Anti-anginal Drugs

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Angina

- 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.
- Women develop angina at a later age than men and are less likely to have classic substernal pain.

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)

Antianginal Drugs

- Antianginal drugs are those that prevent, abort or terminate attacks of angina pectoris.
- Types of angina – Atherosclerotic angina (classic angina [common form]): Attacks are predictably provoked (stable angina) by exercise, emotion, eating or coitus and subside when the increased energy demand is withdrawn. Rest, by reducing cardiac work, usually leads to complete relief of the pain within 15 min. Atherosclerotic angina constitutes about 90% of angina cases.

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- Vasospastic angina (rest angina, variant angina, or Prinzmetal's angina [uncommon form]): Attacks occur at rest or during sleep and are unpredictable. Vasospastic angina is responsible for less than 10% of angina cases. Coronary artery calibre changes in classical and variant angina
- Unstable angina (crescendo angina, also known as acute coronary syndrome): It is characterized by increased frequency and severity of attacks that result from a combination of atherosclerotic plaques, platelet aggregation at fractured plaques, and vasospasm.

Treatment of Angina Pectoris

- Drugs used in angina exploit two main strategies: – reduction of oxygen demand – increase of oxygen delivery to the myocardium

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
- 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:

- 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 Ca2+ and leads to the relaxation of smooth muscle cells in a broad range of tissues.

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- 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. Mechanism of action:
- 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.
- 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.

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- 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.
- 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 O2 balance in the marginal partially ischaemic zone.• 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.

β Blockers

- The β-adrenergic blockers decrease the oxygen demands of the myocardium by blocking β1 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 β1 + β2 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

- Calcium channel blockers – Phenyl alkylamine: Verapamil – Benzothiazepine: Diltiazem – Dihydropyridines: Nifedipine, Felodipine, Amlodipine, Nitrendipine, Nimodipine, Lacidipine, Lercanidipine, Benidipine
- Pharmacological actions: • Smooth muscle: The CCBs cause relaxation by decreasing intracellular availability of Ca2+. The dihydropyridines (DHPs) have the most marked smooth muscle relaxant and vasodilator action; verapamil is somewhat weaker followed by diltiazem.• 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.

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- 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.
- 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.

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- 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.
- 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.

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- 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 INa) 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.

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