

# Drugs used in treatment of Cardiovascular System

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## Angina

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# Angina

- Angina is a characteristic sudden, severe, pressing chest pain radiating to the neck, jaw, back, and arms.
- It is caused by coronary blood flow that is insufficient to meet the oxygen demands of the myocardium, leading to ischemia. The imbalance between oxygen delivery and utilization may result during exertion, from a spasm of the vascular smooth muscle, or from obstruction of blood vessels caused by atherosclerotic lesions.
- The oxygen requirement of myocardium depend on:
  1. Heart rate.
  2. Contractility.
  3. Wall tension:
    - A- thickness of the wall.
    - B- preload or venous return or end diastolic volume.
    - C- after load or intraventricular pressure.
- The blood flow in the coronary arteries depend on:
  1. Duration of diastole.
  2. Aortic pressure during diastole.

# Clinical types of Angina

1. **Stable angina (typical angina pectoris)**: is the most common form of angina. It is characterized by a burning, heavy, or squeezing feeling in the chest. It is caused by the reduction of coronary perfusion due to atherosclerotic plaque. The heart becomes vulnerable to ischemia whenever there is increased demand, such as that produced by physical activity, emotional excitement, or any other cause of increased cardiac workload.
2. **Prinzmetal's angina (variant angina)**: is an uncommon pattern of episodic angina that occurs at rest and is due to coronary artery spasm. Although individuals with this form of angina may have significant coronary atherosclerosis, the angina attacks are unrelated to physical activity, heart rate, or blood pressure.
3. **Unstable angina**: lies between stable angina on the one hand and myocardial infarction on the other. In unstable angina, chest pains occur with increased frequency and are precipitated by progressively less effort.
4. **Mixed forms of angina**: Patients with advanced coronary artery disease may present with angina episodes during effort as well as at rest, suggesting the presence of a fixed obstruction associated with endothelial dysfunction.

# Treatment of Angina

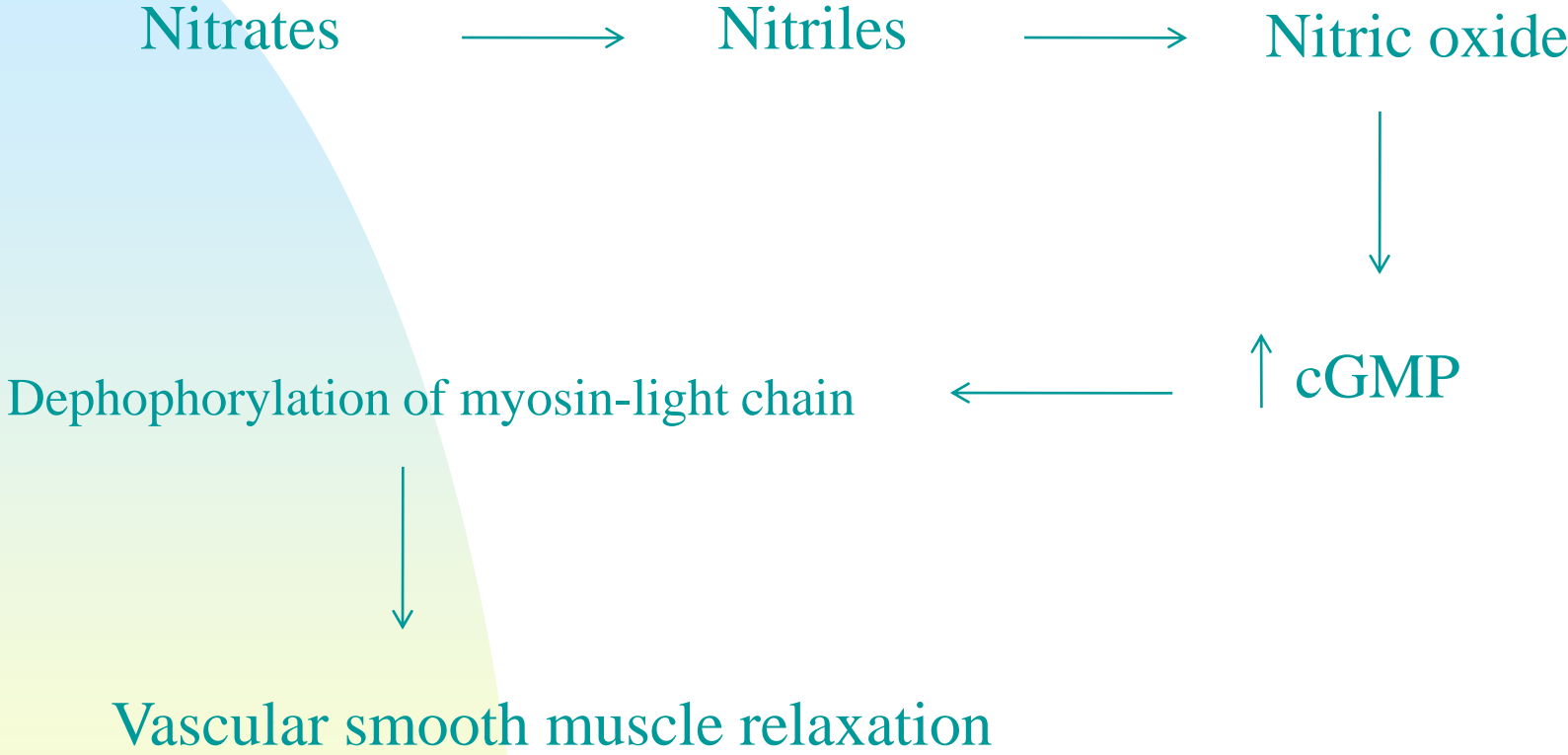
- Three classes of drugs are effective either alone or in combination in treating patients with stable angina:
  1. Nitrates.
  2. BB.
  3. CCB.
  
