

Pharmacology of vasoactive drugs

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Vasoactive drugs may be defined as those which modify the caliber of the vasculature resulting in either vasoconstriction or vasodilatation. These are respectively called as **vasopressors and vasodilators**.

Understanding the physiology of the vascular smooth muscle cells and various mechanisms involved in the regulation of their tone is a prerequisite not only for understanding the pharmacology of the existing vasoactive drugs but also for the invention of new drugs.

Vascular smooth muscle cells (VSMC):

These are present in the entire vasculature apart from capillary bed and small post capillary venules. VSMC exhibit some degree of contraction that determines the diameter and hence the tone of the vessel. Vascular tone refers to the degree of constriction experienced by a blood vessel relative to its maximally dilated state. Vascular tone is determined by many different competing vasoconstrictor and vasodilator influences acting on the blood vessels.

These influences can be either intrinsic or extrinsic.

Intrinsic Factors include:

1. Myogenic mechanisms
2. Endothelial Factors

3. Local Hormones
4. Metabolic byproducts

Extrinsic Factors include:

1. Autonomic nervous system
2. Humoral Factors
 - a. Renin - Angiotensin system
 - b. Atrial natriuretic peptide

VSMC undergoes slow sustained tonic contractions. It contains actin and myosin but lacks the regulatory protein troponin. The arrangement of the myofilaments is not organized into distinct bands as in cardiac muscle.

Contraction in VSMC can be initiated by mechanical, electrical and chemical stimuli. Passive stretching initiates contraction that originates from the smooth muscle itself and is therefore myogenic. Electrical depolarization of the VSMC membrane opens voltage-gated (L-type) calcium channels increasing intracellular calcium concentration and hence increases contraction. The chemical stimulants include norepinephrine, angiotensin II, vasopressin, endothelin-1, and thromboxane A₂.

Vascular tone is dependent on the intracellular calcium concentration. Increased intracellular calcium occurs either by opening of calcium channels on cell membrane or by release of calcium from internal stores in sarcoplasmic reticulum (SR). The free calcium binds to calmodulin (CAL). Ca⁺⁺- CAL activates myosin light chain kinase (MLCK). MLCK phosphorylates MLC in the presence of ATP leading to cross-bridge formation between the myosin heads and the actin filaments and hence contraction. Calcium is re-sequestered by SR by a ATP dependent calcium pump or transported extracellularly either by a ATP dependent calcium pump or sodium-calcium exchanger.

VASOPRESSORS:

The vasopressors that are routinely used can be classified as:

1. α_1 agonists
 - a. direct acting
 - b. indirect acting
2. V₁ receptor agonists

NOREPINEPHRINE (NEPI):

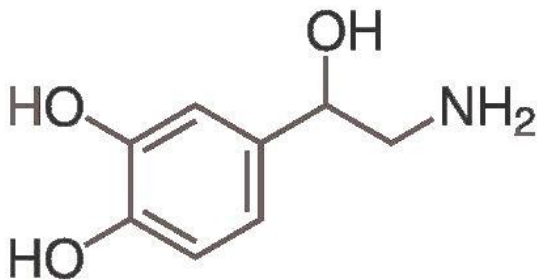


Fig 1: Norepinephrine

It is a naturally occurring catecholamine synthesized from phenylalanine / tyrosine.

Mechanism: α_1 Agonist and modest β -agonist activity.

Dynamics: Vasoconstriction; increase in systolic as well as diastolic blood pressure; reflex bradycardia. Coronary flow is increased owing to elevated diastolic blood pressure and indirect stimulation of the cardiac myocytes which release local vasodilators. The vasoconstrictive effect is dependent on the basal vascular tone which may be altered in critically ill and trauma patients.

Preparation: Available as clear colourless solution in 2 ml ampoules containing 2mg/ml of norepinephrine tartarate equivalent to norepinephrine 1mg/ml.

