ANTI-ANGINAL DRUGS

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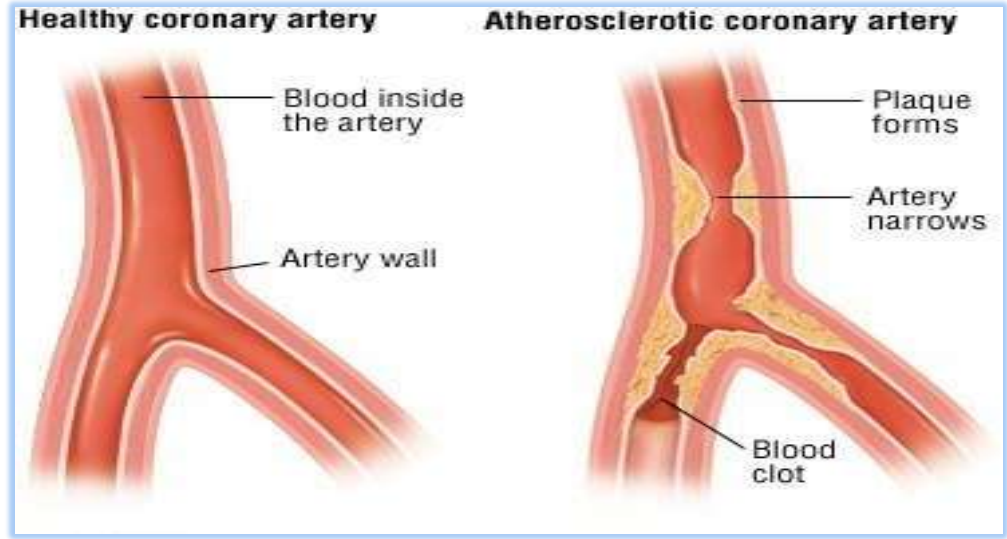
INTRODUCTION

- **ANGINA PECTORIS:–** Chest pain due to imbalance between the oxygen requirement of the heart and oxygen supplied to it via the coronary vessels.

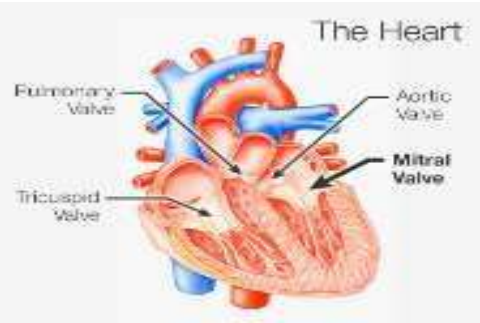
  Angina pectoris refers to a strangling or pressure-like pain caused by cardiac ischemia.

  The pain is usually located substernally but is sometimes perceived in the neck, shoulder and arm, or epigastrium.



Causes of chest pain

- Pericarditis (caused by a variety of infectious agents, e.g., bacteria, fungi, and viruses, autoimmune disorders, renal failure, and trauma)
- Mitral Valve Prolapse
- Pulmonary Embolism (is an infarct of the lung)
- Pleurisy (is chest pain associated with inflammation of the pleural lining of the lungs)
- Hyperventilation Syndrome (is caused by fear or panic induced hyperventilation)
- Trauma/Rib Fracture
- Chest Wall Twinge Syndrome (Precordial Catch) (is due to intercostal muscle spasm)
- Costochondritis (an inflammation of the cartilage between the rib end and the sternum)
- Esophagitis, Acute or Chronic (GERD)



Reference: Chest Pain. In: Herrier RN, Apgar DA, Boyce RW, Foster SL. eds. *Patient Assessment in Pharmacy* New York, NY: McGraw-Hill; 2015.

TYPES OF ANGINA PECTORIS

1. Classical angina (Stable angina) –

- due to atherosclerosis of coronary arteries

2. Variant/ Prinzmetal's angina –

- due to coronary vasospasm

3. Unstable angina –

- progressive occlusion of the coronary artery

- rupture of an atheromatous plaque & platelet aggregation at the ruptured plaque

Reference: Drugs Used in the Treatment of Angina Pectoris. In: Trevor AJ, Katzung BG, Kruidering-Hall M. eds. *Katzung & Trevor's Pharmacology: Examination & Board Review, 11e* New York, NY: McGraw-Hill; 2015.

