

Antianginal drugs:

- Organic nitrates:

Glyceryl trinitrate (GTN), Isosorbide mononitrate (ISMN)
The long-acting form of GTN.

Basic effect is non-specific relaxation of SM. (Vasodilation is the most prominent action, while all kinds of SM are affected. (Details in Note). Antianginal effects due to dilation of peripheral arteries and veins. In some cases, dilation of collateral vessels is important. Also useful in coronary spasm (variable angina)

Side effects: headache + hypotension, risk of fainting.

- β - antagonists (e.g. Atenolol)

\downarrow heart rate, while longer filling time may \uparrow O₂ demand of heart to do more work.

Prophylactic and therapeutic use.

- Calcium channel antagonist

Nifedipine, verapamil, diltiazem. (Differ in actions see Note Table)

Block L-type VGCC. Depression of conduction (particular in dysrhythmias associated with slow response). Cardiac slowing due pacemaker depression.

Depression of force of contraction, reduces T_I current (inhibits ectopic beats)

↑ resistance to ischaemic damage due to reduced cardiac work.

Vasodilation.

- Dipyridamole (use minimal)

Vasodilator. Inhibit platelet aggregation (prevent thrombosis in angina).
Shown to inhibit adenosine uptake by tissue (adenosine accumulation may be involved in vasodilation)

- Nicorandil potassium channel activators.

- Other drugs:

Aspirin, Statins (eg simvastatin), Heparins

anti-platelet Treat atherosclerotic disease anti-coagulation.

Abciximab, tirofiban: glycoprotein IIb / IIIa inhibitors — Inhibit platelet activation by antagonizing IIb / IIIa receptors.

Antihypertensive drugs

Diuretics:

Thiazide (e.g. bendroflumethiazide = bendrofluazide) Mentioned previously, K⁺ channel openers for VSM relaxation, decrease cardiac output (diuretic effect) and lower BP. Long term: Cardiac output and plasma volume returns but BP remains lower due to reduced peripheral resistance. Mechanism involved is unclear (as VSM vasodilation is caused by some diuretics, not all)

Vasodilators: (All of these drugs will cause the baroreceptor reflex to be activated)
[As β_1 -adrenoceptors are not blocked: there will be an associated reflex tachycardia and activation of the renin angiotensin system]

ATP sensitive K⁺ channels (K_{ATP}) openers: Diaxoxide, Minoxidil.

ATP binding closes K_{ATP} channels, preventing hyperpolarization. The drugs block ATP binding to open the channels → Greater hyperpolarization closes L-type VGCC, vasodilation is resulted in. K_{ATP} expressed in cardiac, smooth muscle and β -cell (hyperpolarization reduces insulin release)

Diazoxide: used in hypertensive emergencies, but diabetogenic.

Minoxidil: used in severe hypotension, whereas causing hypertrichosis.

hydralazine: considered to be a selective arteriolar vasodilator (unknown mechanism)

Calcium channel blockers:

Inhibiting Ca²⁺ influx into arterial SM and, to a variable extent,

myocardial cells. Nifedipine: selective blocker for the L-type VGCC in VSM.

Verapamil: pronounced effects on the heart (decrease cardiac output, ↓ heart rate
↓ A-V conduction)

Nitrovasodilators

e.g. Sodium nitroprusside: Break down to release NO.
(for severe hypertensive crisis)
(Not used for day to day treatment of hypertension)

Indirect vasodilators: Alpha adrenoceptor antagonist:

{ α_1 antagonist: prazosin: blocking the effects of sympathetic stimulation to the vasculature. Side effect: fainting due to hypotension in the first dose.
Longer acting agents (e.g. doxazosin) found to be better tolerated.
Side effect: postural hypotension, tachycardia

Adrenergic blocking agents:

Prevent NA from releasing by the post-ganglionic sympathetic neurones.
(e.g. guanethidine)

Side effects: postural hypotension, failure of ejaculation, nasal congestion.
(Some side effects due to inhibition of sympathetic activity to all tissues and not just the vasculature)

Ganglion blocking drugs:

Hexamethonium: Side effects include those from blocking both sympathetic and parasympathetic nervous systems.

