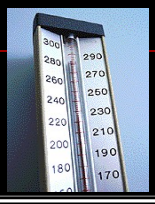
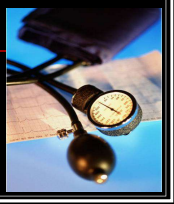
ANTI-HYPERTENSIVE DRUGS





Occurrence

Types & Etiology

Treatment

- Non Pharmacological
- Pharmacological

Vertical integration with medicine

HYPERTENSION

Current definition (W.H.O.)

A level of systolic blood pressure of 140 mm Hg or above, or a level of diastolic blood pressure of 90mm Hg or above, by repeated measurements over periods of several weeks.

It may be systolic or diastolic.

Vertical integration with medicine

Blood Pressure Regulation

Hypertension

Category	Systolic (mmHg)	Diastolic (mm Hg)
optimal	<120	< 80
normal	< 130	< 85
high-normal	130-139	85-89
Hypertension		
stage 1	140-159	90-99
stage 2	160-179	100-109
stage 3	≥ 180	≥110

Malignant Hypertension SBP 200 or more DBP 120 or more

Vertical integration with medicine

BP = CO × PVR

Normal regulation of blood pressure

- **Postural Baroreflex (short term)**
- **Renal Response to Decreased BP (long term)**

Spiral regulation with physiology

Regulation of Blood Pressure

- **Baroreceptors & the ANS:** for rapid moment to moment control
- **Renal responses:** Renin Angiotensin – Aldosteron system ---- for long term control.
- **Others:** Endothelin
  Nitric oxide
  Vasopressin

Spiral regulation with physiology

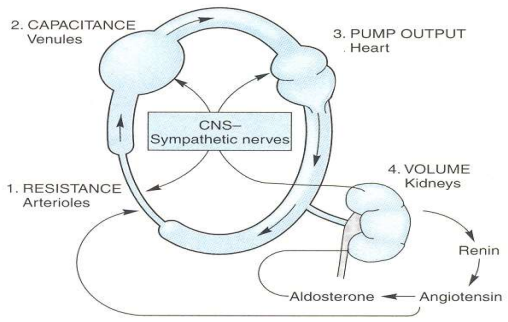


Figure 11–1. Anatomic sites of blood pressure control.

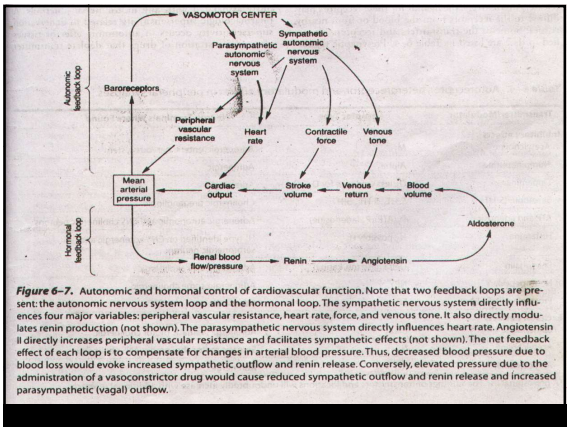


Figure 6–7. Autonomic and hormonal control of cardiovascular function. Note that two feedback loops are present: the autonomic nervous system loop and the hormonal loop. The sympathetic nervous system directly influences four major variables: peripheral vascular resistance, heart rate, force, and venous tone. It also directly modulates renin production (not shown). The parasympathetic nervous system directly influences heart rate. Angiotensin II directly increases peripheral vascular resistance and facilitates sympathetic effects (not shown). The net feedback effect of each loop is to compensate for changes in arterial blood pressure. Thus, decreased blood pressure due to blood loss would evoke increased sympathetic outflow and renin release. Conversely, elevated pressure due to the administration of a vasoconstrictor drug would cause reduced sympathetic outflow and renin release and increased parasympathetic (vagal) outflow.

Why to Treat Hypertension ?

Anatomic site of blood pressure control

- The major blood vessels controlling blood pressure are referred to as

1. The resistance vessels
2. The capacitance vessels

Spiral regulation with physiology

- Why do we treat hypertension?
- Sustained elevations in blood pressure lead to complications such as **stroke**, **heart attack**, **kidney failure** and other organ damage

BP = CO x PVR

cardiac factors

heart rate
contractility

1. Beta Blockers
2. CCB's
3. C.A. Adrenergics

circulating volume

salt
aldosterone

ACEi's
Diuretics

CCB = calcium channel blockers
CA Adrenergics = central-acting Adrenergics
ACEi's = angiotensin-converting enzyme inhibitors

A. DIURETICS

Thiazides & related agents

- Hydrochlorothiazide
- Chlorthiazide
- Benzthiazide
- Chlorthalidone
- Indapamide

Loop diuretics

- Furosemide
- Bumetanide
- Ethacrynic acid

BP = CO x PVR

Hormones

1. vasodilators
2. ACEI's
3. CCB's

Peripheral Sympathetic

Receptors

alpha: 1. alpha blockers
beta: 2. beta blockers

Central Nervous System

1. CA Adrenergics

Local Acting

1. Peripheral-Acting vasodilators

Potassium Sparing Diuretics

- Triamterene
- Spironolactone
- Amlioride

CLASSIFICATION
Main Groups

- DIURETICS
- SYMPATHOPLEGICS
- CALCIUM CHANNEL BLOCKERS
- DRUGS ACTING ON RENIN ANGIOTENSIN SYSTEM
  - ACE INHIBITORS
  - ANGIOTENSIN RECEPTOR BLOCKERS
- VASODILATORS

