1. Development of the plasma fibrinolytic state:
   Several biological changes occur after the administration of thrombolytic agents. Some of these are listed below:
   a. Circulating plasminogen activator
   b. Plasminogen converted to plasmin
   c. Antiplasmin complexes with and inhibits plasmin
   d. Free plasmin
   e. Plasmin degradation of fibrinogen
   f. Degradation of other plasma clotting factors
   g. Hypocoagulable state

2. Major effects of Thrombolytic Therapy:

   Besides dissolving the clots, thrombolytic agents produce multiple actions. Some of these can be summarized in the following:

<table>
<thead>
<tr>
<th>EFFECT</th>
<th>EVENT</th>
<th>PATHOGENESIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Benefit</td>
<td>Thrombolysis</td>
<td>Degradation (solubilization) of fibrin in the thrombus</td>
</tr>
<tr>
<td>Side-effect</td>
<td>Systemic lytic state</td>
<td>Degradation of plasma fibrinogen by circulating plasmin</td>
</tr>
<tr>
<td>Complication</td>
<td>Bleeding</td>
<td>Degradation of fibrin in hemostatic plugs (possibly also the hypocoagulable state) adversely influenced by prolonged duration of treatment</td>
</tr>
</tbody>
</table>
Effect of Thrombolytic Therapy on the Fibrinogen and Plasminogen Levels (Note the decrease in fibrinogen after thrombolytic agents).
3. Clinical Usage of Thrombolytic Agents:

Thrombolytic agents are now routinely used for a variety of thrombotic conditions. Their clinical acceptance is gradually increasing.

a. Acute Myocardial Infarction:

Large numbers of patients with myocardial infarction have a thrombus in the coronary vessels, with the incidence of occlusion being 70% after the onset of pain. Several thrombolytic agents are currently used for the treatment of myocardial infarction.

Acute occlusion of the coronary artery leading to the formation of a fibrin-rich clot, which may lead to myocardial infarction.

A fresh thrombosis in the coronary artery. Platelet aggregates forming of a thrombus resulting in plaque rupture leading to a fresh clot formation and a myocardial infarction.

Time plays a crucial role for the success of thrombolytic therapy. Older clots are less susceptible to the lytic action of thrombolytic agents.

b. Peripheral Arterial Occlusion:

Thrombolytic agents such as urokinase and streptokinase have been routinely used in the dissolution of arterial occlusions. Both intravenous and localized treatments are used.

c. Deep Venous Thrombosis:

Both streptokinase and urokinase were initially used for the treatment of DVT. Both localized and systemic treatment can be used.

d. Pulmonary Embolism:
Both streptokinase and urokinase were originally used in large multicenter clinical trials in the U.S.A. Both local and systemic infusions of streptokinase and urokinase have been used. t-PA is not used in this indication.

e. Thrombotic stroke. Acute management of thrombolytic and ischemic stroke

f. Catheter Clearance:

For shunts, grafts and extracorporeal circulation, these agents offer very efficient cleansing effects.

D. Clinical Results on the Use of Thrombolytic Agents in Myocardial Infarction:

Thrombolytic agents have been successfully used in various conditions such as DVT, pulmonary embolism, peripheral occlusive disorders and other thrombotic conditions.

E. Complications of Thrombolytic Therapy:

1. Bleeding
2. Re-occlusion
3. Stroke
4. Others

F. Absolute Contraindication of Thrombolytic Therapy:

1. Intracranial bleeding
2. Massive hemorrhage

G. Other Contraindications

H. Drug Interactions with Thrombolytic Agents:

1. Antiplatelet Drugs
2. Heparin
3. Dextrans
I. Pharmacologic Antagonist for Thrombolytic Agents:

1. EACA (Epsilon-amino caproic acid)
2. Tranexemic Acid (Trans-4-Aminoethylcyclohexane 1-Carboxylic Acid)
3. Aprotonin (Trasylol)

III. DEFIBRINOGENATING ENZYMES

A. General Considerations:

A number of venoms and biologics contain enzymes that can digest fibrinogen. Some of these agents have been found to be useful for therapeutic purposes.

1. Ancrod is tested in stroke

IV. CORONARY ANGIOPLASTY AND STENTS

A. Anticoagulants during coronary angioplasty.

B. Stents

1. Bare metal stents
2. Drug eluting stents
3. Disposable stents
Drugs used to treat Hyperlipidemia I & II

**Date:** Tuesday, October 1st, 2013 – 8:30 am – 10:30am


**Key Concepts and Learning Objectives:**
1. List the presently accepted values for desirable, borderline and high serum LDL-cholesterol, HDL and triglyceride levels.

2. List the principal indications for each of the major classes of hypolipidemic drug agents

3. Describe the mechanism of action of each of the major classes of hypolipidemic drug agents.

4. Describe the principal therapeutic effect of each of the major classes of hypolipidemic drug agents on the serum levels of LDL, HDL and triglycerides

5. List the major adverse effects of each of the major classes of hypolipidemic drug agents

6. List the principal contraindications for each of the major classes of hypolipidemic drug agents.

7. Describe the effects of clinically relevant drug interactions on the serum concentration of the statin class of hypolipidemic drug agents

8. Identify which of the major classes of hypolipidemic drug agents would be most effective for the treatment of: hypercholesterolemia, hypertriglycerideremia, and combined hyperlipidemia.

9. Discuss how hypolipidemic drug agents can be combined effectively in the treatment of dyslipidemia.
Drugs to be covered in this lecture:

1. The STATINS
   Atorvastatin (Lipitor®)
   Fluvastatin (Lescol®)
   Lovastatin (Mevacor®)
   Simvastatin (Zocor®)
   Pravastatin (Pravachol®)
   Rosuvastatin (Crestor®)

2. Bile Acid-binding resins
   Cholestyramine (Questran®)
   Colestipol (Colestid®)
   Colesevelam (Welchol®)

3. Cholesterol Absorption Inhibitor
   Ezetimibe (Zetia®)

4. Niacin

5. The Fibrates
   Fenofibrate (Tricor®, Lofibra®)
   Gemfibrozil (Lopid®)

6. omega-3 fatty acids
   Eicosapentaenoic acid: Docosahexaenoic acid (Lorvaza®)
Drugs in the treatment of hyperlipidemia I& II

(A) Background

A1. ATHEROSCLEROSIS & HYPERLIPIDEMIA/HYPERLIPOPROTEINEMIA

a) Atherosclerosis is strongly associated with hyperlipidemia: the presence of elevated/abnormal levels of lipids (i.e. cholesterol and triglycerides) and/or lipoproteins (e.g. LDL & VLDL) in the blood

b) The most important risk factor in the development of atherosclerosis is an elevated level of Low Density Lipoproteins (LDL)-a class of lipoprotein that is rich in cholesterol- the so called “bad cholesterol”.

c) Elevated serum triglycerides levels are an independent risk factor for atherosclerosis and cardiovascular disease, as well as being a risk factor for pancreatitis

d) Decreased levels of HDL-cholesterol (“good cholesterol”) is an independent risk factor for the development of cardiovascular disease

A2. Causes of Hyperlipoproteinemia

a) Genetics: Either Monogenic (e.g. defective LDL receptor in Familial Hypercholesterolemia) or polygenic (e.g. Familial Combined Hyperlipoproteinemia)

b) Lifestyle (e.g. high fat diet) and other secondary causes (e.g. type-2 diabetes, lipodystrophy & hypothyroidism)

c) Combination of genetics, lifestyle and secondary causes.

A3. The Primary Hyperlipoproteinemias (The Fredricskon Classification)

<table>
<thead>
<tr>
<th>Type</th>
<th>Synonyms</th>
<th>Frequency</th>
<th>Defect</th>
<th>Effects on Lipoproteins</th>
<th>Atherosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>Familial Hyperchylomicronemia</td>
<td>Very rare</td>
<td>LPL deficiency/ ApoCII deficiency</td>
<td>Chylomicrons</td>
<td>–</td>
</tr>
<tr>
<td>Type IIa</td>
<td>Familial Hypercholesterolemia</td>
<td>0.2%</td>
<td>LDL receptor defect Binding of LDL to LDLR</td>
<td>LDL</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Familial apoB100 defect</td>
<td>0.1%</td>
<td>Relatively common</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Polygenic Hypercholesterolemia</td>
<td>Unknown defects result in impaired clearance of LDLs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type IIb</td>
<td>Familial Combined Hyperlipidemia</td>
<td>0.5%</td>
<td>Unknown (polygenic): Overproduction of B100 &amp; triglycerides (VLDL) and decreased clearance of LDL</td>
<td>VLDL &amp; LDL</td>
<td>+++</td>
</tr>
<tr>
<td>Type III</td>
<td>Familial DysbetaIoproteinemia</td>
<td>0.02%</td>
<td>Mutant ApoE: Increased production/decreased clearance of VLDL remnants</td>
<td>IDL</td>
<td>+++</td>
</tr>
<tr>
<td>Type IV</td>
<td>Familial Hypertriglyceridemia</td>
<td>1%</td>
<td>Overproduction/decreased clearance of VLDL remnants</td>
<td>VLDL</td>
<td>–/+</td>
</tr>
<tr>
<td>Type V</td>
<td>Familial Mixed Hypertriglyceridemia</td>
<td>Rare 1/1,000,000</td>
<td>Unknown: Overproduction/decreased clearance of VLDL &amp; chylomicrons</td>
<td>VLDL &amp; Chylomicrons</td>
<td>–/+</td>
</tr>
</tbody>
</table>
**A4. Secondary causes of hyperlipoproteinemias**

<table>
<thead>
<tr>
<th>Hypertriglyceridemia</th>
<th>Hypercholesterolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity &amp; overweight</td>
<td>Dietary excess: Cholesterol &amp; sat. Fats</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>Hypopituitarism</td>
</tr>
<tr>
<td>Excess alcohol intake</td>
<td>Acute intermittent porphyria</td>
</tr>
<tr>
<td>High carbohydrate diet (&gt;60%)</td>
<td>Biliary cirrhosis</td>
</tr>
<tr>
<td>Stress</td>
<td>Type-2 diabetes</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Anorexia Nervosa</td>
</tr>
<tr>
<td>Certain Diseases:</td>
<td>Corticosteroid treatment</td>
</tr>
<tr>
<td>type-2 diabetes</td>
<td>Antiviral protease therapy</td>
</tr>
<tr>
<td>Nephritis</td>
<td>Lipodystrophy</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>Certain Drugs:</td>
</tr>
<tr>
<td>Lipodystrophy</td>
<td>Estrogens</td>
</tr>
<tr>
<td>Certain Drugs:</td>
<td>Corticosteroid excess</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Antiviral protease therapy</td>
<td>Antiviral protease therapy</td>
</tr>
</tbody>
</table>

**2004 NCEP Treatment Goals**

<table>
<thead>
<tr>
<th>Risk</th>
<th>Cardiovascular Risk Factors</th>
<th>LDL Goal</th>
<th>Initiate lifestyle change if LDL is</th>
<th>Consider drug therapy if LDL is</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very High Risk</td>
<td>Cancer, CHD, other factors</td>
<td>&lt;70 mg/dl</td>
<td>&gt;100 mg/dl</td>
<td>&lt;100 mg/dl</td>
</tr>
<tr>
<td>High Risk</td>
<td>Prior CHD, Diabetes, 2+ risk factors</td>
<td>&lt;100 mg/dl (optional &lt;70)</td>
<td>&gt;100 mg/dl</td>
<td>&gt;100 mg/dl</td>
</tr>
<tr>
<td>Moderately High Risk</td>
<td>2 risk factors, 10-20% 10yr risk</td>
<td>&lt;130 mg/dl (optional &lt;100)</td>
<td>&gt;130 mg/dl</td>
<td>&gt;130 mg/dl</td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>2 risk factors, &gt;20% 10yr risk</td>
<td>&lt;130 mg/dl</td>
<td>&gt;130 mg/dl</td>
<td>&gt;130 mg/dl</td>
</tr>
<tr>
<td>Lower Risk</td>
<td>0-1 risk factors</td>
<td>&gt;160 mg/dl</td>
<td>&gt;160 mg/dl</td>
<td>&gt;190 mg/dl</td>
</tr>
</tbody>
</table>

Modified from 2004 NCEP ATP III panel guidelines

**A5. Treatment options for Hyperlipoproteinemia**

**A5.1 Hypercholesterolemia (elevated LDL-C)**

The treatment for hypercholesterolemia is dependent upon the degree of LDL-cholesterol elevation and the calculated cardiovascular risk (see Table).

- a) For moderate hyperlipidemia with low cardiovascular risk factors lifestyle changes maybe sufficient to normalize lipoprotein levels.
  - (i) Dietary reduction of cholesterol intake
  - (ii) Exercise- improves lipoprotein metabolism
  - (iii) Weight reduction- improves lipoprotein metabolism

- b) For patients with more severe hypercholesterolemia and/or with a high cardiovascular risk, drug therapy should be initiated. The initial drug of choice is a **STATIN** (see below).

**A5.2 Hypertriglyceridemia (elevated triglycerides)**

- a) Lifestyle change: very low fat diet and exercise

- b) If necessary (i.e. TG> 500mg/ml), triglyceride-lowering drugs such as a fibrate or niacin can be initiated (see below).

N.B. Drug therapy needs to be continued indefinitely as withdrawal of drug will result in rebound of abnormal lipid profile

**(B) Drugs used in the treatment of Hypercholesterolemia**

**B1. HMG-CoA reductase inhibitors (“STATINS”)**

Atorvastatin (Lipitor®), Fluvastatin (Lescol®), Lovastatin (Mevacor®), Simvastatin (Zocor®), Pravastatin (Pravachol®), & Rosuvastatin (Crestor®)

- **B1.1 Primary clinical effect**
  - Significant reduction in LDLs (20-60%- dose and drug specific)
  - Modest reduction in triglycerides (10-20%)
  - Modest 5-10% increase in HDLs

- **B1.2 Mechanism of Action**
  - a) Inhibition of HMG-CoA reductase
The statins are analogs of 3 hydroxy-3 methylglutarate, a key metabolite of cholesterol biosynthesis and inhibit HMG-CoA reductase— the rate limiting step in cholesterol biosynthesis, thereby inhibiting endogenous cholesterol synthesis and the production of VLDLs.

- Inhibition of HMG-CoA reductase results in the depletion of intracellular cholesterol, which activates the SREBP transcription factor resulting in the increased transcription of the gene encoding the LDL receptor.

- Increased LDL receptor expression at the plasma membrane results in the uptake of additional LDL from the circulation and the overall reduction of plasma LDL-cholesterol levels.

- Other properties of Statins that contribute towards their beneficial effects in the treatment of atherosclerosis:
  i. Inhibit the adhesion of monocytes to the endothelium and migration to the arterial wall
  ii. Inhibit monocyte proliferation
  iii. Inhibit the expression of adhesion molecules expressed on the endothelium
  iv. Inhibit the oxidation of LDL to ox-LDL
  v. Inhibit SMC proliferation
  vi. Inhibit immune and inflammatory responses
  vii. Stabilize the endothelium making atherosclerotic plaques less likely to rupture

**B1.3 Therapeutic Uses**

a) Drug of choice for treating patients with increased plasma LDL-C levels in all types of hyperlipidemia
b) The dose response relationship of STATIN drugs is non-linear: Doubling the
STATIN dose only results in a 5-6% further decrease in LDL-C, while increasing
potential toxicity.

c) Patients with Familial hypercholesterolemia benefit much less because of defect
in LDL receptor.

d) Drug of choice for patients with high risk of cardiovascular disease irrespective of
plasma cholesterol levels.

Numerous clinical trials have demonstrated that the use of either Atorvastatin
(Lipitor®) or Simvastatin (Zocor®) in patients with a high cardiovascular risk (i.e.
previous history of coronary heart disease, high blood pressure + smoking or
type-2 diabetes) can significantly decrease (25-30%) their risk of future
cardiosternal events (i.e. heart attack and stroke) and death due to CHD no
matter what their initial baseline serum LDL-cholesterol levels.

B1.4 Pharmacokinetics

a) Statins are directly taken up into the liver by a specific anion transporter OATP2

b) There is extensive 1st pass extraction in the liver- consequently these drugs
primarily exhibit their dominant effect in the liver

c) Lovastatin (Mevacor®), Simvastatin (Zocor®) & Atorvastatin (Lipitor®) are
metabolized by CYP3A4 mechanisms

d) Fluvastatin (Lescol®) and Rosuvastatin (Crestor®) are metabolized by CYP2C9
mechanisms

e) Pravastatin (Pravachol®) is not metabolized via the cytochrome P450 pathway

f) Half-lives for Lovastatin (Mevacor®), Simvastatin (Zocor®), Pravastatin
(Pravachol®) & Fluvastatin (Lescol®) are ~ 1.5-2hrs

g) Half-life for Atorvastatin (Lipitor®) is 14hrs and for Rosuvastatin (Crestor®) is 19
hrs

h) All Statin drugs are glucoronidated in the liver: enhances metabolism and
secretion

B1.5 Adverse Effects

a) Generally well tolerated- patients that can tolerate one statin can generally
tolerate another- mild GI disturbances, headache or rash may occur

b) Biochemical abnormalities in liver function have also been reported (1-2%)

c) Small risk in type-2 diabetes, although benefit clearly outweighs the risk

d) Myalgia (muscle pain; 2-11%) and Myopathy (muscle weakness) are common
and increase with increasing dose of drug

e) Rhabdomyolysis (muscle disintegration), although reported, is rare and occurs
primarily at high doses of drug – can lead to renal failure and even death (8% of
cases)

Symptoms: fever, malaise, diffuse myalgia and/or tenderness, marked elevation
of serum creatine kinase and myoglobin present in the urine
- More common in patients with either acute/chronic renal failure, obstructive liver disease, or hypothyroidism
- Can be observed with drug interaction especially inhibitors of CYP3A4 e.g. cyclosporin, tacrolimus, ketoconazole/itraconazole, HIV Protease inhibitors (see below) and gemfibrozil
- Fewer muscle effects are observed with Pravastatin (Pravachol®)

B1.6 Drug interactions.

a) **All** statins with the exception of Pravastatin (Pravachol®) are metabolized in the liver by the cytochrome P450 system

b) Drugs that inhibit cytochrome P450 enzymes will **increase** the concentrations of statins leading to increased risk of adverse effects such as myopathy and Rhabdomyolysis

- CYP3A4 inhibitors lead to elevated levels of Lovastatin (Mevacor®), Simvastatin (Zocor®) & Atorvastatin (Lipitor®)

CYP3A4 inhibitors associated with increased risk of Rhabdomyolysis
- Immunosuppressants: cyclosporin & tacrolimus
- Macrolide antibiotics: erythromycin, clarithromycin
- Calcium channel blockers: diltiazem, verapamil
- Anti-arrhythmia drugs: amiodrone
- Azole anti-fungal agents: itraconazole, ketoconazole
- HIV anti-retrovirals: amprenavir, indinavir, neflinavir & ritonavir
- Anti-coagulants: warfarin

- Inhibitors of CYP2C9 increase the plasma concentration of Fluvastatin (Lescol®) and Rosuvastatin (Crestor®) e.g. ketoconazole, itraconazole, metronidazole, sulfinpyrazone,

c) Grapefruit juice in large amounts (>1 liter/day) may also increase the plasma concentrations of Lovastatin, Simvastatin & Atorvastatin via inhibition of CYP3A

d) Drugs such as phenytoin, griseofulvin, barbiturates, rifampin and thiazolindiones that **increase** expression of CYP3A4 can **reduce** plasma concentrations of Lovastatin (Mevacor®), Simvastatin (Zocor®) & Atorvastatin (Lipitor®).

e) Pravastatin (Pravachol®) is **not** metabolized by the cytochrome P450 system and is therefore the drug of choice for use with verapamil, the ketoconazole group of fungal agents and macrolide antibiotics.

f) Gemfibrozil (a fibrate -see below) inhibits the metabolism of **ALL** statin drugs (including pravastatin) by inhibiting statin glucoronidation, which is involved in the metabolism of all Statin drugs, thereby acting to increase statin drug concentrations and increasing the risk of myopathy and rhabdomyolysis. Gemfibrozil also affect Statin drug concentrations by inhibiting the OATP2 transporter-mediated uptake of Statins into the liver.

B1.7 Contraindications.
a) Pregnancy and Nursing Mothers- statins have been shown to induce birth defects  
b) Patients with Liver disease  
c) Patients taking Gemfibrozil have an increased risk of myopathy and rhabdomyolysis.