Classification of antianginal drugs

- **Nitrates**
  - **Short acting:** Glyceryl trinitrate (GTN, Nitroglycerine)
  - **Long acting:** Isosorbide dinitrate (short acting by sublingual route), Isosorbide, mononitrate, Erythrityl tetranitrate, Pentaerythritol tetranitrate
- **β Blockers:** Propranolol, Metoprolol, Atenolol and others.
- **Calcium channel blockers**
  - **Phenyl alkylamine:** Verapamil
  - **Benzothiazepine:** Diltiazem
  - **Dihydropyridines:** Nifedipine, Felodipine, Amlodipine, Nitrendipine, Nimodipine, Lacidipine, Lercanidipine, Benidipine

Classification of antianginal drugs

- **Potassium channel opener:** Nicorandil
- **Others:** Dipyridamole, Trimetazidine, Ranolazine, Ivabradine, Oxyphedrine

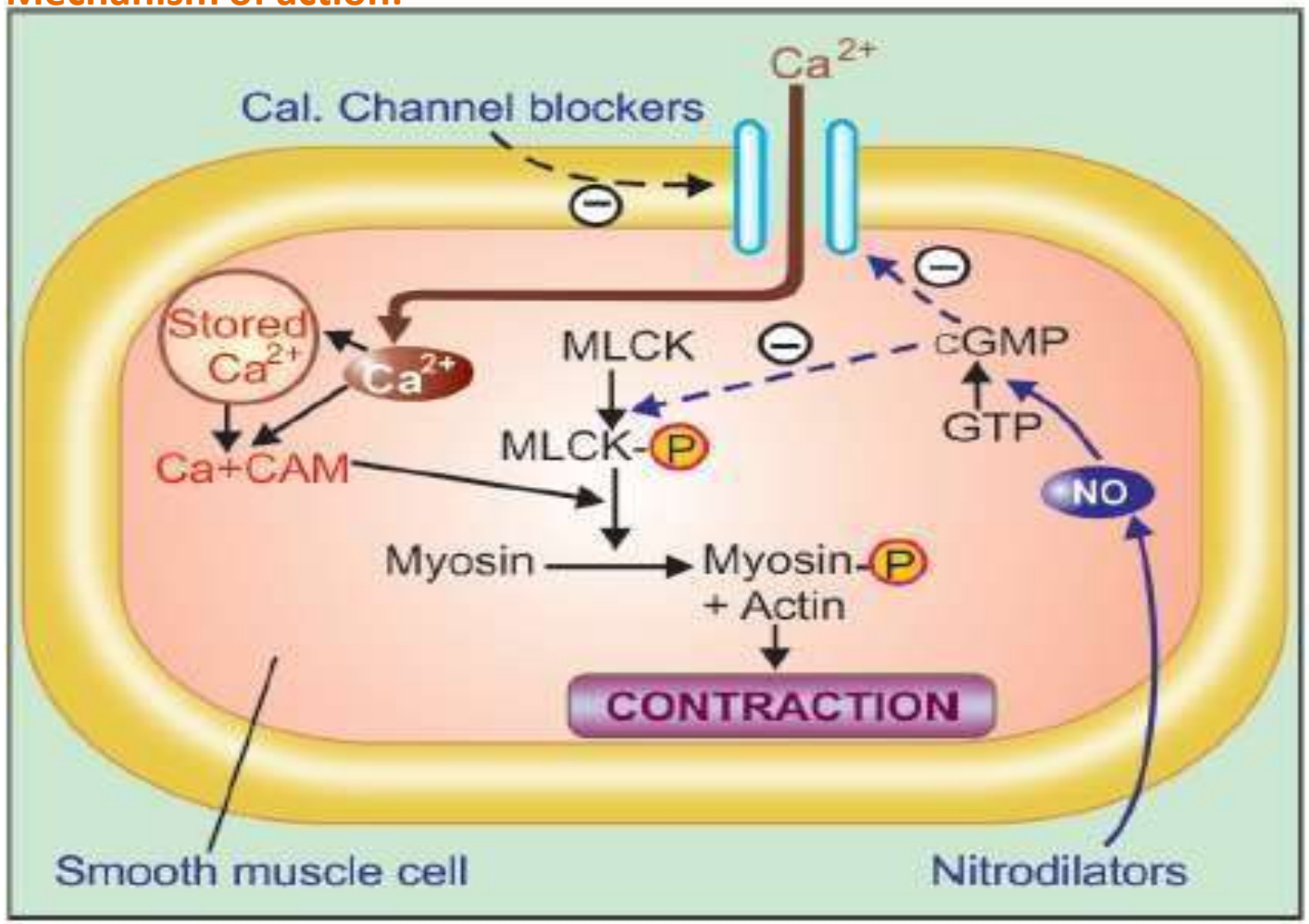
- **Clinical classification**
- **Used to abort or terminate attack:** GTN, Isosorbide dinitrate (sublingually).
- **Used for chronic prophylaxis:** All other drugs.