B. SYMPATHOPLEGICS

1. Centrally acting drugs

- Methyldopa
- Clonidine
- Guanabenz
- Guanfacine

2. β-Adrenergic receptor antagonists

- Propranolol
- Metoprolol
- Atenolol

SYMPATHOPLEGICS

3. α-Adrenergic receptor antagonists

- Prazosin
- Terazosin
- Doxazosin
- Phenoxybenzamine
- Phentolamine

4. Alpha & Beta Blockers

- Labetalol
- Carvedilol

Non-dihydropyridines

Phenylalkylamines

Verapamil (Calan)

Gallopamil

Diphenylpiperazines

Flunarizine

Trimetazidine

Ranolazine

SYMPATHOPLEGICS

5. Adrenergic Neuron Blockers

- Guanethidine
- Reserpine

6. Ganglion Blocking Agents

- **Trimetaphan**

Non-dihydropyridines continue…

Benzothiazepines

Diltiazem (Herbessor)

Diarylaminopropylamine

Bepridil

C. CALCIUM - CHANNEL BLOCKERS

Dihydropyridines

Nifedipine (Adalat)

Nicardipine

Nimodipine

Amlodipine

Nisoldipine

Nitrendipine

Felodipine

Isradipine

D. DRUGS ACTING ON RENIN ANGIOTENSIN SYSTEM

Angiotensin Converting Enzyme (ACE) Inhibitors

- Captopril
- Enalapril
- Lisinopril
- Benzapril
- Perindopril
- Quinapril
- Ramipril
- Trandolapril

Angiotensin II Receptor Blockers (Competitive antagonists)

- Losartan
- Valsartan
- Candesartan
- Eprosartan
- Irbesartan
- Telmisartan
- Saralasin

Diuretics

- Used to adjust volume in hypertension, acute and chronic heart disease, acute and chronic renal failure.
- Four main classes used in hypertension:
  - Carbonic anhydrase inhibitors (proximal tubule and collecting duct)
  - Thiazides and thiazide-like agents (Distal convoluted tubule)
  - Loop diuretics (Thick ascending limb)
  - Potassium sparing diuretics (Late Distal tubule and collecting duct)

E. VASODILATORS

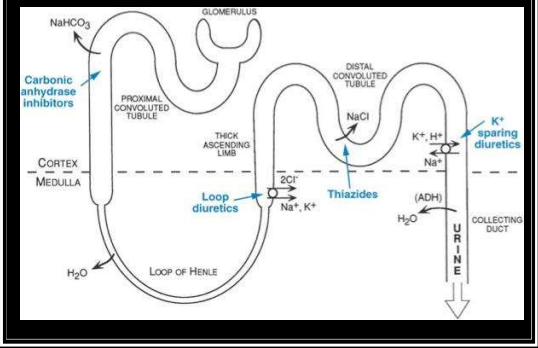
1. Arterial

Oral:	Hydralazine	Minoxidil
Parenteral:	Diazoxide	Fenoldopam

2. Venodilators: Nitroglycerine

3. Aterial and Venous:

Sodium Nitroprusside



MONOTHERAPY VERSUS POLYPHARMACY

- Thiazide diuretics reduce the re-absorption of **sodium** and **chloride** in the early part of the distal convoluted tubule of the kidney.
- This results in the delivery of increased amounts of sodium to the distal tubule, where some of it is exchanged for potassium.
- The net result is increased excretion of sodium, potassium and water.
- Circulating volume is diminished, reducing preload on the heart and, thus, cardiac output and blood pressure.
- With long-term therapy, auto-regulation by the body's own compensatory mechanisms results in vasodilatation, reduction of peripheral vascular resistance and return of the cardiac output to normal.
- Thiazides also have some direct vasodilatory properties.

Other diuretics

- Loop diuretics act on the ascending limb of the loop of Henle and inhibit the reabsorption of **chloride**, **sodium** and **potassium**.
- They produce a rapid but short-lived diuresis and are thus unsuitable as first-line agents for hypertension, as they do not provide 24-hour control.
- However, they do have a role in patients with impaired renal function in whom thiazides are ineffective, and in patients with hypertension resistant to multiple drug therapy, who are often fluid overloaded.
- Furthermore, they may be synergistic with agents such as the ACE inhibitors.

Core -Pharmacology

Diuretics To be avoided in

Young active hypertensive
Diabetes or family history of diabetes
Gout or family history of gout
Abnormal lipid profile
Pregnancy induced hypertension

Core -Pharmacology

- Potassium-sparing diuretics, such as **amiloride** and **triamterene**, produce little reduction in blood pressure themselves.
- They may be useful in combination with other diuretics to prevent hypokalemia.
- **Spironolactone** is a specific aldosterone antagonist, with a particular role in primary hyperaldosteronism or Conn's syndrome.

Core -Pharmacology

B. SYMPATHOPLEGICS

- Moderate to severe hypertension, most effective when used concomitantly with a diuretic
- Classified according to the site at which they impair the sympathetic reflex arc
- Can elicit compensatory effects through mechanisms not dependent on adrenergic NS (retention of Na^+ by the kidney)

Core -Pharmacology

Diuretics - Situations favoring

- Elderly patients
- Isolated systolic hypertension
- Obese patients with volume overload
- Renal disease with Na^+ retention
- Low cost therapy

Core -Pharmacology

SYMPATHOPLEGICS

1. Centrally acting drugs
- Methyldopa
- Clonidine
- Guanabenz
- Guanfacine

2. β-Adrenergic receptor antagonists
- Propranolol
- Metoprolol
- Atenolol

3. α-Adrenergic receptor antagonists
- Prazosin
- Terazosin
- Doxazosin
- Phenoxybenzamine
- Phentolamine

Core -Pharmacology

SYMPATHOPLEGICS

4. Alpha & Beta Blockers

- Labetalol
- Carvedilol

5. Adrenergic Neuron Blockers

- Guanethidine
- Reserpine

6. Ganglion Blocking Agents

- Trimetaphan

Core -Pharmacology

MOA - α-Methyldopa…

- α -Methyl NE is released instead of NE & acts as agonist at **post synaptic α2 receptors in VMC in the brain stem**.
- Inhibits adrenergic neuronal out flow from the brain stem to the peripheral sympathetic NS.
- Methyl Nor epinephrine ↓ Blood pressure mainly by↓ PVR , HR & CO variably ↓
- Methyl NE is not a substrate for MAO like Nor epinephrine.
- At periphery α -Methyl NE acts as vasoconstrictor ,so it is not MOA as anti-hypertensive

Core -Pharmacology

Centrally acting sympathoplegic drugs:

These drugs are central α_2 receptor agonists.