**B2. Bile acid-binding resins**  
Cholestyramine (Questran®), colestipol (Colestid®), colesevelam (Welchol®)

**B2.1 Primary clinical effect**  
- Modest 10-25% reduction in LDLs (less effective than statins)  
- can potentially cause a small increase in serum triglycerides

**B2.2 Mechanism of Action.**

a) Bile acid-binding resins are cationic polymers that act as anion exchangers that bind to negatively charged bile acids/salts and prevent their reabsorption in the small intestine  

b) Resin/Bile acid complexes are excreted in the feces (~10-fold increase in excretion)  

c) The decreased concentration of re-circulating bile acids upregulates the expression of cholesterol 7-α hydroxylase (rate limiting enzyme in the synthesis of bile acids) thereby promoting the enhanced hepatic conversion of cholesterol into additional bile acids, this lowers the concentration of hepatic cholesterol thereby increasing expression of LDL receptors (via activation of SREBP-see above), which promotes the hepatic uptake of LDL from the plasma, resulting in an overall decrease in the plasma LDL concentration  

d) N.B. the decrease in hepatic cholesterol can also lead to the increased expression of HMG-CoA reductase, resulting in increased hepatic cholesterol synthesis and the generation of additional VLDLs- this can actually increase serum triglyceride levels in patients with type III dyslipoproteinemia.
B2.3 Therapeutic Use.
a) Because of the clinical efficacy of statins, bile acid-binding resins have largely been relegated to second line drugs that are mainly used for the treatment of primary hyperlipidemias in the young (<25 yrs) and in patients for whom statins do not effectively lower plasma LDL-cholesterol

b) Resins can be used together with low dose STATIN in combination therapy to aggressively reduce serum LDL-C concentrations (~50% lower than a statin alone)- allows aggressive reduction of LDL-C without increasing STATIN dose where toxicity may occur.

c) Drug of choice for treating hypercholesterolemia in children and women of child bearing age who are lactating, pregnant, or could become pregnant.

OTHER NON-HYPOLIPIDEMIC INDICATIONS
d) Resins can also be used to relieve pruritus (itching) caused by accumulation of bile acids in patients with biliary obstruction

e) To prevent diarrhea in Crohn’s Disease by preventing build up of bile acids in the large intestine of those that have undergone an ileal resection

f) Treatment of C. difficile infections- where they are used to prevent diarrhea by promoting the absorption of the C. diff A and B toxins

g) Treatment of drug overdose with digoxin, leflunomide & levothyroxine- form resin-drug complexes thereby preventing drug absorption and promoting elimination.

B2.4 Pharmacokinetics
a) Not absorbed or metabolically altered by the intestine
b) Totally excreted in the feces

B2.5 Adverse Effects
a) Since these agents are not absorbed or metabolized they are very safe with few side effects
b) GI disturbances are the most common side effects e.g. constipation, bloating, nausea and flatulence

At high concentrations Cholestyramine (Questran®) and colestipol (Colestid®), but not colesevelam (Welchol®) can impair the absorption of the fat soluble vitamins A, D, E and K – decreased Vitamin K can result in bleeding.

B2.6 Drug interactions.
a) Cholestyramine (Questran®) and colestipol (Colestid®), but not colesevelam (Welchol®), interferes with the intestinal absorption of many drugs e.g. tetracycline, Phenobarbital, digoxin, warfarin, paravatatin, fluvastatin, aspirin and thiazide diuretics. - These Drugs should be taken either 1-2 hrs before or 4-6 hrs after bile acid-binding resins
B2.7 Contraindications
a) Dysbetalipoproteinemia and raised triglycerides (>400 mg/dL) due to risk of further increasing triglyceride levels

B3. Inhibitors of intestinal sterol absorption.
Ezetimibe (Zetia®)

B3.1 Primary clinical effect
- Reduces LDL levels by ~18%
- Minimal effect on HDL and triglycerides

B3.2 Mechanism of action
a) Ezetimibe (Zetia®) inhibits the action of the Niemann-Pick C1-like protein (NPC1L1) involved in the absorption of both dietary and biliary cholesterol in the small intestine
b) This decreases the delivery of dietary cholesterol to the liver, thereby reducing the production of VLDLs. Since VLDLs are the precursors of LDLs, this also leads to a reduction in the serum concentration of LDL-cholesterol.
c) In addition, the reduction in hepatic cholesterol will also result in an increase in the expression of LDL receptors, thereby promoting increased LDL clearance.

B3.3 Therapeutic uses.
a) Reduces LDL levels in patients with primary hypercholesterolemia
b) Significant LDL lowering effects when combined with a STATIN - a further 25% decrease in LDL versus STATIN-treatment alone.
c) The combination of Ezetimibe (Zetia®) together with a STATIN allows the use of a lower dose of the STATIN drug, thereby avoiding potential STATIN-associated adverse effects (e.g. Rhabdomyolysis).

B3.4 Pharmacokinetics
a) Rapidly absorbed by the enterocytes
b) Recirculates enterohepatically several times/day. This acts to continuously recirculate the drug back to its site of action and limits systemic exposure.

B3.5 Adverse effects
a) Generally well tolerated
b) Flatulence is most common effect
b) Diarrhea and myalgia can occur
d) Low incidence of impaired liver function (reversible)
B3.6 Drug interactions.
   a) Cyclosporin increases concentration of Ezetimibe (Zetia®)
   b) Bile acid resins interfere with the absorption of Ezetimibe (Zetia®), and if used concurrently should be taken several hours apart

B3.7 Contraindications.
   a) Hypersensitivity to Ezetimibe (Zetia®)
   b) Patients with mild to severe hepatitis
   c) Pregnant women

(C) Drugs used in the treatment of Hypertriglyceridemia

Treatment Options for hypertriglyceridemia

1. When serum triglyceride levels are borderline high (150-199 mg/dL) a lifestyle change is indicated including a low fat diet, exercise and cessation of smoking/alcohol

2. When serum triglyceride levels are high (200-499 mg/dL) initial emphasis should be on reducing non-HDL cholesterol (i.e. LDL-C and VLDL) using a LDL-C lowering drug such as a STATIN or the addition of niacin or a fibrate- ie. To reduce the risk of atherosclerosis

3. When serum triglyceride levels are very high (>500 mg/dL) the initial goal should be to reduce triglyceride levels with either niacin or a fibrate to reduce the risk of pancreatitis. Once triglyceride levels are below 500 mg/dL then LDL-C goals should be addressed

C1. Niacin

Niacin (nicotinic acid/vitamin B3) is a water-soluble vitamin that, at physiological concentrations is used in the synthesis of NAD & NADP, both important co-factors in intermediary metabolism. The pharmacological effects of niacin require large doses (1,500- 3,000 mg/day) and are independent of conversion to NAD & NADP.

C1.1 Primary clinical effect
   • 30-80% reduction in triglycerides
   • 10-20% reduction in LDLs
   • 10-30% increase in HDLs-most effective drug at reducing HDL

C1.2 Therapeutic Uses
   a) Lowers both plasma cholesterol and triglycerides
   b) Particularly useful in the treatment of familial combined hyperlipidemias and familial dysbetalipoproteinemia (elevation of both triglycerides and cholesterol)
   c) Most effective agent at elevating HDL levels.
   d) Often combined with another lipid lowering drug such as a statin or a resin
   e) Niacin has been shown to reduce the incidence of myocardial reinfarctions and overall mortality in patients with a history of previous MI
   f) The use of Niacin is often limited by poor tolerability (see below).

C1.2 Mechanism of Action
   a) Niacin improves virtually all lipid parameters resulting in decreased free fatty acids (FFA), VLDL & LDL and increased HDL
   b) Niacin acts via its Gi-coupled GPCR (GPR109A) expressed in adipose tissue to inhibit cAMP-induced lipolysis (stimulated via the Gs-coupled beta-adrenergic receptor.
   c) The reduced levels of lipolysis reduce the release of free FFA to the liver
d) Decreased FFA to the liver causes a reduction in the synthesis of triglycerides that in turn reduces production of VLDLs

e) Reduced VLDLs in turn reduce the production of LDL-C

f) Niacin inhibits DGAT2 (Diacylglycerol acyltransferase)- the rate limiting step in hepatic triglyceride synthesis, thereby decreasing hepatic VLDL production

g) Niacin decreases the expression of apoCIII (secreted inhibitor of Lipoprotein Lipase) resulting in increased LPL activity and a corresponding increase in VLDL clearance

h) Niacin acts to decrease macrophage recruitment to atherosclerotic plaques

i) Niacin also increases the half-life of apoAI, the major apolipoprotein present in HDL, which in turn increases the plasma concentration of HDL and promotes reverse cholesterol transport (the HDL-mediated transport of cholesterol from the peripheral tissues to the liver where it can be excreted).

j) Niacin also significantly reduces the levels of Lp(a) lipoprotein, which is a modified form of LDL that is covalently coupled to the Lp(a) protein. The Lp(a) protein is homologous to plasminogen and is found in atherosclerotic plaques, where it is thought to contribute towards atherosclerosis by antagonizing the activation of plasminogen thereby inhibiting thrombolysis. Niacin is the only lipid lowering drug to significantly reduce the levels of Lp(a) lipoprotein.
C1.4 Pharmacokinetics
a) Administered orally
b) Is converted in the body to nicotinamide and is incorporated into NAD+
c) Excreted in the urine unmodified and as several metabolites

C1.5 Adverse effects.
a) Most patients experience skin flushing, itching (pruritis) and a sensation of warmth – this prostaglandin-mediated effect can be diminished by prior treatment with Aspirin or Ibuprofen

b) Some patients experience GI distress, nausea and abdominal pain.

c) Niacin inhibits tubular secretion of uric acid and therefore predisposes to hyperuricemia and gout (20% of patients)

d) Can cause insulin resistance (generally reversible) and hyperglycemia may be worsened in susceptible patients i.e. Type-2 diabetes

e) Hepatic toxicity has been reported

f) Niacin can exacerbate peptic ulcer and is therefore contraindicated in patients with severe peptic disease

g) Poor tolerability often limits the use of the drug

C1.6 Contraindications
a) Peptic Ulcer disease
b) Patients with a history of Gout
c) Caution should be observed in diabetics
d) Caution should be observed in patients with impaired liver function

C2. Fibrates.
Fenofibrate (Tricor®, Lofibra®), Gemfibrozil (Lopid®)

C2.1 Primary clinical effect
- 40-60% reduction in triglycerides
- mild (10-20%) reduction in LDL
- 10-20% increase in HDL

C2.2 Mechanism of action
a) Fibrates are derivatives of fibric acid and act as ligands for the nuclear hormone transcription factor peroxisome proliferator-activated receptors alpha (PPAR\(\alpha\))
b) Fibrates activate PPARα, which then binds to its responsive element in the promoters of numerous genes involved in lipoprotein structure and function.

c) PPARα activation acts to decrease plasma triglyceride concentrations by:
   (i) increasing the expression of lipoprotein lipase in muscle, thereby resulting in increased muscle lipolysis leading to enhanced uptake and catabolism of triglyceride-rich lipoproteins.
   (ii) decreasing the hepatic expression of apolipoprotein CIII (a known inhibitor of lipoprotein lipase), which acts to enhance overall lipoprotein lipase activity, thereby increasing the catabolism of triglyceride-rich lipoproteins.
   (iii) increasing the expression of genes involved in fatty acid transport and fatty acid oxidation in hepatocytes, which results in increased fatty acid catabolism, thereby reducing hepatocyte triglyceride synthesis and decreasing the hepatic production of VLDLs.

**Overall effect:** Increased peripheral VLDL clearance and decreased hepatic TG production = ↓serum [VLDL]

d) PPARα activation increases the plasma concentration of HDLs by increasing the synthesis of apoAI and apoAII, the major apolipoproteins found in HDL. This promotes reverse cholesterol transport.

e) PPARα activation also induces the upregulation of the SR-B1 scavenger receptor in hepatocytes, which binds to HDL and promotes increased transfer of cholesterol from HDLs to hepatocytes, thereby leading to increased secretion of cholesterol into the bile duct. This can lead to increased risk of gallstone formation (see below).
C2.3 Therapeutic Uses
a) Effective at decreasing serum triglyceride levels
b) Useful for increasing concentration of serum HDL-C levels
c) Used in the treatment of hypertriglyceridemias, especially in patients with severe hypertriglyceridemia at risk of pancreatitis and in hypertriglyceridemia with low HDL-C
d) Therapy of choice for patients with Familial dysbetalipoproteinemia (Type III hyperlipoproteinemia: increased plasma triglycerides and lipoprotein remnants)
e) Long-term fibrate usage has been clinically proven to reduce the incidence of coronary events (22%), stroke (25%), and transient ischemia events (59%).

C2.4 Pharmacokinetics
a) Both drugs are completely absorbed after oral administration
b) Drugs are distributed widely and are bound to serum proteins
c) Both drugs undergo extrahepatic circulation
d) Half-life for gemfibrozil is 1.5 hrs and for fenofibrate is 20 hrs

C2.5 Adverse effects
a) Generally well tolerated
b) most common side effects are mild GI disturbances
c) Predisposition to gallstone formation due to increased cholesterol excretion in the bile. Fibrates inhibit expression of cholesterol 7alpha-hydroxylase (the rate-limiting enzyme in bile acid production), thereby decreasing bile acid production resulting in increased secretion of free cholesterol, which can result in the formation of gallstones
d) Myopathy and rhabdomyolysis have been reported (esp. Gemfibrozil: increased risk when given with a STATIN)
e) Hepatitis

C2.6 Drug interactions
a) Both drugs are strong protein binders and can therefore displace other protein-bound drugs from albumin resulting in an increased serum drug concentration.
   • potentiates the effects of oral anti-coagulants (e.g. warfarin) leading to increased risk of bleeding. Anticoagulant drug concentrations should be reduced by 30% when given together with a STATIN
   • enhances hypoglycemic effects of sulfonylureas

b) Gemfibrozil increases the serum concentration of STATINS leading to increased risk of STATIN-induced adverse effects such as myopathy and rhabdomyolysis
   • Gemfibrozil inhibits the transporter responsible for hepatic uptake of STATINS
   • Gemfibrozil inhibits STATIN glucuronidation that is involved in the metabolism and excretion of all STATINS
c) Fenofibrate does not affect STATIN metabolism and is therefore the drug of choice for use with a STATIN in combination therapy.

d) Because both drugs are renally excreted, drug concentrations are elevated in patients with renal insufficiency, thereby increasing the risk of drug interactions.

C2.7 Contraindications
a) Pregnant/lactating women

b) Patients with severe hepatic dysfunction—due to increased risk of hepatic damage

c) Patients with severe renal dysfunction—since both drugs renally secreted

d) Patients with pre-existing gallbladder disease

e) Caution should be observed in patients taking a STATIN because of increased risk of Rhabdomyolysis

C3. Fish Oils: Omega-3 long chain polyunsaturated fatty acids
A mixture of Eicosapentaenoic acid and Docosahexanoic acid (Omacor/Lorvaza)

C3.1. Primary clinical effect
- Lowers serum triglyceride levels by 50%
- Minor increase in HDL
- Can increase LDLs in some individuals

C3.2. Mechanism of Action.
- Unclear, but appears to involve the inhibition of hepatic triglyceride synthesis and the increased triglyceride clearance

C3.3. Therapeutic Uses
- Currently approved only as an adjunct to diet and lifestyle interventions in the treatment of hypertryglyceridemia in patients with TG levels >500 mg/dl

C3.4. Adverse Effects
a) Fishy after taste
b) GI: nausea, bloating, diarrhea, flatulence
c) reduces serum concentrations of vitamin E

C3.5. Drug Interactions
a) None
b) Unlike fibrates, fish oils are not associate with an increased risk of Rhabdomyolysis when given together with a STATIN
D. Combination drug therapy.
Combined drug therapy is useful when:

a) LDL-cholesterol levels are not sufficiently reduced in high-risk patients even with the highest dose of STATIN
   - A STATIN + either a Resin, Ezetimibe or Niacin
     Synergistic reduction of LDL-cholesterol with drug combination

b) Both LDL and VLDL levels are elevated (e.g. combined hyperlipoproteinemia)
   - STATIN + Niacin – more effective than either agent alone
   - STATIN + fibrate - in cases where TG and LDL are very high- however should be used with caution as increased risk of myopathy especially with Gemfibrozil (Fenofibrate is preferred drug in this case)

c) When LDL or VLDL levels are not normalized with a single drug regime

d) When HDL deficiency co-exists with other hyperlipidemias
   - Either Niacin or a fibrate is added to increase HDL

e) When VLDL levels are increased during treatment of hypercholesterolemia with a bile acid-binding resin
   - Niacin is added to control elevated VLDL levels

### Review of lipid-lowering drug effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on LDL</th>
<th>Effect on Triglycerides</th>
<th>Effect on HDL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niacin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile acid Binding resins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol Absorption inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pharmacology &amp; Therapeutics</strong></td>
<td>Drugs to treat Hyperlipidemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Common mechanisms</strong></td>
<td><strong>Interactions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Increase levels of VLDL</td>
<td>(a) Muscle atrophy/motility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Reduce levels of HDL</td>
<td>(b) Increased secretion of VLDL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(c) Increase levels of LDL</td>
<td>(c) Hepatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(d) Reduce levels of HDL</td>
<td>(d) Reduce HDL levels</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Effects**

- Low HDL
- Low VLDL
- Increased HDL levels
- Decreased LDL levels

**Pharmacological effects**

- Low HDL levels
- Increased VLDL levels
- Decreased HDL levels
- Reduced LDL levels

**Adverse effects**

- Muscle atrophy/motility
- Hepatitis

**Interactions**

- Muscle atrophy/motility
- Hepatitis

**Mechanisms of action**

- Increased secretion of VLDL
- Reduced HDL levels

**Indications**

- Low HDL levels
- Increased VLDL levels
- Decreased HDL levels
- Reduced LDL levels
PHARMACOLOGY OF NITRIC OXIDE

Date: October 2, 2013-10:30 am
Katzung and Trevor’s Pharmacology, Examination & Board Review. 8th Ed., pp. 163-165.

KEY CONCEPTS & LEARNING OBJECTIVES

1. Recall that the originally described endothelium derived relaxing factor (EDRF) is now known to be nitric oxide.
2. Describe the physiologic process which can generate endogenous nitric oxide.
3. Identify that arginine is the main endogenous source of nitric oxide.
4. Identify the isoforms of the enzymes responsible for the synthesis of nitric oxide.
5. Compare the beneficial and toxic effects of nitric oxide.
6. Identify drugs which can increase the levels of endogenous nitric oxide.
7. List two drugs that spontaneously or enzymatically breakdown in the body to release NO.
8. Describe some of the therapeutic uses of nitrates.
9. Describe the term nitric oxide donor.

LIST OF DRUGS COVERED IN LECTURE

1. Nitroglycerine
2. Iso-sorbide dinitrite
3. Amyl nitrate
4. Nitroprusside
5. Hydralazine (vasodilator)
6. Nitric oxide (INOmax)
7. Furoxans (Furazolidone, antiprotozoal)
8. L-Arginine
PHARMACOLOGY OF NITRIC OXIDE

I. INTRODUCTION

Nitric oxide, a gaseous signaling molecule that diffuses vascular and cellular sites and regulates a wide range of physiologic and pathological processes including cardiovascular, cerebrovascular, inflammatory, immune and neuronal pathways.

Nitric oxide produces profound pharmacologic actions, some of which are listed below.

1. Smooth muscle
   - relaxation
2. Cell adhesion
   - decreased adhesion
3. Inflammatory response

II. DISCOVERY OF NITRIC OXIDE

1. Endogenous nitric oxide (NO) is generated from the oxidation of the guanidine group of arginine. Exposure to bacterial lipopolysaccharide result in the generation of NO in the macrophage. Infection of bacterial endotoxin to animals also increases the NO levels.

2. Upon stimulation with acetylcholine and carbochol, the vascular endothelium release a vasodilatory substance known as the endothelin derived growth factor (EDRF). This EDRF was later characterized to be NO.

Nitric oxide counteracts the vasoconstrictor effects of various mediators.
III. BIOLOGIC SYNTHESIS AND THE INACTIVATION OF NITRIC OXIDE

1. Synthesis of Nitric Oxide

Nitric oxide designated as NO or simply NO, is a highly diffusible gas composed of one atom of nitrogen and oxygen each. Nitric oxide is synthesized by a family of enzymes collectively termed as nitric oxide synthase (EC.1.14.13.49). Three isoforms of these enzymes have been identified and are summarized in the following table.