Nitrates/ Organic Nitrates

- **Preload reduction:** Peripheral pooling of blood → decreased venous return (preload reduction).
- **Afterload reduction:** Nitrates also produce some arteriolar dilatation → slightly decrease total peripheral resistance or afterload on heart.
- **Redistribution of coronary flow:** In the arterial tree, nitrates preferentially relax bigger conducting (angiographically visible) coronary arteries than arterioles or resistance vessels.

Nitrates/ Organic Nitrates

Mechanism of action:



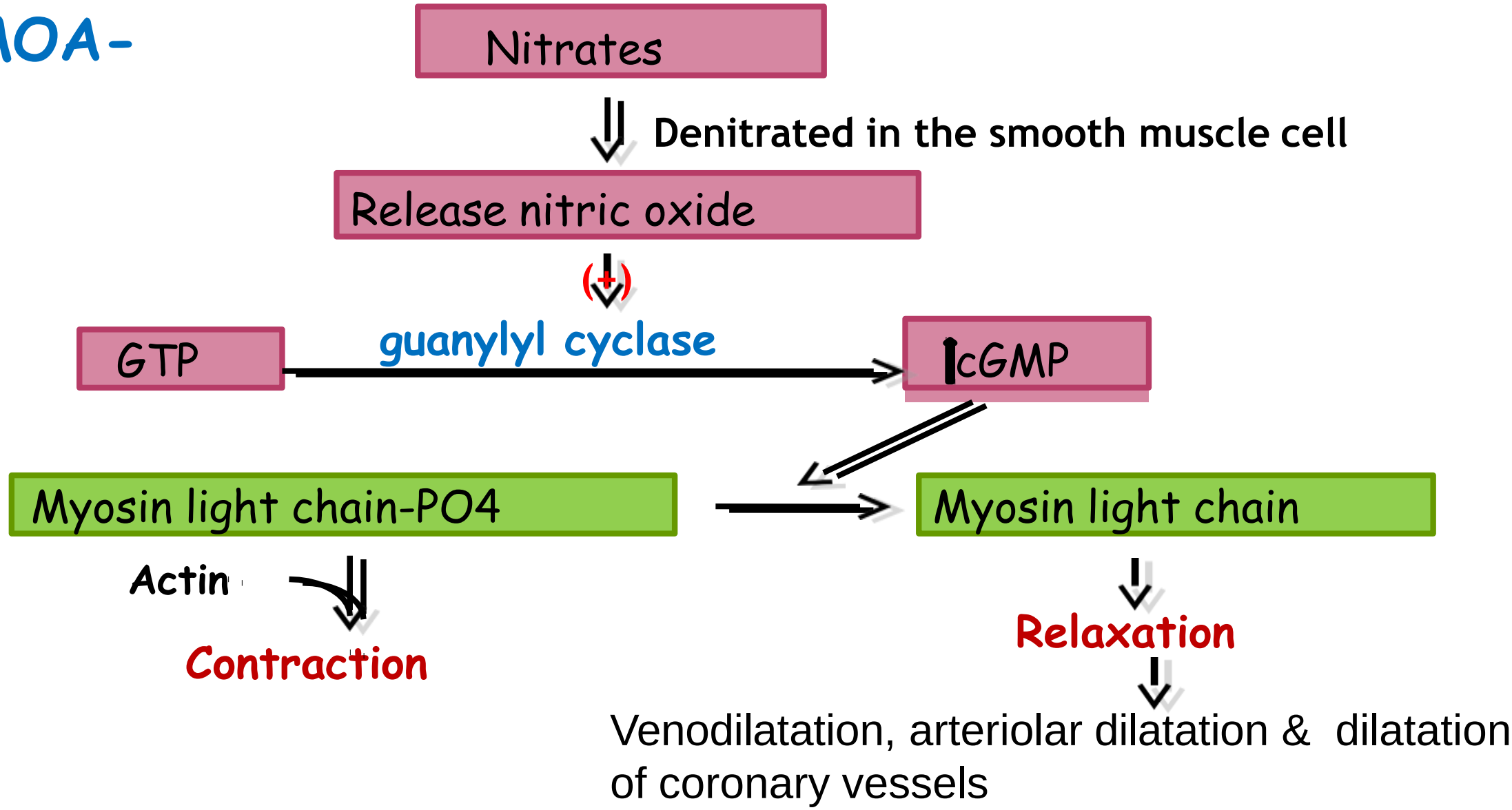
Mechanism of vascular smooth muscle relaxant action of nitrodilators like glyceryl trinitrate and calcium channel blockers