- Reduce sympathetic out flow from vasomotor centers in the brain stem
- Allow these centers to retain or even increase their sensitivity to baroreceptors.
- Their effects are not dependent on posture
- The drugs are:
  - Methyldopa
  - Clonidine
  - Guanabenz
  - Guanfacine

Core -Pharmacology

Therapeutic uses

1. Antihypertensive

- Widely used in the past for mild to moderate hypertension along with a diuretic.
- Now preferred drug in pregnancy, effective & safe for both mother & fetus.
- Valuable in hypertensives with renal insufficiency , no dosage adjustment required.
- In Hypertensive crisis; may be given I/V.

Vertical integration with medicine

MOA - α-Methyldopa

- Pro-drug , an analog of L - DOPA
- Taken up into the adrenergic nerve terminals by uptake -1
- Metabolized to active metabolite α-methyl Nor-epinephrine ,like synthesis of Nor-epinephrine
- α-Methyldopa → α-Methyldopamine → α-methyl Nor-epinephrine (α -Methyl NE)
- α -Methyl NE replaces Nor epinephrine in the vesicles.

Core -Pharmacology

Adverse effects

- Sedation– the most common specially at onset of treatment.
- On long term use:
  - Persistent lassitude & impaired mental concentration.
  - Mental Depression , Nightmares , vertigo.
  - Extrapyramidal symptoms-- Parkinsonian signs.
  - Hyperprolactinemia--- lactation in males & females.
- Postural hypotension ; only in volume depleted patients
- Positive Coombs test in 10-20 % cases treated for longer than12 months.

Vertical integration with medicine

Clonidine

- Clonidine is a 2-imidazoline derivative
- Act on alpha 2 adreno-receptors in brain stem to decrease sympathetic outflow leading to decrease in baro-receptor reflex arc and decrease in peripheral vascular resistance
- Clonidine also decreases heart rate & cardiac output

Core -Pharmacology

Beta Blockers

- **Mild to moderate hypertension**
- In **severe** hypertension - in combination therapy with direct vasodilators to prevent compensatory tachycardia.
- In hypertensive emergencies (Labetalol , Esmolol)
- Intra-operative & Postoperative hypertension (Esmolol)
- Hypertension with chronic heart failure (Carvedilol , Metoprolol, Bisoprolol)
- Hypertension with Pheochromocytoma use β- blockers after α blocker. (If given before Alpha blockers, there will be enhanced effects of catecholamines on alpha receptors--- further rise in blood pressure)

Vertical integration with medicine

Adverse effects of Clonidine

- Sedation –centrally mediated & dose dependent.
- Xerostomia (dry mouth) -centrally mediated & dose dependent.
- Depression (withdraw the drug if present). C/I in patients at risk of depression
- Hypertensive crisis on sudden withdrawal

(Marked rise in blood pressure if drug is stopped abruptly)

Vertical integration with medicine

Beta Blockers Suitable for patients of hypertension

1. Low cost therapy.
2. Young patient; less effective in elderly & blacks.
3. Coexisting anxiety or tachycardia , Angina.
4. Non-obese, high renin hypertensive.
5. Post-MI patients
6. Pregnancy (cardioselective & β blocker with ISA)

Vertical integration with medicine

β-Adrenergic receptor antagonists

i) Non-selective (β_1, β_2) blockers

Propranolol , Pindolol , Nadolol, Carteolol , Penbutolol

ii) Cardioselective (β_1) blockers

Acebutolol , Atenolol, Betaxolol , Bisoprolol , Esmolol, Nebivolol & Metoprolol

iii) Both α & β blockers

Labetalol & Carvedilol

Usual Predominance of Sympathetic or Parasympathetic Tone at Various Effector Sites, and Consequences of Autonomic Ganglionic Blockade

Site	Predominant Tone	Effect of Ganglionic Blockade
Arterioles	Sympathetic (adrenergic)	Vasodilation; increased peripheral blood flow; hypotension
Veins	Sympathetic (adrenergic)	Dilation: peripheral pooling of blood; decreased venous return; decreased cardiac output
Heart	Parasympathetic (cholinergic)	Tachycardia
Iris	Parasympathetic (cholinergic)	Mydriasis
Ciliary muscle	Parasympathetic (cholinergic)	Loss of visual accommodation
Gastrointestinal tract	Parasympathetic (cholinergic)	Reduced tone and motility; constipation; decreased gastric and pancreatic secretions
Urinary bladder	Parasympathetic (cholinergic)	Urinary retention
Salivary glands	Parasympathetic (cholinergic)	Xerostomia
Sweat glands	Sympathetic (cholinergic)	Anhidrosis
Genital tract	Sympathetic and parasympathetic	Decreased stimulation