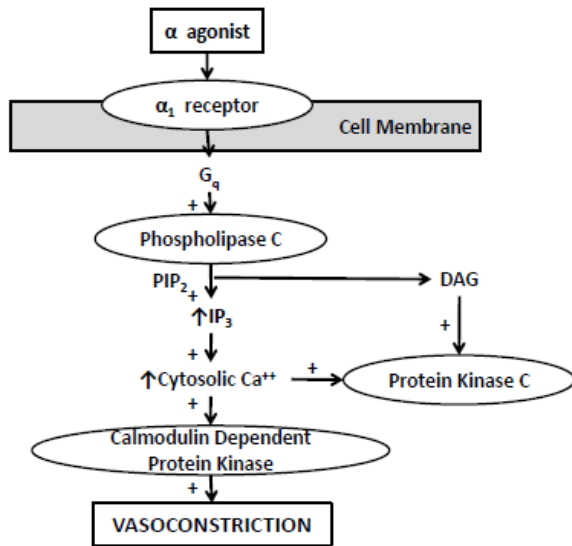


Fig 2: Intracellular Mechanism of α -agonist

Dilution: Usually 4mg (or 2mg) is diluted in 50 ml 5%D or NS for infusion.

Route: IV infusion

Dose: 0.01 to 3.0 $\mu\text{g}/\text{kg}/\text{min}$ as infusion

Kinetics: Norepinephrine is normally rapidly eliminated from the blood and the half-life is 2 to 2.5 minutes. It undergoes methylation (by COMT) oxidation (by MAO) and the metabolites – vanilylmandelic acid (VMA), 3,4-dihydroxymandelic acid, 3-Methoxy-4-hydroxyphenylglycol (MHPG), and 3,4-dihydroxyphenylglycol – which are inactive are excreted in the urine.

Indications:

1. Sepsis and septic shock
2. Vasodilatory shock
3. Post cardiopulmonary bypass
4. Subarachnoid block (rare)

Note: Ensure adequate volume resuscitation before starting vasoconstrictors.

Adverse Effects:

1. Reduce cardiac output
2. Reflex bradycardia

3. Severe vasoconstriction skin necrosis if extravasated. Central venous access is a safer than peripheral vein for norepinephrine infusion.

PHENYLEPHRINE:

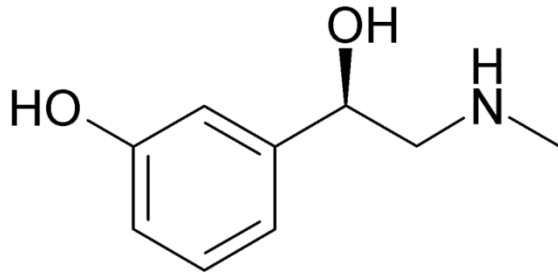


Fig 3: Phenylephrine

Mechanism: α_1 Agonist.

Dynamics: Vasoconstriction; hypertension; reflex bradycardia; increase in afterload and hence increase in myocardial oxygen consumption. Reflex bradycardia might be helpful to offset the increase in oxygen demand and also by increasing the supply due to the increase the diastolic time /pressure.

Preparation: Available as clear colourless solution in 1 ml ampoules containing 10 mg phenylephrine /ml.

Dilution: Usually diluted in 100 ml normal saline to get a concentration of 100 μ g/ml for adult cases and further dilution to 10 μ g/ml for paediatric cases.

Route: IM / SC / IV

Dose: IM /SC – 2 to 5 mg

IV – 1 to 4 μ g/kg as bolus

20 to 50 μ g/min as infusion

Oral – not for vasopressors

Topical Spray - Decongestant

Kinetics: Subject to extensive pre-systemic metabolism and the oral bioavailability is 40% compared to intravenous administration. PE rapidly distributes into the peripheral tissues on IV administration. The volume of distribution (V_D) is large – 200 to 500 liters. Does not cross placental or blood brain barrier (BBB). It is extensively metabolized in the gut wall and liver.

