Drug used in IHD

Principles of drug therapy

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Angina

- **IHD – most common cardiovas disease in the world**
- **Angina**: when oxygen demand **>** supply - ischaemia
- Occurs when there is a:

  1. Sudden increase in demand for oxygen in a chronically ischaemic heart (stable angina)

  2. When there is a spasm in a coronary artery (variant / atypical angina)

  3. Rupture of an atheromatous plaque (unstable angina, an acute coronary syndrome

Angina

- Worsened by exercise, alleviated by rest
- Pointer to coronary artery disease
- Atheromatous obstruction of large coronary vessels (CAD) – commonest cause

Therapeutic strategies

(i) Increase oxygen supply / delivery

(ii) Reduce oxygen demand

Achieved by:

- reduce preload - vasodilators **(nitrates)**
- reduce afterload - vasodilators **(CCB)**
- reduce heart rate / contractility **(beta blockers)**
- reduce coronary arterial tone **(nitrates)**

Treatment of angina

- General management
- Medical management
  - Prognostic: Aspirin / clopidogrel / statins
  - Symptomatic: nitrates, ß-blockers, CCB, nicorandil
- Revascularization
  - Angioplasty / bypass surgery

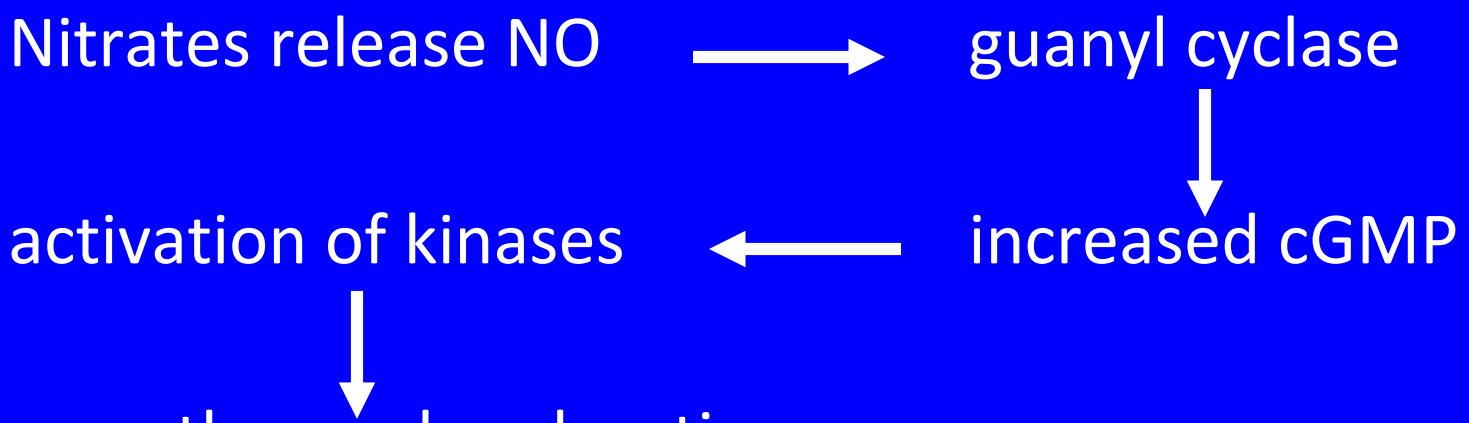
Nitrates

Pharmacological effects useful in angina

- Dilates syst. veins - reduced venous return & lowers LV end-diastolic pressure/volume (preload)
- Dilates large coronary arteries to:
  - redistribute blood along collaterals & from epicardial to endocardial regions
  - relieve coronary artery spasm including arterial constriction induced by exercise
- Dilates arterioles (larger doses) - reduced PR (reduced myocardial O_2 consumption)

Nitrates - mechanism of action

Act by relaxing smooth muscle



- NO does not require an intact endothelium for vasodilatation
- Nitrates dilate blood vessels in the presence of endothelial dysfunction
- ?Reduced platelet aggregation

Nitrates - kinetic data

GTN - first pass metabolism in the liver

- Usually given sublingually (0.5 mg) - effect begins in one / two min and lasts up to 30 min
- Well absorbed through skin - transdermal patches - sustained effect (12 - 14 hours)
- For occasional treatment - sublingual spray (indefinite shelf-life)

Nitrates - kinetic data

Isosorbide di & mononitrate (ISDN/ISMN)

- Longer acting than GTN - similar actions
- Taken orally (5 - 30 mg t.d.s. / 40 mg b.d.)
- Half-life about 4 hours - for prophylaxis
- Slow release formulations for once/day use
  - smooth kinetic profile & avoids tolerance
- ISMN preferred to ISDN - predictable response

Nitrates - adverse effects

- Vasodilatation - headache, flushing, reflex tachycardia, dizziness, syncope
- Orthostatic hypotension – syncope
- Tolerance - with prolonged use, mainly with skin patches (remove patches overnight)
- Formation of methaemoglobin - ineffective as an oxygen carrier

Nitrates - clinical uses

- Stable chronic angina
  - treatment (acute attack): sublingual GTN
  - prevention: regular ISMN / demand GTN
- Unstable angina - iv GTN (with other drugs)
- LVF - to reduce cardiac preload (mainly for those who cannot tolerate ACE inhibitors)
- Acute pulmonary oedema
- Hypertensive emergencies (iv GTN)

Calcium channel blockers (CCB)

- **CCB** reduce myocardial oxygen demand
  - reduce arterial & intraventricular pressure
  - reduced heart rate (verapamil & diltiazem)
- **CCB** also reduce focal coronary artery spasm in variant angina – most effective prophylactic treatment for this type of angina

Beta-blockers

- Although not vasodilators most useful in effort angina:
- reduced heart rate: reduced O2 demand & increased diastolic perfusion time & coronary perfusion
- reduced BP
- reduced myocardial contractility
- Reduces myocardial O2 demand – rest & exercise

RCTs – better outcome & symptomatic improvement in patients with stable angina than CCB

Nicorandil

- Powerful vasodilator – coronary arteries
- Activates cardiac ATP-dependent K channels
- One large RCT – reduction of fatal / non-fatal coronary events with this drug
- Registered for use in some countries including SL

Figure 2. Invention of therapeutic drugs contributes to reduction in deaths from cardiovascular disease (*A*) and AIDS (*B*). *A*, Adapted by permission from Reference 22; *B*, Adapted by permission from Reference 23.

Reduction in deaths from CV disease after introduction of statins

Other medications:

- Anti-platelet drugs
- Lipid lowering agents