Antihypertensive drugs

By dr. Gamal Ahmed
HYPERTENSION

Current definition (W.H.O.)
A level of systolic blood pressure (SBP) of 140 mm Hg or above, or a level of diastolic blood pressure (DBP) of 90 mm Hg or above, by repeated measurements over periods of several weeks. It may be systolic or diastolic.
## Stages of Hypertension

<table>
<thead>
<tr>
<th>Stage</th>
<th>Diastolic Range (mm Hg)</th>
<th>Systolic Range (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Normal</td>
<td>85-89</td>
<td>130-139</td>
</tr>
<tr>
<td>Stage 1</td>
<td>90-99</td>
<td>140-159</td>
</tr>
<tr>
<td>Stage 2</td>
<td>100-109</td>
<td>160-179</td>
</tr>
<tr>
<td>Stage 3</td>
<td>&gt; 109</td>
<td>&gt; 179</td>
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</tbody>
</table>
Chronic high blood pressure (hypertension) left untreated can lead to:

- Stroke
- Blood vessel damage (arteriosclerosis)
- Heart attack or heart failure
- Kidney failure
Types of Hypertension

- **Essential**
  - A disorder of unknown origin affecting the Blood Pressure regulating mechanisms

- **Secondary**
  - Secondary to other disease processes

Environmental Factors

- Stress
- ↑ Na+ Intake
- Obesity
- Smoking

**BP=CO x PVR**

**Ways of Lowering Blood Pressure**

1. Reduce cardiac output (β-blockers, Ca^{2+} channel blockers)
2. Reduce plasma volume (diuretics)
3. Reduce peripheral vascular resistance (vasodilators)
Classification of Antihypertensive drugs

A. Diuretics

B. Sympathoplegics

C. Calcium Channel blockers

D. Drug acting on renin angiotensin system
   1. Angiotensin converting enzyme inhibitors (ACEI)
   2. Angiotensin receptor blocker (ARB)

E. Vasodilators
Low dose diuretic therapy is safe and effective in preventing HTN complications

Types

1. Thiazides related agents (congeners)
   - Hydrochlorothiazide
   - Benzthiazide
   - Chlorthalidone
   - Indapamide

2. Loop diuretics
   - Furosemide
   - Bumetanide
   - Ethacrynic acid

3. K+ sparing diuretics
   - Spironolactone, triamterene and amiloride
A. Thiazide diuretics

1. Most effect. diuretics to ↓ BP in patients with norm. renal function
2. The antihy. doses are lower that those required for diuretic effect

MOA of Thiazide diuretics

↓ blood volume and cardiac output and no effect on PVR

After 6-8 weeks of continuous therapy, IV volume and CO return to normal while PVR ↓ and this may probably related to

a. Depletion of Na⁺ stores which leads to
   i. ↓ of interstitial fluid volume
   ii. ↓ in smooth muscle Na⁺ concentration that in turn ↓ intracellular Ca++ concentration
   iii. Change in response of cell surface Receptors to vasoconstrictor hormones

b. Induction of renal prostaglandin biosynthesis

c. Opening of K channels
Clinical uses of Thiazide diuretics

1. Used for monotherapy of mild hypertension (20/10 mmHg drop in 60% of patients) and for polydrug therapy of more severe cases
2. Used in combination with sympathoplegics, ACEI, Ca-channel blockers & vasodilators in more severe HTN (they counteract the compensatory mechanisms → Sodium Retention)
3. Used for treatment of hypertension in patients with osteoporosis because they are Ca sparing
4. Active by oral route and duration of action is 6-12hrs

Side effects of Thiazide diuretics

1. **K loss** (minimized by using low doses, diet, use of comb. with K-sparing diuretics)
2. **Hyperuricemia** (bad for gout)
3. **Hyperglycemia**, glucose intolerance (bad for diabetes)
4. ↑ **LDL & VLDL** (bad for atherosclerosis)
2. Loop diuretics

**MOA of loop diuretics**
Inhibit the cotransport of Na, K and Cl at the thick ascending loop of henle

**Examples of loop diuretics**
Prototype: Furosemide
Others: Bumetanide, Torsemide, ethacrynic acid

Short acting usually 4 hrs

**Uses of loop diuretics**
1. They are preferable to thiazides in malignant hypertension and concomitant chronic kidney disease
2. Used in CHF or cirrhosis

**Toxicity of loop diuretics**
Hypokalemic metabolic acidosis
2. Potassium sparing diuretics

MOA of Potassium sparing diuretics
Inhibit cotransport of Na, K and Cl at the thick ascending loop of henle

Examples of Potassium sparing diuretics
Triamterene, Spironolactone, Amlioride

Uses of Potassium sparing diuretics
1. They are only used in combination with thiazides to counteract hypokalemia.