- (- - -→) Inhibition
- CAM—Calmodulin;
- NO—Nitric oxide
- MLCK—Myosin
- light chain kinase
- MLCK-P—Phosphorylated MLCK
- GTP—Guanosine triphosphate;
- cGMP—Cyclic guanosine monophosphate

References: Tripathi, K. (2013). Essentials of medical pharmacology (7th ed.). New Delhi: Jaypee Brothers.

Nitrates

MOA-



Nitrates/ Organic Nitrates

Mechanism of action:

- The organic nitrate agents are prodrugs that are sources of NO. **NO activates the soluble isoform of guanylyl cyclase**, thereby **increasing intracellular levels of cGMP**. In turn, **cGMP promotes the dephosphorylation** of the myosin light chain and the **reduction of cytosolic Ca^{2+} and leads to the relaxation of smooth muscle** cells in a broad range of tissues.

References: Eschenhagen T. Treatment of Ischemic Heart Disease. In: Brunton LL, Hilal-Dandan R, Knollmann BC. eds. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e* New York, NY: McGraw-Hill

Pharmacological actions

1. Vascular smooth muscles –

- Preload reduction (prominent action)
- Afterload reduction
- Redistribution of coronary blood flow

a) Dilatation of capacitance vessels

⇓

Pooling of blood in veins Decrease

⇓

venous return to heart

⇓

decrease preload

⇓

decrease in end diastolic pressure decrease

⇓

in O_2 demand

b) Arteriolar dilatation

↓

decrease peripheral resistance

↓

decrease afterload decrease in

↓