C. CALCIUM - CHANNEL BLOCKERS

Dihydropyridines

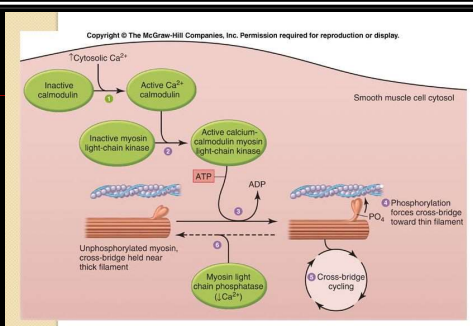
Nifedipine (Adalat)	Nicardipine
Nimodipine	Amlodipine
Nisoldipine	Nitrendipine
Felodipine	Isradipine

Non-dihydropyridines

Phenylalkylamines

Verapamil (Calan)

Gallopamil



Activation of smooth muscle contraction by calcium

CALCIUM - CHANNEL BLOCKERS

Diphenylpiperazines

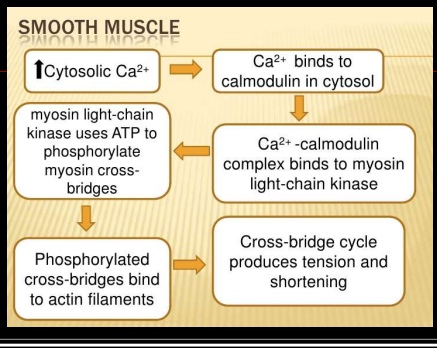
Flunarizine	Trimetazidine
Ranolazine	

Benzothiazepines

Diltiazem (Herbessor)

Diarylaminopropylamine

Bepridil



Type of Voltage-gated / Voltage-dependent Calcium Channels

- **L Type**
  - All types of Muscle , Neurons, bone
  - Heart (ventricular) more sensitive to Verapamil
- **T Type**
  - Neurons , bone
  - Heart (pace maker cell)
- **N Type**
  - Neurons
- **P Type**
  - Cerebellar purkinje neurons

Mechanism of Action in Blood Vessels

Blocking of voltage gated L-type calcium channels

↓

Reduced Ca^{++} in smooth muscle cells

↓

Reduced formation of Ca^{++} / Calmodulin complex

↓

No activation of myosin light chain kinase

↓

No Phosphorylation of myosin light chain → No contraction

↓

Vasodilatation

↓

Decreased Peripheral Resistance

Decreased BP

ON HEART

Blockade of voltage gated calcium channels

↓

Reduced Ca^{++} influx into cardiac cells

↓

No breaking of troponin bridge

↓

Less force & rate of contraction

↓

Decreased BP

Other Effects

- Anti-platelet effect (interfere with platelet aggregation)
- Effect on other smooth muscles (relaxation of bronchiolar, GIT and uterine sm. muscles)
- No action on Skeletal muscles
- Decreased release of insulin - Verapamil
- Decrease secretion of exocrine glands – less effect because of difference of Ca channels

Ph. Kinetics

Nifedipine

- Complete oral absorption
- Peak plasma levels 20-45 Min
- Detectable plasma levels 6 Min D.O.A 8-12 hrs

Diltiazem

- Elimination half life 3-6 hrs.
- Extensive metabolism in liver.
- Verapamil and Nifedipine excreted in urine Diltiazem excreted in faeces.

THERAPEUTIC USES

- Hypertension
- Angina
- Supraventricular arrhythmias
- Hypertrophic cardiomyopathy
- Prevent increase in infarct size
- Migraine Prophylaxis
- Raynaud's phenomenon
- Atherosclerosis
- Subarachnoid hemorrhage (Nimodipine)

Pharmacological Actions / Effects

Group Actions On Heart

- Anti Anginal (↓PVR &↓ CO)
- Anti hypertensive(↓PVR & ↓CO)
- Anti arrhythmic (Verapamil & Diltiazem)
- Useful in Myocardial infarction (↓O_2 requirements)

Toxicity (extension of therapeutic actions)

Cardio-depression, AV blocks, Hypotension Bradycardia, Cardiac failure

Minor AEs

Constipation, Nausea

Edema of dependent parts

Skin rashes, Flushing, Dizziness

DRUGS ACTING ON RENIN ANGIOTENSIN SYSTEM

ACE INHIBITORS

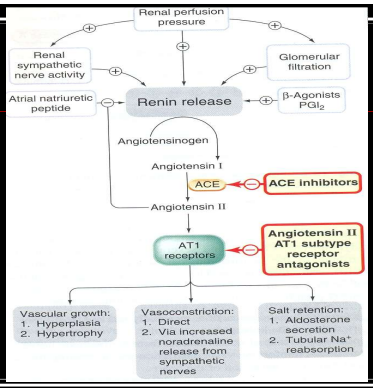
ANGIOTENSIN RECEPTOR BLOCKERS

MOA of ACE Inhibitors

- Renin is released from JGA
- Renin acts upon Angiotensinogen, to split off the inactive decapeptide Angiotensin I .
- Angiotensin I is then converted primarily by endothelial angiotensin converting enzyme(ACE) to Octapeptide, angiotensin II.
- Angiotensin II - most powerful vasoconstrictor.
- Also stimulates the synthesis and secretion of aldosterone which retains sodium & water.
- ACEIs inhibit the converting enzyme peptidyl dipeptidase & prevents formation of Angiotensin II. The same enzyme (under the name of plasma kininase) inactivates bradykinin, so it accumulates
- Bradykinin produces vasodilation directly as well as through ↑ PG synthesis.