- 1. Typical angina pectoris is promptly relieved by rest or nitroglycerin (a vasodilator).
- 2. Prinzmetal's angina generally responds promptly to coronary vasodilators, such as nitroglycerin and calcium-channel blockers, but BB are contraindicated.
- 3. Unstable angina requires hospital admission and more aggressive therapy to prevent death and progression to myocardial infarction. The symptoms are not relieved by rest or nitroglycerin. Unstable angina is treated by anticoagulant plus the three classes of drugs.

# 1- Organic Nitrate

- They are effective in stable angina as well as in unstable angina and variant angina.
- **Effects on CVS:**
  1. **Dilation of the large veins:** resulting in pooling of blood in the veins. This diminished preload (venous return to the heart) and reduce the work on the heart.
  2. **Dilation of coronary vasculature:** providing high blood supply to the heart muscle.
  3. **Relaxing of arterioles:** high dose can causing diminished after load.
  4. **Other effects:**

Relaxation of the smooth muscle of the bronchi, GIT, biliary system and genitourinary tract, has been demonstrate experimentally. A decrease in platelet aggregation may result from the increasing in cyclic GMP.

# Mechanism of action



# Pharmacokinetic

- Organic nitrate are volatile, destroyed by heat, not affected by light and are not explosive.
- The bioavailability of traditional oral organic nitrates (nitroglycerin & isosorbide dinitrate) is very low because of high capacity of hepatic organic nitrate reductase.
- The sublingual route which avoids the 1<sup>st</sup> pass effect is therefore preferred to achieving therapeutic blood level rapidly. But the duration of action is brief.

# Preparation of organic nitrate

## 1. Glyceryl Trinitrate (Nitroglycerin):

### ■ The drug of choice for:

1. Prompt relief of an ongoing attack of angina precipitated by exercise or emotional stress.
  2. It may be also taken for prophylaxis before any exertion known to produce angina.
- It is available as sublingual tablets, lingual spray, percutaneous ointment and transdermal patches.
  - Sublingual nitroglycerin has a rapid onset of action (1-3 mins) and a short duration of action (20-30 mins).



## 2- Isosorbide (Mono& Di nitrate):

- It is an oral active nitrate. It is less rapidly metabolized in the liver and smooth muscle.
- It has lower potency than nitroglycerin in relaxing vascular smooth muscle.
- The drug is used for prophylaxis of angina and maintenance therapy.
- It is given sublingually also.
- The time to peak effect is 15 min. and the duration of action is 1 hr.

# Tolerance

with continuous exposure to nitrates, smooth muscle may develop complete tolerance (tachyphylaxis)

- Factors responsible for tolerance:

1. Diminished release of nitric oxide.
2. Systemic compensation by significant symp. Discharge & Na-water retention.

- Tolerance to the action of nitrates develops rapidly and can overcome by:

1. Provision of a daily nitrate free interval to restore sensitivity to the drug. This interval is typically (6-8 hrs.) usually at night because there is decrease demand on the heart at that time.
2. The nitrate free interval of patient of variant angina should be late afternoon because angina worsens early in the morning.

# Necorandil:

- It's an alternative to nitrate when tolerance to these is a problem.
- Nicorandil is a vasodilator with a mixed nitrate and ATP-dependant K-channel opening action.

# Adverse Effects:

1. Headache: 30-60% due to stretching of the pain sensitive tissues around the meningeal arteries.
2. Postural hypotension.
3. Facial flushing.
4. Tachycardia.
5. Methemoglobinemia (rare).

# 2- Calcium Channel Blockers:

- All CCB are vasodilators.
- In the cardiac muscles, these drugs cause a reduction in contractility throughout the heart and decrease in S.A. node (pace maker rate) & in A.V. node conduction velocity.
- They decrease arteriolar tone & systemic vascular resistance resulting in decrease in arterial pressure (decrease afterload).
- **Verapamil** mainly affects the myocardium, whereas **Nifedipine** exerts a great effect on s.m. in peripheral vasculature. **Diltiazem** is intermediate in its action.

# Chemical Classes of CCB

1. Dihydropyridines: Nifedipine is arteriolar vasodilator with minimal effect on heart rate. It is useful in variant angina.
2. Benzothiazepines: Diltiazem affects both cardiac & vascular s.m.
3. Diphenylalkylamines: Verapamil slows cardiac conduction directly and thus dec. H.R. & O<sub>2</sub> demand.

# 3- B-adrenoceptor blockers

- ❖ Decrease H.R. , B.P. and contractility which reduces myocardial oxygen demand at rest and during exercise.
- ❖ Lower H.R. is also associated with inc. in diastolic perfusion time that may inc. myocardial perfusion.
- ❖ It's not used for acute anginal attacks.
- ❖ BB reduces frequency and severity of anginal attacks
- ❖ BB contraindicated in patient with DM, PVD and COPD.

# End of Angina

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