

Part II

Anti Ischemic Drugs

"Although life is full of sufferings, it is full also of the overcoming of it"

Hellen Keller

- CHAPTER 7: NITRATES.
- CHAPTER 8: BETA-ADRENERGIC BLOCKERS.
- CHAPTER 9: CALCIUM ANTAGONISTS.
- CHAPTER 10: METABOLIC ANTI ANGINAL DRUGS.
- CHAPTER 11: SELECTIVE HEART RATE-LOWERING AGENTS.

ANTI ISCHEMIC DRUGS

- The main indication of this group is the relief of anginal pains.
- Other important indications of some members are treatment of hypertension, arrhythmias and heart failure.

- Anti ischemic drugs include:
 1. Nitrates.
 2. Beta-adrenergic blockers.
 3. Calcium antagonists.
 4. Metabolic antianginal drugs.
 5. Selective heart rate-lowering agents.

- Myocardial ischemia is the result of imbalance between myocardial oxygen supply and demand. Anti ischemic drugs produce their beneficial effect by either improving myocardial O₂ supply or decreasing demand or both.

- Causes of decreased myocardial oxygen supply:
 1. Progressive narrowing of epicardial coronary arteries by atherosclerotic (ASO) plaques.
 2. Sudden enlargement of ASO plaque.
 3. Sudden narrowing or complete occlusion of an epicardial coronary artery by an intracoronary thrombus following rupture or erosion of an ASO plaque.
 4. Coronary artery spasm usually in association with ASO disease e.g. vasospastic (Prinzmetal) angina.
 5. Microvascular disease: disease of the small intramyocardial arteries secondary to abnormalities in vasomotor tone as in syndrome X or secondary to coronary microemboli from thrombi or ruptured atherosclerotic plaque in epicardial coronary artery.
 6. Other causes: coronary embolism, abnormal coronary rheology slow flow, compression of epicardial coronary artery by myocardial bridge, coronary ectasia.

- Causes of increased myocardial oxygen demands:

The following are the major determinants of myocardial oxygen demand. Any increase of one or more of these factors will increase demand:

 1. Heart rate.
 2. Arterial pressure.
 3. Myocardial inotropic state (contractility).

4. LV wall stress which is determined by the internal LV cavity dimensions and intraventricular pressure. LV dilatation will increase wall stress.
 5. An increase in LV muscle mass (LVH).
 6. Metabolic: free fatty acids, the major source of myocardial fuel require more oxygen to generate an equivalent amount of ATP when compared to glucose.
- Causes of myocardial ischemia with normal epicardial coronary arteries:
Though atherosclerosis is the chief cause of coronary artery disease producing narrowing of coronary arteries, myocardial ischemia can occur in patients with normal coronary angiograms:
 1. Coronary spasm.
 2. Microvascular disease.
 3. Valvular heart disease: mitral valve prolapse, aortic valve disease, mitral stenosis.
 4. Pulmonary hypertension.
 5. Left ventricular hypertrophy: hypertrophic cardiomyopathy, arterial hypertension.

Majority of these conditions are more common in women than in men.

Chapter (7)

Nitrates

- Mechanism of Action
- Clinical Indications
- Contraindications
- Preparations
- Uses in Acute Coronary Syndromes
- Nitrate Tolerance

- Three organic nitrates are currently used:
 1. Nitroglycerin (NTG).
 2. Isosorbide dinitrate (ISDN).
 3. Isosorbide mononitrate (ISMN).
- They are prodrugs and undergo biotransformation in which nitrite ion (NO_2^-) is released and metabolized to nitric oxide (NO).

MECHANISM OF ACTION:

A. Increase coronary blood supply.

1. Dilatation of large coronary arteries and arterioles (>100 μm in diameter), this will lead to increased perfusion of ischemic zones. Nitrates dilate both normal and abnormal coronary arteries.
2. Relief of coronary artery spasm.
3. Dilatation of coronary collaterals and enhancement of collateral flow.
4. Redistribution of transmural coronary blood flow from subepicardial to subendocardial ischemic regions.

B. Decrease myocardial oxygen consumption

This is the chief mechanism for relief of ischemia by nitrates.

Systemic venous relaxation in the extremities and splanchnic circulation results in sequestration of the circulating blood volume away from the heart and lungs and fall in venous return and cardiac filling.

1. Venous dilatation with decreased LV filling pressure and decreased preload can reduce ventricular volume and decrease LV wall stress – a major determinant of myocardial oxygen consumption. The fall in preload is more pronounced with sitting or standing.
Vasodilatation develops at low nitrate concentration and is near maximal at moderate dosage.
2. Arterial dilatation: nitrates dilate large and small arteries with fall in vascular impedance and decrease in arterial pressure, resulting in reduction in after-load.