Angiotensin Converting Enzyme (ACE) Inhibitors

- Captopril
- Enalapril
- Lisinopril
- Benzapril
- Perindopril
- Quinapril
- Ramipril
- Trandolapril



Angiotensin II Receptor Blockers (Competitive antagonists)

- Losartan
- Valsartan
- Candesartan
- Eprosartan
- Irbesartan
- Telmisartan
- Saralasin

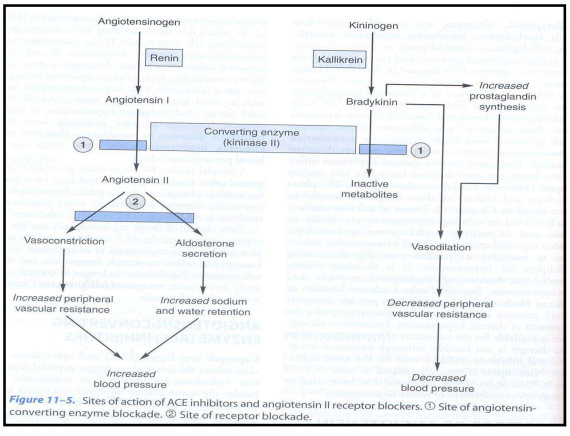


Figure 11–5. Sites of action of ACE inhibitors and angiotensin II receptor blockers. ① Site of angiotensin-converting enzyme blockade. ② Site of receptor blockade.

Actions of Angiotensin – II

- Generalized vasoconstriction, especially marked in efferent arterioles of the kidney. Is 40 times more powerful vasoconstrictor than NE.
- ↑ release of nor- epinephrine from sympathetic nerve terminals, reinforcing vasoconstriction & ↑ the rate and force of contraction of the heart
- Stimulation of proximal tubular re-absorption of Na^+
- Stimulates secretion of aldosterone from the adrenal cortex which retains sodium & water.
- Cell growth (Mitogenesis) in the heart and in arteries.

Pharmacokinetics

Mostly prodrugs, Orally active

Absorption : Rapid from GIT (B.A=70%) ↓ B.A ē food
Metabolism : Conjugation in liver
Distribution : Well but not to C.N.S
Excretion : Kidneys except fosinopril & moexipril
Pro -drugs : **to active drugs by hydrolysis in Liver.**
Enalapril → **De-esterified** → **Enalaprilat – t ½ 11 hrs**

Most of ACEIs excreted by kidneys so dosage should be ↓ in renal insufficiency.

PHARMACOLOGICAL EFFECTS - Antihypertensive effect

- **Due to inhibitory action on the Renin - Angiotensin System**
  Decreased Angiotensin II less vasoconstriction, hence Vasodilatation ⟶ Decreased PR.
- **Due to increased bradykinin** ⟶ Bradykinin degradation is prevented, accumulation of bradykinin – **a potent vasodilator**
- So↓ B.P principally by ↓ P.R.
- CO & H.R. not significantly changed
- No reflex tachycardia (Safe in patients ē I.H.D) due to
  - Downward resetting of baroreceptors OR
  - ↑ Parasympathetic activity.
- Effective in Patients ē High & Normal Renin Levels

Adverse Effects

- Altered Taste
- Allergic Skin Rashes
- Drug Fever

} 10% cases, less with newer long acting drugs

- Marked Hypotension ē First Dose in hypovolemic patients
- Acute Renal Failure In Renal Artery Stenosis
- Hyperkalemia (more likely in renal insufficiency & diabetic pts)
- Dry-cough, sometimes with wheezing because of ↑ Bradykinin
- Angioedema because of ↑ Bradykinin
- Neutropenia serious but rare, in Autoimmune diseases
- Proteinuria In Renal insufficiency ē High Doses of Captopril.
- **Teratogenc Effects**
  In 2nd & 3rd Trimester; Fetal Hypotension, Anuria & Renal Failure, Sometimes Fetal malformations/Death – CI in pregnancy

PHARMACOLOGICAL EFFECTS…

Effect on Nephropathy in D.M.

- ↓ Proteinuria
- Stabilize Renal Function.
- Improve intra renal hemodynamics

Even in the absence of lowering of BP

Effect on Heart

- Useful in C.C.F
  ↓ After Load & Preload.
- Useful after Myocardial Infarction
  ↓ Post Myocardial Infarction Remodeling

Drug Interactions

- With K^+ Supplements /K^+ Sparing Diuretics (Marked hyperkalemia)
- Non Steroidal Anti. Inflammatory Drugs may impair the hypotensive effect which is mediated through Bradykinin

Contraindications Pregnancy

Therapeutic Uses

- Hypertension -with a thiazide diuretic or beta blockers
- Congestive Cardiac Failure
- Diabetic Nephropathy
- Myocardial Infarction

Angiotensin II type I (AT_1)Receptor Blockers (Competitive antagonists)

Peptide Antagonists: Saralasin

Non-Peptide Antagonists:

Losartan , Valsartan
Candesartan , Eprosartan
Irbesartan , Telmisartan

M.O.A- Angiotensin-II Receptor Blockers

Competitive Blockers of Angiotensin –II AT_1 Receptors
So effects like ACEIs, with following differences:

- **No Effect on Bradykinin**, so no dry cough and no angioedema
- **More effective than ACEIs** (Angiotensin - II also generated by other Enzymes)
- Prolonged treatment disinhibits renin secretion & ↑ angiotensin-II levels → ↑stimulation of AT_2 Producing vasodilatation and other beneficial effects.

Adverse Effects: Like ACEIs except Dry cough & Angioedema

Angiotensin-II Receptor Blockers

Two types: AT_1 & AT_2

1. AT_1:

Location predominate in vascular smooth muscles.
Group G protein coupled.
Effector Phospholipase C
Second messenger IP_3 & DAG.
Response Smooth muscle contraction within seconds

VASODILATOR DRUGS

Drugs that dilate B.Vs by acting directly on smooth muscles through non autonomic mechanisms

- Arterial vasodilators
  - Hydralazine, Minoxidil, Diazoxide, Fenoldopam
- Arterial & Venous vasodilator
  - Sodium Nitroprosside
- Venous
  - Nitroglycerine
- Calcium Channel Blockers

2. AT_2

Location in all tissues in fetus
In adults adrenal medulla, reproductive tissues, vascular endothelium & parts of the brain.
Group G protein coupled.
Effector Phospholipase A_2, nitric oxide
Second messenger cGMP.
Functions

- Fetal tissue development
- Inhibition of growth & proliferation
- Cell differentiation
- Apoptosis
- Possibly vasodilatation.