cardiac work

c) Relaxation of coronary arteries

↓

redistribution of blood flow to ischaemic areas in angina patients

2. Relaxation of smooth muscles of the bronchi, biliary tract & esophagus

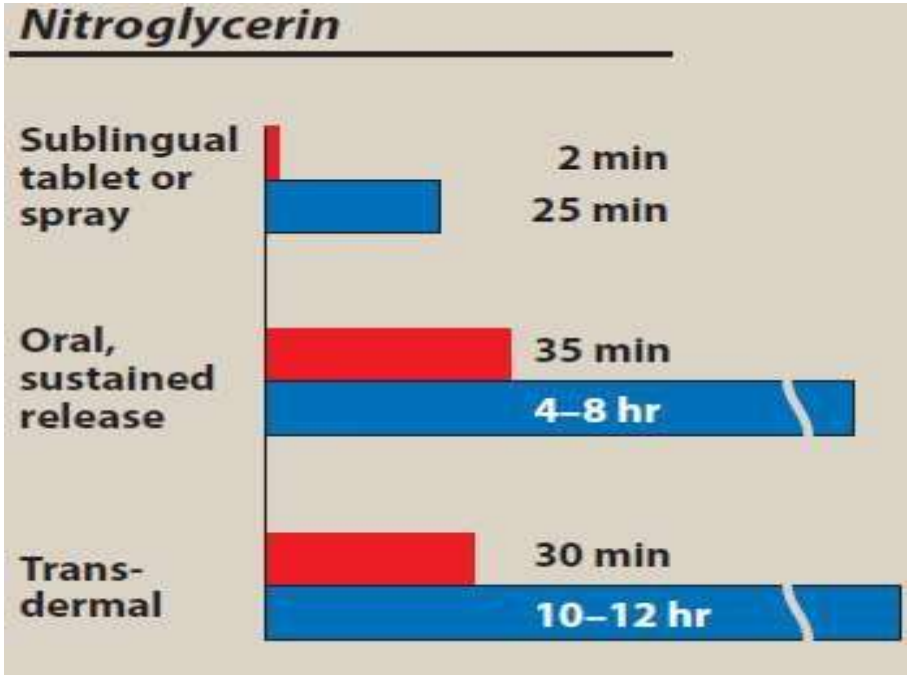
Nitrates/ Organic Nitrates

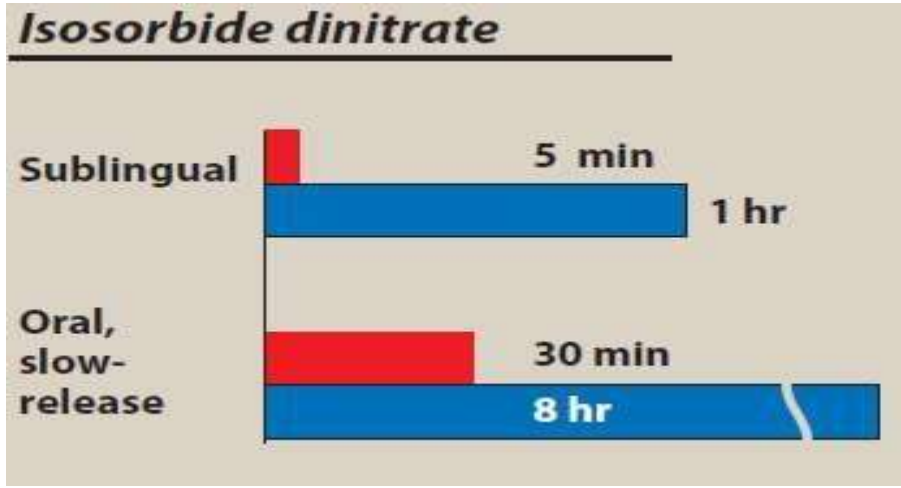
Pharmacokinetics:

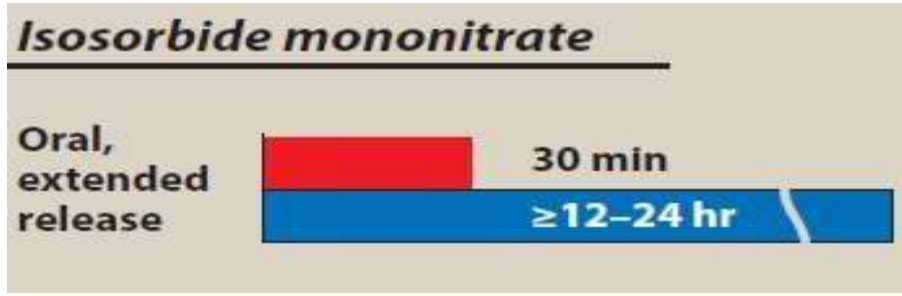
- Organic nitrates are lipid soluble, well absorbed from buccal mucosa, intestines and skin.
- Ingested orally, **all except isosorbide mononitrate** undergo extensive and variable first pass metabolism in liver. They are rapidly denitrated by a glutathione reductase and a mitochondrial aldehyde dehydrogenase.

Nitrates/ Organic Nitrates

Pharmacokinetics:







Nitrates/ Organic Nitrates

Adverse effects:

- Headache is the most common adverse effect of nitrates. High doses of nitrates can also cause postural hypotension, facial flushing, and tachycardia.
- Phosphodiesterase type 5 inhibitors such as **sildenafil** potentiate the action of the nitrates. To preclude the **dangerous hypotension** that may occur, this combination is contraindicated.

Nitrates/ Organic Nitrates

Tolerance:

- Tolerance to the actions of nitrates develops rapidly as the blood vessels become desensitized to vasodilation. Tolerance can be overcome by providing a daily "**nitrate- free interval**" to restore sensitivity to the drug.