OTHER ACTIONS

1. Pulmonary arterial bed relaxation: beneficial in subjects with secondary pulmonary hypertension.
2. Antiplatelet action: decreased platelet activation resulting in inhibition of platelet aggregation and less thrombosis. Stimulation of platelet guanylate cyclase by nitrates prevents fibrinogen binding to platelet GP IIb/IIIa receptors.

Molecular Mechanism of Action

- Nitrates act through endothelial-independent pathway to relax all types of vascular smooth muscle cells to varying degrees.
- Nitrates are converted to nitric oxide, which then activates guanylate cyclase. Guanylate cyclase, in turn, produces cyclic guanosine monophosphate (cGMP) which leads to increased levels of intracellular cGMP and vasodilatation through decrease in intracellular calcium level.
- In platelets, increases in cGMP exert an antiaggregatory action.

CLINICAL INDICATIONS

1. Chronic stable angina. Treatment and prophylaxis of anginal attacks.
2. Acute coronary syndromes: unstable angina and MI.
3. Congestive heart failure.
4. Diastolic LV dysfunction.
5. Hypertensive emergencies (parenteral nitroglycerin).
6. Acute pulmonary oedema secondary to LV failure.

CONTRAINDICATIONS

1. Patients who have taken sildenafil (Viagra) within 24 hours because of the risk of severe hypotension.
2. Patients with hypertrophic cardiomyopathy even those without a resting gradient across left ventricular outflow tract.
3. Patients with suspected right ventricular infarction because of risk of hypotension.
4. Use cautiously in patients with severe aortic stenosis or with volume depletion.

NITRATE PREPARATIONS

✓ Nitroglycerin (NTG)

- Available in many formulations, parenteral, sublingual, buccal, ointment and patch.
- It has a very short half-life of several minutes; cessation of an intravenous NTG infusion or removal of transdermal patch results in a rapid fall of NTG plasma level within 20 to 40 minutes.
- Veins take up NTG more avidly than arteries.
- *Dosages*
 - *Sublingual NTG*: 0.3-0.6 mg, onset of action is 2-5 minutes and its duration is 20-30 minute. The usual tablet dose is 0.3 mg to 0.4 mg repeated every five minutes for a total of three doses. NTG tablets are both heat and light sensitive. They should be stored in a

tightly capped dark bottle in the refrigerator. Prescription should be renewed every three to six months.

- *NTG patch*: 0.4-0.8 mg/h, the patch should be applied for only 12-14 hours each day.
- *Oral NTG*: has no reliable data supporting its effectiveness.
- Intravenous NTG: initiated at a rate of 10 mcg per minute through continuous infusion and increased by 10 mcg/min every 3-5 minutes until symptom relief or blood pressure response is noted.
 - o If no response is seen increments of 20 mcg/min can be used. If symptoms and signs of ischemia are not relieved, the dose should be increased until a blood pressure response is observed.
 - o Caution should be used when systolic blood pressure falls below 110 mmHg in previously normotensive patients or to a greater than 25% below the starting mean arterial blood pressure if hypertension was present.
 - o Maximal dose of 400 mcg/min should not be exceeded.

✓ Isosorbide Dinitrate (ISDN)

- The most widely used long acting nitrate.
- Available as short-acting and sustained-release formulation.
- Onset of action is within 15 to 30 minutes and the duration of action is three to six hours. There is low bioavailability from hepatic metabolism.
- *Dosage*: 10 to 40 mg three times daily. There is no added benefit with 60 and 120 mg doses.
 - Tolerance has limited the usefulness of ISDN as a chronic antianginal agent. Development of tolerance occurs despite higher plasma concentrations of ISDN during maintenance therapy.
 - To prevent the development of tolerance, it is recommended to give ISDN at 8 AM, 1 PM and 6 PM. This regimen can offer antianginal protection for at least six hours.
 - Begin with a dose of 10 mg three times daily and advance to 40 mg three times daily as needed.

✓ Isosorbide Mononitrate (ISMIN)

- Onset of action is within 30 minutes, and the duration of action is six to eight hours. It is completely bioavailable.
- The usual starting dose is 20 mg twice daily to be increased to 40 mg twice daily if necessary. Seven hours interval between doses followed by 17 hours nitrate-free interval.
- Extended (sustained) release preparation is given once daily and lasts 12 hours.

- A minimum of 60 mg per day is recommended, higher doses such as 120 or 240 mg daily may be necessary for sustained antianginal efficacy without tolerance. Sustained release preparation action lasts for 12 hours, nocturnal or rebound angina may develop.
- ISMN preparations in Egypt (tablet size):
 - Regular: 20, 40 mg
 - Sustained release (SR): 25, 50 mg
- Extended release preparations are preferable. Starting dose is 30 mg once daily can be titrated to 120 mg once daily as needed.