The principal routes of metabolism are oxidation by monoamine oxidase (MAO), sulphate and glucuronide conjugation. The metabolites are inactive and excreted in urine.

Adverse Effects:

1. Reduce cardiac output
2. Reflex bradycardia
3. Severe vasoconstriction skin necrosis if extravasated.

VASOPRESSIN:

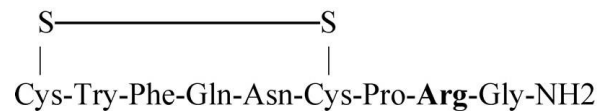


Fig 4: Vasopressin (Nonapeptide)

It is a nonapeptide, synthesized as a pro-hormone in magnocellular neurone cell bodies of the paraventricular and supraoptic nuclei of the posterior hypothalamus. Normal plasma concentrations are < 4pg/ml.

Mechanism of Action: Vasopressin acts on V1, V2, V3 and ocytocin-type receptors (OTR). Systemic vasoconstriction is mediated through G-protein coupled V1 receptors. Activation of phospholipase C occurs via Gq G protein, which ultimately leads to an increase in intracellular calcium. In the pulmonary circulation vasodilatation is produced via the release of nitric oxide. V1 receptors are also present on myometrium and platelets.

V2 receptors are located in the distal tubule and collecting ducts of the kidney, stimulation of which results in mobilization of aquaporin channels into the apical membrane. V2 receptors are essential for plasma volume and osmolality control. V2 receptors are also present on vascular endothelium and result in the release of von Willebrand factor.

V3 receptors are found in the pituitary. They are thought to be involved in ACTH release, memory consolidation and temperature regulation.

Preparation: Available as clear colourless solution in one ml ampoules/vials containing 20 IU /ml of synthetic vasopressin.

Dilution: in 20 ml or 50 ml of NS or 5%D.

Route: IV

IM / SC

Dose: 40 IU IV bolus in asystolic cardiac arrest

5 to 20 IU SC / IM in diabetes insipidus every 4th hourly.

20 IU intravenously over 15 minutes to initially control bleeding varices.

Infusion – 0.0003 to 0.002 IU/kg/min or 0.01 to 0.1 IU / min.

Kinetics: It is metabolized by the liver and intestine and has a half life of 24 minutes. It is also filtered into the glomerulus, reabsorbed and metabolized in PCT and excreted in the urine.

Indications:

1. Vasodilatory shock
2. Sepsis
3. Post CPB
4. Asystolic Cardiac arrest
5. Bleeding oesophageal varices
6. Diabetes insipidus
7. Improve platelet function (as Desmopressin)

Adverse effects:

1. Severe vasoconstriction – resulting in ischemia of the gut and the limbs especially when continued at higher doses or in combination with noradrenaline.
2. Extravasation – skin necrosis.

DOPAMINE:

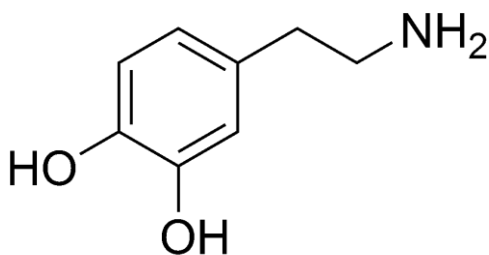


Fig 5: Dopamine

Dopamine is an endogenous neurotransmitter synthesized from tyrosine / phenylalanine and is the natural precursor of norepinephrine and epinephrine.

Mechanism: Acts on dopamine, β_1 , β_2 and α_1 receptors depending on the dose administered.

Table 1: Dose and Dopamine effects			
Dose ($\mu\text{g}/\text{kg}/\text{min}$)	Receptor	Effect	
<5	D	Renal and mesenteric vasodilatation	
5-10	β	Inotropic and chronotropic	
>10	α	Vasoconstriction	

Availability: as clear colourless solution in 5ml ampoule containing 200 mg dopamine.

Dilution: 200 mg in 50 ml NS or 5%D

Route: Intravenous

Dose: Given as intravenous infusion.