Centrally acting antihypertensives:

Drugs decreasing sympathetic outflow:

Clonidine: α_2 (G_i) agonist.

α -methyl DOPA \longrightarrow α -methyl NA: More selective to α_2 .

B adrenoceptor antagonist:

Non-selective β , selective
Propantheline, atenolol probably cross the blood brain barrier (BBB) to inhibit sympathetic excitation: "switching off" the baroreceptor reflex by lowering peripheral resistance and dampen down the renin secretion from juxtaglomerular cells. (\downarrow sympathetic drive)
Oxprenolol partial agonists: cause less bradycardia, useful in patients with incipient cardiac failure or peripheral vascular disease.

Angiotensin converting enzyme inhibitors:

Captopril, enalapril (long acting), Angiotensin II: potent vasoconstrictor.
side effect: hypotension, hyperkalaemia, etc.

Angiotensin I receptor antagonists.

Losartan competitive antagonist at AT₁, metabolised in the liver to a non-competitive AT₁-antagonist.
side effect: dry cough (bradykinin accumulation).

Anticoagulants and fibrinolytics.

factors constrain spontaneous coagulation:

Thrombomodulin: on endothelial cells, bind reversibly to thrombin (factor IIa)

Antithrombin III: α_2 -globulin, neutralises the serine proteases: IIa , IXa , Xa
 XIa & XIIa (inhibits)

Heparin cofactor II: Inhibits factor IIa (thrombin)

Drugs used for haemostasis modification can target:

- ① Fibrin formation
- ② Platelet adhesion and activation.
- ③ Fibrin removal (fibrinolysis)

Agents promoting blood coagulation:

Vitamin K (K_1 (phytomenadione) and K_2) acts as a cofactor for the gamma-carboxylation of glutamic acid residues on the N-terminus of precursor glycoproteins: This process yields the zymogens: II , VII , IX and X .
Vitamin K deficiency normally acquired as a consequence of liver disease.

Whole blood / plasma / Factor VII / Factor IX concentrate

Agents which decrease blood coagulation:

Injectable anticoagulants: Heparin

Found in mast cells & plasma.

A polysaccharide often found in mucus: Mucopolysaccharide

prevents blood coagulation both in vivo and in vitro.

↳ Inactivates thrombin (II^{a}) And factors $\text{IX}^{\text{a}}, \text{X}^{\text{a}}, \text{XI}^{\text{a}} \& \text{XII}^{\text{a}}$.
↳ Achieved by combining with and accelerating the action of antithrombin III.

Prolonged use: deplete stores of antithrombin III → diminish the effects of heparin.

Can reduce the risk of deep venous thrombosis and pulmonary embolism.

Adverse effect: haemorrhage, prevented by protamine sulphate, a heparin antagonist.

- Other anticoagulants which don't involve antithrombin III:

Hirudin, lepirudin, bivalirudin: Inhibitors of thrombin.

Useful for patients who develop an immune response to heparin.

Plaxin: Inhibitor of Factor X.

Danaparoid: Inhibitor of Factor X^{a} .

NAPc2 (nematode anticoagulant complex)

Drugs that enhance endogenous anticoagulant activity (protein C-activated protein C)

Anicrod acts on fibrinogen to produce unstable fibrin fibres leading to depletion of fibrinogen.

- Oral anticoagulants (e.g. Warfarin)

Interfere with the reduction of Vitamin K (a cofactor in the post-translational γ -carboxylation of glutamate residues at the N-terminus) → producing non-functional factors II, VII, IX and X

Main adverse effect: excessive bleeding, counteracted by increasing vitamin K intake

The drug effect only when the existing pool of active factors is depleted.