COMPENSATORY RESPONSES TO VASODILATOR DRUGS & BASIS FOR COMBINATION THERAPY

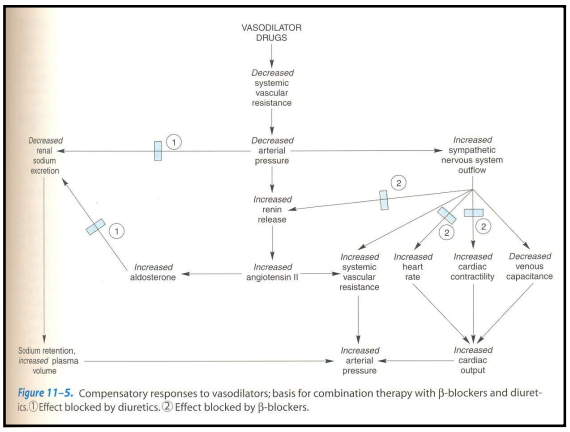
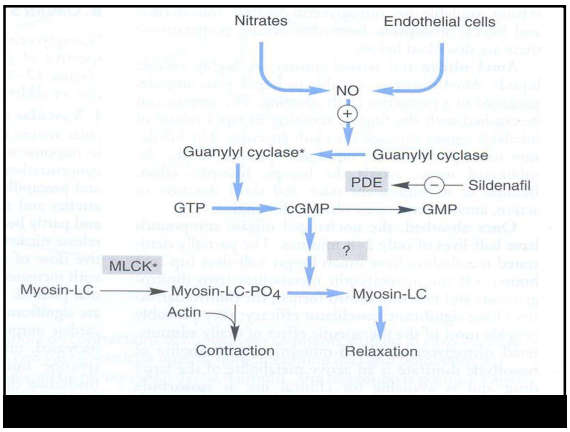


Figure 11–5. Compensatory responses to vasodilators; basis for combination therapy with β-blockers and diuretics. ① Effect blocked by diuretics. ② Effect blocked by β-blockers.



↑ sympathetic out flow & ↑ rennin release

- ↑ HR. & Cardiac contractility-------- Increased CO--- ↑ blood pressure
- Vasoconstriction--- ↑ PR-- ↑ blood pressure
- ↑ renin ------ ↑ Angiotensin –II ----Vasoconstriction--- ↑ PR-- ↑ blood pressure & ↑ Aldosterone---- ↓ renal sodium excretion-- ↑ plasma volume---- ↑ blood pressure

So vasodilators are used in combination therapy with Diuretics & β Blockers

Core –Pharmacology

HYDRALAZINE…

Ph.k

- Well abs from GIT
- Rapid first pass metabolism in liver low B.A (25%)
- Metabolized by *Acetylation* - Slow or Rapid Acetylators due to genetic factors
- Rapid Acetylators →
  Greater First pass metabolism less B.A
- Slow Acetylators →
  Less First pass metabolism more B.A.
- Half Life : 2 - 4 hrs.

Core –Pharmacology

HYDRALAZINE

Oral vasodilator

Hydrazine derivative

MOA

Direct arteriolar dilator

Do not dilate veins

MOA not clear it probably acts through release of nitric oxide from endothelium

Core –Pharmacology

HYDRALAZINE…

Ph. Effects

Arteriolar dilatation leads to decreased peripheral resistance & hence decreases blood pressure.

Postural hypotension - uncommon.

Hypotensive effect elicits compensatory responses

Vasodilatation → Hypotension which causes:

Increased sympathetic out flow & increased rennin release.

- Increased HR & contractility-------- Increased CO
- Increased PR----- Increased BP
- Increased Renin ------Increased Angiotensinogen---- Increased Aldosterone----Decreased renal sodium excretion-- ----Increased plasma volume-----*Increased BP*

Core –Pharmacology

HYDRALAZINE…

Therapeutic uses

- **Anti-hypertensive** – in pregnancy for short term Rx, in severe cases in combination
- **In CCF** – decrease after load

Toxicity

- Headache,
- Nausea, anorexia, sweating & flushing
- Palpitation, Dizziness Angina / arrhythmias (in Pt. ē I.H.D)
- Syndrome like Systemic Lupus Erythematosis in slow acetylators (reversible) / in high doses
- With high doses - Arthralgia, Myalgia, Skin rashes, Fever
- Rare side effects: Peripheral Neuropathy, Drug fever.

Vertical integration with medicine

MINOXIDIL…

Ph. Kinetics

- Well absorbed from GIT, BA:90%
- Metabolized by conjugation
- DOA: 24 Hrs
- Only given orally

Toxicity

- Tachycardia, palpitations, angina
- Edema---When doses of beta blockers & diuretics are inadequate.
- Headache, sweating & hirsuitism

(Topically used for baldness)

Core –Pharmacology

MINOXIDIL - Oral Arteriolar vasodilator

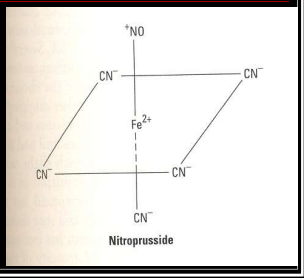
MOA

- Pro drug, converted to Minoxidil sulphate, an active metabolite which is K^+ channel opener.
- causing hyperpolarization of cell membranes, and makes contraction less likely & hence relaxation of vascular smooth vasodilatation⟶Decreased PR ⟶Decreased BP
- Compensatory responses are elicited, so combined with Diuretic or a Beta blocker.

