

Anti- Anginal drugs

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Overview

2

- ▶ **Coronary Heart Disease (CHD)** includes **chronic angina pectoris (stable angina)** and a group of acute coronary syndromes consisting of **unstable angina** and **myocardial infarction (MI)**
- ▶ Two forms MI can be distinguished by the presence or lack of ST segment elevation on the electrocardiogram
- ▶ All of these conditions are caused by coronary artery ischemia (inadequate blood flow) resulting from atherosclerosis, formation of thrombi or coronary vasospasms
- ▶ Generally, **typical angina** results from formation of atherosclerotic plaques in vessel walls that limit coronary blood flow and the supply of oxygen to the myocardium
- ▶ **Angina pectoris** is the chest pain that is experienced to reduced blood flow and subsequent insufficient oxygen supply to the part of the heart

Phases of coronary artery disease

3

- ▶ Though the disease progression is not always followed, below is the established diseases disease phases progression
- ▶ Asymptomatic disease → stable angina → progressive angina → unstable angina → non-ST-segment elevation MI, and ST-segment elevation MI

Symptoms of Angina

- ▶ Chest pain and discomfort that sometimes radiates to shoulders, arms, neck, jaw, abdomen or back and may even feel like indigestion
- ▶ Heavy weight or pressure on the chest (Chest heaviness)
- ▶ Dizziness
- ▶ Fatigue
- ▶ Nausea
- ▶ Shortness of breath
- ▶ Sweating

Types of angina

Stable angina

- ▶ This involves the symptoms occurring due to increased physical activity like exercises where oxygen supply becomes insufficient

Unstable angina

- ▶ This is when the frequency and severity of attacks increases over time
- ▶ It may be caused by occlusion of a coronary vessel by small platelet thrombi and ruptured atheromatous plaque and most oftenly a forerunner of MI

Variant angina (Prinzmetal angina)

- ▶ This is caused by acute coronary vasospasm and may occur at rest or during sleep

Drugs use in management of Angina

Types or categories of anti – angina drugs

- ▶ Vasodilators
 - Nitrites or nitrates
 - Calcium channel blockers
- ▶ Beta blockers
- ▶ Myocardial metabolism modifiers

Vasodilators

1. Nitrates

- ▶ Amyl nitrite
- ▶ Nitroglycerine (Glyceryl trinitrate)
- ▶ Isorsobide mononitrate
- ▶ Isorsobide dinitrate

2. Calcium Channel blockers

- ▶ Nifedipine
- ▶ Amlodipine
- ▶ Nimodipine
- ▶ Diltiazem
- ▶ Verapamil

Organic nitrites or nitrates

9

- ▶ Onset of action and duration of action is dependent on the physical properties, route of administration and rate of biotransformation
- ▶ Amyl nitrite has the most rapid onset and shortest duration of action
- ▶ Isosorbide compounds have the slowest onset of action and the longest duration of action

Amyl nitrite

10

- ▶ Volatile liquid that can be inhaled and absorbed through the lungs
- ▶ Its action is rapid in action (30 seconds) and brief in duration (3 to 5 minutes)

Indications for Amyl nitrite

- ▶ Very effective for management of acute angina attacks
- ▶ Management of Cyanide where its used until sodium nitrite and sodium thiosulfate
- ▶ Nitrites oxidise hemoglobin to methemoglobin which in comparison haemoglobin has a greater affinity for cyanide
- ▶ It is therefore used to trap the compound in the form of cyanmethemoglobin and then
- ▶ Sodium thiosulfate is administered to convert cyanide to thiocyanate

**NITROGLYCERINE , ISORSOBIDE DINITRATE
AND
ISORSOBIDE MONONITRATE**

Nitroglycerine (Glyceryl trinitrate)

- ▶ Nitroglycerine is available for sublingual, transdermal, topical, oral and i.V administration
- ▶ Its solubility in water and lipids permits its rapid dissolution and absorption after sublingual or buccal administration for treatment of acute angina attacks
- ▶ The patches slowly release for absorption through the skin into circulation and is used in the prevention of angina attacks

Nitroglycerine (Glyceryl trinitrate) Cont'd

- ▶ Ointments are used for horizontal patients with angina or MI
- ▶ Sustained release capsules are used for prevention of angina pectoris
- ▶ The drug is well absorbed from the gut but undergoes considerable first pass metabolism and hence calling for larger doses when administered orally

Isorsobide dinitrate

14

- ▶ Can be administered orally and sublingually
- ▶ Used for both treatment and prevention of angina attacks
- ▶ Produces same effects as nitroglycerine but it has slightly lower onset of action and a greater duration of action
- ▶ It is converted to an active compound, isorsobide mononitrate which is now available as a drug preparation itself

