Chapter 4. Anti-Anginal Drugs

Syllabus:

**Vasodilators:** Amyl nitrate, Nitroglycerin*, Pentaerythritol tetranitrate, Isosorbidedinitrite*

Dipyridamole

**Calcium channel blockers:** Verapamil, Bepridil hydrochloride, Diltiazem hydrochloride, Nifedipine, Amlodipine, Felodipine, Nicardipine, Nimodipine

4.1. **ANGINA PECTORIS**

Angina pectoris is a condition of myocardial ischemia.

Angina occurs due to imbalance between myocardial oxygen demand and myocardial oxygen supply.

Oxygen supply not meet as per demand lead to hypoxia condition resulting in myocardial tissue injury and followed to myocardial infarction.

Main reason is the coronary vasospasm and atherosclerosis that impaired the blood flow to the heart

4.1.1. Classification of Angina Pectoris

**Classical Angina:** occurs due to increase cardiac workload by exercise, emotional stress and cold condition. Atherosclerosis is the main reason. Depressed S-T segment in ECG. Treated by antiplatelet drugs and thrombolytics.

**Unstable Angina:** attack in rest condition (Pre-Infarct). Occurs due to extensive coronary artery blockage due to atheroma and vasospasm. Treated by vasodilators and antiplatelet drugs.

**Variant or Prinz metal Angina:** unpredictable and attack during sleep and rest. Coronary vasospasm is the main reason which is caused by stress, cold, smoking, etc. Elevation of S-T segment in ECG. Treated by vasodilators.

**Silent Angina:** Ischemia without symptoms.

Pharmacology/Pathophysiology lectures of Angina Pectoris

Pathophysiology: [https://youtu.be/0BgkxP-SY0I](https://youtu.be/0BgkxP-SY0I)

Drug Classification and MOA: [https://youtu.be/7xUAuwGYNMk](https://youtu.be/7xUAuwGYNMk)

Antiplatelet drugs: [https://youtu.be/EnuW_tOm0Yc](https://youtu.be/EnuW_tOm0Yc)
4.2. **ANTIANGINAL DRUGS**

Drugs which are used to treat angina pectoris are called antianginal drugs.

The basic goal is to improve the coronary blood flow and discard the atheroma.

**Drug Classifications**

**A. Vasodilators**

1. Nitrates:
   
   (a) *Short acting*: Glyceryl trinitrate (GTN, Nitroglycerine)
   
   (b) *Long acting*: Isosorbide dinitrate (short acting by sublingual route), Isosorbide mononitrate, Erythrityl tetranitrate, Penta erythritol tetranitrate

2. β *Blockers*: Propranolol, Metoprolol, Atenolol and others.

3. Calcium channel blockers:
   
   (a) *Phenyl alkylamine*: Verapamil
   
   (b) *Benzothiazepine*: Diltiazem
   
   (c) *Dihydropyridines*: Nifedipine, Felodipine, Amlodipine, S(-) Amlodipine, Nitrendipine, Lacidipine, Benidipine, Lercanidipine

4. Potassium channel opener: Nicorandil

**B. Others**

Dipyridamole, Trimetazidine, Ranolazine, Ivabradine, Oxyphedrine

**4.2.1. Medicinal Chemistry of Antianginal Drugs**

1. **Nitrates:**
   
   Organic Nitrates are the polyester of nitric acid (-C-O-NO2), which donate NO a potent vasodilator
   
   **MOA**: NO activates the soluble guanylyl cyclase enzyme which is responsible for production of cGMP and further cGMP promotes the vasodilation by activation of myosin light chain phosphatase (MLCP).
   
   **Uses**: Angina pectoris, myocardial ischemic diseases, cerebral or peripheral vascular disorders.
   
### Name | Structure and IUPAC name | Uses
---|---|---
**Amyl Nitrite** | ![Structure of Amyl Nitrite](image) 3-methyl-1-nitrosoxy butane | - Ischemic heart diseases  
- Antidotes for Cyanide poisoning by oxidation  
- In industries used as a cleaning agent

**Amyl Nitrate** | ![Structure of Amyl Nitrate](image) Pentyl nitrate | - Ischemic heart diseases

**Nitroglycerine (Glyceryl trinitrate; GTN)** | ![Structure of Nitroglycerine](image) 1,2,3-Trinitroxypropane | - Ischemic heart diseases  
- Heart failure  
- Taken sublingually in acute angina condition

Animated Video link: [https://youtu.be/OxOHprGvbpk](https://youtu.be/OxOHprGvbpk)
### Pentaerythritol tetranitrate

- 3-nitrooxy-2,2-bis(nitrooxymethyl)propyl] nitrate
- Ischemic heart diseases
- Also used as an explosive by military

### Isosorbide dinitrate

- 1,4:3,6-dianhydro-2,5-di-O-nitro-D-glucitol.
- Ischemic heart diseases
- Taken sublingually in acute angina condition