2 to 20 $\mu\text{g}/\text{kg}/\text{min}$

Kinetics: Dopamine is an intermediary product during the synthesis of norepinephrine and epinephrine. Dopamine has a plasma half life of two minutes and is broken down by COMT, MAO and conjugated to form various inactive metabolites which are excreted in urine.

Indications:

1. Hypotension
2. Inotropy and vasopressors effect
3. For chronotropy
4. Post cardiopulmonary bypass

Side Effects:

1. Tachycardia
2. Ventricular arrhythmia
3. Severe hypertension (especially if on non selective β – blockers)
4. Cardiac ischemia

EPHEDRINE

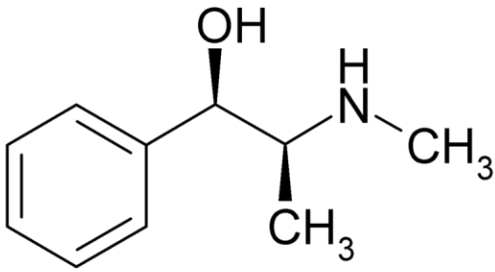


Fig 6: Ephedrine

Mechanism: Ephedrine acts directly on β_1 and β_2 receptors, and indirectly on α_1 receptors by causing noradrenaline release.

Action: It causes a rise in blood pressure and heart rate, and some bronchodilation.

Preparation 3% or 5% solution: 1 ml ampoules.

Dose 3-10 mg boluses iv, repeat until effective. Maximum dose is 60mg.

Length of action 5-15 minutes, repeated doses less effective (i.e. it demonstrates tachyphylaxis)

Indications: Low blood pressure due to vasodilation e.g. following spinal or epidural anaesthesia and drug overdoses. Best vasopressor to use in pregnancy as it does not reduce placental blood flow.

Adverse effects:

1. Tachycardia
2. Hypertension.
3. Possible arrhythmias if used with halothane.

METARAMINOL:

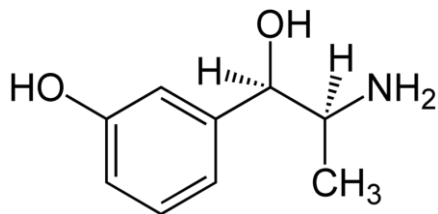


Fig 7: Metaraminol

Mechanism: Acts directly on α_1 receptors and also causes noradrenaline and adrenaline release.

Actions: Increases blood pressure and cardiac output. It is less likely to cause a reflex bradycardia than methoxamine or phenylephrine. Onset of action is within 1-2 minutes of intravenous administration and persists for 10 to 30 minutes.

Preparation: Available in 1 ml ampoule as 1% (10mg/ml) solution.

Route: IV / IM / SC

Dose: 2-10mg IM / SC,

1 mg IV boluses

IV infusion at 1-20mg/hr.

Kinetics: It is metabolized in the liver and excreted by the kidney.

Indications:

1. Hypotension during GA / Spinal anaesthesia

Adverse Effects:

1. Tachycardia
2. Hypertension
3. Cardiac ischemia

VASODILATOR DRUGS:

Vasodilators can be classified based on their action as follows:

1. Alpha-adrenoceptor antagonists
2. ACE Inhibitors
3. Angiotensin receptor blockers (ARBs)
4. β_2 adrenergic agonists
5. Calcium channel blockers (CCB)
6. Centrally acting sympatholytics
7. Direct acting vasodilators
8. Endothelin receptor antagonists
9. Ganglionic blockers
10. Nitrodilators
11. Phosphodiesterase inhibitors
12. Potassium channel Openers
13. Renin inhibitors

ALPHA- ANTAGONISTS:

These drugs block the effect of norepinephrine released from the sympathetic nerves. These can be further classified as:

- a. Competitive blockers

- i. Selective alpha 1
 - Prazosin
 - Terazosin
 - Doxazosin
 - Trimazosin
- ii. Non-selective
 - Phentolamine
- b. Non-competitive
 - i. Phenoxybenzamine

Actions: These dilate both arteries and veins, however the vasodilator effect is more pronounced in the arterial resistance vessels.