Mechanism of action of Nitrates

15

- ▶ Promotes the release of aldehyde dehydrogenase in the release of nitric oxide
- ▶ Nitric oxide is a gas that activates guananyl cyclase and hence leading to the formation of cyclic Guanosine Monophosphate (cGMP)
- ▶ cGMP activates cGMP dependent kinases that cause relaxation of vascular smooth muscles preferentially the venous smooth muscle
- ▶ This leads to venous pooling of blood, a decrease in venous blood return to the heart and decrease in ventricular volume, pressure, and wall tension
- ▶ By doing this nitrates cardiac work and oxygen demand and thereby, relieving or preventing angina pectoris

Tolerance to Nitrates

16

- ▶ Continuous administration of nitroglycerine and other organic nitrates often leads to pharmacodynamic tolerance to their vasodilative effects
- ▶ It has been demonstrated to occur with intravenous, transdermal and oral administration of nitrates
- ▶ To prevent nitrate tolerance and loss of therapeutic effect, skin patches should be removed for at least 10 hours each day
- ▶ Furthermore, each long acting oral medication should only be administered only once or twice daily

Mechanism of Tolerance to Nitrates

- ▶ Studies suggest that anion free radicals (O^{2-}) are formed during the release of nitric oxide from organic nitrates and mitochondrial aldehyde dehydrogenase
- ▶ These free radicals then inactivate aldehyde dehydrogenase and thereby leading to tolerance

Side effects of nitrates

- ▶ Most common adverse effects of organic nitrates which are caused by excessive vasodilation include
 - ▶ Headache
 - ▶ Hypotension
 - ▶ Dizziness
- ▶ Reflex tachycardia (this can increase oxygen demand and counteract the effects of nitrates – Patients should avoid excessive doses)
- ▶ To prevent reflex tachycardia, a beta blocker can be used together with an organic nitrate or other type of vasodilator
- ▶ Sildenafil and other 5 – phosphodiesterase inhibitors used in erectile dysfunction usually potentiate the hypotensive effects of organic nitrates (They both increase cGMP levels , leading to vasodilation)
- ▶ This concurrent use should must therefore, be avoided as this profound hypotensive effect causes tachycardia which in some episodes has been fatal

CALCIUM CHANNEL BLOCKERS (CCBs)

Examples of CCBs

Dihydropyridines

- ▶ Nifedipine
- ▶ Amlodipine
- ▶ Nicardipine
- ▶ Felodipine
- ▶ Nimodipine

Non –dihydropyridines

i. Diphenylalkylamines

- ▶ Verapamil

ii. Benzothiazepines

- ▶ Diltiazem

Mechanism of action CCBs in angina

21

- ▶ Calcium channel ions are located in the plasma membranes of smooth muscle and cardiac tissues
- ▶ There are two types of channels, the L and the T types which are both found in the vascular smooth muscles, sinoatrial (SA) and atrioventricular (AV) nodes however, only the L-Type channels are found in the muscle cells of the heart
- ▶ The influx of calcium through these channels lead to membrane depolarisation thus initiating or strengthening muscle contraction
- ▶ CCBs bind to these calcium channels and alter their conformation leading to preventing the influx of calcium into cells
- ▶ This produces smooth muscle relaxation and eventually suppresses cardiac activity
- ▶ Whereas all CCBs cause vascular smooth muscles to relax, they differ markedly in their effects on their effects on cardiac muscles with non - dihydropyridines (diltiazem and verapamil) exhibiting more cardiac effect than dihydropyridines

Descriptions of specific drugs

22

- ▶ Amlodipine, nifedipine, nicardipine and felodipine are approved for treatment of angina
- ▶ Amlodipine has long elimination half life and is administered once daily
- ▶ Felodipine and nifedipine are available in sustained release formulations given once daily
- ▶ Nimodipine is not used in angina but reserved in for the purpose of reducing complications of Subarachnoid haemorrhage which is one of the causes of stroke
- ▶ Nimodipine achieves its effect by dilating small cerebral vessels and hence improving collateral circulation to the affected areas of the brain
- ▶ Nimodipine should only be administered by mouth or feeding tube and never by I.V that has caused severe hypotension, cardiac arrest and fatalities

Description of specific drugs (Cont'd)

23

- ▶ Diltiazem and verapamil are effective treatments of typical and variant angina
- ▶ Caution should be exercised when administering these drugs in patients with heart failure because of their ability to suppress cardiac contractility especially verapamil
- ▶ In patients with angina but without heart failure, these drugs have an advantage of reducing the heart rate and contractility in addition to their effects on myocardial wall tension
- ▶ Both verapamil and diltiazem reduce the clearance of digoxin thereby leading to increased serum digoxin levels and hence precipitating digoxin toxicity
- ▶ Therefore digoxin doses should be reduced when being taken along side diltiazem and verapamil

Side effects of CCBs

24

- ▶ Fatigue
- ▶ Headache
- ▶ Dizziness
- ▶ Flushing

- ▶ Peripheral edema

- ▶ Higher incidence of Myocardial infarction and cardiac failure especially the immediate release formulations
 - In this vain, it is recommended that long acting or sustained release formulations used to avoid occurrence of complications