<table>
<thead>
<tr>
<th>Property</th>
<th>NOS-1 (nNOS, neuronal NOS)</th>
<th>NOS-2 (iNOS, inducible NOS)</th>
<th>NOS-3 (eNOS, endothelial NOS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other names</td>
<td>nNOS</td>
<td>iNOS</td>
<td>eNOS</td>
</tr>
<tr>
<td>Tissue</td>
<td>Neuronal, epithelial cells</td>
<td>Macrophages, smooth muscle cells</td>
<td>Endothelial cells</td>
</tr>
<tr>
<td>Expression</td>
<td>Constitutive</td>
<td>Transcriptional induction</td>
<td>Constitutive</td>
</tr>
<tr>
<td>Calcium requirement</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Chromosome</td>
<td>12</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Approximate mass</td>
<td>150-160 kDa</td>
<td>125-135 kDa</td>
<td>133 kDa</td>
</tr>
</tbody>
</table>

These isoforms are heme containing flavoproteins employing L-arginine as a substrate and requiring NADPH, Flavin adenine dinucleotide and tetrahydrobiopterin as cofactors. The conversion of L-arginine to L-citrulline is inhibited by several arginine analogues such as N-monomethyl-L arginine.

Some nitric oxide donors such as oxygenated nitroprusside, spontaneously generates NO, whereas others such as the furoxan and organic nitrates and nitrites such as nitroglycerin require the presence of a thiol compound such as cysteine. Once generated NO interacts with the heme moiety of soluble guanyl cyclase in the cytoplasm of the cell. Upon activation this enzyme converts GTP to cyclic GMP.

Nitric oxide undergoes both oxidative and reductive reactions resulting in the formation of a variety of oxides of nitrogen. These are described in the following table.
2. Inactivation of Endogenous Nitric Oxide

NO is inactivated by heme and by free radicals superoxide. The scavenger of superoxide such as the enzyme superoxide dismutase may protect nitric oxide and augment its potency and duration of action. On the other hand, superoxide may interact with NO to generate peroxynitrite (ONOO⁻) which complexes with the sulphydryal groups of several key enzymes. The effects of peroxynitrile are regulated by glutathione. Nitrosoglutathione is a more stable form of cytosolic NO. In cardiovascular diseases and diabetes cellular levels of glutathione are reduced and contribute to the vascular pathology.

IV. INHIBITORS OF NITRIC OXIDE

Several approaches can be used to reduce endogenous nitric oxide levels and thus inhibit its effects. These include:

1. L-arginine derivatives (L-NMMA, L-NAME)
2. Inhibitors of nitric oxide synthase synthesis

3. Inhibitor of binding of arginine to NOs

4. Scavengers of NO

Most of the inhibitors are substrate analogues. Heme is a scavenger for NO. In sepsis and other inflammatory conditions, NOS-2 is induced and results in an increased production of NO. Excess production of NO results in the generation of peroxynitrite which is toxic to cells. Thus, NO inhibitors may be helpful in the treatment of sepsis related disorders.

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Mechanism</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>N\textsuperscript{\textalpha}Monomethyl-l-arginine (l-NMMA)</td>
<td>Competitive inhibitor, binds arginine-binding site in NOS</td>
<td>Nonselective NOS inhibitor</td>
</tr>
<tr>
<td>N\textsuperscript{\textalpha}Nitro-l-arginine methyl ester (l-NAME)</td>
<td>Competitive inhibitor, binds arginine-binding site in NOS</td>
<td>Nonselective NOS inhibitor</td>
</tr>
<tr>
<td>7-Nitroindazole</td>
<td>Competitive inhibitor, binds both tetrahydrobiopterin and arginine-binding sites in NOS</td>
<td>Partially selective for NOS-1 in vivo</td>
</tr>
<tr>
<td>BBS-2</td>
<td>Inhibits iNOS dimerization</td>
<td>Also weakly inhibits nNOS and eNOS</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>NO scavenger</td>
<td></td>
</tr>
</tbody>
</table>


V. EFFECTS OF NITRIC OXIDE

NO’s major effects are mediated by the activation of guanyl cyclase resulting in the generation of cyclic GMP. NO can also generate several reactive nitrogen derivatives by interacting with molecular oxygen and superoxide radicals.

These oxides of nitrogen are highly reactive and unstable, interact with numerous proteins, lipids, nucleic acids and metabolize. Thus, these reactive species alter the physiologic
disposition of cells and tissues and mediate several physiologic and pathologic effects. The beneficial effects include smooth muscle relaxation, vasodilation, immune regulation, anesthetic and anti-atherosclerotic responses. The pathologic responses include free radical formation, nitrosation and irritant effects.

1. Vascular Effects

NO is involved in the regulation of normal vascular tone. Decreased NO levels in blood vessels may result in an increase in blood pressure.

*Katzung 11\textsuperscript{th} Ed. Pp.194.*
NO is also a potent inhibitor of the white cells adhesion to the endothelial surface. It decreases the release of adhesion molecules such as the E-Selectin on the endothelial surface. NO has been shown to protect against ischemic and reperfusion injury.

2. Respiratory Effects
Nitric oxide improves cardiopulmonary function in adults with pulmonary hypertension and is approved for this indication (INOmax). It is administered by inhalation. It is also used in children with acute respiratory distress syndrome (ARDS). Nitric oxide also relaxes airway smooth muscle and acts as a bronchodilator.

3. Septic Shock
Bacterial infection and lipopolysaccharide B activate inducible nitric oxide synthase (NOs-2) resulting in hypotension, shock and possible death. This effect is reversed by NO inhibitors such as the L-NMMA.

4. Atherosclerosis
Vascular plaque and endothelial damage in atherosclerosis results in impaired nitric oxide formation. Decreased release of NO results in vascular defects and increased cellular proliferation. L-arginine and nitric oxide donors are useful in the treatment of atherosclerotic disorders.

5. Platelets
Nitric oxide is a potent inhibitor of platelet adhesion, activation and aggregation and regulates the release of serotonin, growth factors and thromboxane from platelets. Platelets also contain the constitutive and inducible NOs. Cyclic GMP plays an important role in platelet protection. NO also indirectly enhances fibrinolysis by inhibiting the release of antiplasmin for the platelets.

6. Organ Transplantation
Accelerated graft atherosclerosis following organ transplantation is a chronic condition and is a major cause of graft failure. Platelet activation results in the generation of growth factors such as the PDGF. Cellular proliferation causes ischemic and reperfusion injury. **Nitric oxide acts as a cytoprotective agent and prevents cellular and platelet adhesion.** **Dietary L-arginine increases plasma NO levels has been shown to reduce the graft atherosclerosis.** In some cases excessive production of NO may be harmful and promote graft rejection.

7. The Central Nervous System

NO is known to play a major role in the CNS as a neurotransmitter, as a modulator of receptors and the release of other transmitters. NO is implicated in neurmodulatory process and has impact on stroke and vascular dementia. NO has multiple roles in the CNS which are beyond the scope of this discussion.

8. Peripheral Nervous System

Nonadrenergic, noncholinergic (NANC) are widely distributed peripheral tissues. Some NANC neurons release nitric oxide. Erectile responses are thought to be caused by the release of NO from NANC neurons. Nitric oxide donors may be useful in impotence. Such agents as nitroglycerine ointment and nitroglycerin patches have been used. Another approach is to inhibit CGMP degradation by phosphodiesterase 5 with such drugs as Sildenafil (Viagra). Potent interactions between NO donors and Viagra have been reported resulting in hypotension.

9. Inflammation

Nitric oxide has a role in both the acute and chronic inflammation. NOs-3 is involved in the vasodilation associated with acute inflammation. Nitric oxide promotes edema and vascular permeability. In inflammatory bowel disease, arthritis and other diseases of
inflammation, NOs-3 is elevated and generates excessive NO levels.

VI. NITRATES AS NO DONORS

Nitrates represent the most widely used donors of nitric oxide (NO). Denitration of such drugs as the nitroglycerin result in the formation of NO which is responsible for the smooth muscle relaxation.

1. Classification and pharmacokinetics
   a. Nitroglycerine
   b. Isosorbide dinitrate (sublingual/oral)
   c. Amyl nitrates (volatile rapid acting)
      Rarely prescribed

2. Pharmacokinetics

<table>
<thead>
<tr>
<th>Type</th>
<th>Example</th>
<th>Duration of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra short</td>
<td>Inhaled amyl nitrate</td>
<td>3-5 minutes</td>
</tr>
<tr>
<td>Short</td>
<td>Sublingual nitroglycerin iso-sorbide dinitrate</td>
<td>10-30 minutes</td>
</tr>
<tr>
<td>Intermediary</td>
<td>Oral or sustained release nitroglycerine or</td>
<td>4-8 hours</td>
</tr>
<tr>
<td></td>
<td>iso-sorbide dinitrate</td>
<td></td>
</tr>
<tr>
<td>Long</td>
<td>Transdermal nitroglycerine</td>
<td>8-10 hours</td>
</tr>
</tbody>
</table>

3. Mechanism of action

   Primarily produce smooth muscle relaxation by releasing endogenous NO which produces the following effects.
   a. Stimulates guanyl cyclase
   b. Increased production of cGMP
   c. Dephosphorylation of myosin
VII. THERAPEUTIC USE OF NITRIC OXIDE.

1. Methods of Administration

Commercial NO systems are available which can accurately deliver inspired NO concentrations between 0.1 and 80 ppm and simultaneously measure NO and NO$_2$ concentrations. A consistent inspired level of NO is maintained by administering NO in nitrogen to the inspired limb of the ventilator circuit as intermittent or continuous delivery. NO can be administered via a closely fitted mask. It is administered mostly in the management of primary pulmonary hypertension. After the administration, NO should be gradually discontinued to avoid complications such as rebound.

2. Indications

a. Selective pulmonary vasodilation

b. Treatment of newborn with persistent pulmonary hypotension (improves oxygenation)

c. Beneficial effects in cardiopulmonary bypass in adults, congestive heart disease, primary pulmonary hypertension, pulmonary edema, lung transplantation and sickle cell crisis.
PHARMACOLOGY OF VASOACTIVE PEPTIDE

Date: October 3, 2013-10:30 am
Reading Assignment: Katzung 12th Ed. Pp. 295-312

KEY CONCEPTS & LEARNING OBJECTIVES

1. Identify the enzyme responsible for the conversion of angiotensinogen to angiotensin I. Atrial Natriuretic Peptide
2. Discuss the effects of angiotensin converting enzyme (ACE).
3. Describe two drugs which are known as angiotensin converting enzyme inhibitors (ACE Inhibitors).
4. Discuss the pharmacologic actions of bradykinins and Atrial Natriuretic Peptide.
5. Compare the actions of kallikreins and endothelins.
6. List four of the potent vasoactive peptide
7. Describe the functions of vasoactive intestinal peptide (VIP), substance P and calcitonin gene-related peptide (CGRP).
8. Describe the effect of desmopressin on endothelial cells
9. Describe the effects of aprotonin on the actions of kallikrein

LIST OF DRUGS COVERED IN LECTURE

1. Captopril (ACE inhibitor)
2. Enalapril (ACE inhibitor)
3. Losartan (Angiotensin receptor inhibitor)
4. Valsartan (Angiotensin receptor inhibitor)
5. Icatibant (Bradykinin receptor inhibitor)
6. Aprotonin (Kallikrein inhibitor)
7. Desmopressin (Vasopressin analogues, release vW factor)
8. Bosentan (ET$_A$-ET$_B$ receptor inhibitor)
PHARMACOLOGY OF VASOACTIVE PEPTIDE

I. PHARMACOLOGY OF VASOACTIVE PEPTIDES

Vasoactive peptides are comprised of a wide group of polypeptides of endogenous origin that function as local and plasmatic hormones and neurotransmitters. Of these peptides the angiotensin, the kinins, endothelins and vasopressin play an important role in the overall regulation of hemodynamics and its pathogenesis. Some of these peptides are listed below.

1. Angiotensins (I, II and III)
2. Bradykinin and related kinins
3. Vasopressin
4. Atrial natriuretic peptides and related peptides
5. Endothelins
6. Vasoactive intestinal peptides and related peptides
7. Substance P
8. Neurotensins
9. Calcitonin gene-related peptide
10. Adrenomodulin
11. Neuropeptide Y
12. Urotensin

Mechanisms of Actions

These peptides all act on cell surface receptors. Most act via G protein-coupled receptors and cause the production of second messengers, some may open ion channels.
II. ANGIOTENSIN AND RELATED PEPTIDES

Angiotensin

Angiotensin is formed by the action of renin on angiotensinogen releasing angiotensin I, a decapeptide. Angiotensin I is converted to angiotensin II, an octapeptide by the action of converting enzyme. Angiotensin II is degraded into inactive peptide by the action of angiotensinases. Of these angiotensin I, angiotensin II and angiotensin III, only angiotensin II is active and produces profound vasoconstriction and other pharmacologic responses.

1. Angiotensinogen

A circulating protein from which renin cleaves angiotensin I. It is a glycoprotein. Angiotensin production is increased by a variety of drugs including corticosteroids,
estrogens, thyroid hormones and Angiotensin II. The plasma levels of angiotensinogen are also increased in pregnancy related hypertension.

2. Angiotensin I

A decapeptide with virtually no biologic activity. It must be converted to the octapeptide, angiotensin II by the action of angiotensin converting enzyme (ACE). Plasma or tissue aminopeptides convert angiotensin II into angiotensin III.

- Angiotensin I Decapeptide (inactive)
- Angiotensin II Octapeptide (active)
- Angiotensin III Heptapeptide (inactive)
- Angiotensin III fragment <Tetrapeptides (inactive)

3. Angiotensin Converting Enzyme

Angiotensin converting enzyme is also known as

- Peptidyl dipeptidase
- Kininase II

It catalyzes the cleavage of dipeptide from the carboxyl terminal of angiotensin I (decapetide) into angiotensin II (octapeptide). This enzyme is widely distributed in the vasculature mostly located on the luminal structure of the endothelial cells. It has been the primary target to develop antihypertensive drugs.

4. Angiotensinase

A group of peptidases which hydrolyze angiotensin II and angiotensin III into smaller fragments. These peptide fragments are inactive.

5. Pharmacologic Actions of Angiotensin II

Short plasmatic half life (15-60 secs.). This peptide exerts profound effects in the regulation of vascular tone, fluid and electrolyte balance. Excessive production of this peptide results in
hypertension and disorders of hemodynamics. On a molar basis, it is 40 times more potent than nor-epinephrine, stimulates autonomic ganglion, increases the release of epinephrine and nor-epinephrine from the adrenal medulla and facilitates autonomic transmissions. It stimulates aldosterone production from the adrenal cortex. At higher concentrations it produces glucocorticoid biosynthesis. Angiotensin is a potent mitogenic agent for the vascular and cardiovascular muscle cells and may contribute to cardiac hypertrophy. Angiotensin converting enzyme inhibitors inhibit the mitogenic responses of angiotensin II.

6. Inhibitors of Angiotensin

Numerous drugs are now available that block the formation of the action of angiotensin II. These include drugs blocking the rennin secretion and action, conversion of angiotensin I to angiotensin II and block angiotensin receptors.

III. ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACE INHIBITORS)

ACE inhibitors not only block the conversion of angiotensin I to angiotensin II but also inhibit the degradation of other vasoactive peptides such as the bradykinin, substance P and enkephalin. The action of ACE inhibition to block bradykinin metabolism contributes significantly to the observed hypotensive effect and has been reported to cause severe side effects including cough, angioedema and hypotensive shock.

Captopril and Enalapril are two of the most commonly used ACE inhibitors.

Enalapril is a prodrug ethyl ester, converted endogenously into active product.
IV. ANGIOTENSIN ANTAGONISTS

Substitution of certain amino acids such as sarcosine for the phenylalanine in position 8 of the angiotensin II is responsible in the formation of potent peptides antagonist of the action of angiotensin II. The best known of these is saralasin. Another class includes the nonapeptide antagonists such as the losartan and valsartan. Clinical benefits of the angiotensin receptor antagonists and ACE are almost the same.

Questions.

1. Do the angiotensin antagonists have any effect on the actions on ACE?
2. Can these angiotensin antagonists be given to a hypertensive patient with sepsis?
V. BRADYKININS AND RELATED PEPTIDES –KININS

Kinins represent one of the most potent groups of vasodilators peptides produced by the endogenous actions of enzymes known as kallikreins or kininogenases. These enzymes act on plasma proteins known as kininogenases.

Kallikreins are glycoprotein enzymes produced in the liver as prekallikreins and are present in plasma and several tissues including kidney, pancreas, gastrointestinal tract, sweat glands and salivary glands. Plasmatic prekallikrein is also known as Fletcher factor and promotes coagulation process via intrinsic system. Plasma prekallikrein can be activated by factor XIIa (Hageman factor).
Pancreatic kallikrein can be activated by trypsin. The active kallikrein can generate kinins and exert profound action on hemodynamics (hypotension). Many of the patients with consumption coagulopathies (DIC) develop hypotension due to increased kallikrein production.

2. Kininogen

Kininogens represent plasma lymph and interstitial protein substrates for the kallikreins. Two different types of kininogens are present in plasma. A low molecular weight kininogen (LMWK) and a high molecular weight kininogen (HMWK). The HMWK is also known as the Fitzgeald factor and is involved in the promotion of coagulation process in the intrinsic pathway. Plasma kallikrein cleaves the HMWK to generate bradykinin.

3. Formation of Kinins in Plasma and Tissues

Three different types of kinins are found in mammalian systems. Each kinin is formed by the action of different enzymes on kininogen. 1.) Bradykinin is released by plasma kallikrein; 2.) Lysyl bradykinin (kallikrein) is released by glandular kallikrein (pancreas kidney) and 3.) Meth-lysylbradykinin is released by pepsin and pepsin like enzymes. All of theses three kinins are found in plasma and urine. In most pathologic conditions related to hypotensive shock. Bradykinin is the predominant peptide.
4. Actions of Kinins

a. Hemodynamic effects

Marked vasodilation in several vascular beds, including the heart, liver, kidney, intestine, skeletal muscles and liver. These agents are 10 times more potent than histamine. Kinins stimulate the release of nitric oxide and prostaglandins PGE₂ and PGI₂. Kinins promote water and solution passage from the blood to extracellular fluid resulting in edema.

b. Effect on Endocrine and Exocrine Gland

Kinins produced in the pancreas, kidney and glandular site may enter the blood circulation and contribute to the localized hypotensive and inflammatory responses.

c. Role in Inflammation and Pain

Kinins promote redness, local heat, swelling and pain. Kinins are potent algesic agents. They produce pain by nociceptive afferents in the skin and viscera.

5. Mechanisms of Action of Kinins
The biologic actions of kinins are mediated by specific receptors localized on the membranes of the target tissues. Two types of receptors are identified, namely the B₁ and B₂ on the basic agonists potencies. B₁ receptors are the predominant receptors for the mediation of the biologic responses of kinins. Thus, drugs to block the actions of bradykinin target B₂ receptors.

6. Metabolism of Kinins

Kinins are metabolized rapidly (half life 15 seconds) by non-specific kininases. Two plasma kininases have been well characterized namely kinanase I and kininase II. Kinanase II is the same enzyme as the angiotensin converting enzyme and is capable of inactivation the bradykinin and it also converts angiotensin I into angiotensin II. Angiotensin converting enzyme inhibitors such as captopril therefore can inhibit the generation of angiotensin II simultaneously bradykinin levels may increase resulting in hypotension.

Case Report

An elderly hypotensive hospitalized patient was treated with an ACE inhibitor, namely captopril. During hospitalization she became septic due to an infection. Soon after she went into severe hypotensive shock.

What is the likely cause of the hypotensive shock in this patient?

7. Drugs Effecting the Kallkrein Kinin System

At this time a specific antagonist of the action of kinins is not available. Several inhibitors of both the B₁ and B₂ receptors have been designed and used in animal models, and human trials have been proven useful. Ictibant is a second generation B₂ receptor inhibitor which
has undergone limited clinical trials in pain and inflammation. Several other B₂ antagonists are available only for experimental purposes. β₂ receptor inhibitors may be useful for the treatment of hypotension and myocardial hypertrophy. The generation of kallikreins can be inhibited with a kallkrein inhibitors, aprotonin. Thus, the bradykinin generated is blocked. Aspirin is also known to block the algesic effects of prostaglandins generated by bradykinin. On the other hand, the action of kinin can be augmented by ACE inhibitors, which block the degradation of this peptide.

FVI. VASOPRESSIN

Vasopressin (Anti-diuretic hormone, ADH) plays an important role in the long term control of blood pressure through its action on the kidney to increase water resorption. It has short term vasoconstrictor actions.

Several selective analogues of vasopressin have been synthesized. Of these one clinically used preparation is 1-diamino [D-Arg⁶] arginine vasopressin (dDAVP) or desmopressin. This agent was initially developed for the treatment of patients with diabetes insipidus. Desmopressin increase the factor VIII activity of patients with mild hemophilia and von Willebrand disease. It is effective in the control of bleeding in mild surgical process. It can also be administered intranasally. In blood banking procedures this agent is also used to increase the factor VIII and von Willebrand factor in plasma of donor blood.

