ANTIANGINAL DRUGS

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Angina pectoris

• Disease affecting the coronary arteries which supply oxygenated blood from left ventricle to heart tissues

• The lumen of artery become restricted and it becomes less efficient in supplying the blood and oxygen to heart called as ischemia
Definition of Angina
GOALS OF TREATMENT

• Therapy of angina is mainly directed to minimize the Anginal attacks

• By restoring the balance between oxygen supply/oxygen demand to cardiac muscles or dilating coronary vessels

• Reversing and preventing myocardial ischemia

SUPPLY AND DEMAND.

• Improve the quality of life.
TYPES OF ANGINA

- Stable or classical
- Unstable angina or acute coronary syndrome
- Prinzmetal or variant angina
• What antianginal drugs do?

• Decrease the demand of oxygen or increase the supply of oxygen

• Dilates coronary arteries

• Decrease the after load
CLASSIFICATION

1) NITRATES:
a) **Short acting:** Glyceryl trinitrate (GTN)
b) **Long acting:** Isosorbide dinitrate, Isosorbide mononitrate, Erythrityl tetranitrate, Pentaerythrityl tetranitrate

2) B blockers: Metoprolol, Atenolol, Bisoprolol, Celiprolol

3) Calcium Channel Blockers:
a) Verapamil, Diltiazem
b) Dihydropyridine --- Nifedipine, Amlodipine, Nitrendipine, Nimodipine

4) Potassium Channel opener: Nicorandil, Pinacidil, Cromakalim, Minoxidil, Diazoxide

5) Cytoprotective drugs: Trimetazidine, Ranolazine.
Organic Nitrates

These are esters of simple organic alcohols or polyols with nitric acid

Glyceryl trinitrate (GTN)
Amyl nitrate
Isosorbide mononitrate,
Erythrityl tetranitrate,
Pentaerythrityl tetranitrate
I. Nitrites and Nitrates

1) Nitrates:
   a) Short acting: Glyceryl trinitrate (GTN)
   b) Long acting: Isosorbide dinitrate, Isosorbide mononitrate, Erythrityl tetranitrate, Pentaerythrityl tetranitrate

2) β-blockers: Metoprolol, Atenolol, Bisoprolol, Celiprolol

3) Calcium Channel Blockers:
   a) Verapamil, Diltiazem
   b) Nifedipine, Amlodipine, Nitrendipine, Nimodipine

4) Potassium Channel opener: Nicorandil, Pinacidil, Cromakalim, Minoxidil, Diazoxide

5) Cytoprotective drugs: Trimetazidine, Ranolazine.
Nitrates/nitrites

Mechanism of action:
Synthesis of nitrates

Isopentyl alcohol + HNO₃ → Amyl nitrite

Propene-1,2,3-triol + HNO₃ → Nitroglycerine
Synthesis of nitrates

Erythritol → Erythrityl Tetranitrate

Pentaerythritol + HNO₃/ H₂SO₄ → Pentaerythritol tetranitrate
Nitrates

**uses**
- Stable angina
- Unstable angina
- Cyanide poisoning

**Adverse effects**
- Head ache
- Palpitation
- Tolerance
Calcium channel blockers

- The contraction of the cardiac and vascular smooth muscle is dependent on extracellular calcium concentration.

- Transport of calcium into cardiac and vascular smooth muscle is regulated voltage-gated channel.
• Calcium channel blockers interacts L type channels and reduces the calcium flux through the channels

• This reduces the availability of intracellular calcium and leads to
  • Relaxation of arteriolar smooth muscle
  • Depress myocardial contractility
Calcium channel blockers

1,4-Dihydro Pyridines

<table>
<thead>
<tr>
<th>Compound</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>X</th>
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</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>-CH₂O(CH₂)₂NH₂</td>
<td>-C₂H₅</td>
<td>-CH₃</td>
<td>2-Cl</td>
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<tr>
<td>Felodipine</td>
<td>-CH₃</td>
<td>-C₂H₅</td>
<td>-CH₃</td>
<td>2,3-Cl</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>-CH₃</td>
<td>-CH₃</td>
<td>-CH₃</td>
<td>2-NO₂</td>
</tr>
</tbody>
</table>
Calcium channel blockers

Diphenyl alkylamines
Verapamil

[Chemical structure of Verapamil]
Calcium channel blockers

Benzothiazepine derivatives
Diltiazem

[Chemical structure diagram]
Synthesis of Nifedipine

Hantczsh
Synthesis of Verapamil

2-(3,4-Dimethoxyphenyl)acetonitrile + 2-Chloropropane → 3,4-Dimethoxy-2-isopropylvaleronitrile

NaNH₂ - HCl
Verapamil contd

3,4-Dimethoxy-2-isopropyl valero nitrile

3,4-Dimethoxy phenyl ethyl-N-methyl-3-chloro propylamine

Verapamil
Calcium channel blockers

- **Uses**
  - Hypertension
  - Vasospastic angina
  - Migraine
  - Preterm labour

- **Adverse effects**
  - Constipation
  - Bradycardia
  - Heart block
  - Gum hyperplasia
Beta Blockers

• Drugs that block the action of cathecholamines through beta receptors

• Non selective - Propranalol, nadolol
• Cardioselective – Metoprolol, atenolol, esmolol
• With additional alpha blocking - labetalol
BETA BLOCKERS

Synthesis

α-Naphthol + Epichlorohydrin → Propranolol
METAPROLOL

Route II: From p-(2-Methoxy ethyl) phenol

\[
\begin{align*}
\text{p-(2-Methoxy ethyl)phenol} & \quad \text{Epichlorhydrin} \\
\text{H}_2\text{COH}_2\text{CH}_2\text{C} & \quad \text{H}_2\text{COH}_2\text{CH}_2\text{C} \\
\text{OH} & \quad \text{OH} \\
\downarrow & \quad \downarrow \\
\text{Cl} & \quad \text{Cl} \\
\text{C} & \quad \text{C} \\
\text{CH}_2 & \quad \text{CH}_2 \\
\text{O} & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{NH}_2\text{CH(CH}_3\text{)}_2 & \quad \text{NH}_2\text{CH(CH}_3\text{)}_2 \\
\end{align*}
\]

Metoprolol
Potassium channel opener

- Nicorandil

- These drug opens the ATP – sensitive K channels

- Opening of this leads to hyper polarisation

- Followed by closing of calcium channels

- Less intracellular calcium -- muscle relaxation
Nicorandil

v. Nicorandil (Nicoram, Cortflo, Zynicor)

Synthesis:

Methyl nicotinate + 2-Aminoethanol → Nicorandil

HNO₃
Trimetazidiné

- Calcium Channel Blocker
- Protective effect on ischemic myocardium & left ventricular function
- used in Exertional angina
Thank you