Dependence:

- Sudden withdrawal after prolonged exposure has resulted in spasm of coronary and peripheral blood vessels. ***Withdrawal of nitrates should be gradual***.

Nitrates/ Organic Nitrates

Uses:

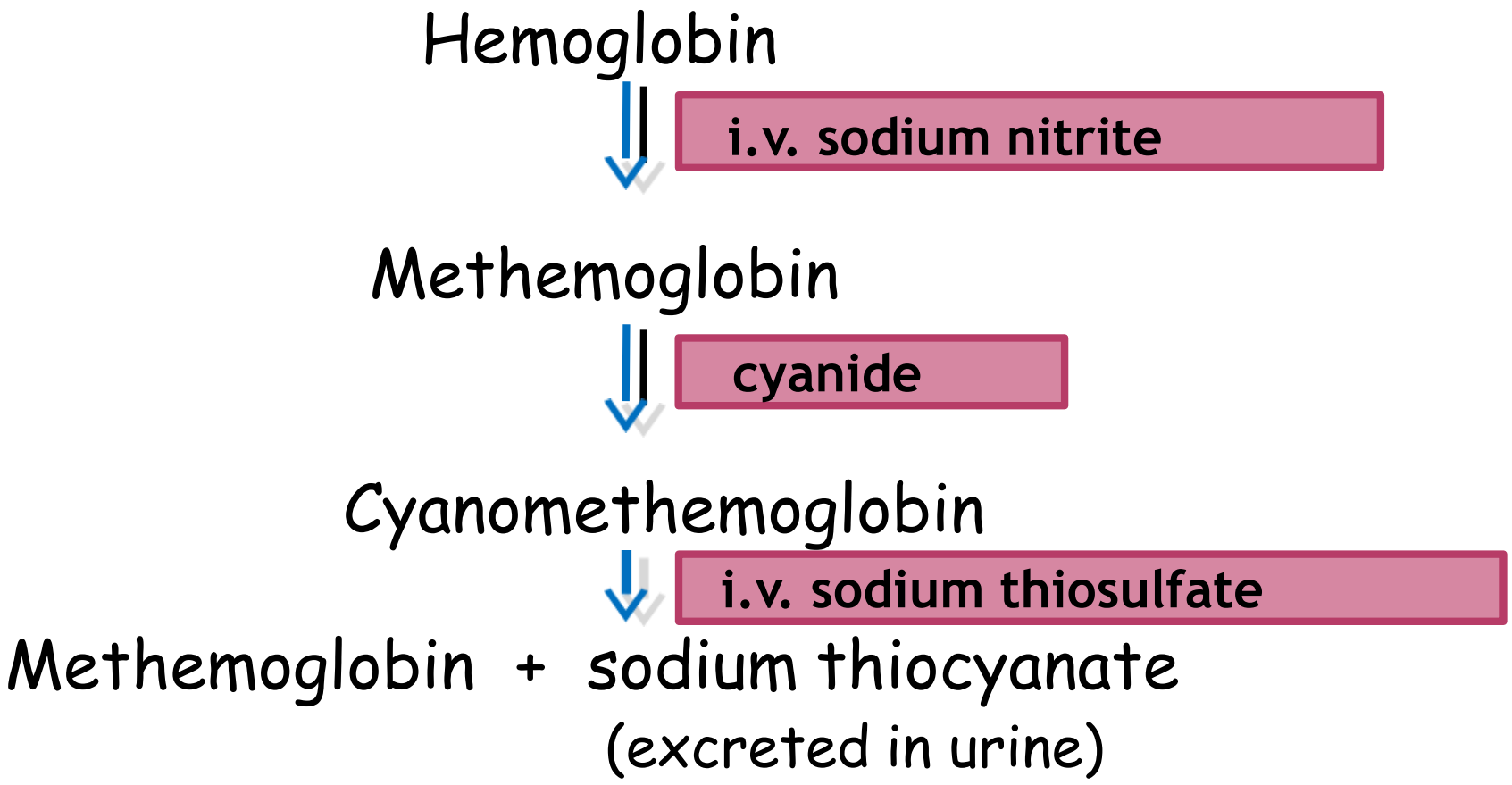
- ***Angina pectoris:*** GTN produces relief within 3 min in 75% patients, the rest may require another dose or take longer (upto 9 min).
- ***Acute coronary syndromes:*** Nitrates are useful by decreasing preload as well as by increasing coronary flow.
- ***Myocardial infarction (MI):*** GTN is frequently used during evolving MI with the aim of relieving chest pain, pulmonary congestion and limiting the area of necrosis by favourably altering O_2 balance in the marginal partially ischaemic zone.