Suggestions for Nitrate Dosing

- Start nitrate therapy with small doses and build up to maximally tolerated amount.
- Some individuals are extremely sensitive to nitrates; others experience little or no side effects.
- Headache and dizziness are the limiting symptoms with nitrate administration. They usually decrease or disappear over time.
- Many patients are underdosed e.g. 10 mg ISDN, 30 or 40 mg ISMN-SR or 0.2 to 0.4 mg/h of the NTG patch are less likely to be clinically effective doses.
- In congestive heart failure, the dosage of nitrates to achieve a significant hemodynamic effect is considerably higher than in patients with normal LV function. Patients with congestive heart failure tolerate large doses.
- In patients with primarily exertional angina, nitrates are given during the day when the patient is more active.
- In patients with nocturnal angina or congestive heart failure, therapy at night is advised.
- When given in adequate dosage, there is no difference in efficacy between ISDN, ISMN and transdermal NTG.

Table 7-1: Common Nitrate Preparations

Preparation	Route of administration	Onset of action, minutes	Duration of action	Dose
Nitroglycerin	Sublingual tablet	2-5	15-30 min	0.15-0.9 mg
	Sublingual spray	2-5	15-30 min	0.4 mg
	Ointment	2-5	Up to 7 hours	2 percent, 15x15 cm (7.5 to 40mg)
	Transdermal	30	8-14 hours	0.2-0.8 mg/hour
	Oral sustained release	30	4-8 hours	2.5-13 mg
	Intravenous	2-5	Drug infusion	5-200 µg/min
Isosorbide dinitrate	Sublingual	2-5	Up to 60 min	2.5-15 mg
	Oral	30	Up to 8 hours	5-80 mg BID or TID
	Spray	2-5	2-3 min	1.25 mg/day
	Chewable	2-5	2-2.5 hours	5 mg
	Oral slow release	30	Up to 8 hours	40 mg OD or BID
Isosorbide mononitrate,	Oral	30	6-8 hours	20-40 mg BID 60-240 mg/day
Isosorbide mononitrate, extended release	Oral	30-60	12 hours	30-120 mg once daily
Pentaerythroid tetranitrate	Sublingual	2-5	Not known	10 mg as needed
Erythritol tetranitrate	Sublingual	2-5	Not known	5-10 mg as needed
	Oral	30	Not known	10-30 mg TID

USE OF NITRATES IN ACUTE CORONARY SYNDROMES

▼ Unstable Angina

- IV NTG is preferable because of its short half life and feasibility of rapid dose titration. Tolerance may develop after 24 hours with recurrence of chest pain. Such patients respond to dose increases.
- Once the patient has been stabilized, IV NTG can be tapered gradually, and intermittent therapy with long-acting oral nitrate can be started about 1-2 hours, before discontinuation of the nitrate infusion.
- No evidence that nitrates reduce the risks of developing infarction or death.

✓ Acute Myocardial Infarction

- Intravenous nitrates are helpful in reducing pain and decrease LV filling pressures in AMI complicated by congestive heart failure.
- Nitrates provide no additional survival benefit when compared with placebo.
- Current data do not support their routine use in patients with AMI.
- Recent guidelines recommend the use of nitrates for the first 24 to 48 hours in patients with AMI who have an indication for nitrate therapy such as: recurrent ischemia, heart failure or hypertension. The infusion of IV NTG should be initiated at 5 to 10 mcg/min and gradually increased. The goal is a 10% reduction in systolic blood pressure for normotensive subjects and approximately a 30% reduction in systolic blood pressure in hypertensive patients, avoiding hypotension.
- The major concern with continuous infusion of NTG is the development of nitrate tolerance that occurs in most patients within 24 hours.
- IV NTG is discontinued within 24 to 48 hours. Long acting oral nitrates may be indicated in patients with significant residual ischemia or heart failure.

NITRATE TOLERANCE

- Attenuation and sometimes abolition of hemodynamic and antianginal effects of nitrates.

✓ Proposed Mechanisms

1. Increased vascular oxygen free radical generation (O_2^-). The sources include membrane NAD(P)H and xanthine oxidases. Hydralazine, by inhibiting NAD(P)H oxidases, modifies the development of tolerance. Superoxide anions inactivate nitric oxide.
2. Depletion of sulfhydryl groups necessary for biotransformation of nitrate to nitric oxide (NO).
3. NTG impairs the function of nitric oxide synthase (NOS), reducing NO production.
4. NTG stimulates counter regulatory responses mediated by sympathetic nervous system and renin-angiotensin-aldosterone axis. The vasoconstriction induced by these responses has been implicated in the rebound ischemia after NTG withdrawal. Neurohormonal responses may play a role in free radical generation. Angiotensin II stimulates membrane NAD(P)H oxidases.
5. Plasma volume expansion with chronic use.

✓ Prevention

- Intermittent therapy with an adequate nitrate-free interval. It is thought that a nitrate-free interval permits the generation of reduced sulfhydryl groups.
- Other proposed methods, none as yet used clinically:

- Folic acid (10mg/day).
- L. arginine.
- Anti oxidants e.g. carvedilol.