VII. NATRIURETIC PEPTIDES AND RELATED PEPTIDES

The atria and other tissues of mammals contain a family of peptides with nitriuretic diuretic, vasorelaxant and other properties. The family includes the atrial natriuretic peptide (ANP). The brain natriuretic peptide (BNP) and the C-type natriuretic peptide.

All of these peptides have a short half-life in the circulation. BNP is shown to improve the
hemodynamics and renal excretion of sodium in patients with congestive heart failure. Several analogues of ANP have also been derived. Vasopeptide inhibitors are a new class of drugs that inhibit metaloproteases. Thus, these drugs increase the levels of natriuretic peptides and decrease the formation of angiotensin II. Recently developed drugs include omapatrilat, sampartilat and fasidotrilat. These drugs enhance vasodilation, reduce vasoconstriction and increase sodium excretion.

VIII. ENDOTHELINS

The endothelins represent a series of peptides with potent vasoconstricting properties that were first isolated from aortic endothelial cells.

Three isoforms of endothelin are identified, namely ET₁, ET₂ and ET₃. Each endothelin is a 21 amino acid peptide. It is predominantly present in vascular endothelium. The endothelin are rapidly cleared from the circulation.

Endothelins produce a dose dependent vascular constriction in most vascular beds. Two receptor subtypes are found for endothelins. ETₐ and ETₐ. Endothelins have multiple actions such as vasoconstriction, proliferation and vasodilation which are mediated through the ETₐ and ETₐ receptors.

Inhibition of Endothelin

Both the selective (ETₐ and ETₐ) and non-selective antagonists for the actions of endothelins have been developed. An example of non-selective antagonists is Bosentan. It is active both orally and intravenously.
IX. VASOACTIVE INTESTINAL PEPTIDE

Vasoactive intestinal peptide (VIP) is a 28 amino acid peptide related to secretin and glucagons. VIP is present in the central and peripheral nerves where it functions as a neuromodulator. VIP produces marked vasodilation. Specific VIP receptor inhibitors are developed for research purposes only.

X. SUBSTANCE P

Substance P belongs to the tachykinin family which shares the carboxy terminal sequence Phe-X-gly-leu-meth. Other mediators of this family are neurokinin A and neurokinin B which are decapeptides. Substance P induced vasodilation by stimulating the release of nitric oxide. Several inhibitors of substance P have been developed.

XI. NEUROTENSIN

Neurotensin is a tridecapeptide and is synthesized in association with neuromodulin N (hexapeptide) in a big protein. In peripheral circulation it causes vasodilation, hypotension, vascular permeability, hyperglycemia and inhibition of gastric motility. Several analogues of neurotensin have also been synthesized.

XII. CALCITONIN GENE RELATED PEPTIDE

CGRP is a 37 amino acid containing peptide which is related to the calcitonin family of
peptidases. CGRP is present in large amounts in the thyroid gland. CGRP is also found in the
CNS and GI tract with substance P. Intravenous administration of CGRP can cause
hypotension and tachycardia.

XIII. ADRENOMODULIN

Adrenomodulin is a 52 amino acid and peptide which was first isolated from the adrorenal
medullary pheochromocytoma tissues. It is widely distributed and circulates in blood and
mediates hypothyroid responses. Circulating adrenomodulin levels are increased during
intensive exercise, patients with hypertension, renal failure and septic shock.

XIV. NEUROPEPTIDE Y

Neuropeptide Y is one of the most abundant neuropeptides in both the central and peripheral
nervous system. It consists of 36 amino acids. Besides a CNS effect it produces
vasoconstriction and mediates hypertensive responses. Selective neuropeptide Y antagonists
are now available and are useful the role of this peptide in hemodynamic disorders

XV. UROTENSIN

Urotensin is an undecapeptide with a conserved cyclic heptapeptide sequence. It is a potent
vasoconstrictor primarily acting on arterial beds. It is one of the most potent vasoconstrictors,
Urotensin levels are increased in patients with end stage heart failure. Specific antagonists of
urotensin are also available for research purposes only. These may be useful in patients with
end stage heart failure.
DIURETICS

Recommended Reading: Goodman & Gilman’s Manual of Pharmacology and Therapeutics Chapter 28; Basic & Clinical Pharmacology (Katzung, 10th edition) Chapter 15

KEY CONCEPTS AND LEARNING OBJECTIVES

1. To understand the importance of the organic anion transport system and protein binding to the renal action of diuretics.
2. To know the sites of action and the mechanism of action of the diuretics.
3. To know the effects of the different diuretics on electrolyte excretion patterns.
4. To understand the therapeutic applications of diuretics.
5. To know conditions and/or drug interactions that interfere with or contraindicate diuretic use.

DRUGS:

A. Carbonic Anhydrase Inhibitors (acetazolamide, dichlorphenamide, methazolamide, dorzolamide)

B. Osmotic Diuretics (mannitol)

C. Loop Diuretics (furosemide, bumetanide, torsemide, ethacrynic acid)

D. Thiazides (chlorthalidone, chlorothiazide, hydrochlorothiazide, metolazone, indapamide)

E. Potassium-sparing Diuretics (spironolactone, eplerenone, triamterene, amiloride)

F. ADH Antagonists (demeclocycline, lithium, tolvaptan, conivaptan, mozavaptan)
1. INTRODUCTION

A. History of Diuretics

- Diuretics effective for the treatment of edema have been available since the 16th century. Edema is defined as an excessive accumulation of fluid in tissues or cavities.
- Mercurochlorous chloride was known by Paracelsus to be diuretic.
- In 1930, Swartz discovered that the antimicrobial sulfanilamide could be used to treat edema in patients with congestive heart failure—effect attributed to an increase in renal excretion of Na⁺.
- Most modern diuretics were developed when side effects of antibacterial drugs were noted, which included changes in urine composition and output.
- Except for spironolactone, diuretics were developed empirically, without knowledge of specific transport pathways in the nephron.
- Diuretics are currently among the most commonly prescribed drugs in the U.S. They are useful for treatment of diverse clinical conditions ranging from kidney stones to heart failure, but they can also have an extremely wide range of adverse effects.

B. Function of the Kidney

- Kidneys control the extracellular fluid (ECF) volume by adjusting NaCl and H₂O excretion.
- Each day the kidney filters more than 22 moles of Na. To maintain NaCl balance approximately 3 lbs. of NaCl must be reabsorbed by the renal tubules on a daily basis.
- Edema can develop when NaCl intake exceeds NaCl excretion, as may occur in congestive heart failure or renal failure.
- Na⁺ reabsorption is driven primarily by Na⁺/K⁺ adenosine triphosphatase (ATPase) located at the basolateral (blood side) membrane of epithelial cells throughout the nephrons, the units of the kidney where reabsorption takes place.
- The Na⁺/K⁺ ATPase is an energy-requiring pump which exchanges 3 Na⁺ for 2 K⁺, thereby keeping a low Na⁺ concentration and a high K⁺ concentration within the cell.
- On the luminal side of the tubule epithelium, cell-specific pathways exist for passive movement of Na⁺ down its electrochemical gradient from lumen to cell. These pathways form the physiological basis of diuretic action.
C. Review of Renal Anatomy

The substance of the kidney may be divided into an outer cortex and an inner medulla. The medulla is arranged into pyramid-shaped units called medullary pyramids, which are separated by extensions of cortical tissue. The medullary pyramids convey ducts which converge to discharge urine at their apices; the apices of the pyramids are known as renal papillae. Calyces are funnel-shaped spaces into which one or more renal papillae project. The calyces converge to form the larger funnel-shaped renal pelvis from which the urine is conducted to the bladder by the ureter.

See Figure 16.2 From: B. Young, J.S. Lowe, A. Stevens, and J.H. Heath, Wheater's Functional Histology, 2006, p. 303

Blood enters the kidney via the renal artery which branches to the interlobar, arcuate, and interlobular arteries, and finally to an afferent arteriole, which supplies a glomerulus. A glomerulus is a tightly coiled network of capillaries within a capsule of flattened epithelial cells called Bowman’s capsule. Blood exits the glomerulus via an efferent arteriole.

Elements of plasma are filtered from the glomerular capillaries into Bowman’s space and the glomerular filtrate then passes into the renal tubule. The renal tubule is up to 55 mm long in humans and is lined by a single layer of epithelial cells. The primary function of the renal tubule is the selective reabsorption of water, inorganic ions, and other molecules from the glomerular filtrate.

See Figure 16.4 From: B. Young, J.S. Lowe, A. Stevens, and J.H. Heath, Wheater’s Functional Histology, 2006, p. 304
2. **DIURETIC PHARMACOLOGY**

A. **GENERAL CONSIDERATIONS**

- The most common therapeutic goal of diuretic use is to reduce edema by reducing the extracellular fluid (ECF) volume.
- For this to occur, NaCl output (excretion) MUST exceed NaCl intake (in diet).
- Diuretics primarily prevent Na\(^+\) entry into the renal tubule epithelial cell, thereby increasing the excretion of Na\(^+\).
- Once a diuretic enters the tubule fluid, the nephron site at which it acts determines its effect. In addition, the site of action also determines which electrolytes, other than Na\(^+\), will be affected.
- **Except for spironolactone, eplerenone, and ADH antagonists, diuretics generally exert their effects from the luminal side of the nephron.**
  - It is necessary for diuretics to get into the tubule fluid in order to be effective.
  - Mannitol does this by filtration at the glomerulus.
  - Most other diuretics are tightly protein bound and undergo little filtration. They reach the urine via secretion across the proximal tubule (organic acid or base secretory pathway).
Decreased renal blood flow or renal failure reduces diuretic effectiveness as do drugs which compete for the secretory pump (for example, probenecid and NSAIDs compete with acidic drugs and cimetidine competes with basic drugs).

- Tubule epithelial cells: a single cell layer between tubule lumen and interstitial space.
  - Na\(^+\) reabsorption is driven primarily by Na\(^+\)/K\(^+\) ATPase at the basolateral (blood side) membrane of epithelial cells throughout the nephron.
  - The Na\(^+\)/K\(^+\) ATPase is an energy-requiring pump which exchanges 3 Na\(^+\) for 2 K\(^+\), thereby keeping a low Na\(^+\) concentration and a high K\(^+\) concentration within the cell.
  - On the luminal side, cell-specific pathways exist for passive movement of Na\(^+\) down its electrochemical gradient from lumen to cell.
  - Reabsorption occurs from the tubule lumen, across the epithelium to the interstitial space, and finally into the adjacent blood vessels.
B. PROXIMAL CONVOLUTED TUBULE DIURETICS

- The proximal convoluted tubule (PCT) determines the rate of Na\(^+\) and H\(_2\)O delivery to the more distal portions of the nephron.

- A wide variety of transporters couple Na\(^+\) movement into the cell to the movement of amino acids, glucose, phosphate, and other solutes.

**Carbonic anhydrase (CA) inhibitors (acetazolamide, dichlorphenamide, methazolamide, dorzolamide)**

- Mechanism of Action: Bicarbonate is primarily reabsorbed in the proximal tubule. H\(^+\) secreted into the lumen can combine with filtered bicarbonate (HCO\(_3^-\)) to form H\(_2\)CO\(_3\) that is then converted to CO\(_2\) and H\(_2\)O (catalyzed by carbonic anhydrase). CO\(_2\) diffuses into the proximal tubule where it recombines with H\(_2\)O to form H\(_2\)CO\(_3\) (catalyzed by cytosolic carbonic anhydrase). H\(_2\)CO\(_3\) dissociates into H\(^+\) and HCO\(_3^-\). HCO\(_3^-\) exits the proximal tubule on the blood side, while H\(^+\) is again secreted into the tubule lumen. This results in HCO\(_3^-\) reabsorption. If CA activity is inhibited, HCO\(_3^-\) reabsorption is reduced and therefore much larger amounts of HCO\(_3^-\) are delivered to the distal nephron. Because Na\(^+\) is the most abundant cation present in proximal tubule fluid, it is the major cation which accompanies HCO\(_3^-\) out of the proximal tubule. In the distal nephron, Na\(^+\) is largely reabsorbed (unlike HCO\(_3^-\)) and is exchanged for K\(^+\).

Therefore **CA inhibitors primarily cause an increase in urinary HCO\(_3^-\), K\(^+\), and water excretion.** Effectiveness is reduced with continued therapy because plasma [HCO\(_3^-\)] falls, reducing the amount of HCO\(_3^-\) that appears in the urine.
Pharmacodynamics: Inhibits reabsorption of $\text{HCO}_3^-$ in the proximal convoluted tubule.

Pharmacokinetics: CA inhibitors are relatively weak diuretics. Well absorbed orally; effect begins within 30 minutes and is maximal within 2 hours; duration of effect is 12 hours. Renal secretion is via the organic acid transporter.

Adverse effects: **Metabolic acidosis** (with prolonged use, due to urinary loss of bicarbonate) and **hypokalemia** (with acute treatment, due to increased delivery of $\text{Na}^+$ and $\text{HCO}_3^-$ to the collecting tubule and the resulting increase in $\text{K}^+$ excretion). Calcium phosphate stones (due to alkalinization of tubular fluid). Drowsiness, paresthesias & hypersensitivity rxns.

Contraindications: Hepatic cirrhosis (increased urine pH reduces $\text{NH}_3$ secretion and thereby increases serum $\text{NH}_3$; this exacerbates hyperammonemia that can lead to encephalopathies).

Indications: Generally given for reasons other than diuresis. Because ocular fluid and CSF production are dependent on CA, inhibitors can be used to treat glaucoma or increased CNS pressure. CA inhibitors can be given in conditions where urine alkalinization is beneficial (certain drug overdoses). CA inhibitors can also be used to prevent altitude sickness -- the decrease in serum pH lowers hemoglobin’s affinity for oxygen, thereby increasing oxygen delivery to the tissues.

**Osmotic Diuretics (mannitol)**

- **Mechanism of Action:** Mannitol is a non-metabolizable osmotic diuretic and is filtered into the tubular space where it markedly increases tubular fluid osmolality. This change in osmotic gradient results in impaired reabsorption of fluid with a resultant increased excretion of water (some $\text{Na}^+$ accompanies). Acts primarily in segments of the nephron that are permeable to water (PCT, descending limb of Henle’s loop, and CT (in the presence of ADH)).

- **Pharmacodynamics:** IV administration causes expansion of intravascular volume; powerful diuretic effect once it reaches the kidney.

- **Pharmacokinetics:** **NOT** orally absorbed—must be injected IV to reach the kidneys. In pts with normal renal function $t_{1/2}$ is approx. 1.2 hr.

- **Adverse effects:** The major toxicity is due to increased plasma osmolality. Particularly with reduced glomerular filtration rate (in diseases such as congestive heart failure (CHF) or renal failure), mannitol is distributed in the extracellular fluid (ECF). This moves water out of cells into ECF potentially worsening heart failure. $\text{Na}^+$ follows water movement out of cells leading to hyponatremia.

- **Contraindications:** CHF, chronic renal failure, acute pulmonary edema.

- **Indications:** Maintain or increase urine volume; reduce intracranial pressure or intraocular pressure (ophthalmological procedures or glaucoma—requires intact blood-brain or blood-ocular barrier); promote renal excretion of toxic substances.
C. LOOP DIURETICS

Thick Ascending Limb:

- Impermeable to H₂O.
- Na⁺/K⁺/2Cl⁻ cotransporter on luminal membrane driven by the Na⁺ gradient (maintained by the basolateral Na⁺/K⁺ ATPase).
- Influx of K⁺ from both sides raises intracellular [K⁺].
- K⁺ diffuses back into the lumen creating (+) charge in lumen.
- The (+) charge improves paracellular diffusion of other positively charged ions like Ca²⁺ and Mg²⁺.

Loop Diuretics (e.g. furosemide):

- Mechanism of Action: All loop diuretics act primarily by blocking the Na⁺/K⁺/2Cl⁻ co-transporter in the apical membrane of the thick ascending limb of Henle’s loop.

- Pharmacodynamics: Because this is the same site responsible for concentrating extracellular fluid (ECF) and diluting urine, loop diuretics decrease these processes. The thick ascending limb is a major site of Ca²⁺ and Mg²⁺ reabsorption, processes that are dependent on normal Na⁺ and Cl⁻ reabsorption. Therefore, loop diuretics increase urinary water, Na⁺, K⁺, Ca²⁺, and Mg²⁺ excretion. The loop diuretics also cause dilation of the venous system and renal vasodilation, effects that may be mediated by prostaglandins.

- Pharmacokinetics: loop diuretics generally act within 20 min and t₁/₂ is approx. 1-3 hr. They are rapidly absorbed from the gut (renal secretion mechanism--organic acid transporter) and can be given i.v. This class of diuretics are the most efficacious available and can cause excretion of up to 20% of the filtered Na⁺. Rate of absorption is decreased in CHF.

- Adverse effects: All loop diuretics can cause predictable electrolyte imbalances, including hyponatremia, hypokalemia, Ca²⁺ and Mg²⁺ depletion, metabolic alkalosis and volume contraction. Ototoxicity (impaired hearing) and hypersensitivity reactions may also occur. Loop diuretics can also induce mild hyperglycemia (perhaps due to hypokalemic-induced inhibition of insulin release).
Contraindications: Caution in patients susceptible to hypokalemia. Adverse effects of digoxin are also more common in patients with low potassium levels (hypokalemia), since digoxin normally competes with K⁺ ions for the same binding site on the Na⁺/K⁺ ATPase pump.

Indications: Loop diuretics may be used for conditions refractory to less potent diuretics, or where a short acting diuretic is indicated. Specific indications include lowering blood pressure, reduction of acute pulmonary edema or edema associated with congestive heart failure, reduction of acute hypercalcemia or acute hyperkalemia.

Additional Loop Diuretics

- **BUMETANIDE**
  - About 40X more potent than furosemide
  - Shorter half-life than furosemide: ~ 1 hr
  - 50% metabolized by the liver

- **TORSEMIIDE**
  - Longer half-life than furosemide: ~ 3 hrs
  - Longer duration of action, too: ~ 5-8 hrs
  - Better oral absorption than furosemide
  - 80% metabolized by the liver

- **ETHACRYNIC ACID**
  - Last resort; used only when others exhibit hypersensitivity
  - No CA inhibition
  - Nephrotoxic and ototoxic
D. DISTAL CONVOLUTED TUBULE DIURETICS

Distal Convoluted Tubule:

- Impermeable to H₂O.
- The Na⁺ gradient drives the Na⁺-Cl⁻ cotransporter.
- Ca²⁺ reabsorption is controlled by parathyroid hormone (PTH), which regulates production of Ca²⁺ channels inserted in the luminal membrane.
- Intracellular Ca²⁺ is pumped out the basolateral border by:
  - Na⁺/Ca²⁺ countertransport; high capacity exchanger.
  - The Ca²⁺ ATPase pump; low capacity pump.

Thiazides (hydrochlorothiazide) and thiazide-like drugs (metolazone, indapamide):

- Mechanism of Action: This is the most commonly prescribed class of diuretics. They inhibit Na⁺ and Cl⁻ co-transport in the cortical thick ascending limb and early distal tubule.

- Pharmacodynamics: They have a milder diuretic action than do the loop diuretics because this nephron site reabsorbs less Na⁺ than the thick ascending limb. In addition, if glomerular filtration rate falls, less fluid reaches the distal tubule and thiazides may only have a small impact on Na⁺ and water excretion. These compounds then are relatively ineffective in renal insufficiency. Thiazide diuretics tend to increase Ca²⁺ reabsorption.

- Pharmacokinetics: All are well absorbed from the gut. Onset of action is within approx. 1 hr; effects can be long lasting but vary with the drug used (6-48 hr). Bioavailability is decreased in patients with renal disease, hepatic disease, and CHF.

- Adverse effects: Hyponatremia & hypokalemia, dehydration, metabolic alkalosis, hyperuricemia, hyperglycemia*, hyperlipidemia*, weakness, fatigue, paresthesias & hypersensitivity reactions.