Indications:

1. Primary hypertension
2. Hypertensive emergencies – phaeochromocytoma

Adverse effects:

1. Orthostatic hypotension
2. Nasal congestion
3. Headache
4. Reflex tachycardia
5. Fluid retention

Doses of intravenous alpha blockers:

Phentolamine

Bolus - 1 to 5 mg IV direct

Infusion – 0.1 to 2.0 mg/min

Phenoxybenzamine

1mg/kg/day infused at least over 2 hours.

ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS:

These produce by inhibiting the formation of angiotensin II. Renin released by the kidneys lyses angiotensinogen to form angiotensin I which is then converted to angiotensin II by ACE in lungs. Bradykinin is levels also increase as they are broken down by ACE. This results in dry cough.

Drugs used are: Captopril, enalapril, fosinopril, lisinopril, ramipril, moexipril, quinapril, benazepril.

Actions:

1. Vasodilatation
2. Decrease blood volume

- a. Natriuretic effect
- b. Diuretic effect
3. Depress sympathetic activity
4. Inhibit cardiac and vascular hypertrophy.

Kinetics: All ACE inhibitors bind to tissue and plasma proteins. The free drug is eliminated predominantly by glomerular filtration. Enalapril and later ACE inhibitors are prodrugs. Captopril and Lisinopril are active by themselves.

Indications:

1. Hypertension
2. Heart failure

Adverse Effects: Low incidence.

1. Dry cough (10%)
2. Hypotension
3. Angioedema
4. Hyperkalemia
5. Impairment of renal function
6. Taste disturbance
7. Skin rashes

ANGIOTENSIN RECEPTOR

TOR BLOCKERS (ARB):

ARBs antagonize the action of angiotensinII in a highly selective manner at the angiotensinII AT1-receptor which mediates all classical effects of angiotensin. The functional role of AT2-receptors is unclear.

Examples: Candesartan, Eprosartan, Irbesartan, Losartan, Olmesartan, Telmisartan, Valsartan.

Mechanism: Many ARBs or active metabolites bind to AT1 receptor in a manner which is competitive but slowly surmountable, so that the duration of action is prolonged.

Kinetics: All ARBs are well absorbed after oral administration. Losartan is converted to active metabolite EXP 3174. Candesartan is the active constituent of the prodrug candesartan cilexetil.

Adverse Effects:

1. Hyperkalemia
2. Impairment of renal function
3. Dizziness and syncope
4. Angioedema – very rare.

BETA 2 ADRENERGIC AGONISTS:

Beta 2 receptors are located on the vascular smooth muscles and on bronchial smooth muscle cells.

Mechanism: β_2 receptors are coupled with Gs-G protein which stimulates the formation of cAMP. cAMP inhibits myosin light chain kinase that is responsible for phosphorylating smooth muscle myosin thereby resulting in smooth muscle relaxation – vasodilatation and bronchodilatation.

Examples: Dobutamine, Isoprenaline, Salbutamol, Albuterol.

These are primarily used either for inotropy (Dobutamine), chronotropy (Isoprenaline) or for bronchodilatation.

Uses:

1. Bronchial asthma
2. Inotropy
3. Chronotropy
4. Uterine relaxation in premature labour

Adverse Effects:

1. Hypotension
2. Tachycardia
 - a. Reflex
 - b. β_1 stimulation
3. May reduce coronary perfusion pressure and result in cardiac ischemia.

CALCIUM CHANNEL BLOCKERS (CCB):

CCBs are widely used drugs in cardiovascular medicine to control hypertension, manage angina and tachyarrhythmias

Examples: Amlodipine, Diltiazem, Felodipine, Isradipine, Lacidipine, Lercanidipine, Nicardipine, Nifedipine, Nisoldipine, Verapamil.