Nitrates/ Organic Nitrates

Uses:

- CHF and acute LVF: Nitrates afford relief by venous pooling of blood → reduced venous return (preload) → decreased end diastolic volume → improvement in left ventricular function.
- Biliary colic
- Esophageal spasm
- Cyanide poisoning: Nitrates generate methaemoglobin
- which has high affinity for cyanide radical and forms cyanomethaemoglobin.

Cyanide poisoning –



Adverse effects

- Flushing of face, throbbing headache
- Postural hypotension & tachycardia
- Palpitation, weakness, dizziness
- Tolerance – 'Monday disease'
- Methaemoglobinemia – high doses

β Blockers

- The β-adrenergic blockers decrease the oxygen demands of the myocardium by blocking β_1 receptors, resulting in decreased heart rate, contractility, cardiac output, and blood pressure.
- All β blockers are nearly equally effective in decreasing frequency and severity of attacks and in increasing exercise tolerance in classical angina, but cardioselective agents (atenolol, metoprolol) are preferred over nonselective $\beta_1 + \beta_2$ blockers (e.g. propranolol).
- Agents with intrinsic sympathomimetic activity (ISA) such as **pindolol** should be avoided in patients with angina and those who have had a MI.

Calcium channel blockers

Voltage sensitive calcium channels			
	L-type (Long lasting current)	**T-type** (Transient current)	**N-type** (Neuronal)
1. Conductance	25 pS	8 pS	12–20 pS
2. Activation threshold	High	Low	Medium
3. Inactivation rate	Slow	Fast	Medium
4. Location and function	• Excitation-contraction coupling in cardiac and smooth muscle • SA, A-V node—conductivity • Endocrine cells—hormone release • Neurones—transmitter release	• SA node—pacemaker activity • 'T' current and repetitive spikes in thalamic and other neurones • Endocrine cells—hormone release • Certain arteries—constriction	• Only on neurones in CNS, sympathetic and myenteric plexuses—transmitter release
5. Blocker	Nifedipine, diltiazem, verapamil	Mibefradil, flunarizine, ethosuximide	ω-Conotoxin

Calcium channel blockers

- **Phenyl alkylamine:** Verapamil
- **Benzothiazepine:** Diltiazem
- **Dihydropyridines:** Nifedipine, Felodipine, Amlodipine, Nitrendipine, Nimodipine, Lacidipine, Lercanidipine, Benidipine

Calcium channel blockers (CCBs)

MOA –

CCB's

↓

binds to α_1 subunit of L- type Ca^{2+} channels & block their activity

↓

decrease in transmembrane calcium current smooth muscle

↓

relaxation, decreased

contractility in cardiac muscle, decrease in pacemaker activity & conduction velocity

Calcium channel blockers

Pharmacological actions:

- **Smooth muscle:** The CCBs cause relaxation by decreasing intracellular availability of Ca^{2+}. The dihydropyridines (DHPs) have the most marked smooth muscle relaxant and vasodilator action; verapamil is somewhat weaker followed by diltiazem.

Calcium channel blockers

Pharmacological actions:

- **Heart:** Calcium influx is increased in ischemia because of the membrane depolarization that hypoxia produces. The calcium channel blockers protect the tissue by **inhibiting the entrance of calcium** into cardiac and smooth muscle cells of the coronary and systemic arterial beds and **decreases smooth muscle tone and vascular resistance, afterload**.