*Hyperglycemia has been linked to diuretic-induced hypokalemia. K⁺ deficiency inhibits insulin secretion by pancreatic β cells, although diuretic-induced changes in glucose metabolism are not conclusively related to altered K⁺ homeostasis—impaired glucose tolerance has been observed even when low dose thiazide diuretic therapy is combined with a K⁺-sparing diuretic. Hyperglycemia with diuretic therapy may be exacerbated by an increase in sympathetic nervous system activity, which also decreases peripheral glucose utilization.
Hyperglycemia tends to increase with increasing doses of thiazide diuretics, is less common with loop diuretics, and is generally reversible on termination of the diuretic therapy. Short-term thiazide diuretic therapy can dose-dependently elevate serum total cholesterol levels, modestly increase low-density lipoprotein cholesterol levels and raise triglyceride levels, while minimally changing high-density lipoprotein cholesterol concentrations. The mechanisms of diuretic-induced dyslipidemia remain uncertain, but have been related to worsened insulin sensitivity and/or reflex activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system in response to volume depletion. Supporting this latter notion is the fact that doses of diuretics which are low enough so as not to activate the sympathetic nervous system, do not increase lipid values; in contrast, higher diuretic doses are more apt to be associated with reflex sympathetic nervous system activation and dyslipidemia.

- **Contraindications:** Caution in patients that are susceptible to hypokalemia.

- **Indications:** Hypertension treatment. They can be used in CHF, nephrotic syndrome and other Na⁺-retaining states. Thiazides can also be used to reduce tubular Ca²⁺ concentration to prevent kidney stones.

### Additional thiazide or thiazide-like diuretics:

<table>
<thead>
<tr>
<th>Diuretic</th>
<th>Relative Potency</th>
<th>Half-life</th>
<th>Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHLORETIAZIDE</td>
<td>1/10th of HCTZ</td>
<td>1.5 hrs</td>
<td></td>
</tr>
<tr>
<td>METOLAZONE</td>
<td>10X more potent</td>
<td>4-5 hrs</td>
<td></td>
</tr>
<tr>
<td>INDAPAMIDE</td>
<td>20X more potent</td>
<td>10-22 hrs</td>
<td>Metabolized</td>
</tr>
<tr>
<td>CHLORTHALIDONE</td>
<td>Same potency</td>
<td></td>
<td></td>
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</tbody>
</table>

- Metolazone is a quinazoline diuretic that has the same sites of action and side effects as the thiazides. **Metolazone is the strongest inhibitor of Na⁺ and water reabsorption of the thiazide and thiazide-like diuretics.** It is one of the few distal nephron diuretics that can be efficacious in patients with severe renal insufficiency and may be given in combination with a loop diuretic in these patients if diuresis with either agent alone is inadequate.
E. COLLECTING TUBULE DIURETICS

**Principal Cells:**
- The Na\(^+\) gradient drives influx of Na\(^+\) through its channel.
- The efflux of K\(^+\) follows its concentration gradient.
- Na\(^+\) absorption exceeds K\(^+\) secretion causing net (–) charge in the tubular lumen.
- Net (–) charge repels Cl\(^–\) and attracts K\(^+\) into lumen.
- Aldosterone increases expression of Na\(^+\)/K\(^+\) ATPase & channels
- ADH regulates water channels and water reabsorption.

**Intercalated Cells:**
- Luminal membrane
  - Proton pumps actively transport H\(^+\) into the lumen (expression is increased by aldosterone).
- Basolateral membrane
  - HCO\(_3\)\(^–\)/Cl\(^–\) passive countertransporter

THE TRANSPORT PROPERTIES OF THE COLLECTING TUBULE ACCOUNT FOR SOME ADVERSE EFFECTS OF DIURETIC DRUGS THAT EXERT DIRECT EFFECTS AT MORE PROXIMAL SEGMENTS OF THE NEPHRON:

**Hypokalemic effects of CA inhibitors:**
1. Increased HCO\(_3\)\(^–\) in tubule leads to increased lumen negative potential.
2. The lumen-negative potential enhances K\(^+\) efflux from the principal cells.

**Hypokalemic effects of Loop & Thiazide diuretics:**
1. Increased Na\(^+\) and Cl\(^–\) in tubule leads to increased lumen negative potential.
2. The lumen-negative potential enhances K\(^+\) efflux from the principal cells.

**Metabolic alkalosis with Loop & Thiazide diuretics:**
1. Increased Na\(^+\) and Cl\(^–\) in tubule leads to increased lumen negative potential.
2. The lumen-negative potential enhances H\(^+\) efflux from the intercalated cells.
Potassium sparing diuretics

These agents are often given to avoid the hypokalemia that accompanies the agents previously described. They should never be given in the setting of hyperkalemia or in patients on drugs or with disease states likely to cause hyperkalemia. The latter include diabetes mellitus, multiple myeloma, tubulointerstitial renal disease, and renal insufficiency. Potassium supplements and ACE inhibitors/ARBs can cause hyperkalemia and should not be combined with K+ sparing diuretics.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors/ARBs</td>
<td>Prevent angiotensin-II (AngII) -induced aldosterone release</td>
</tr>
<tr>
<td>Renin inhibitors</td>
<td>Prevent AngII production &amp; its stimulation of aldosterone release</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Block prostaglandin-induced renin secretion/aldosterone release</td>
</tr>
<tr>
<td>Digitalis overdose</td>
<td>Inhibits the Na+/K+-ATPases of the renal tubule epithelial cells</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>A cationic antibiotic agent, trimethoprim blocks Na+ channels in the apical membrane of the principal cells of the collecting tubules</td>
</tr>
<tr>
<td>Pentamidine</td>
<td>Same mechanism as trimethoprim—blocks distal potassium secretion into the collecting ducts</td>
</tr>
<tr>
<td>Heparin</td>
<td>Decreases aldosterone release by reducing both the number and affinity of the AngII receptors in the zona glomerulosa</td>
</tr>
<tr>
<td>Salt substitutes</td>
<td>Contain potassium—absorbed into circulation to directly elevate serum potassium levels</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>Activates AChR in neuromuscular junction moves potassium from intracellular to extracellular fluid</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Multifactorial, including hyporenin-hypoaldosteronism and interference with aldosterone action in the principal cells of the collecting tubules</td>
</tr>
<tr>
<td>β blockers</td>
<td>Prevent sympathetic activation of renin release</td>
</tr>
</tbody>
</table>

Spironolactone and eplerenone

- **Mechanism of Action**: Spironolactone & eplerenone are competitive antagonists of aldosterone binding to the cytosolic mineralocorticoid receptor in the principal cells of the collecting tubule — they block the actions of aldosterone (increased Na+ and H2O retention).

- **Pharmacodynamics**: Block aldosterone-stimulated Na+ reabsorption and K+ and H+ secretion in the late distal convoluted tubule and collecting tubule. This results in mild diuresis due to decreased Na+ reabsorption. Also reduce aldosterone-stimulated ammoniagenesis throughout the nephron.

- **Pharmacokinetics**: Given orally, spironolactone takes up to 2 days to be effective with a t1/2 approx. 20 hr. Undergoes substantial hepatic metabolism and acts through the blood side of the tubule. A weak diuretic because its site of action reabsorbs only modest amounts of Na+.

- **Adverse effects**: Major side effects are hyperkalemia and metabolic acidosis. Spironolactone can cause gynecomastia or amenorrhea (mildly enhances estrogen levels/activity) due to cross-reactivity with androgen receptors. Eplerenone is considerably more expensive than spironolactone, but it does not inhibit testosterone binding and therefore it does not induce gynecomastia or other related anti-androgenic side effects.

- **Contraindications**: Do not use in setting of hyperkalemia.
Indications: Greatest efficacy in patients with high plasma levels of aldosterone (e.g. hyperaldosteronism due to adrenal tumor or hyperplasia). Also useful in patients with secondarily elevated aldosterone, e.g. hepatic cirrhosis, CHF. May be effective in treating hypertension, often in combination with loop or thiazide diuretics.

Amiloride and triamterene

Mechanism of Action: Both agents block Na⁺ channels in the apical membranes of the late distal tubule and collecting tubule epithelial cells.

Pharmacodynamics: Because K⁺ and H⁺ secretion in this nephron segment are driven by the electrochemical gradient generated by Na⁺ reabsorption, K⁺ and H⁺ transport into the urine is reduced.

Pharmacokinetics: Both agents are effective orally. Secreted into PCT by organic base transporter. T₁/₂ of amiloride and triamterene are 21 and 4 hr, respectively. These compounds are primarily eliminated by the kidney. Relatively weak diuretics.

Toxicity: The most severe side effect is hyperkalemia, but metabolic acidosis can also occur. Nausea and vomiting are the most frequent side effects while hyponatremia may be problematic in the elderly.

Indications: Usually given together with another diuretic, often a thiazide or loop diuretic. This combination can result in normal K⁺ excretion (hypokalemic effect of thiazide or loop balances hyperkalemic effect of amiloride or triamterene).

Contraindications: similar to Spironolactone -- **Do not use in setting of hyperkalemia.**

ADH Antagonists: Demeclocycline, Lithium, Tolvaptan, Conivaptan, Mozavaptan

Demeclocycline: tetracycline antibiotic – nephrotoxic

Lithium: Psych drug used for treatment of mania – nephrotoxic
  * Both demeclocycline and lithium inhibit ADH-stimulated water reabsorption in the collecting tubule—poorly characterized mechanisms may include reduction of either cyclic AMP formation or insertion of aquaporin 2 water channels in the luminal membrane.

V₂ vasopressin receptor antagonists: tolvaptan, conivaptan, mozavaptan, (lixivaptan, satavaptan, and OPC-31260)
  * Induce increased, dose-dependent production of dilute urine.
  * Tolvaptan is effective orally and has a half-life of 6 to 8 hours.
  * Conivaptan: combined V₁a and V₂ receptor antagonist: intravenous formulation of conivaptan is available for the treatment of euvoelemic hyponatremia.
  * Potential adverse effects: hyernatremia, thirst, dry mouth, hypotension, dizziness.
  * Indications: SIADH; euvoelemic or hypervolemic hyponatremia; congestive heart failure.
### CHANGES IN URINARY ELECTROLYTE PATTERNS IN RESPONSE TO DIURETIC DRUGS

<table>
<thead>
<tr>
<th>Agent</th>
<th>NaCl</th>
<th>NaHCO₃</th>
<th>K⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbonic anhydride inhibitors</td>
<td>++</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Loop agents</td>
<td>+++++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Thiazides</td>
<td>++</td>
<td>±</td>
<td>+</td>
</tr>
<tr>
<td>Loop agents plus thiazides</td>
<td>+++++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>K⁺-sparing agents</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Some diuretic formulations with trade names:

- Acetazolamide (Daimox)
- Amiloride and Hydrochlorothiazide (Moduretic)
- Bumetanide (Bumex)
- Conivaptan (Vaprisol)
- Chlorothalidone (Hygroton, Thalitone)
- Chlorothiazide (Diuril)
- Dichlorphenamide (Daranide)
- Eplerenone (Inspra)
- Ethacrynic acid (Edecrin)
- Furosemide (Lasix)
- Hydrochlorothiazide (Esidrix, Ezide, Hydrodiuril, Microzide, Oretic)
- Indapamide (Lozol)
- Mannitol (Osmitrol)
- Metolazone (Mykrox, Zaroxolyn)
- Methazolamide (GlaucTabs)
- Spironolactone (Aldactone)
- Torsemide Oral (Demadex Oral)
- Triamterene (Dyrenium, Midamor)
- Triamterene and Hydrochlorothiazide (Dyazide, Maxzide)
3. **DIURETIC THERAPY**

A. Edema (excessive accumulation of fluid in the interstitial space)

Capillary Filtration: movement of water across the capillary wall is determined by:

i. Hydrostatic pressure gradient between capillary & interstitial space ($P_{cap} - P_{is}$)

ii. Oncotic pressure ($\pi_{is} - \pi_{cap}$)

\[
\pi = \sigma RT(C_{cap} - C_{is})
\]

Where

$\sigma$ = Reflection coefficient

$R$ = Gas constant

$T$ = Absolute temperature

$C_i$ & $C_o$ = Solute concentrations (i.e. [albumin]) in capillary & interstitial space

iii. Capillary permeability

Diuretics will tend to decrease capillary hydrostatic pressure and increase plasma oncotic pressure to favor absorption over filtration.
B. Kidney Diseases

- Most cause retention of salt & H₂O.
- Renal insufficiency reduces efficacy of most diuretics because of reduced glomerular filtration (cannot sustain naturiesis).
- Diabetic nephropathy—often associated with hyperkalemia—may be treated with thiazides or loop diuretics.

C. Hepatic Cirrhosis

- Portal hypertension, hypoalbuminemia
- Leads to a reduction in plasma volume.
- Activates renin-angiotensin-aldosterone axis.
- $2\text{°}$ hyperaldosteronism results in Na⁺ retention in kidney.
- Associated with ascites and peripheral edema.
- Spironolactone, eplerenone are effective.
- May be somewhat resistant to loop diuretics—limited by hypokalemia.

D. Congestive Heart Failure

- The failure of the heart to effectively pump blood leads to poor renal perfusion, which causes the kidneys to release renin. Plasma renin-angiotensin rises. Angiotensin stimulates aldosterone release, which causes Na⁺ retention (and edema).
- If aldosterone is high and if distal tubular sodium supply is also high, as may occur with thiazide or loop diuretic therapy, kaliuresis will be sustained.
- K⁺ depletion (hypokalemia) can lead to ventricular arrhythmias and impaired cardiac performance (significantly increased risk of coronary events, stroke, and sudden death).
- Spironolactone may be an effective adjunct or alternative diuretic to prevent hypokalemia-induced cardiac dysfunction.
- ACE inhibitors may be combined with thiazide or loop diuretics, but should not be combined with spironolactone.
Heart Failure

- Left heart failure (acute):
  - ↑hydrostatic pressure in lung capillaries.
  - Pulmonary edema.
  - Life-threatening—requires rapid, aggressive therapy such as i.v. loop diuretic.

- Right heart failure (chronic):
  - Redistribution of extracellular fluid volume from arterial to venous circulation.
  - Venous, hepatic, splenic congestion, & peripheral tissue edema.
  - Oral loop diuretics often are effective if carefully managed.

E. Hyponatremia

Hyponatremia, defined as a serum sodium concentration ([Na⁺]) less than 136 mEq/l, is the most common electrolyte disorder in hospitalized patients (Kennedy et al. Br Med J 2:1251-1253, 1978).

Hyponatremia may be associated with:

a) Hypovolemia: causes include diarrhea, vomiting, excessive sweating; infusion of 0.9% saline is usually an effective treatment.

b) Euvolemia: causes include Syndrome of Inappropriate ADH secretion (SIADH), hypothyroidism, adrenal insufficiency; saline infusion may be ineffective or worsen hyponatremia.

c) Hypervolemia: causes include congestive heart failure, cirrhotic liver disease, nephrotic syndrome; saline infusion may not improve hyponatremia, and will likely worsen edema.

In May 2009, tolvaptan (Samsca; Otsuka), a selective vasopressin V₂ receptor antagonist, was approved by the US FDA for the treatment of clinically significant hypervolemic and euvolemic hyponatraemia (serum sodium concentration <125 mmol per litre or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, cirrhosis and SIADH. Conivaptan (Vaprisol; Astellas), a vasopressin V₁a/V₂ receptor antagonist is also approved in the United States for euvolemic and hypervolemic hyponatraemia. (Ghali et al., Nature Reviews Drug Discovery 8, 611-612 (August 2009)). Mozavaptan, another selective vasopressin V₂ receptor antagonist, was approved in October 2006 for hyponatremia caused by SIADH due to ADH producing tumors.
F. Hypertension

SEVENTH REPORT OF THE JOINT NATIONAL COMMITTEE ON PREVENTION, DETECTION, EVALUATION, AND TREATMENT OF HIGH BLOOD PRESSURE.


- For uncomplicated hypertension, a thiazide diuretic should be used in drug treatment for most, either alone or combined with drugs from other classes.

- Two or more antihypertensive medications will be required to achieve goal BP (140/90 mm Hg, or 130/80 mm Hg) for patients with diabetes and chronic kidney disease.

- For patients whose BP is more than 20 mm Hg above the systolic BP goal or more than 10 mm Hg above the diastolic BP goal, initiation of therapy using two agents, one of which usually will be a thiazide diuretic, should be considered.

G. Nephrogenic Diabetes Insipidus

- Characterized by a loss of effect of ADH on the kidney.

- Thiazide diuretics first reported to be an effective therapy in 1959 by Crawford & Kennedy (Nature 183 : 891–892, 1959).

H. Nephrolithiasis

- ⅔ of renal stones contain calcium phosphate or calcium oxalate.

- Hypercalciuria may be treated with thiazide diuretics and ↓NaCl intake.

I. Hypercalcemia

- Potentially life-threatening.

- Can be treated with i.v. loop diuretics and saline infusion.
4. **DIURETIC RESISTANCE**

Edema refractory to a given diuretic drug. Causes include:

- NSAID co-administration (block prostaglandin-induced increase in RBF, increase expression of Na⁺/K⁺/2Cl⁻ co-transport in TAL, compete for organic acid transporter in PCT).
- Congestive heart failure (CHF) or chronic renal failure (reduced RBF decreases delivery of diuretics to tubule; build-up of organic acids competes for secretory transport into tubule).
- Nephrotic syndrome (protein in tubule binds to diuretic drugs and limits their actions).
- Hepatic cirrhosis, CHF, renal failure (decreased GFR results in increased PCT absorption of Na⁺; decreased delivery of Na⁺ to the distal nephron decreases effect of drugs that target Na⁺ transporters or channels in these segments).

Therapeutic strategies may include increasing dose, decreasing dosing interval, or adding another drug with a different site of action (i.e. combination therapy).

5. **COMBINATION THERAPY**

- Loop + Thiazide Diuretics:
  - only in patients refractory to one or the other.
  - may be too robust and lead to K⁺ wasting.

- K⁺-sparing + Loop or Thiazide:
  - prevents hypokalemia.
  - avoid in renal insufficiency.

6. **LIST OF DRUGS COVERED IN LECTURE:**

   **A. Carbonic Anhydrase Inhibitors** (acetazolamide, dichlorphenamidine, methazolamide, dorzolamide)

   **B. Osmotic Diuretics** (mannitol)

   **C. Loop Diuretics** (furosemide, bumetanide, torsemide, ethacrynic acid)

   **D. Thiazides** (chlorthalidone, chlorothiazide, hydrochlorothiazide, metolazone, indapamide)

   **E. Potassium-sparing Diuretics** (spironolactone, eplerenone, triamterene, amiloride)

   **F. ADH Antagonists** (demeclocycline, lithium, tolvaptan, conivaptan, mozavaptan)
<table>
<thead>
<tr>
<th>Diuretic Class (site and mechanism of action)</th>
<th>Main Indications</th>
<th>Other Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carbonic Anhydrase Inhibitors</strong>&lt;br&gt;Acetazolamide, dorzolamide, methazolamide, and dichlorphenamide inhibit CA in luminal membrane of <strong>proximal tubule</strong>, reducing proximal HCO₃⁻ reabsorption.</td>
<td>To reduce intraocular pressure in glaucoma. To lower [HCO₃⁻]ₚ in &quot;mountain sickness&quot;. To raise urine pH in cystinuria.</td>
<td>Hypokalemic periodic paralysis.*&lt;br&gt;Adjunctive therapy in epilepsy.&lt;br&gt;Solid hypoxic tumors?</td>
</tr>
<tr>
<td><strong>Osmotic Diuretics</strong>&lt;br&gt;Freely filterable, non-reabsorbable osmotic agents like mannitol, glycerol, and urea act primarily on the proximal tubule to reduce the reabsorption of H₂O and solutes including NaCl.</td>
<td>To treat or prevent Acute Renal Failure (ARF).&lt;br&gt;To reduce intra-cranial or intra-ocular pressure.&lt;br&gt;To enhance urinary excretion of chemical toxins.</td>
<td></td>
</tr>
<tr>
<td><strong>Loop Diuretics</strong>&lt;br&gt;Furosemide, bumetanide, torsemide, and ethacrynic acid inhibit the Na⁺/K⁺/2Cl⁻ cotransport system in the thick ascending limb of Henle's loop (ALH).</td>
<td>Acute Pulmonary Edema.&lt;br&gt;Hypertension.&lt;br&gt;Congestive heart failure (CHF)—in the presence of renal insufficiency or for immediate effect.&lt;br&gt;ARF, CRF, ascites, and nephrotic syndrome</td>
<td>Hypercalcemia.</td>
</tr>
<tr>
<td><strong>Thiazide</strong>&lt;br&gt;Chlorothiazide, hydrochlorothiazide, chlorthalidone, metolazone, indapamide inhibit NaCl cotransport in early distal convoluted tubule (DCT).</td>
<td>Hypertension.&lt;br&gt;Edema due to CHF, hepatic cirrhosis, renal disease.&lt;br&gt;Idiopathic Hypercalciuria (renal calculi).</td>
<td>Nephrogenic Diabetes Insipidus (prevent further urine dilution from taking place in the DCT).</td>
</tr>
<tr>
<td><strong>K⁺-Sparing Diuretics</strong>&lt;br&gt;Spirofolactone &amp; eplerenone competitively block the actions of aldosterone on the collecting tubules. Amiloride and triamterene reduce Na⁺ entry across the luminal membrane of the principal cells of the collecting tubules.</td>
<td>Chronic liver disease: to treat secondary hyperaldosteronism due to hepatic cirrhosis complicated by ascites (spironolactone, eplerenone). To prevent the hypokalemic effects of other diuretics.</td>
<td>Primary hyperaldosteronism (Conn's syndrome)—spironolactone, eplerenone.</td>
</tr>
<tr>
<td><strong>ADH Antagonists</strong>&lt;br&gt;Doxycycline, lithium, tolvaptan, conivaptan, moxavaptan, etc. prevent ADH-induced water reabsorption in the principal cells of the collecting tubule.</td>
<td>SIADH&lt;br&gt;Euvolemic or hypervolemic hyponatremia.</td>
<td>Congestive Heart Failure (CHF).</td>
</tr>
</tbody>
</table>

*may require dietary potassium supplements to prevent potassium wasting.
# Main Side Effects of Diuretics

## Carbonic Anhydrase Inhibitors
Metabolic acidosis (due to HCO$_3^-$ depletion with prolonged treatment), hypokalemia (acute effect)
Drowsiness, fatigue, CNS depression, and paresthesia.