Mechanism: CCBs promote vasodilatory activity by reducing calcium influx into VSMC by interfering with voltage-operated calcium channels (and to a lesser extent receptor-operated channels) in the cell membrane.

Classification: Categorized according to structural and functional distinctions:

1. Dihydropyridine derivatives – Amlodipine, Felodipine, Isradipine, Nifedipine, Nicardipine.
2. Phenylalkylamines : Verapamil
3. Benzothiazepines: Diltiazem

Dihydropyridine derivatives have pronounced peripheral vasodilator properties resulting in reflex tachycardia. Other two groups reduce the heart rate and are called rate-limiting CCBs.

Kinetics: All CCBs have low and variable oral bioavailability because of extensive first pass metabolism. Half life is less than 12 hours except for amlodipine (40 hrs).

Indications:

1. Hypertension
2. Ventricular Arrhythmia
3. Angina

Adverse Effects:

Dihydropyridines:

1. Headache and flushing
2. Tachycardia and palpitation
3. Swelling of ankles and hands
4. Gum hypertrophy

Rate-limiting CCBs

1. Bradycardia
2. AV conduction delay
3. Constipation (verapamil)

CENTRALLY ACTING SYMPATHOLYTICS:

These include α_2 agonists. These receptors are located in the presynaptic noradrenergic neurons, the stimulation of which inhibits release of noradrenaline.

Examples: Guanabenz, Guanfacine, Clonidine, Alpha methyl dopa, and Dexmedetomidine.

Alpha methyl dopa is a structural analog of dopa and functions as a prodrug.

Mechanism: They activate α_2 receptors and reduce the sympathetic outflow to the heart and vasculature.

Actions: Decrease heart rate, cardiac output and reduce blood pressure. It also reduces vascular tone and result in vasodilatation, reduced systemic vascular resistance and blood pressure.

Adverse Effects:

1. Sedation
2. Dry mouth and nasal mucosa
3. Bradycardia
4. Orthostatic hypotension
5. Impotence
6. Constipation
7. Nausea and gastric upset.

DIRECT ACTING VASODILATORS:

These drugs appear to have multiple direct effects on VSMC.

Examples: Hydralazine, Minoxidil

Mechanisms:

1. K⁺ channel opening
2. Inhibit IP₃-induced release of calcium
3. Stimulates formation of nitric oxide

Action: Its action is highly specific to arterial vessels, reduces SVR and causes reflex tachycardia.

Kinetics: Well absorbed from the GIT. Has complex metabolism depending on the acetylators status. In slow acetylators it undergoes primary oxidative metabolism, while in rapid acetylators it undergoes acetylation.

Indications:

1. Primary arterial hypertension
2. Pulmonary hypertension (rare)
3. Heart failure

Adverse Effects:

1. Reflex tachycardia – cardiac ischemia
2. Headaches
3. Flushing
4. Lupus-like syndrome
5. Hirsutism (with minoxidil)

ENDOTHELIN RECEPTOR ANTAGONISTS (ERA):

Endothelin, a 21 amino acid peptide is a powerful vasoconstrictor which acts through ETA and ETB receptors which are Gq protein coupled.

There are three kinds of ERAs:

1. Selective ETA antagonists: Sitaxentan, Ambrisentan, Atrasentan, zibotentan.
2. Selective ETB antagonists: BQ-788, A192621.
3. Dual antagonists: Bosentan, Macitentan, Tezosentan.

Sitaxentan, Ambrisentan and bosentan are used primarily for the treatment of pulmonary arterial hypertension.

Adverse Effects:

1. Headache
2. Cutaneous flushing
3. Edema formation

GANGLIONIC BLOCKERS:

These drugs block the nicotinic receptors present in both sympathetic and parasympathetic ganglia. By reducing the sympathetic outflow they cause vasodilatation.

Examples: Trimethaphan, hexamethonium, pentolinium, mecamylamine and pempidine.

Indications:

These are used less frequently. Used only infrequently in hypertensive emergencies.