### Synthesis of Nitroglycerine

```
CH₂OH
CHOH
CH₂OH
  Glycerine

3 HNO₃
H₂SO₄

CH₃ONO₂
CH₂ONO₂
Nitroglycerine
```
Synthesis of Isosorbide dinitrate

2. Dipyridamole

2-[2-[bis(2-hydroxyethyl)amino]-4,8-di(piperidin-1-yl)pyrimido[5,4-d]pyrimidin-6-yl]-(2-hydroxyethyl)amino]ethanol

2,2',2'',2'''-[(4,8-dipiperidin-1-yl)pyrimido[5,4-d]pyrimidine-2,6-diyldinitrilo]tetraethanol

MOA: Dipyridamole acts by two pathways

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1) Inhibit the phosphodiesterase (PDE) enzyme and potentiate the cGMP & cAMP dependent effects.

2) Inhibit the cellular uptake of adenosine

**Uses:** It is an antiplatelet drug used along with anticoagulant drugs. It also dilate the blood vessels including coronary artery. It can be used in ischemic heart disease, pulmonary hypertension and thromboembolism.

### 3. Calcium Channel Blockers

(a) *Phenyl alkylamine:* Verapamil

(b) *Diaryl amino propyl amine:* Bepridil

(b) *Benzothiazepine:* Diltiazem

(c) *Dihydropyridines:* Nifedipine, Amlodipine, Felodipine, Nicardipine, Nimodipine

**Pharmacology of CCBs:** [https://youtu.be/7wRm1OY8bT8](https://youtu.be/7wRm1OY8bT8)

**Animated Video Link:** [https://youtu.be/9UMzJjXiNDM](https://youtu.be/9UMzJjXiNDM)

**A) Phenyl alkylamine:**

**Verapamil**

2-(3,4-dimethoxyphenyl)-5-[2-(3,4-dimethoxy phenyl)ethyl-methylamino]-2-propan-2-yl pentane nitrile

[www.youtube.com/pharmacologyconceptsbyrajeshchoudhary](http://www.youtube.com/pharmacologyconceptsbyrajeshchoudhary)
**MOA:** It blocks the l-type calcium channel mainly in myocardiocyte and suppress the cardiac activity. It also dilates arterioles and has some α-adrenergic activity.

**Uses:** It has been used in the treatment of hypertension, angina pectoris, cardiac arrhythmia, and most recently, cluster headaches.

**Dose:** 40 – 120 mg TID (oral).

**The R-enantiomer is more effective at reducing blood pressure compared to the S-enantiomer. However, the S-enantiomer is 20 times more potent than the R-enantiomer at prolonging the PR interval in treating arrhythmias.**

**B) Diaryl amino propyl amine:**

**Bepridil**

![Bepridil structure]

N-benzyl-N-[3-(2-methylpropoxy)-2-pyrroolidin-1-yl propyl] aniline

✓ Used in the treatment of Angina pectoris

**C) Benzothiazepine**

**Diltiazem**

![Diltiazem structure]

(+) cis-3-(acetyloxy)-5-[2-dimethyl amino)ethyl]-2, 3-dihydro-2-(4-methoxy phenyl)-benzothiazepin-4(5H)-one
**MOA:** It blocks the l-type calcium channel in myocardiocytes and blood vessels. Less potent than verapamil and nifedipine  
**Dose:** 30 – 60 mg TID/QID (oral).  
**Uses:** As an antihypertensive, antiarrhythmic & antianginal.

**D) Dihydropyridines**

They are **Vaso-selective** L-type calcium channel blockers, and not or little effects on heart

| **Nifedipine** | ▪ It dilates arterioles.  
▪ Nifedipine has no antiarrhythmic activity  
▪ It is used alone or in combination with diuretics or β-blockers in the management of hypertension.  
▪ It is also used in the prophylaxis of angina & in the treatment of Raynaud’s disease. |
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<tr>
<td><img src="image" alt="Nifedipine Structure" /></td>
<td>Dimethyl 1, 4-dihydro-2, 6-dimethyl-4-(2-nitrophenyl) pyridine-3, 5-dicarboxylate</td>
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| **Amlodipine** | ▪ Used in hypertension  
▪ and stable angina |
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<tr>
<td><img src="image" alt="Amlodipine Structure" /></td>
<td>3-O-ethyl 5-O-methyl 2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydro pyridine-3,5-dicarboxylate</td>
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| **Felodipine** | ▪ Used in hypertension  
▪ and stable angina |
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"www.youtube.com/pharmacologyconceptsbyrajeschoudhary"
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<tr>
<th>Compound</th>
<th>Molecular Structure</th>
<th>Properties</th>
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| Nicardipine         | ![Nicardipine Structure](image) | - It is a potent vasodilator, dilate the coronary artery and improve the blood flow  
- Used in ischemic heart disease  
- Also used in hypertension |
| Nimodipine          | ![Nimodipine Structure](image) | - It effectively dilates the cerebral blood vessels  
- Used in treatment of cerebral vascular disease |

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