Hypertension

Normal BP:	<120/<80
Prehypertension:	120-139/80-89
Hypertension stage1	140-159/90-99
Hypertension stage 2	≥160/100
Emergency	>210/>120
Resistant hypertension three regimen	Failure of BP control with drug
Isolated systolic hypertension	>140/<90

How can we treat hypertension

- Secondary hypertension- treat underlying cause
- Essential hypertension- cause not known
- Factors involved- stress, weight, dietary habits, salt retention, increased angiotensin production, , increased sympathetic tone
- Approaches-

✓Reduce salt/water content of body

✓Reduce sympathetic tone

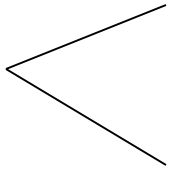
✓Reduce effects of circulating angiotensin II

✓Reduce cardiac force of contraction

✓Dilate peripheral vessels to reduce cardiac filling & consequent stroke volume

Drugs used for treatment of hypertension:

- Diuretics
- Centrally acting agents- methyl dopa, clonidine
- β-Adrenoceptor blockers
- α-Adrenoceptor blockers
- Combined α and β blockers
- ACE inhibitors
- ARBs
- CCBs
- Vasodilators



Hydralazine, Minoxidil, Diazoxide, Fenoldopam (arteriolar)

Sodium nitroprusside (arteriolar + venular)

Need for life-style changes:

- Weight loss/control
- Restricted sodium intake
- Increasing aerobic exercise
- Moderating alcohol consumption

✓These changes in life-style may be sufficient to control hypertension in early stage I

✓They also facilitate pharmacological treatment

Diuretics:

- Thiazides, loop diuretics and K^+ sparing diuretics

✓They are antihypertensive when given alone

✓Also enhance the efficacy of other antihypertensive agents

✓Exact mechanism not known

✓Initially decrease extracellular volume and enhance Na^+ excretion by inhibiting Na^+Cl^- co-transporter which leads to ↓ in CO

✓Long term therapy- CO and extracellular volume returns to pretreatment value due to compensatory mechanisms but antihypertensive effect persists due to decrease in PVR

✓↓ in PVR may occur due to direct vasodilatory effect of thiazides or due to their effect on kidney

Thiazides should be avoided in patients with concommitant:

- Diabetes mellitus
- Gout
- Hyperlipidaemia
- Renal insufficiency

High efficacy (ceiling) diuretics

- Severe reduction in blood volume & electrolyte imbalance
- Strong diuretic
- Weak antihypertensive than thiazide diuretics
- Indicated in HT when complicated by
  - ✓Chronic renal failure
  - ✓Coexisting CHF
  - ✓Severe edema due to use of potent vasodilators

Sympatholytic agents:

- Centrally acting: α methyldopa, clonidine
- β Adrenoceptor blockers
- α Adrenoceptor blockers
- Combined α and β adrenoceptor blockers- labetalol, carvedilol

Methyldopa:

- It is an analog of DOPA (dihydroxyphenylalanine)
- It is a pro drug- metabolized in brain by L-aromatic amino acid decarboxylase in adrenergic neurons to α methyl dopamine and then converted to α methyl norepinephrine
- α Methyl norepinephrine is stored in the vesicles in place of NE and released in response to stimulus
- Acts in the CNS to reduce sympathetic outflow from brain stem

- Also, probably acts an an agonist of central presynaptic α_2 receptors to reduce central sympathetic outflow
- Rapidly absorbed, t½ approximately 2 h
- Even after i.v. injection effects starts after a delay of about 6-8 h

•Why the delay in action? probably due to time taken for transportation to brain and conversion to methyl NE

•ADRs:

✓Sedation, transient

✓Dryness of mouth

✓Parkinsonian signs

✓Hyperprolactenemia leading to gynecomastia or galactorrhoea

Clonidine, Guanbenz and Guanfacine:

- Stimulate α_{2A} subtype of α_2 receptors in the brain stem and reduce the central sympathetic outflow
- ↓ in plasma concentration of NE correlates with the decrease in BP
- Decreased sympathetic outflow also reduces cardiac output & HR
- In supine position, when the sympathetic tone to vasculature is low, the effect is mainly by reducing HR and stroke volume

- In upright position, the vasculature tone is high and effect is mainly by reducing the PVR
- Since they block peripheral vasoconstriction, postural hypotension may occur

ADRs:

- Sedation
- Xerostomia
- Dryness of eye, nasal mucosa
- Parotid swelling
- Postural hypotension
- Erectile dysfunction
- Bradycardia, sinus arrest, AV block
- Rebound hypertension

Guanadrel:

- Exogenous false neurotransmitter
- Actively transported to adrenergic neuron by NET (NE transporter)
- Previously NET was known as Uptake 1
- Stored in adrenergic neurons where it is concentrated in storage vesicles and replaces NE
- Released in place of NE and acts as false neurotransmitter
- It has no activity on adrenergic receptors

- This inhibits the functioning of peripheral adrenergic neurons
- Antihypertensive effect is achieved by reduction in PVR
- Postural hypotension

β-Adrenergic blockers:

- Decrease HR, output and stroke volume (β_1)
- Inhibit renin release from JG apparatus (β_1)
- Block β-receptors of peripheral blood vessels so they constrict (β_2)
- PVR increases initially but gradually returns to pretreatment values or less
- Those crossing the BBB also reduce central sympathetic tone

- Do not cause retention of salt and water
- Often combined with diuretics- additive effect
- Highly preferred drugs for hypertensive patients with complications like angina, MI or CHF

β-Adrenoceptor blockers produce:

- Decreased myocardial contraction & cardiac output (β_1)
- Decreased renin secretion (β_1)
- Decreased central sympathetic activity (Presynaptic β_2 effect)

All β-adrenoceptor blockers produce:

- Reduced exercise tolerance
- Mild chronic fatigue
- Sedation
- Increased airway resistance
- Bradycardia
- Sleep disturbances- ↓ melatonin release

- All β-adrenoceptor blockers initially produce vasoconstriction by blocking vascular β-receptors that relax vascular smooth muscles
- This vasoconstriction disappears after some time (adaptability ?)

β-Adrenoceptor blockers with intrinsic sympathomimetic activity:

Advantages:

- Less bradycardia & myocardial suppression- useful in patients having low cardiac reserve
- Less likely rebound hypertension
- Less worsening of lipid profile
- Less effect on exercise tolerance

β-Adrenoceptor blockers with intrinsic activity:

- Oxeprenolol
- Pindolol
- Penbutolol
- Acebutolol

Nebivolol: β_1 selective antagonist

- Promotes vasodilation due to ↑ production of NO in arterial smooth muscle
- Has antioxidant properties also

α_1-Adrenoceptor blockers:

- Block α_1-adrenoceptors on smooth muscles of arterioles
- Reduce arteriolar resistance and increase venous capacitance
- Reflex increase in HR and plasma renin activity
- Return to normal during long term therapy
- Postural hypotension may occur depending on plasma volume

- Reduce total plasma concentration of triglycerides and LDL
- Increase plasma levels of HDL- beneficial effect
- Effect on lipids persists even when combined with diuretics
- Preferred in hypertensive patients with BPH

Combined α and β adrenoceptor blockers:

- Labetalol and carvedilol
- Labetalol is a mixture of four stereoisomers- one isomer is α blocker like prazosin, another is a non-selective β blocker with partial agonist activity like pindolol
- Other two isomers are inactive
- Carvedilol is a β receptor antagonist with α_1 receptor blocking activity
- Pheochromocytoma

Vasodilators: Hydralazine:

- ✓Directly relaxes the arteriolar smooth muscle
- ✓Mechanism uncertain
- ✓Does not relax venous smooth muscle
- ✓Compensatory reflex increase in sympathetic outflow
- ✓Increase in HR, cardiac output, plasma renin activity and fluid retention
- ✓Selective decrease in vascular resistance in coronary, cerebral and renal vascular beds
- ✓Postural hypotension- uncommon because it does not dilate veins