Adverse Effects:

1. Orthostatic hypotension
2. Tachycardia
3. Dry mouth, GIT atony
4. Urine retention

NITRODILATORS:

Nitrodilators are drugs that mimic the actions of endogenous NO by releasing NO or forming NO within tissues.

Mechanism: NO activates the guanyl cyclase – cyclic GMP pathway leading to vasodilatation. Release of NO involves both enzymatic and non-enzymatic pathways.

There are two important drugs used commonly in anaesthesia practice

1. Nitroglycerine (NTG)
2. Sodium Nitroprusside (SNP)

Nitroglycerine (NTG):

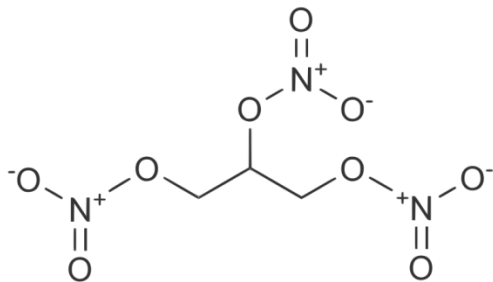


Fig 8: Nitroglycerine

Actions: NTG is a prodrug and must be first denitrated to produce active metabolite nitric oxide (NO).

Preparation: Available in 5 ml ampoules containing 5mg/ml.

Dilution: usually 25 mg NTG is diluted in 50 ml of NS or 5%D for infusion.

Kinetics: Bioavailability orally is only 50 % and sublingually it is 88 to 90%. The onset is quick after sublingual administration and the half-life is about 1 to 3 minutes. By intravenous the onset is very quick and the half-life is about 1 to 3 minutes.

Dose: 0.5 to 10 µ/kg/min as continuous infusion.

Uses:

1. Angina
2. Acute myocardial infarction

3. Severe hypertension
4. Coronary artery spasms

Adverse Effects:

1. Headaches
2. Severe Hypotension
3. Reflex tachycardia and sometimes bradycardia
4. Potentiation of other vasodilators
5. Nitrate tolerance

Sodium Nitroprusside (SNP):

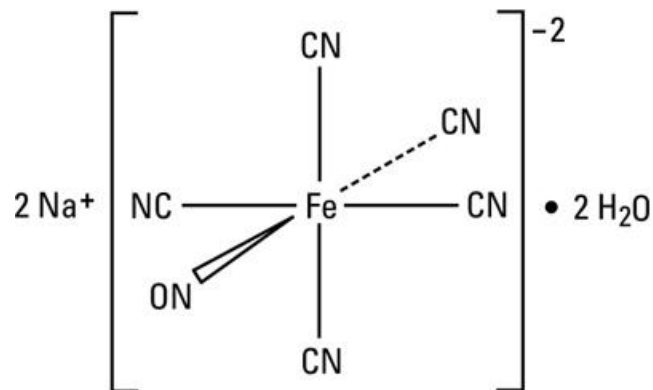
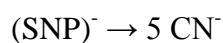
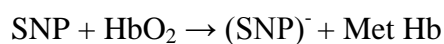


Fig 9: Sodium Nitroprusside

Actions: Dilates both arterioles and venules resulting in venous pooling and reduced systemic vascular resistance. Cardiac output tends to fall due to preload reduction in patients with normal ventricular function but tends to increase in those with severely impaired LV function due to predominant effect on the arterial impedance.

Kinetics: SNP is an unstable molecule that decomposes under strongly alkaline conditions or when exposed to light. The drug must be given by continuous infusion to be effective. Onset is within 30 sec, peak action at 2 minutes and the effect disappears within 3 minutes.

Metabolism is by reduction followed by the release of cyanide and nitric oxide. Cyanide is further metabolized in the liver to thiocyanate and eliminated in urine.