Core –Pharmacology

Sodium Nitroprusside

Complex of Iron, Cyanide, Nitroso Group



Core-Pharmacology

MINOXIDIL…

Therapeutic uses

- In severe hypertension in combination therapy
- Topically for baldness

Vertical integration with medicine

Sodium Nitroprusside..

Powerful parenteral vasodilator of Arterioles & Veins

- Given by I/V infusion – t ½ = few min
- **OOA:** within Seconds
- **DOA:** brief 1-10 min
- Rapidly metabolized by uptake in to RBCs with liberation of cyanide
- Cyanide metabolized to thiocynate in presence of sulphur donor by mitochondrial enzyme (rhodanase)
- Thiocynates excreted by kidneys slowly

Sodium Nitroprusside..

M.O.A

Activate guanylyl cyclase, either via release of nitric oxide or by direct stimulation of the enzyme.

↓

Increase intracellular cGMP,

↓

Relaxation of S.M of Arterioles + Veins

↓

Vasodilatation

↓

↓ P.R

↓

↓ B.P

Sodium Nitroprusside..

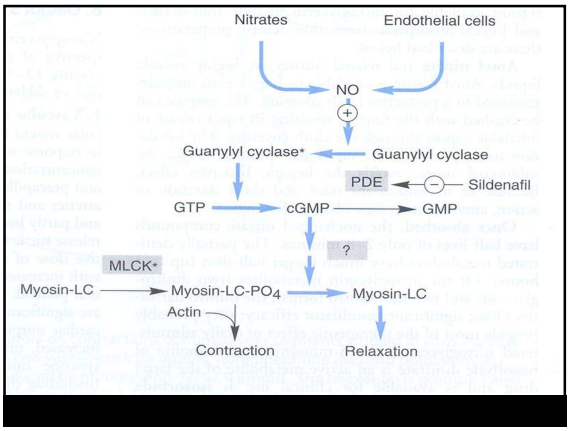
AEs

- **Excessive hypotension.**
- **Palpitation**
- **Nausea, vomiting, perspiration.**

AEs due to Cyanide Toxicity

- Metabolic Acidosis
- Arrhythmias
- Excessive hypotension
- Death

Prevented By Soduim Thiosulphate or Hydroxycobolamine



Sodium Nitroprusside..

AEs because Of thiocyanate

- Weakness, Disorientation, Psychosis, Muscle Spasm & convulsions
- Delayed Hypothyroidism

Met-hemoglobinaemia during infusion may occur

Sodium Nitroprusside..

Ph. Effects

Rapid ↓ in B.P, In Supine position & Upright position, more marked in upright position.

Effect disappears within 1-10min on stopping infusion

Hypotension is due to decreased PR,

C.O- normally no change / slight ↓

Low C.O→Because Of:

↓ After Load.

↓ Preload.

DIAZOXIDE Long Acting arteriolar vasodilator

MOA

Prevents Vascular Sm. muscle contraction by opening ATPase sensitive K^+ Channel

↓

Stabilization of Membrane Potential at RMP

↓

No Contraction → Relaxation

↓

↓ P.R→ ↓ B.P

DIAZOXIDE…

Ph. Effects

dilates only Arterioles → ↓P.R & Rapid ↓ in B.P
↑ H.R → ↑ C.O (Compensatory Mechanism)

Ph.K

Given I/V, bound To P.Proteins & Vascular Tissue
Exc - 30% unchanged, 70% Metabolites

Pharmacokinetics - FENOLDOPAM

- Rapid metabolism by conjugation
- Half-life: 10 min – given by continues IV infusion
- Initiated at low dose (0.1 mcg/kg/min)
- Titrated upward every 15-20 min to a max dose of 1.6 mcg/kg/min until the desired BP reduction is achieved

DIAZOXIDE

Ad. Effects

- Excessive Hypotension – stroke & MI, the reflex sympathetic response can provoke angina
- Salt & Water retention
- Hyperglycemia - Secretion of insulin from β-cells is inhibited

Th. Uses

- Hypertension – Severe
  With β Blocker / Diuretics
- In Insulinoma to treat Hypoglycemia

(Diazoxide also inhibits the secretion of insulin)

FENOLDOPAM…

Th. Uses

- Used for hypertensive emergencies and postoperative hypertension - Given by intravenous infusion

AEs

- **Major toxicities** are reflex tachycardia, headache, flushing. & even hypokalemia may occur
- Increase in IOP. --- C/I in glaucoma

FENOLDOPAM

- Recently discovered peripheral arteriolar dilator
- Racemic mixture, R isomer is Pharmacologically active.

MOA

Acts primarily as an agonist of dopamine D1 receptors, resulting in dilatation of peripheral arteries & natriuresis

TREATMENT OF HYPERTENSIVE EMERGENCIES

(Hypertensive Crisis / Malignant hypertension)

An emergency condition resulting from untreated primary hypertension – can prove lethal if not managed in time

- B.P. 200/120 mm Hg.
- If not treated
  - Cerebral Hemorrhages
  - Epistaxis
  - Acute Heart Failure
  - Retinal Hemorrhages

TREATMENT OF HYPERTENSIVE EMERGENCIES....

- Pt. is monitored in an intensive care unit with continuous recording of arterial B.P.
- Fluid in-take & out-put monitoring.
- Daily measurement of body weight.

Vertical integration with medicine

Mono / single drug therapy

desirable because

- Better compliance
- Cost effective
- Generally A/E are fewer – no drug interactions

Thiazide diuretics, β blockers, ACEIs, AT_1 blockers & Ca^{++} channel blockers ----- all reduce the complication of hypertension

Vertical integration with medicine

TREATMENT OF HYPERTENSIVE EMERGENCIES...