Calcium channel blockers

Phenyl alkylamine: Verapamil:

- It dilates arterioles and decreases total peripheral resistance.
- It slows atrioventricular (AV) conduction directly and decreases heart rate, contractility, blood pressure, and oxygen demand.
- It also has some α adrenergic blocking activity.
- Verapamil has greater negative inotropic effects than amlodipine, but it is a weaker vasodilator.
- **Verapamil should not be given with β blockers, digoxin, cardiac depressants like quinidine and disopyramide.**

Calcium channel blockers

Benzothiazepine: Diltiazem:

- Diltiazem also slows AV conduction, decreases the rate of firing of the sinus node pacemaker, and is also a coronary artery vasodilator.
- Diltiazem can relieve coronary artery spasm and is particularly useful in patients with variant angina.
- It is somewhat less potent vasodilator than nifedipine and verapamil, and has modest direct negative inotropic action, but direct depression of SA node and A-V conduction are equivalent to verapamil.

Calcium channel blockers

Dihydropyridine (DHP) calcium channel blockers: Nifedipine:

- Nifedipine is the prototype DHP with a rapid onset and short duration of action. It causes arteriolar dilatation and decreases total peripheral resistance.
- Nifedipine is usually administered as an extended-release oral formulation.
- It causes direct depressant action on heart in higher dose.

- **ADR:** Frequent side effects are palpitation, flushing, ankle edema, hypotension, headache, drowsiness and nausea. Nifedipine has paradoxically increased the frequency of angina in some patients.

Calcium channel blockers

Other dihydropyridine (DPH) calcium channel blockers:

- **Amlodipine**, an oral dihydropyridine, functions mainly as an arteriolar vasodilator.
- **Nitrendipine**, is a calcium channel blocker with aditional action of vasodilatation action. **Vasodilation action is due to release NO from the endothelium and inhibit cAMP phosphodiesterase**.
- **Lacidipine**, is a highly vasoselective newer DHP.
- Nimodipine, is short-acting DHP which penetrates blood- brain barrier very efficiently due to high lipid solubility.
- **DPH with long duration of action:** Lercanidipine, Benidipine.

Calcium channel blockers

Pharmacokinetic characteristics of calcium blockers: channel

	Drug	Bioavailability	Vd (L/Kg)	CL (L/hr/Kg)	Active metabolite	Elimin. t½ (hr)
1.	Verapamil	15–30%	5.0	0.9	Yes	4–6
2.	Diltiazem	40–60%	3.0	0.7	Yes	5–6
3.	Nifedipine	30–60%	0.8	0.42	Minor	2–5
4.	Felodipine	15–25%	10.0	1.0	None	12–18
5.	Amlodipine	60–65%	21.0	0.42	None	35–45

Calcium channel blockers

Uses:

- **Calcium channel blockers can be safely given to patients with obstructive lung disease and peripheral vascular disease in whom β blockers are contraindicated.**
- CCB are used for the treatment of
  - angina pectoris
  - hypertension
  - cardiac arrhythmias
  - hypertrophic cardiomyopathy

Potassium Channel Openers

Nicorandil:

- Antianginal action of nicorandil is mediated through ATP sensitive K+ channels (KATP) thereby hyperpolarizing vascular smooth muscle.
- Nicorandil is well absorbed orally, nearly completely metabolized in liver and is excreted in urine. Administered
  i.v. during angioplasty for acute MI, it is believed to improve outcome.
- ADR: Flushing, palpitation, weakness, headache, dizziness, nausea and vomiting.

Other antianginal drugs

Dipyridamole	• Dipyridamole inhibits platelet aggregation • It is a powerful coronary dilator
Trimetazidine	• This antianginal drug acts by nonhaemodynamic mechanisms. • The mechanism of action of trimetazidine is uncertain, but it may improve cellular tolerance to ischaemia by inhibiting mitochondrial long chain 3-ketoacyl-CoAthiolase.
Ranolazine	• This **novel antianginal drug** primarily acts by inhibiting a late Na^+ current (late I_{Na}) in the myocardium.
Ivabradine	• This **'pure' heart rate lowering antianginal drug** has been introduced recently as an alternative to β blockers. • It blocks cardiac pacemaker (sino-atrial) cell 'f' channels.
Oxyphedrine	• Improve myocardial metabolism.

Avoid Tobacco
Tobacco smoke
Stress
High blood pressure
High blood cholesterol
Be More Active
Physical inactivity
Stress
High blood pressure
High blood cholesterol
Obesity
Alcohol
Stress
High blood pressure
High blood cholesterol
Diabetes mellitus
Obesity
Choose Good Nutrition

THANK YOU