## Osmotic Diuretics
Acute expansion of ECF volume and increased risk of pulmonary edema, hyponatremia (with impaired renal function); hypernatremia (prolonged use with normal GFR). Nausea and vomiting; headache.

## Loop Diuretics
Hypokalemia; hypomagnesemia; hyponatremia; hypovolemia; hyperuricemia*
Metabolic alkalosis
Ototoxicity and diarrhea (mainly with ethacrynic acid)

## Thiazide
Hypokalemia; hyponatremia; hypovolemia;
Hyperuricemia due to enhanced urate reabsorption* and hypercalcemia due to enhanced Ca$^{2+}$ reabsorption
Metabolic alkalosis
Hyperglycemia (insulin resistance); hyperlipidemia.
Hypersensitivity (fever, rash, purpura, anaphylaxis); interstitial nephritis.

## K$^+$ - Sparing Diuretics
Spironolactone: hyperkalemia, gynecomastia, hirsutism; menstrual irregularities; testicular atrophy (with prolonged use).
Amiloride: hyperkalemia, glucose intolerance in diabetic pts.
Triamterene: hyperkalemia; megaloblastic anemia in pts with liver cirrhosis.

## ADH Antagonists
Lithium, doxycycline: nephrotoxic
Tolvaptan, conivaptan, mozavaptan: hypernatremia, thirst, dry mouth, hypotension, dizziness

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*: The proximal tubule is the major site of uric acid handling; both reabsorption and secretion occur in this segment, with the net effect being the reabsorption of most of the filtered uric acid. Thiazide and loop diuretics decrease uric acid excretion by increasing net uric acid reabsorption; this can occur either by enhanced uric acid reabsorption or by reduced uric acid secretion—or a combination of both effects. **Hyperuricemia can cause gout.**
<table>
<thead>
<tr>
<th>Interacting Drugs</th>
<th>Potential Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE inhibitors /</strong></td>
<td></td>
</tr>
<tr>
<td>K⁺ - sparing diuretics</td>
<td>⇒ increased hyperkalemia ⇒ cardiac arrhythmias (monitor serum K⁺ closely)</td>
</tr>
<tr>
<td><strong>Aminoglycosides /</strong></td>
<td></td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>⇒ ototoxicity and nephrotoxicity. (monitor hearing and serum creatinine closely)</td>
</tr>
<tr>
<td><strong>Anticoagulants /</strong></td>
<td></td>
</tr>
<tr>
<td>Thiazide &amp; Loop diuretics</td>
<td>⇒ increased anti-coagulant activity with loop diuretics; decreased anti-coagulant activity with thiazide</td>
</tr>
<tr>
<td>diuretics</td>
<td></td>
</tr>
<tr>
<td><strong>β- Blockers /</strong></td>
<td></td>
</tr>
<tr>
<td>Thiazide &amp; Loop diuretics</td>
<td>⇒ hyperglycemia, hyperlipidemia, hyperuricemia.</td>
</tr>
<tr>
<td></td>
<td>⇒ increased plasma levels of propranolol</td>
</tr>
<tr>
<td><strong>Carbamazepine or chlorpropamide /</strong></td>
<td></td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>⇒ increased risk of hyponatremia (monitor Na⁺)</td>
</tr>
<tr>
<td><strong>Digoxin /</strong></td>
<td></td>
</tr>
<tr>
<td>Thiazide &amp; Loop diuretics</td>
<td>⇒ hypokalemia ⇒ increased digoxin binding &amp; toxicity (monitor K⁺ and cardiac function)</td>
</tr>
<tr>
<td><strong>NSAIDs /</strong></td>
<td></td>
</tr>
<tr>
<td>Thiazide &amp; Loop diuretics</td>
<td>⇒ reduced diuretic effect, increased risk of salicylate toxicity with high doses of salicylates (thiazide &amp; loop d.).</td>
</tr>
<tr>
<td>K⁺ sparing diuretics</td>
<td>⇒ increased risk of hyperkalemia with K⁺ sparing diuretics</td>
</tr>
<tr>
<td><strong>Quinidine /</strong></td>
<td></td>
</tr>
<tr>
<td>Loop &amp; thiazide diuretics</td>
<td>⇒ polymorphic ventricular tachycardia (<em>torsade de pointes</em>)</td>
</tr>
<tr>
<td><strong>Sulfonylureas /</strong></td>
<td></td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>⇒ hyperglycemia</td>
</tr>
<tr>
<td><strong>Steroids /</strong></td>
<td></td>
</tr>
<tr>
<td>Thiazide &amp; Loop diuretics</td>
<td>⇒ increased risk of hypokalemia (monitor serum K⁺ closely)</td>
</tr>
</tbody>
</table>
REVIEW QUESTIONS:

1. How do diuretic drugs reach their sites of action?

2. Why does acetazolamide produce an alkaline urine (pH = 8.2)?

3. Why do thiazide and loop diuretics cause potassium loss?

4. How do thiazide and loop diuretics affect calcium excretion?

5. How do carbonic anhydrase inhibitors cause a diuresis?

6. Which class of diuretics would cause increased excretion of magnesium?

7. What is the mechanism of action of amiloride?

8. What class of diuretics interferes with sodium reabsorption in the proximal tubule?

9. How would the combination of a loop diuretic and thiazide diuretic influence sodium excretion?

10. What are the effects of spironolactone on urinary potassium excretion?

11. What is the most common reason for diuretic use?

12. What are the most common adverse effects associated with diuretic therapy?

13. Which diuretic drugs would be indicated to reduce edema/ascites in patients with hepatic cirrhosis?

14. Which thiazide-like diuretic is most likely to be efficacious in patients with severe renal insufficiency?
KEY CONCEPTS AND LEARNING OBJECTIVES

A. To briefly review the pathophysiological basis for the development of angina pectoris and other ischemic coronary syndromes.
B. To examine the mechanisms by which nitrates, beta-blockers, calcium-channel blockers and ranolazine relieve angina.
C. To briefly discuss nonpharmacological approaches to the relief of angina and other ischemic coronary syndromes.

LIST OF IMPORTANT DRUGS

Organic Nitrates: Nitroglycerin
Isosorbide dinitrate

Calcium Channel Blockers: Nifedipine
Nicardipine
Amlodipine
Verapamil
Diltiazem

Beta Receptor Antagonists: Propranolol
Nadolol
Atenolol
Metoprolol
Carvedilol

pFOX Inhibitor Ranolazine
ANTI-ANGINAL DRUGS

I. MYOCARDIAL ENERGY BALANCE
   A. Oxygen Supply and Oxygen Demand are tightly coupled
   B. Oxygen Supply to Myocardium = Myocardial O2 delivery + Myocardial O2 extraction
      1. Myocardial O2 extraction is nearly maximal at rest (75% of available O2)
      2. Any increase in O2 supply must occur by increase in O2 delivery (increased coronary blood flow)
   C. Determinants of Coronary Blood Flow
      1. Diastolic Perfusion Pressure (Aortic Diastolic Pressure - End-diastolic Pressure)
      2. Coronary Vascular Resistance (extrinsic compression and intrinsic regulation)
   D. Regulation of Coronary Vascular Resistance
      1. Mechanical Compression: Majority of blood flow occurs during diastole-compression of intra-myocardial blood vessels during systole
      2. Metabolic Regulation - increased myocardial work ⇒ increased myocardial blood flow
         a) Adenosine
         b) O2
         c) CO2
         d) K+
         e) Lactate
         f) NO2
      3. Neural Regulation
         a) Sympathetic stimulation causes vasoconstriction, but
         b) Sympathetic stimulation also causes increased myocardial work, with increased production of metabolites, and therefore,
         c) net effect is VASODILATION

II. DETERMINANTS OF MYOCARDIAL OXYGEN CONSUMPTION (DEMAND)
   A. Heart Rate
   B. Myocardial Wall Stress - LaPlace’s Law: \( \sigma = \text{Pressure} \times \text{RADIUS} / 2 \times \text{thickness} \)
      1. Pressure is the INTRAVENTRICULAR PRESSURE (pressure inside the chamber)
      2. Ventricular Volume (Preload) – affects diastolic wall stress
      3. Impedence to ejection (Afterload) – affects systolic wall stress
   C. Contractility (Force of Contraction)

III. PATHOPHYSIOLOGY OF MYOCARDIAL ISCHEMIA
   A. Myocardial Ischemia occurs when O2 Demand EXCEEDS O2 Supply
      1. Increased Myocardial O2 Demand in Setting of Fixed Coronary Artery Obstruction
         a) Exercise
         b) Sympathetic Stimulation (emotional stress, fear, drugs)
         c) Arrhythmias (especially tachycardias)
2. Acute Reduction in Coronary Blood Flow
   a) Decreased Perfusion Pressure (hypotension)
   b) Vasospasm
   c) Thrombus/Emboli
B. Hypoxia vs. Ischemia (reduced O2 vs. reduced flow/increased demand)
C. Cardiac Functional Impairment Caused by Ischemia
   1. Decreased LV Compliance (increased myocardial stiffness – Increased LVEDP)
   2. Decreased force of contraction - Regional wall motion abnormalities
   3. Decreased C.O. in severe or global ischemia
   4. Electrical instability (ventricular arrhythmias)
   5. Cell Death
D. Ischemia leads to infarction (cell death) if there is an absolute reduction of flow for a sufficient period of time
   1. No flow \(\rightarrow\) Irreversible injury in 30-45 min
   2. Marginal flow \(\rightarrow\) Infarction may not occur for several hours
   3. Coronary Collateral Vessels - some degree of protection from ischemia
E. Common Causes of Myocardial Ischemia
   1. Atherosclerotic Coronary Artery Disease
   2. Severe Aortic Stenosis
   3. Severe Hypertension
   4. Severe Anemia
   5. Congenital Heart Disease

IV. ANGINA PECTORIS – Clinical Manifestation of Myocardial Ischemia
A. Anginal Syndromes – Clinical Presentations
   1. Exertional Angina
   2. Unstable (Crescendo Angina)
   3. “Silent Ischemia”
   4. Variant Angina
B. Acute Myocardial Infarction

V. THERAPY OF MYOCARDIAL ISCHEMIA
A. Drug Therapy
   1. Organic Nitrates
   2. Calcium Channel Blockers
   3. Beta Adrenergic Receptor Blockers
   4. Ranolazine
B. Coronary Revascularization
   1. Percutaneous Coronary Interventions (PCI) – Balloon angioplasty, stenting, atherectomy, etc.
   2. Coronary Artery Bypass Grafting (CABG)
VI. ORGANIC NITRATE THERAPY (Rx) for EXERTIONAL and VASOSPASTIC ANGINA

A. Mechanism of Action in Smooth Muscle
1. Organic Nitrates (R-O-NO₂) combine with cysteine residues (R-SH) in vessel wall to form Nitrosothiols that release Nitric Oxide (NO)
2. NO directly stimulates Guanylyl Cyclase in vascular smooth muscle to produce cGMP
3. cGMP → activates a cGMP-dependent phosphatase
4. Phosphatase de-phosphorylates myosin light chain leading to smooth muscle relaxation
5. Organic nitrate-induced vasodilatation is ENDOTHELIUM-INDEPENDENT

B. Systemic Effects of Organic Nitrates
1. Dilate venous capacitance vessels and decrease venous return
2. Reduced wall tension and myocardial oxygen consumption
3. Reduced afterload (systemic arteriolar vasodilator)
4. Direct coronary artery vasodilator

C. Clinical Use of Organic Nitrates
1. Angina Pectoris (Exertional, Unstable, Variant)
2. Hypertensive Emergencies
3. Congestive Heart Failure

D. Most Commonly Used Organic Nitrate Preparations
1. Nitroglycerin
   a) Sublingual

---

From Katzung, 10th Ed. Figure 12-3, pg. 187 Effects of nitroglycerin (NTG) on contractions of human vein segments in vitro.

Vein segments denuded of endothelium were first “contracted” with either potassium chloride (K⁺) to cause membrane depolarization and calcium influx (upper panel); or with norepinephrine (NE) to cause release of calcium from intracellular stores (lower panel). The veins were then treated with nitroglycerin (NTG), which caused vasodilation.

Modified by AMS from Opie and Gersh, Drugs for the Heart, 6th edition.
b) Transdermal (ointment, patches)
c) Intravenous
2. Isosorbide dinitrate
   a) Sublingual
   b) Chewable
   c) Oral

E. Nitrates Use in Exertional Angina
   1. Terminate exercise-induced myocardial ischemia (Sublingual Nitroglycerin)
   2. Prevent exercise-induced myocardial ischemia
      a. Sublingual Nitroglycerin
      b. Oral isosorbide Dinitrate
      c. Nitroglycerin patch or ointment
   3. Terminate coronary artery spasm

F. Nitrate Side-Effects
   1. Exaggeration of Therapeutic Effects
      a) Orthostatic Hypotension
      b) Reflex Tachycardia
      c) Headache
   2. Nitrate Tolerance
      a) Repeated exposure to high doses of long-acting nitrates - depletion of cysteine stores?
      b) Nitrate-free intervals - reduces tolerance

VII. Ca\(^{2+}\) CHANNEL BLOCKERS Rx for ANGINA
   A. Mechanism of Action in Smooth Muscle
      1. Vascular smooth muscle contraction is highly dependent on \([Ca^{2+}]_i\)
      2. \([Ca^{2+}]_i\) - Ca influx vs. release of Ca\(^{2+}\) from intracellular stores.
      3. Vascular smooth muscle cells express L-type Ca\(^{2+}\) channels
      4. Little or no Ca\(^{2+}\) induced Ca\(^{2+}\) release in VSM
      5. Other ways to increase \([Ca^{2+}]_i\): Release of Ca\(^{2+}\) from IP\(_3\)-sensitive stores (\(\alpha_1\)-adrenergic agonists, endothelin, vasopressin, angiotensin II)
      6. \([Ca^{2+}]_i\) rise required for activation of Ca\(^{2+}\)-calmodulin dependent Myosin Light Chain Kinase (MLCK)

Katzung, 10\(^{th}\) Ed., Fig 12-1, pg. 184.
Cellular actions of calcium channel blockers on smooth muscle
7. Unlike cardiac muscle, myosin phosphorylation is required for activation of smooth muscle myosin ATPase activity.
8. Therefore, Ca\(^{2+}\) channel blockers reduce \([\text{Ca}^{2+}]_i\) entry, and thus decrease \([\text{Ca}^{2+}]_i\), preventing smooth muscle contraction.
9. Ca\(^{2+}\) channel blockers are potent arteriolar vasodilators, but have little or no effect on venous capacitance vessels.

B. Ca\(^{2+}\) channel blockers also affect Ca\(^{2+}\) entry in CARDIAC muscle
1. Negative inotropic agents
2. Decrease rate of SA nodal Phase IV depolarization (decrease heart rate)
3. Slow AV nodal conduction velocity

C. Clinical Use of Calcium Channel Blockers
1. Angina Pectoris
2. Hypertension
3. Arrhythmias
4. Hypertrophic Cardiomyopathy
5. Migraine
6. Raynaud’s Phenomenon

D. Calcium Channel Blockers for Exertional Angina
1. Dihydropyridines
   a) Nifedipine (short acting)
   b) Nicardipine (intermediate acting)
   c) Amlodipine (long-acting)
2. Phenylalkylamines - verapamil
3. Benzothiazepine - diltiazem
4. Diarylaminopropylamine ether – bepridil

E. Calcium Channel Blocker Characteristics – Systemic Effects
1. Negative Inotropic Effects (decreases myocardial O2 consumption)
   • Verapamil>diltiazem>nifedipine
2. Negative Chronotropic Effects (decreases myocardial O2 consumption)
   • Verapamil>diltiazem>nifedipine
3. Vasodilatory Effects (decrease afterload ⇒ decrease myocardial O2 consumption)
   • Nifedipine>diltiazem>verapamil
4. Dilate coronary vasculature and prevent coronary artery spasm

F. Calcium Channel Blocker Side-Effects
1. Verapamil and Diltiazem
   a) Bradycardia
   b) Heart Block
   c) Congestive Heart Failure
   d) Hypotension
2. Dihydropyridines
   a) Reflex Tachycardia
   b) Peripheral Edema
   c) Hypotension

VIII. BETA BLOCKER Rx for ANGINA
A. Beta Receptor Subtypes
1. $\beta_1$ Receptors - Cardiac Muscle
2. $\beta_2$ Receptors
   a) Cardiac muscle
   b) Bronchial Smooth Muscle
   c) Vascular Smooth Muscle

B. Mechanism of Action - Related to Cardiac Effects (not vasodilators)
1. $\beta_1$ adrenergic receptor - present in variety of myocardial cells (conduction system + muscle cells)
2. Regulates $\text{Ca}^{2+}$ influx (L-type $\text{Ca}^{2+}$ channels) and $\text{Ca}^{2+}$ storage/release by sarcoplasmic reticulum (Ryanodine receptors (RyR) and SR $\text{Ca}^{2+}$ ATPase (SERCA2-Phospholamban))
3. $\beta_1$ adrenergic stimulation causes -
   a) Increased heart rate
   b) Increased AV nodal conduction velocity
   c) Increased force of contraction (positive inotropy)
4. $\beta_1$ receptor antagonists therefore counteract the effects of sympathetic stimulation on the heart
   a) Decrease HR
   b) Decrease myocardial contractility (i.e., they are negative inotropes)
   c) Decrease mean arterial blood pressure (decrease afterload)
   d) All three interventions markedly decrease myocardial $\text{O}_2$ consumption
5. Decrease in heart rate increases myocardial $\text{O}_2$ delivery - increased diastolic perfusion time, decreased vascular compression.

C. Clinical Use of Beta Blocking Agents
1. Exertional Angina Pectoris
2. Hypertension
3. Arrhythmias
4. Dissecting Aortic Aneurysm
5. Mitral Valve Prolapse
6. Post-MI prophylaxis
7. Hyperthyroidism
8. Migraine

D. Beta Blocker Characteristics
1. Cardioselectivity (nonselective vs. $\beta_1$ selective)
2. Duration
3. Lipid Solubility
4. Routes of Elimination
5. Intrinsic Sympathomimetic Activity

E. Beta Blockers in Common Use for Exertional Angina

1. Nonselective
   a) Propranolol
   b) Nadolol
2. Cardioselective
   1. Metoprolol
   2. Atenolol
3. Nonselective with Intrinsic Sympathomimetic Activity
   a) Labetalol
   b) Pindolol
4. Cardioselective with Intrinsic Sympathomimetic Activity
   (Acebutolol)

F. Routes of Elimination: Liver vs. Kidney (see adjacent figure).

G. Beta Blocker Side-Effects

1. Bronchospasm
2. Peripheral vasospasm
3. Exaggeration of cardiac therapeutic effects (bradycardia, heart block, acute CHF)
4. Central nervous system effects (insomnia, depression, fatigue)

H. Relative Contraindications to Beta Blocker Therapy

1. Acute congestive heart failure
2. Marked bradycardia (<55 bpm)
3. Advanced heart block (1st, 2nd, 3rd degree)
4. Severe peripheral vascular disease
5. Insulin-dependent diabetes mellitus
6. Sexual impotence
7. Bronchospasm (COPD, Asthma)

IX. RANOLAZINE – A NEW CLASS OF ANTI-ANGINAL DRUGS

A. pFOX inhibitors inhibit mitochondrial enzymes of beta oxidation.

1. Under normal conditions the heart can use either glucose or fatty acids to generate ATP.
2. Metabolism of glucose uses oxygen more efficiently than the metabolism of fatty acids.
3. During acute myocardial ischemia, fatty acids rise precipitously, inhibiting pyruvate dehydrogenase. As a consequence, glucose oxidation is depressed. This is particularly undesirable when oxygen supply is limited as in myocardial ischemia.
4. Ranolazine partially inhibits fatty acid oxidation, allowing the heart to use more glucose as a fuel by relieving the inhibition on pyruvate dehydrogenase.
5. The net result is reduced lactic acid accumulation, less intracellular acidosis, and a reduction in the severity of the myocardial ischemic response.