Anti H.T Drugs Used

- I/V Sodium Nitroprusside/fenoldopam as infusion.
- Nifedipine sublingually
- Methyl Dopa I/V
- ACE inhibitors (Captopril). Hydralazine orally
- Prazosin (α Blockers) & β- Blockers - orally
- Labetalol orally
- Diuretics to prevent volume expansion - Furosemide is the drug of choice.
- Dialysis may be a necessary alternative to the loop diuretics in patients with oliguric renal failure.

Clonidine is contraindicated.

Vertical integration with medicine

Rationale of Combination therapy / Polypharmacy

- **To eliminate compensatory responses** Vasodilators with diuretics & β blockers.
- **Inadequate responsiveness** to one drug:
  - 2nd drug with different MOA is added
  - Some patients may require a 3rd drug.

Vertical integration with medicine

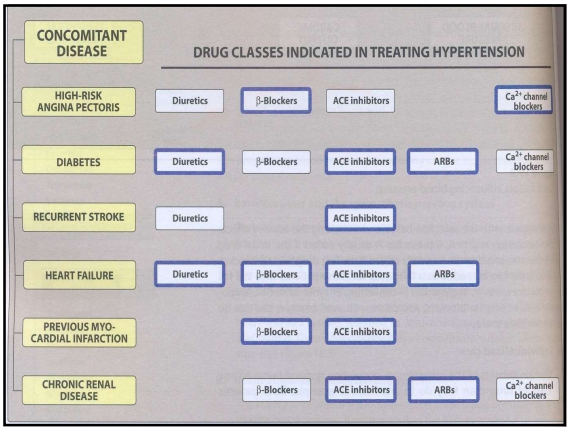
TREATMENT OF HYPERTENSIVE EMERGENCIES...

The Diastolic B.P should not be normalized but kept at 100-110mmHg in first few hours to prevent cerebral Hypoperfusion, Brain injury.

Because chronic hypertension is associated ē Auto regulatory changes in cerebral Blood Flow.

Subsequently B.P. is normalized by Oral Antihypertensive drugs over several Weeks.

Vertical integration with medicine



Patient's compliance:

Generally hypertensive patients are asymptomatic so compliance is poor due to A/E of drugs.

To improve compliance :

- Individualize choice of the drug.
- Educate patient regarding the disease / complication & drug .
- Dosing regimens should be simplified.
- Advise monitoring of blood pressure at home.

Vertical integration with medicine

ARTIFICIAL INTELLIGENCE

Table 1. Potential artificial intelligence applications for the prevention and management of hypertension

	AI applications
Predicting development of hypertension	- Predict the risk of developing HTN by using medical data,[17–20] treadmill stress test,[21] behavioral, environmental, socioeconomic factors, and genetics.[22–25]
	- Identify new genes associated with HTN.[26]
Diagnosing hypertension	- Accurately diagnosing HTN by using demographic data, vital signs, traditional CV risk factors, and routine laboratories in large patient cohorts.[27,28]
Predicting blood pressure	- Predict BP from demographic data, lifestyle (alcohol, smoking, and exercise),[29] and retinal fundus images.[30]
Measuring Blood Pressure	- Estimate BP by analyzing PPG signal from pulse oximeter with ML algorithms[31–37] and DL algorithms.[37,38]
	- Estimate BP from PPG signal recorded by a smartphone[39] and a smartwatch.[40]
Predicting cardioavascular risk in hypertension	- Predict CV outcomes in HTN patients,[41–44] and stratify patients based on their risk.[45–47]
Predicting and identifying barriers to blood pressure control	- Predict the risk of developing uncontrolled BP.[48,49]
	- Identify factors contributing to treatment adherence[50–52] and success.[53]
Refining blood pressure targets	- Uncover factors associated with CV outcomes[54,55] and adverse events[56] in major RCTs suggesting different BP targets.

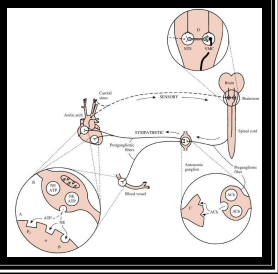
Abbreviations: AI, artificial intelligence; BP, blood pressure; CV, cardiovascular; DL, deep learning; HTN, hypertension; ML, machine learning; PPG, photoplethysmograph; RCTs, randomized, controlled trials.

RESEARCH

- *This is a potentially major development in hypertension. There has not been a new class of drug licensed for the treatment of high blood pressure in the last 17 years. This novel approach leads to a substantial reduction in blood pressure, both by day and night, that lasts for around six months after a single injection. This is attractive because it helps avoid the difficulty with adherence to treatment seen with current medicines. The next stage of clinical trials will focus on developing robust safety data, and broader evidence of efficacy, before zilebesiran can be licensed for use.*
- *https://www.ed.ac.uk/news/2023/promising-new-drug-to-manage-high-blood-pressure*
- *Professor David WebbChristison Chair of Therapeutics and Clinical Pharmacology at the University of Edinburgh, who led the Edinburgh study site*

EOLA

Identify the site of action of different anti-hypertensive drugs acting on sympathetic reflex



BIOETHICS

- ***Potential strategies to encourage and improve adherence include***:
  - Educating patients at the time of the initial prescription about their medicine(s) and how it works; this message should be reinforced at each appointment. In particular, if a decision is made to initially prescribe two low dose antihypertensives together, emphasise why it is important that both are taken consistently, i.e. to maximise blood pressure control while reducing the risk of adverse effects (compared with high dose monotherapy).
  - Selecting antihypertensives with once daily dosing
  - Reducing polypharmacy, e.g. using a fixed-dose combination, if available
  - Using pill boxes, blister packaging or electronic reminders (e.g. smartphone apps)
  - If adverse effects are problematic, consider night-time dosing, which can limit the perception of adverse effects