$CN^- + Met\ Hb \rightarrow CyanMet\ Hb$ OR

$CN^- + Thiosulfate \rightarrow Thiocyanate$ OR

$CN^- + Cyt\ Oxidase \rightarrow Cyanide\ Toxicity$

Fig 10: SNP Metabolism

Mean elimination half-time of thiocyanate is 3 days in those with normal renal function and is prolonged in renal insufficiency.

Adverse Effects:

1. Hypotension, Tachycardia
2. Severe lactic acidosis because of toxic accumulation of cyanide.

PHOSPHODIESTERASE INHIBITORS:

These drugs block the enzyme phosphodiesterase (isoenzyme 3) which breaks down cAMP increasing intracellular cAMP levels. This has an inotropic effect on the myocardial cells and results in vasodilatation by relaxing the vascular smooth muscle cells. Hence these are called as inodilators.

Examples: Amrinone, Milrinone

Actions: The effects on the vasculature are: Vasodilatation, increased organ perfusion, decreased SVR, decreased arterial pressure. The effects on the cardiopulmonary system are: increased contractility and heart rate, increased stroke volume and ejection fraction, decreased ventricular preload and decreased pulmonary capillary wedge pressure.

Availability: Milrinone is available as 1mg/ml in 10 ml vial.

Dilution: 10 mg is diluted in 50 ml of NS or 5% dextrose solution.

Dose: Loading dose 50µg/kg. Infusion is administered at 0.375 to 0.5µg/kg/min.

Uses:

1. Short-term intravenous treatment with acute decompensated heart failure.
2. Post cardiopulmonary bypass in severe LV dysfunction
3. Inotropic support in congenital heart disease patients with pulmonary artery hypertension.

Adverse reactions:

1. Hypotension – especially during administration of bolus dose because of vasodilatation.
2. Ventricular ectopic activity
3. Headaches
4. Hypokalemia
5. Tremor
6. Thrombocytopenia.

POTASSIUM CHANNEL OPENERS:

These are drugs which facilitate ion transmission through potassium channels resulting in hyperpolarization of the membrane.

Examples: Minoxidil, Nikorandil, Diazoxide

Actions: Minoxidil and diazoxide produce arteriolar vasodilatation with no effect on the capacitance vessels. SVR falls and reflex tachycardia occurs. Minoxidil is a potent stimulant for rennin secretion

Kinetics: Minoxidil is well absorbed from the GIT. Minoxidil is itself not active. In the liver it is metabolized to the active metabolite minoxidil N-O Sulfate. Has a half life of 3-4 hours, but its duration of action is 24 hours or even longer.

Uses:

1. Reserved for severe hypertension responding poorly to other antihypertensive medications.

Adverse effects:

1. Retention of salt and water
2. Fall in SVR, reflex tachycardia
3. Pericardial effusion
4. Flattened / inverted T waves
5. Hypertrichosis

RENIN INHIBITORS

Renin inhibitors produce vasodilatation by inhibiting the activity of rennin, which is responsible for stimulating angiotensin II formation.

Examples: Aliskiren

Preparation: Available as 150 mg tablets

Dose: 150 to 300 mg once a day.

Actions:

1. Dilate arteries and veins by blocking angiotnesin II formation.
2. Down regulate sympathetic adrenergic activity
3. Promote renal excretion of sodium and water.
4. Inhibit cardiac and vascular remodeling associated with chronic hypertension, heart failure and myocardial infarction.

Kinetics: Orally active nonpeptide drug with a half-life of 24 hours and is dosed once per day. It takes about 2 weeks of dosing to achieve maximal antihypertensive effect. It is metabolized by the liver and eliminated renally.

Uses:

1. Antihypertensive
2. Prevent cardiac and vascular remodeling

Adverse Effects:

1. GI side effects like diarrhea
2. Cough
3. Angioedema
4. Hyperkalemia
5. Hypotension
6. Risk of birth defects.

CONCLUSION:

Vascular tone is determined by complex balance between endogenous vasodilators and vasoconstrictors. Thorough understanding of its physiology in health and disease and the pharmacologic effects of vasoactive drugs helps in better management of the patients.