ADRs:

- Extension of pharmacological effects: headache, flushing, hypotension, palpitation, tachycardia, dizziness, nausea
- Can precipitate angina or MI due to increased myocardial O_2 demand
- Immunological reactions- drug induced lupus syndrome, serum sickness, hemolytic anemia
- Pyridoxine responsive polyneuropathy- probably because hydralazine combines with pyridoxine to form hydrazone

Minoxidil:

- Converted in liver to active form- minoxidil N-O sulphate
- Produces arteriolar vasodilation
- No effect on venous capacitance vessels
- Causes increase in cardiac output
- Blood flow to skin, skeletal muscles, GIT and heart is increased
- Dilates renal artery, nett effect depends on hypotension and extent of dilatation

- Potent stimulator of renin secretion- by increasing sympathetic outflow and effecting renal regulation of renin release
- Minoxidil sulphate opens ATP-modulated K^+ channels
- K^+ efflux occurs, cell is hyperpolarized

- ✓May precipitate severe bradycardia/sinus arrest
- ✓Hepatotoxicity- Coombs test (antiglobulin) necessary because autoantibodies are produced against Rh antigen
- ✓Preferred drug for treatment of hypertension during pregnancy

ADRs:

•CVS: same as hydralazine

•Hypertrichosis: (abnormal hair growth in the body) may occur

Uses:

•Severe hypertension- should never be given alone; always with a diuretic to prevent fluid retention and a sympatholytic drug to control reflex CVS changes

•Baldness- topical

Diazoxide:

- Chemically related to thiazide diuretics but has no diuretic activity
- Instead causes retention of sodium and water
- Acts by opening K^+ channels in arteriolar smooth muscle cells
- No effect on venules
- Causes hyperglycemia
- Used for short term treatment of hypertensive emergencies
- Often combined with a diuretic and a β blocker

Fenoldopam:

- Agonist of dopamine D_1 receptors
- Causes dilatation of arterioles and natriuresis
- Oral bioavailability is poor
- t½ approx. 5 min
- Onset of action is rapid
- Increases renal output, creatinine clearance and sodium excretion so concomitant use of diuretic or β blocker is not required
- ADRs: reflex tachycardia, headache, flushing
- Increases intraocular pressure so should be avoided in glaucoma

Sodium nitroprusside:

- Releases NO which dilates the blood vessels
- Mechanism of NO release not known but mimics endogenous NO release by vascular endothelial cells
- No development of tolerance (it occurs to nitroglycerine)
- Dilates both arterioles and venules
- CO falls due to venous pooling and reduction in PVR
- Plasma renin activity increases
- Unlike arteriolar dilators hydralazine, minoxidil and diazoxide, it causes only modest increase in HR and reduces cardiac O_2 demand

- Used to treat hypertensive emergencies, aortic dissection, controlled hypotension during anesthesia
- Effect of light on drug

Toxicity:

- Headache, nausea, vomiting-disappear after the drug is discontinued
- Cyanide or thiocyanate accumulation
- Thiocyanate toxicity- psychosis, disorientation and convulsions
- Methemoglobinaemia- due to cyanide

- Administration of sodium thiosulfate and hydroxycobalamine
- Sodium thiosulfate- acts as a sulfur donor and facilitates metabolism of thiocyanates
- Hydrocobalamine- combines with cyanide ion to form non-toxic cyanocobalamine

Pregnancy

•If taken before pregnancy, most anti-HTN can be continued except ACE inhibitors and angiotensin II receptor blockers.

•Methyldopa is most widely used for hypertension during pregnancy.

•Beta-blockers are not recommended early in pregnancy.

Drugs to be avoided for treatment of hypertension associated with other diseases:

Pregnancy	ACEI, ARBs, β-blockers, diuretics
Diabetes mellitus IIDDM)	Diuretics, β-blockers
Angina pectoris	Vasodilators
Bronchial asthma	β-blockers
Peripheral vascular disease	β-blockers
CHF	CCBs except amlodipine, α and β-blockers