B. Ranolazine is a relatively new drug - approved by FDA in January, 2006
C. Use originally limited to patients who continue to have angina despite nitrates, beta blockers and calcium channel blockers
D. Now approved for “first-line” use in exertional angina
E. Electrophysiological Effects – blocks late Na⁺ current, prolongs action potential duration (Risk of EADs and Torsades de Pointe)

X. USE OF PHARMACOLOGICAL AGENTS IN PATIENTS WITH ANGINA PECTORIS

A. Double Product
   1. Myocardial Oxygen Consumption ~ Heart Rate x Systolic Blood Pressure
   2. Improved exercise tolerance as an indicator of drug efficacy

B. Symptom-limited Exercise Stress Testing (see adjacent figure)
C. How long can a patient exercise before developing signs and symptoms of myocardial ischemia?
D. Development of Angina
E. Development of ST-T wave changes on exercise ECG
F. Effects of Anti-Anginal Drugs on Treadmill Exercise Performance
   1. Increased exercise duration
   2. Angina and ST segment changes occur at same double product
G. Benefits of Anti-Anginal Drugs Translate to Activities of Daily Living
   1. Less frequent anginal episodes
   2. Shorter duration of anginal episodes
   3. Increased exercise tolerance
H. Pharmacological Treatment of Exertional Angina
   1. Nitrates, Ca²⁺ channel blockers and beta blockers all increase time to onset of angina and ST segment depression in patients with exertional angina
2. Increased exercise tolerance without significant change in angina threshold (angina occurs at same double product)
3. Nitroglycerin - effective in aborting anginal episode as well as in prophylaxis
4. Long-acting nitrates - prophylaxis of exertional angina
5. Monotherapy vs. Combination therapy
   a) nitrate + beta blocker
   b) nitrate + Ca$^{2+}$ channel blocker
   c) nitrate + Ca$^{2+}$ channel blocker + Beta blocker: reserved for patients with normal LV function, refractory to single or double combination
   d) Beta blocker or verapamil block reflex tachycardia and increased contractile activity associated with nitrates
   e) Beta blocker or Ca$^{2+}$ channel blocker useful in patients with angina and hypertension
   f) Beta blockers contraindicated in patients with ASTHMA, COPD, and **acute** CHF.

I. Pharmacological Treatment of Vasospastic Angina (Prinzmetal’s variant angina)
   1. Nitrates and Ca$^{2+}$ channel blockers are much more effective than beta blockers
   2. Revascularization if fixed obstructive lesions also present

J. Pharmacological Treatment of Silent Ischemia
   1. Silent ischemia usually associated with increase in heart rate and BP (increased double product)
   2. Beta blockers particularly effective in reducing total ischemic time

K. Pharmacological Treatment of Unstable Angina

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From Katzung, 8th Ed., Fig. 12-6, pg. 195. Metoprolol Effects on Heart Rate and Normalized Ischemic Time
1. Triple drug therapy if tolerated (nitrates, beta blockers, Ca channel blockers)
2. IV nitroglycerin
3. Aspirin and heparin

XI. NONPHARMACOLOGICAL TREATMENT OF ANGINA PECTORIS
   A. Exercise Training (“Training Effect”)
   B. Percutaneous Transluminal Coronary Angioplasty (PTCA)
   C. Coronary Artery Stents
      1. Bare Metal Stents
      2. Drug Eluting Stents
   D. Intra-Aortic Balloon Pump (IABP)
   E. Coronary Artery Bypass Grafts (CABG)
XII. REVIEW QUESTIONS

1. What are the mechanisms by which organic nitrates decrease the severity of myocardial ischemia?

2. What are the mechanisms by which the calcium channel antagonists decrease the severity of myocardial ischemia?

3. How can a beta-blocker increase blood flow to an area of ventricular muscle supplied by a stenotic coronary artery?

4. Why should nadolol be expected to cause less mental depression and fatigue than propranolol?

5. What would be the hemodynamic effects of the administration of a nitrate in combination with a beta-blocker?

6. Why are “pure” arteriolar vasodilators such as dipyramidole not effective in treating myocardial ischemia?

7. What can be done to minimize nitrate tolerance?

8. What drugs are useful in treating variant angina?

9. What are the major side-effects of nifedipine?
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Indications</th>
<th>Mechanism of Action</th>
<th>Clinical Effect</th>
<th>Adverse Effects</th>
<th>Contraindications</th>
</tr>
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<tbody>
<tr>
<td><strong>NITRATES</strong></td>
<td>Exertional angina; Variant Angina; Unstable angina</td>
<td>Reacts with cysteinyl residues in vessel wall to increase the concentration of Nitric Oxide in vascular smooth muscle cells, causing vasodilation, especially of venous capacitance vessels</td>
<td>Terminates episodes of exercise-induced angina; prevents exercise-induced and vasospastic angina</td>
<td>Orthostatic Hypotension; Reflex Tachycardia; Headache; Nitrate Tolerance</td>
<td>Systemic hypotension</td>
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<td>Nitroglycerin</td>
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<td>Isosorbide dinitrate</td>
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<td>Erythrityl tetranitate</td>
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<td><strong>CALCIUM CHANNEL BLOCKERS</strong></td>
<td>Exertional angina; variant angina; Unstable angina</td>
<td>Blocks calcium influx via L-type Ca channels in vascular smooth muscle cells and cardiac myocytes, thereby causing vasodilation and decreased contractility</td>
<td>Prevents episodes of exercise-induced and vasospastic angina</td>
<td>Bradycardia; Heart Block; Congestive Heart Failure; Hypotension; peripheral edema; reflex tachycardia (nifedipine)</td>
<td>Advanced heart block; Congestive heart failure; Systemic hypotension</td>
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<td>Nifedipine</td>
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<td>Nicardipine</td>
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<td>Amlodipine</td>
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<td>Verapamil</td>
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<td>Diltiazem</td>
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<td><strong>BETA BLOCKERS</strong></td>
<td>Exertional angina; Unstable angina</td>
<td>Blocks β-receptors in cardiac myocytes to reduce contractility</td>
<td>Prevents exercise-induced myocardial ischemia</td>
<td>Bronchospasm; Peripheral vasospasm; Bradycardia; Congestive heart failure; Heart block; Depression, fatigue; blocks sympathetic response to insulin-induced hypoglycemia impotence</td>
<td>Advanced heart block; Acute CHF; insulin-dependent diabetes mellitus; asthma, COPD</td>
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<td>Propranolol</td>
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<td>Nadolol</td>
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<td>Atenolol</td>
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<td>Metoprolol</td>
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<td>Carvedilol</td>
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<td><strong>RANOLAZINE</strong></td>
<td>Originally indicated for use in patients with chronic stable angina unresponsive to other agents; now approved for initial use in exercise-induced angina</td>
<td>Inhibits fatty acid beta oxidation in cardiac myocyte mitochondria</td>
<td>Chronic exertional angina</td>
<td>Prolongs QT interval</td>
<td>Long QT syndrome; contraindicated for use with other drugs that prolong QT interval.</td>
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DRUGS TO TREAT CONGESTIVE HEART FAILURE

Date: Thursday, October 17, 2013 – 9:30 am
Reading Assignment: Katzung 12th edition, Chapter 13

KEY CONCEPTS & LEARNING OBJECTIVES:

A. To briefly review the pathophysiological basis for the development of ACUTE congestive heart failure.
B. To examine the rationale for the use of diuretics, inotropic drugs, and vasodilators in the treatment of acute congestive heart failure.
C. To briefly discuss nonpharmacological approaches for the treatment of acute congestive heart failure.
D. To briefly review the pathophysiological basis for the development of ventricular remodeling and CHRONIC congestive heart failure.
E. To examine the rationale for the use of digitalis, diuretics, ACE inhibitors, ARB’s, beta blockers and aldosterone antagonists in the treatment of chronic congestive heart failure.
F. To briefly discuss nonpharmacological approaches for the treatment of chronic heart failure

LIST OF IMPORTANT DRUGS

Loop diuretics: Furosemide
Other Diuretics: Thiazides
                       Spironolactone
                       Eplerenone
Organic nitrate vasodilators: Nitroglycerin
                       Isosorbide Dinitrate
                       Nitroprusside
Other vasodilators: Niseritide
                       Hydralazine
Inotropic agents: Isoproterenol
                       Dopamine
                       Dobutamine
                       Norepinephrine
                       Digoxin
<table>
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<tr>
<th>Category</th>
<th>Drugs</th>
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<tr>
<td>Phosphodiesterase inhibitors:</td>
<td>Inamrinone (a.k.a. amrinone)</td>
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<td></td>
<td>Milrinone</td>
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<td>Angiotensin Converting Enzyme (ACE) Inhibitors:</td>
<td>captopril, enalapril, lisinopril</td>
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<tr>
<td>Angiotensin Receptor Blockers (ARB):</td>
<td>losartan, valsartan, irbesartan, candesartan</td>
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<td>Other vasodilators:</td>
<td>hydralazine</td>
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<tr>
<td>*Beta-blockers:</td>
<td>carvedilol, metoprolol, bucindolol</td>
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TREATMENT OF CONGESTIVE HEART FAILURE

I. CONGESTIVE HEART FAILURE SYNDROMES
   A. Acute Congestive Heart Failure
   B. Acutely Decompensated Chronic Congestive Heart Failure (ADHF)
   C. Chronic Congestive Heart Failure
      1. Systolic Heart Failure (Heart Failure with Reduced Ejection Fraction)
      2. Diastolic Heart Failure (Heart Failure with Normal or Near-Normal Ejection Fraction)

II. TREATMENT OBJECTIVES IN ACUTE CONGESTIVE HEART FAILURE
   A. Early recognition and treatment
   B. Decrease symptoms
      1. Rapidly reduce pulmonary congestion (reduce preload)
         a) Diuretics
         b) Venodilators
         c) Niseritide
      2. Increase forward cardiac output
         a) Inotropic agents (beta adrenergic agonists; phosphodiesterase inhibitors; digitalis glycosides)
         b) Arteriolar vasodilators (nitroprusside)

III. DIURETICS
   A. Mechanism of Action in Acute CHF
      1. Reduce intravascular volume to reduce filling pressure (preload)
      2. Reduce extracellular fluid, thereby reducing edema formation
      3. Preload reduction can have little effect on cardiac output in patients with CHF (flat portion of Frank-Starling Curve)
   B. Clinical Use in Acute CHF
      1. Loop Diuretics (inhibit Na⁺K⁺/2Cl⁻ Transporter in the Loop of Henle)
         a) Furosemide (Lasix®)
         b) Bumetanide
         c) Torsemide
      2. Thiazide diuretics (inhibit Na⁺ and Cl⁻ reabsorption in distal tubule) can be added in combination with Loop Diuretics in patients ‘resistant’ to furosemide
         a) chlorothiazide
         b) chlorthaladone
   C. Adverse Effects of Diuretics
      1. Overdiuresis - can precipitate low output state.
      2. Hypokalemia - may precipitate arrhythmias (increased automaticity)
3. Hypokalemia - increases binding of digoxin to Na pump. Potentiates digitalis toxicity
4. Hypomagnesemia
5. Hyperuricemia
6. Ototoxicity (Loop Diuretics)
7. Allergy (Loop and Thiazides are sulfa drugs!)
8. Diuretic resistance-overcome by using combination of diuretics acting at different sites in the nephron

IV. VENO DILATORS
   A. Organic Nitrates
      1. Aim of therapy is to increase venous capacitance and reduce central venous filling pressure (DECREASE PRELOAD).
      2. Reduced preload will ultimately reduce pulmonary capillary hydrostatic pressure and filtration of fluid across capillary membrane, thus reducing interstitial edema formation - (i.e., reduce Backward Failure)
      3. Nitroglycerin (IV, sublingual, topical)
      4. Isosorbide dinitrate (oral)

   B. Niseritide
      1. Human Recombinant Brain Natriuretic Peptide (hBNP)
      2. “Normally” produced by ventricular myocardium in response to “chronic” stretch
      3. Activates vascular smooth muscle and renal BNP receptors
      4. Raises cGMP levels in VSMC and renal epithelial cells, leading to both vasodilatation (especially of the glomerular afferent arteriole) to increase GFR
      5. Induces vasodilatation and natriuresis

V. INOTROPIC AGENTS USED TO TREAT ACUTE CHF
   A. Beta-Adrenergic Agonists
      1. Mechanism of action
         a) Activation of Adenylyl Cyclase, causing increased production of cAMP.
         b) cAMP activates Protein Kinase A (PK-A), which phosphorylates key intracellular regulatory proteins.
         c) Phospholamban (PLB) - major target for beta adrenergic effects in cardiac muscle. PLB phosphorylation de-represses inhibition of SERCA2 (SR Ca Pump).
         d) PLB phosphorylation therefore increases SR Ca loading- more Ca for EC coupling.
e) PK-A also phosphorylates L-type Ca channels, increasing Ca current - more Ca trigger.

f) PK-A also phosphorylates the RyR receptor, altering its gating properties.

g) PK-A also phosphorylates TnI, reducing myofilament Ca sensitivity.

2. Mechanical effects of beta adrenergic agonists
   a) Increased velocity of fiber shortening and force of contraction
   b) Increased ventricular emptying (Stroke Volume increases)
   c) Decreased end systolic and end-diastolic volume
   d) Increased Heart Rate; AV nodal conduction velocity
   e) Increased Myocardial O2 consumption

3. Systemic effects of beta adrenergic agonists
   a) Increased CARDIAC OUTPUT
   b) Increased renal perfusion

4. Clinical Use of Beta Adrenergic Agonists
   a) Acute Heart Failure following CV surgery
   b) Used in conjunction with arteriolar vasodilators in Acute Mitral Regurgitation and other conditions.
   c) Cardiogenic Shock and other forms of Shock
   d) less useful in Acutely Decompensated Chronic CHF because of down-regulation of cardiac β receptors and toxicity of chronic beta adrenergic stimulation

5. Isoproterenol (IV, short half life)
   a) activates cardiac β1 and β2-receptors
   b) Increases heart rate more than contractility (useful in heart block, idioventricular rhythm); not useful in CHF due to ischemic heart disease
   c) Reduces vascular resistance in kidney, skeletal muscle
   d) can produce systemic hypotension

6. Dopamine
   a) catecholamine-like IV drug with short half-life
   b) Low doses (0.5-5 µg/kg/min) of dopamine activate cardiac β1-receptors, releases norepinephrine from sympathetic nerve terminals, and causes renal vasodilatation
   c) High doses (5-10 µg/kg/min) activates α1-adrenergic receptors and causes vasoconstriction

7. Dobutamine
   a) Synthetic analog of dopamine; given IV with short half-life
   b) Directly stimulates β1-receptors. Increases contractility more than heart rate (opposite of isoproterenol)

B. Phosphodiesterase Inhibitors (Inamrinone, Milrinone)

1. Mechanism of Action
   a) Inhibit the degradation of cAMP, thereby increasing cAMP levels in cardiac muscle.
   b) Vasodilators, perhaps by inhibiting degradation of cGMP
2. Systemic Effects of Phosphodiesterase Inhibitors
   a) Increased C.O.
   b) Reduce pulmonary capillary wedge pressure
   c) Reduce peripheral vascular resistance (direct)
   d) No change in heart rate, systolic BP.

3. Clinical Use of Phosphodiesterase Inhibitors
   a) Especially useful in patients with acute decompensation of chronic CHF (ADHF), as drugs bypass β receptor down-regulation.
   b) Can be used in patients who are receiving β-blockers
   c) Oral agent (Milrinone) increased mortality in chronic CHF, probably by increasing frequency of arrhythmias.

C. Digitalis Glycosides
   1. Mechanism of Action
      a) Partial inhibition of Na/K ATPase (Sarcolemmal Na Pump)
      b) Increased [Na⁺]i leads to enhanced Na/Ca Exchange
      c) Increased [Ca²⁺]i stored in Sarcoplasmic Reticulum
      d) More Ca released from SR stores during each contraction.

   2. Mechanical Effects of Digitalis Glycosides on Cardiac Performance
      a) Increased velocity of fiber shortening and force of contraction
      b) Increased ventricular emptying (SV increases)
      c) Decreased end-systolic and end-diastolic volume

   3. Systemic Effects of Digitalis Glycosides in CHF
      a) Increased C.O.
      b) Increased renal perfusion
      c) Decreased sympathetic tone (reduced heart rate, vasoconstriction)

   4. Parasympathomimetic Effects of Digitalis Glycosides
      a) Sensitizes baroreceptors
      b) Increases central vagal stimulation
      c) Prolongs AV nodal conduction velocity and Effective Refractory Period

   5. Direct Electrophysiological Effects of Digitalis Glycosides
      a) Increased Ca causes activation of K conductance
      b) Shortening of AP Duration
      c) Membrane depolarization (Na pump inhibition)
      d) Delayed afterdepolarizations (DAD’s) and abnormal automaticity
      e) Digitalis Intoxication - VPBs, V tach, junctional tachycardia, etc.

   6. Clinical Use of Digitalis Glycosides
      a) Because of potential for side-effects, digoxin is now primarily used in patients with CHF and Atrial Fibrillation with rapid ventricular response (slows ventricular rate)
      b) DIGOXIN - know your pharmacokinetics!
      c) Incidence of toxicity reduced by frequent measurement of serum levels (Therapeutic range of Digoxin = 1-2 ng/ml; Toxic range >2.5 ng/ml)
      d) Digibind antibodies used to treat digitalis toxicity
VI. OTHER INTRAVENOUS VASODILATORS

A. Nitroprusside
   1. Effective in acute hypertensive emergencies and severe CHF
   2. Rapidly lowers systemic vascular resistance, must be titrated to avoid hypotension
   3. Often used in conjunction with dobutamine in acute CHF (cardiogenic shock, acute valve rupture, etc.)
   4. Limited by accumulation of cyanide, and thiocyanate (short-term use only)

VII. NONPHARMACOLOGICAL THERAPY FOR ACUTE CHF

A. PCI/Surgical Therapy
   1. Acute Revascularization
   2. Urgent Valve Repair/Replacement
B. Ultrafiltration
C. Intra-aortic balloon pump (IAPB)
D. Ventricular assist devices (VADs)
   1. Impella Percutaneous LVAD
   2. Heartmate (I and II)

VII. TREATMENT OBJECTIVES IN CHRONIC CONGESTIVE HEART FAILURE

A. Early recognition of ventricular dysfunction even in the ABSENCE of symptoms
B. Prevent Ventricular Remodeling
C. Decrease symptoms once they develop:
   1. Reduce pulmonary congestion
   2. Increase cardiac output
   3. Improve exercise capacity
   4. Increase quality of life
D. Improve survival

VIII. VENTRICULAR REMODELING

A. Post-MI ventricular remodeling
   Mitchell and Pfeffer: “LV enlargement and distortion of regional and global ventricular geometry occurring after myocardial infarction.”
   Whittaker and Kloner: “Any architectural or structural change that occurs after myocardial infarction in either the infarcted or noninfarcted regions of the heart.”
   Samarel: Hypertrophy and dilatation of noninfarcted segments occurring weeks to years after acute MI.

B. Early Recognition and Treatment of Ventricular Dysfunction
1. Structural changes in the ventricular myocardium represent a disease process.
2. Remodeling often PRECEDES the development of symptoms of CHF (dyspnea, PND, edema, etc.) by months to years.
3. Remodeling is predominantly a growth-mediated response, and results from an interplay between mechanical factors, and systemic and locally derived neurohormonal factors.

4. Efforts directed at preventing or slowing the progression of ventricular remodeling will prevent or delay the development of CHF.