- Direct thrombin inhibitors (DTIs)

Dabigatran

- Drug interactions with oral anticoagulants:

Response to oral anticoagulants is decreased by:

{ Oral contraceptives

{ Prior administration of drugs which cause induction of liver microsomal (P_{450} enzymes) e.g. barbiturates, phenytoin

increased by:

Drugs displacing plasma protein binding of the anticoagulants e.g. aspirin, chloral hydrate etc. (in Note)

-(Acid Citrate Dextrose):

Precipitate Ca^{2+} as an insoluble chelate complex.
(Factor IV)

Fibrinolysis:

Plasminogen : b-globulin.

Fibrinolysis enzymatically breaks down fibrin as well as factors II, V and VII.

Drugs promoting fibrinolysis:

Streptokinase: forms complexes with plasminogen which activates the enzyme. (May act as an antigen) (Plasminogen \rightarrow Plasmin)

Urokinase: directly activates plasminogen through its enzymatic activity.

Adverse effects: Bleeding : reverse with tranexamic acid or fresh plasma.

Hypersensitivity reactions.

Histamine and other mediators of inflammation.

Local hormone (autacoid) include : histamine, 5-hydroxytryptamine (5-HT), kinins, platelet activating factors (PAFs), cytokines (eg interleukins, tumor necrosis factor, interferon).

Enzyme inhibitor α -methyl histidine blocks histidine decarboxylase
(\downarrow histamine formation)

Mediators involved in inflammation and released by cells are autacoids.

Histamine release can be inhibited by β_2 -agonists from basophils or mast cells by \uparrow intracellular cyclic AMP.

Antigen - antibody (IgE class) interaction triggers histamine release -

Complement fragments (5a C3a (anaphylatoxins) also release histamine from most cells. Peptides such as Substance P and vasoactive intestinal polypeptide release histamine. The polybasic molecule Compound 48/80 release histamine from mast cells in some tissue.

Drugs that release histamine: tubocurarine, morphine.

Inflammatory mediators other than histamine:

Kinins (eg. bradykinin, kallidin [lys-bradykinin])

Formed from plasma protein precursors called kininogens by plasma and tissue kallikreins : split the active kinins from the precursors (HMW kininogen)

Kinins are destroyed by carboxypeptidase N and ACE.

Kinins are also vasodilators: acting on β_2 (mostly) and β_1 .

Icatibant: experimental β_2 antagonist

PAF: Membrane precursor: acyl-PAF

PAF formed when released by phospholipase A₂ (PLA₂)

PLA₂ acts on acyl-PAF to produce lyso-PAF → acetylated to yield PAF

PAF: aggregates platelets, also vasoconstrictor ↑ vascular permeability.

Eicosanoids (see later)

Cytokines:

Comprise interleukins, tumor necrosis factor and interferons.

Interleukin-1 (IL-1): has many properties which make it a likely mediator of chronic inflammation. (involved in many mechanisms; see Note)

Antagonist of histamine & treatment of peptic ulcers.

Selective agonists for 3 histamine receptors:

2-methylhistamine → H₁ (G_q)

4-methylhistamine, dimaprit, imipramine → H₂ (G_s)

R-α-methylhistamine → H₃ (G_{i/b})

Selective antagonists at H₁ receptors:

Older compounds cross blood-brain barrier (BBB) have atropine-like action and are sedative.

Newer antihistamine (H₁) don't cross BBB into CNS: No sedative action: Astemizole, terfenadine, cetirizine.

Selective antagonists at H₂:

Cimetidine, Ranitidine (competitive antagonists) inhibit gastric acid secretion.

Selective antagonists at H₃:

Thioperamide Function of H₃ receptors uncertain.

Effects of different histamine receptors at different parts of the body are in Note.

Vasopressin release from posterior pituitary can be triggered by histamine neuron.