- ▶ Occasional gingival hyperplasia

- ▶ Diltiazem and verapamil causes constipation due to reduced peristalsis caused by increased muscle relaxation

Beta Adrenergic Antagonists

Examples of Beta blockers

- ▶ Atenolol, metoprolol, nadolol and propranolol

Mechanism of Action

- ▶ Prevention of exercise induced tachycardia (Improved exercise tolerance)
- ▶ Reduce myocardial oxygen demand
- ▶ Prevention of reflex tachycardia induced by either organic nitrates or dihydropyridine CCBs

Indications

- ▶ Used in the treatment typical angina pectoris and acute MI

Pre – cautions when using beta blockers

- ▶ Beta blockers have a negative inotropic effect that can be hazardous to patients with heart failure if large doses are given
- ▶ Combination of verapamil and beta blockers should be avoided as it may significantly reduce cardiac output
- ▶ The combination of a beta blockers and diltiazem is less hazardous

Modifiers of Myocardial Metabolism

Examples of Myocardial metabolism modifiers

- ▶ Ranolazine
- ▶ Trimetazidine
- ▶ Ischemic heart diseases have for a long time been treated using drugs that decrease heart rate and contractility
- ▶ There is a newer group of drugs whose mechanism is that improving myocardial metabolism without altering heart rate or blood pressure

Ranolazine

- ▶ Approved as first line for chronic stable agent for chronic stable angina

Mechanism of action

- ▶ Primarily blocks the pathologic activation or prolongation of late inward sodium current in the heart cells thereby, leading to excessive intracellular sodium and calcium
- ▶ This leads to in-balance between oxygen supply and demand during ischemia
- ▶ By this mechanism, ranolazine is believed to reduce diastolic tension wall, improve sub-endocardial perfusion and reduce oxygen consumption

Indications

- ▶ Clinically ranolazine increases exercise capacity in angina resulting in fewer angina symptoms and decreasing the need for nitroglycerine use
- ▶ The drug seems to be attractive alternative to the old conventional drugs and can be used with B- blockers and nitrates
- ▶ Clinical trials suggest that ranolazine also improves glycemic control in diabetes, improves vascular endothelial function through increased vasodilation and decreases incidences of atrial fibrillation

Side effects

- ▶ Mild dizziness
- ▶ Headache
- ▶ Nausea
- ▶ Constipation in about 2% of patients

Trimetazidine

- ▶ Under normal circumstances glucose , fatty acids and lactate as a source of energy
- ▶ In all this glucose is metabolised more efficiently and generates more energy per unit of oxygen used
- ▶ Inhibits keto-acyl coenzyme thiolase, a key enzyme in the B-oxidation pathway of fatty acid metabolism
- ▶ This resulting decrease in fatty acid oxidation evokes a compensatory increase in glucose metabolism and reduce oxygen consumption by 20%
- ▶ Trimetazidine has also been found to increase ejection fraction in persons with left ventricular dysfunction

Order of management of Angina Pectoris Sequence

33

Aim of Angina treatment

- ▶ In patients with angina pectoris, the primary objectives of drug therapy are;
 - i. Relieve acute symptoms
 - ii. Prevent ischemic attacks
 - iii. Improve quality of life
 - iv. Reduce risks of Myocardial infarction and other CVS complications
- ▶ Treatment of concurrent hypertension, hyperlipidemia, diabetes and obesity can slow down coronary artery progression
- ▶ Antithrombotic agents reduce coronary thrombosis and myocardial function e.g. Aspirin has been shown to prolong life of angina pectoris patients

Order of management of Angina Pectoris sequence Cont'd

34

- ▶ If a patient only has an occasional angina episode, sublingual nitroglycerin can be used as needed to relieve acute symptoms
- ▶ If episodes occur predictably with exertion, sublingual nitroglycerin or Isorsobide dinitrate can be taken as a prophylactic measure just before exertion
- ▶ Patients with severe angina requiring regular use of sublingual nitroglycerin may benefit from prophylactic therapy with Beta blocker, long acting nitrate or a CCB may be chosen as initial therapy
- ▶ Ranolazine offers an attractive alternative or adjunct to traditional drugs for angina
- ▶ Beta blockers lower the risk MI and possibly improve survival in patients with stable angina reduced angina

Order of management of Angina Pectoris Cont'd

35

- ▶ Patients with unstable angina have a high risk of MI and should receive aspirin or other antithrombotic drugs to prevent thrombus formation
- ▶ Beta blockers are more stable than CCBs in patients with unstable angina
- ▶ CCBs are more effective than Beta blockers in management of variant angina which caused by coronary vasospasm
- ▶ In patients with angina concomitant with asthma, CCBs are more preferred as beta blockers cause bronchospasms
- ▶ In angina with diabetes, CCBs are preferred or Beta 1 agonists or probably a third generation Beta blockers like carvedilol
- ▶ In patients with angina and heart failure, a long acting nitrate may be required for angina prophylaxis

END