C. Drugs That Prevent or Slow the Progression of Ventricular Remodeling and Improve Survival (Anti-Remodeling Rx)
   1. ACE inhibitors (captopril, enalapril, lusinopril)
   2. Angiotensin II receptor antagonists (losartan, valsartan, irbesartan, candesartan)
   3. Beta blockers (carvedilol, metoprolol, bucindolol)
   4. Other vasodilators (hydralazine + isordil)
   5. Aldosterone antagonists (spironolactone, eplerinone)

IX. Angiotensin Converting Enzyme (ACE) Inhibitors (Captopril, Enalapril, Lisinopril)
   A. Mechanism of Action - Block conversion of Ang I to Ang II in lung and other tissues; Also prevents degradation of Bradykinin (kininase inhibitor)
   B. Reduce circulating levels of AngII - potent vasoconstrictor
   C. Reduce aldosterone secretion by adrenal gland
   D. Inhibit local ACE in myocardium, kidneys and blood vessels.
   E. Hemodynamic Effects - Decrease Preload + Decrease Afterload
   F. Studies in chronic CHF indicate that early use of ACE inhibitors improve symptoms, prevent ventricular remodeling, and prolong LIFE.
   G. Now considered first line drugs in patients with chronic CHF
   H. Side effects are due to bradykinin (cough, angioedema).
   I. Other side effects include hypotension, impaired renal function, and hyperkalemia.

X. ANGIOTENSIN II RECEPTOR ANTAGONISTS (ARBs) (Losartan, Valsartan, Irbestartan, Candesartan)
   A. Newer agents, selective AT1 receptor blockers
   B. Unlike ACE inhibitors, they do not prevent bradykinin degradation
   C. Used in patients intolerant to ACE inhibitors

XI. BETA BLOCKERS in CHRONIC CHF
   A. Recent clinical trials have shown that beta blockers (given in addition to digoxin, diuretics and ACE inhibitors) increase survival and prevent deterioration of LV performance over time in patients with mild-moderate chronic CHF.
   B. Mechanism of Action - Thought to involve reduction in heart rate and prevention of deleterious effects of chronic sympathetic stimulation
   1. Prevents activation of the “fetal gene program” (ie., prevents downregulation of αMHC, SERCA2a)
   2. Prevents SR Ca Leak
   3. Prevents beta receptor down-regulation
4. Prevents myocardial apoptosis
5. Decreases structural LV remodeling
C. Must be used with caution – Beta blockers can precipitate worsening of CHF symptoms
D. Specific Agents
   1. Carvedilol (combined $\alpha_1$ and nonselective beta blocker)
   2. Metoprolol (selective $\beta_1$ receptor antagonist)
   3. Bucindolol (combined $\alpha_1$ and nonselective beta blocker)

XII. ALDOSTERONE ANTAGONISTS in CHRONIC CHF (spironolactone, eplerinone)
A. Aldosterone antagonists are Diuretics – inhibit aldosterone effects on distal tubule (prevent Na$^+$ and H$_2$O reabsorption).
B. Aldosterone has other important roles in the pathophysiology of heart failure.
   1. Promotes sympathetic activation
   2. Promotes parasympathetic inhibition
   3. Stimulates myocardial and vascular fibrosis
   4. Causes baroreceptor dysfunction
   5. Impairs arterial compliance
C. RALES Trial – tested effect of adding spironolactone to ACE inhibitor, loop diuretic, and digoxin on long-term outcome in patients with chronic CHF.

XIII. RATIONALE FOR DRUG THERAPY IN SYMPTOMATIC, CHRONIC CHF
A. Similar to Acute CHF, but limited to oral agents
B. Reduce pulmonary congestion and edema formation
   1. Loop Diuretics
   2. Thiazides
   3. Aldosterone antagonists
   4. Venodilators (ACE inhibitors, ARBs, nitrates)
C. Increase Cardiac Output
   1. Increase Contractility - (Digoxin)
   2. Reduce Afterload (ACE inhibitors, ARBs, hydralazine)

XIV. INOTROPIC AGENTS IN CHRONIC CONGESTIVE HEART FAILURE
A. Currently limited to oral Digoxin (partial Na$^+$K$^+$ ATPase inhibitor)
   1. Digoxin has no effect on survival in patients with chronic CHF
   2. Very narrow therapeutic window
B. Other inotropic agents not currently approved by FDA:
   1. Ca$^{2+}$ sensitizers: levosimendan
   2. Myosin activators
   3. Oral phosphodiesterase inhibitors: milrinone–increased mortality in Phase III

XV. OTHER ORAL VASODILATORS
A. Selective Arteriolar Vasodilators (e.g., Hydralazine)
   1. Reduced systemic vascular resistance
   2. Increase forward C.O. (reduced afterload)
3. The magnitude of reduction in vascular resistance is GREATER than the decrease in mean arterial blood pressure - increased output maintains the arterial pressure.
4. Particularly useful in patients with hypertension and CHF.
5. Used in combination with organic nitrates
6. Ca Channel blockers - although they are potent arteriolar vasodilators, they are CONTRAINDICATED IN CHRONIC CHF BECAUSE OF NEGATIVE INOTROPIC EFFECTS

B. Venodilators
5. Aim of therapy is to increase venous capacitance and reduce venous filling pressure (DECREASE PRELOAD). This will reduce capillary hydrostatic pressure and filtration of fluid across capillary membrane, thus reducing interstitial edema formation - (Backward Failure)
6. Isosorbide dinitrate (oral)
7. Nitroglycerin (patch, topical ointment)

XVI. NONPHARMACOLOGICAL THERAPY FOR CHF

A. Revascularization for Chronic Ischemic Heart Disease
B. Valve Repair/Replacement for Chronic Valvular Heart Disease
C. Aneurysmectomy
D. Left ventricular assist devices (LVADs)
   1. Bridge to Transplant
   2. “Destination Therapy”
E. Biventricular pacing (“Cardiac Resynchronization Therapy” or “CRT”) and implantable cardioverter defibrillators (ICDs)
F. Cardiac Transplantation
XVII. REVIEW QUESTIONS

1. What is the rationale for using arteriolar vasodilators to treat acute CHF?

2. How does intravenous nitroglycerin decrease pulmonary edema in acute CHF?

3. What is the goal of diuretic therapy in acute CHF?

4. Why do inotropic drugs like dobutamine cause an increase in urine output in acute CHF?

5. What are the hemodynamic effects of dopamine and how do they differ from the effects of dobutamine?

6. How is niseritide beneficial in acute decompensation of chronic congestive heart failure?

7. Why is inamrinone given to patients who are refractory to dobutamine?

8. What is the mechanism by which digoxin increases cardiac contractility?

9. What are the beneficial effects of digoxin on the autonomic nervous system in CHF?

10. What is the rationale for using arteriolar vasodilators to treat chronic CHF?

11. How does captopril decrease pulmonary edema formation in chronic CHF?

12. What agents have been proven to improve survival in chronic CHF?

13. How would nitroglycerin be beneficial in chronic CHF?

14. Why are beta-blockers given to patients with chronic CHF?

15. What is meant by the term “Destination Therapy”?
### SUMMARY – Drugs to treat Acute CHF and ADHF

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Indications</th>
<th>Mechanism of Action</th>
<th>Clinical Effect</th>
<th>Adverse Effects</th>
<th>Contraindications</th>
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<tbody>
<tr>
<td>DIURETICS</td>
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<tr>
<td>Furosemide</td>
<td>Reduce intravascular volume thereby reducing filling pressures; reduce extracellular fluid thereby reducing pulmonary and peripheral edema formation</td>
<td>Inhibits Na reabsorption by the Na/K/Cl transporter in the Loop of Henle</td>
<td>Diuresis</td>
<td>Overdiuresis; Hypomagnesemia; Hypokalemia, Hyperuricemia; Ototoxicity; Allergy Diuretic resistance</td>
<td>Electrolyte imbalances, volume depletion</td>
</tr>
<tr>
<td>NITRATES</td>
<td></td>
<td>Reacts with cysteinyl residues in vessel wall to increase the concentration of Nitric Oxide in vascular smooth muscle cells, causing vasodilation</td>
<td>Decrease filling pressures, decrease arterial blood pressure</td>
<td>Hypotension; Reflex tachycardia; Methemoglobinemia; Nitrate tolerance</td>
<td>Systemic hypotension</td>
</tr>
<tr>
<td>Nitroglycerin Nitroprusside</td>
<td>Reduce preload by causing vasodilation of venous capacitance vessels; Reduce afterload</td>
<td></td>
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<tr>
<td>NISERITIDE</td>
<td>Acutely decompensated chronic congestive heart failure in hospitalized patients</td>
<td>Activates vascular smooth muscle and renal BNP receptors; raising cGMP levels in VSMC and renal epithelial cells</td>
<td>Vasodilatation (especially of the glomerular afferent arteriole) to increase GFR; Induces vasodilatation and natriuresis</td>
<td>Hypotension, ventricular arrhythmias</td>
<td>Reduced LV filling pressures; systemic hypotension</td>
</tr>
<tr>
<td>BETA ADRENERGIC AGENTS</td>
<td>Low cardiac output due to acute CHF; cardiogenic shock</td>
<td>Stimulates cardiac beta adrenergic receptors to increase myocardial cAMP</td>
<td>Increased heart rate, increased contractility, increased cardiac output</td>
<td>Arrhythmias; increased myocardial O₂ consumption, angina, vasoconstriction (norepinephrine)</td>
<td>Ventricular arrhythmias; severe peripheral vascular disease</td>
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<td>Isoproterenol Dopamine Dobutamine Norepinephrine</td>
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<td>DIGOXIN</td>
<td>Acute CHF; Atrial fibrillation with rapid ventricular response</td>
<td>Partially inhibits NaK ATPase, thereby increasing reverse-mode NaCa exchange and increasing SR Ca stores</td>
<td>Increased contractility; decreased AV node conduction velocity</td>
<td>Arrhythmias; heart block; anorexia; nausea, vomiting</td>
<td>Hx of VT/VF, hypokalemia</td>
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<td>PHOSPHODIESTERASE INHIBITORS</td>
<td>Acutely decompensated chronic congestive heart failure in hospitalized patients, esp. those on beta blockers</td>
<td>Inhibit the degradation of cAMP in cardiomyocytes, thereby increasing cAMP levels in cardiac muscle; Inhibit the degradation of cGMP in vascular smooth muscle, thereby inducing vasodilation</td>
<td>Increased contractility; vasodilation; increased cardiac output</td>
<td>Arrhythmias; hypotension</td>
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</table>
**SUMMARY – Drugs to Treat Chronic CHF**

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<td>Furosemide: Overdiuresis; Hypomagnesemia; Hypokalemia, Hyperuricemia; Ototoxicity; Allergy Diuretic resistance Thiazides: Hyperuricemia, hypercalcemia; Allergy Spironolactone: Hyperkalemia; gynecomastia</td>
<td>Electrolyte imbalances, volume depletion</td>
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<td>ACE INHIBITORS</td>
<td>Chronic CHF</td>
<td>Blocks conversion of Angiotensin I to angiotensin II in lungs and other tissues</td>
<td>Reduces preload by causing vasodilation of venous capacitance vessels; Reduces afterload; prevents LV remodeling</td>
<td>Hypotension Cough</td>
<td>Systemic hypotension</td>
</tr>
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<td>ANGIOTENSIN II</td>
<td>Chronic CHF, especially in patients intolerant to ACE inhibitors</td>
<td>Blocks AT1a receptors in vascular smooth muscle and cardiac myocytes</td>
<td>Reduces preload by causing vasodilation of venous capacitance vessels; Reduces afterload; Prevents LV remodeling</td>
<td>Hypotension</td>
<td>Systemic hypotension</td>
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<td></td>
</tr>
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<td>BETA ADRENERGIC</td>
<td>Chronic CHF</td>
<td>Blocks beta adrenergic receptors on cardiac myocytes</td>
<td>Decreased heart rate, Decreased myocardial damage due to chronic sympathetic stimulation; prevents LV remodeling</td>
<td>Worsening CHF; Bradycardia; Heart block; Depression; bronchospasm; peripheral vasospasm</td>
<td>Acute exacerbation of chronic CHF, asthma, COPD, insulin-dependent diabetes mellitus</td>
</tr>
</tbody>
</table>
ANTI-ARRHYTHMIC DRUGS I & II

I. Ionic Basis of Cardiac Action Potential.

A. Resting membrane potential (RMP).
1. primarily a K⁺ diffusion potential, i.e. high resting K⁺ permeability and low Na⁺ permeability.
2. RMP determined by the K⁺ concentration gradient across the membrane.

B. Fast response action potential (atrial or ventricular)
1. Upstroke (phase 0) - activation of fast Na⁺ channel.
2. Phase 1 - transient outward K⁺ current and inactivation of Na⁺ channels.
3. Phase 2 (plateau) - slow inward Ca²⁺ current and decrease in K⁺ permeability. Ca²⁺ influx, K⁺ efflux.
4. Phase 3 (final repolarization) - increase in K⁺ permeability and inactivation of Ca²⁺ channels.
5. Phase 4 - resting membrane potential - K⁺ permeability high again.
C. Slow response action potential (SA node, AV node)
   1. Depolarization - activation of slow inward Ca\(^{++}\) current
   2. Repolarization - inactivation of Ca\(^{++}\) current and increase in K\(^{+}\) permeability.

D. Pumps and Exchangers
   1. Na\(^{+}\)-K\(^{+}\) pump - maintains Na\(^{+}\) and K\(^{+}\) concentration gradients. Na\(^{+}\) pumped out and K\(^{+}\) pumped in.
   2. Na\(^{+}\)-Ca\(^{++}\) exchange - maintains low intracellular [Ca\(^{++}\)].

E. Functional Aspects of Na Channels.
   1. Resting channel: m activation gate closed; h inactivation gate opened.
   2. Activated channel: m gate opened; h gate opened = Na\(^{+}\) influx
   3. Inactivated channel: m gate opened; h gate closed
   4. Recovery from inactivation: time required to reset channel to resting state.
   5. Recovery from inactivation is both voltage- and time-dependent.
   Under normal conditions, as the action potential repolarizes (voltage) the Na\(^{+}\) channels recovers very rapidly from inactivation (less than 20 ms). Therefore, normally the action potential duration (voltage) is the primary determinant of refractory periods.
   6. However, some anti-arrhythmic drugs can increase the time required for the Na\(^{+}\) channel to recovery from inactivation and therefore increase the refractory period.
   7. Tachy-arrhythmias and premature beats (short cycle lengths) depend on the ability of Na\(^{+}\) channels to activate, inactivate and recover from inactivation RAPIDLY. If a drug prolongs the recovery time of the Na\(^{+}\) channel (or Ca\(^{++}\) channel) then it can block tachycardias and premature beats from occurring.

II. Pathophysiology of Cardiac Arrhythmias
   1. High incidence, approx. 5% of the population, 80% after myocardial infarction
   2. Symptoms range from asymptomatic to severe hemodynamic consequences and death
   3. Etiology is multifactorial
   4. Mechanisms of all cardiac arrhythmias: i.) disturbed impulse formation, ii.) disturbed impulse conduction, or combination of i.) and ii.)
III. Basic Pharmacology of Anti-Arrhythmic Agents.

A. In general, the aim of anti-arrhythmic therapy is to reduce ectopic pacemaker activity and/or modify conduction characteristics to restore normal function.

B. However, anti-arrhythmic drugs DO NOT ACT SPECIFICALLY. They have many untoward side effects including the DEVELOPMENT of LETHAL ARRHYTHMIAS (Cardiac Arrhythmia Suppression Trial (CAST) study). Therefore, pharmacological treatment of asymptomatic or minimally symptomatic arrhythmias should be avoided.

C. Abnormal automaticity (= i.) disturbed impulse formation): drugs are used to i.) reduce phase 4 slope (pacemaker activity), ii.) increase maximal membrane potential, iii.) increase threshold potential or iv.) increase action potential duration.

D. Abnormal conduction: drugs are used to increase the refractory period (by ion channel blockades), thus preventing reentry or premature beats.

E. Use- or state-dependence of drug action:
   - Drugs that are more effective in blocking channels that are being used (activated) frequently or are in an inactivated state (depolarized).
   - Generally, use- or state-dependent anti-arrhythmic drugs have a higher affinity for activated Na⁺ or Ca++ channels (phase 0) or inactivated Na⁺ or Ca++ channels (phase 2 or depolarized) and low affinity for resting channels.
   - Therefore, these drugs block channels in tissues generating rapid electrical activities, i.e. tachycardia, premature beats or tissues with more positive resting membrane potentials, i.e. ischemic or infarcted tissues.

III. General (Vaughan-Williams) Classification of Anti-Arrhythmic Agents.

Generally, anti-arrhythmic drugs are classified by their PREDOMINANT effect on the action potential or their PREDOMINANT cellular mechanism of action. However, many drugs have multiple non-specific effects that are related to different classes of drug action. Metabolites of drugs also may be biological active via different mechanisms of action.

Class I – Na⁺ channel blockers, i.e. local anesthetic action.
   - Class IA - procainamide, quinidine, disopyramide
   - Class IB - lidocaine, mexiletine
   - Class IC - flecainide, propafenone

Class II - β-adrenergic receptor blockers
   - propranolol, esmolol

Class III - prolong action potential duration and effective refractory period (K⁺ channel blocker)
   - amiodarone, dronedarone, sotalol
Class IV - Ca\(^{++}\) channel blockers
  - verapamil, diltiazem

Others
  - adenosine, magnesium, potassium, cardiac glycosides (digitalis)
<table>
<thead>
<tr>
<th>Class 1: Na⁺ channel blockers (local anesthetic action)</th>
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<tbody>
<tr>
<td>Subclasses (A-C) based on kinetics of channel inactivation and effects on action potential duration</td>
</tr>
<tr>
<td>Drug</td>
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<tr>
<td>Class 1A</td>
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<tr>
<td><strong>PROCAINAMIDE</strong></td>
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<td><strong>QUINIDINE</strong></td>
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<td><strong>DISOPYRAMIDE</strong></td>
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<td>Class 1B</td>
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<tr>
<td><strong>LIDOCAINE</strong></td>
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<td><strong>MEXILETINE</strong></td>
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<td><strong>Class 1C</strong></td>
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<tr>
<td><strong>FLECAINAMIDE</strong></td>
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<td><strong>PROPafenONE</strong></td>
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<td>VERAPAMIL</td>
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<td>DILTIAZEM</td>
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# Other drugs (not classified)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Effect</th>
<th>Clinical application</th>
<th>Pharmakokinetics, toxicities, interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADENOSINE</td>
<td>Increases K⁺ conductance (hyperpolarization) and inhibits Ca²⁺ currents via purinergic receptors</td>
<td>Primarily acts on atrial tissues, slows AV node conduction and increases AV node refractoriness, produces transient cardiac arrest</td>
<td>Drug of choice for conversion of paroxysmal supraventricular tachycardia to sinus rhythm</td>
<td>t₁/₂: seconds. Rapid i.v. bolus dose required (initially 6 mg i.v.) Less effective with theophylline/caffeine, potentiated by dipyridamole. Flushing and shortness of breath.</td>
</tr>
<tr>
<td>MAGNESIUM</td>
<td>Mechanism unknown, influences/inhibits Na⁺,K⁺-ATPase, Na⁺, K⁺, Ca²⁺ channels, alters membrane surface charge</td>
<td>Anti-arrhythmic effects in some patients with normal Mg²⁺ levels. May inhibit afterdepolarizations.</td>
<td>Digitalis induced arrhythmias with hypomagnesemia. May be effective against torsade des pointes</td>
<td>I.v.</td>
</tr>
<tr>
<td>POTASSIUM</td>
<td>Hyperkalemia: depolarizes resting membrane potential Hypokalemia: decreases K⁺ permeability</td>
<td>Hyperkalemia: slows conduction (may lead to re-entrant arrhythmias and AV nodal block). Hypokalemia: enhances ectopic automaticity, lengthens action potential duration which can lead to EADs (torsades de pointes).</td>
<td>Maintain normal plasma K⁺</td>
<td>I.v., p.o.</td>
</tr>
<tr>
<td>CARDIAC GLYCOSIDES (DIGITALIS)</td>
<td>Inhibit Na⁺/K⁺-ATPase, thereby affecting Na⁺-Ca²⁺ exchange, increase intracellular Ca²⁺</td>
<td>Positive inotropic actions (used widely in heart failure) Parasympathomimetic effects: increase AV nodal refractoriness and slow AV node conduction.</td>
<td>Atrial arrhythmias. In atrial flutter or fibrillation parasympathomimetic effects slow AV nodal conduction, thereby slowing excessively high ventricular rates.</td>
<td>Long t½: (digoxin: 40 hrs, digitoxin: 160 hrs), loading doses required. Eliminated by the kidney. Narrow therapeutic window. Development of arrhythmias (DAD). Many drug interactions (amiodarone, verapamil, flecainide)!!! Hypokalemia/magnesiumemia enhance toxic effects. Loss of appetite, nausea, blurred vision, visual disturbances (yellow-green), drowsiness, depression. Severe digitalis toxicity can be reversed by digoxin antibodies.</td>
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