2. Spironolactone is used HTN due to hyperaldosteronism

Toxicity of Potassium sparing diuretics
Hypokalemic metabolic acidosis
Diuretics - Situations favoring

1. Elderly patients
2. Low renin hypertension
3. Isolated systolic hypertension
4. Obese patients with volume overload
5. Renal disease with Na⁺ retention
6. Low cost therapy

Diuretics – to be avoided in

1. Young active hypertensive
2. Diabetes or family history of diabetes
3. Gout or family history of gout
4. Abnormal lipid profile
5. Pregnancy induced hypertension
B. SYMPATHOPLEGICS

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

2. β- Blockers
   a. Non-selective (β₁, β₂) blockers
      - Propranolol
      - Pindolol
      - Nadolol
      - Carteolol
      - Penbutolol
   b. Cardioselective (β₁) blockers
      - Acebutolol
      - Atenolol
      - Betaxolol
      - Bisoprolol
      - Esmolol
      - Nebivolol
      - Metoprolol

3. α-Blockers
   - Prazosin
   - Terazosin
   - Doxazosin
   - Doxazosin
   - Phenoxybenzamine
   - Phentolamine

4. α- & β-Blockers
   - Labetalol
   - Carvedilol

5. Adrenergic Neuron Blockers
   - Guanethidinide
   - Reserpine

6. Ganglion Blocking Agents
   - Trimetaphan
1. Centrally acting sympathopregic drugs

These drugs are central $\alpha_2$ receptor agonists
Reduce sympathetic out flow from vasomotor centers in the brain stem and allow these centers to retain or even increase their sensitivity to baroreceptors

**α-Methyldopa**

**MOA**

It is taken up into the adrenergic nerve terminals

$\alpha$-Methyldopa $\rightarrow$ $\alpha$-Methyldopamine $\rightarrow$ $\alpha$-methyl Nor-epinephrine

$\alpha$ -Methyl NE is released instead of NE & acts as agonist at post synaptic $\alpha_2$ receptors in vasomotor center in the brain stem leading to

$\downarrow$ PVR , HR & CO $\rightarrow$ $\downarrow$ BP

Methyl NE is not a substrate for MAO like Nor epinephrine

At periphery $\alpha$ -Methyl NE acts as vasoconstrictor

Gamal Ahmed
Therapeutic uses of α-Methyldopa

1. It is widely used in the past for mild to moderate hypertension along with a diuretic
2. Now it is preferred drug in pregnancy, effective & safe for both mother & fetus
3. It is valuable in hypertensives with renal insufficiency
4. In Hypertensive crisis; it may be given I/V
5. It is usually given together with a diuretic

Adverse effects of α-Methyldopa

1. Sedation, which occurs specially at onset of treatment
2. Mental depression, nightmares, vertigo and parkinsonism occur on long term use
3. Postural hypotension; only in volume depleted patients
Clonidine

It is $\alpha_2$-adrenergic agonist

Therapeutic uses of clonidine

It is second choice drug for therapy of hypertension (usually given together with a diuretic)

Adverse effects of clonidine

1. Sedation and xerostomia (dry mouth) centrally mediated & dose dependent.

2. Depression

3. Hypertensive crisis on sudden withdrawal
2. β-Blockers (olols)

a. Non-selective ($\beta_1$, $\beta_2$) blockers
   Propranolol, Pindolol, Nadolol, Carteolol, Penbutolol

b. Cardioselective ($\beta_1$) blockers
   Acebutolol, Atenolol, Betaxolol, Bisoprolol, Esmolol, Nebivolol & Metoprolol

c. Both α- and β-blockers
   Labetalol & Carvedilol

**MOA of β-blockers**

They block $\beta$-receptors leading to

- a) ↓ CO (blockade of cardiac $\beta_1$-receptors)
- b) Anti-renin effects (blockade of $\beta_1$-receptors in juxtaglomerular cells)
- c) Blockade of Presynaptic $\beta$-receptors → inhibition of NE release
- d) Central effects (blockade of hypothalamic and bulbar $\beta$-receptors)
Guideline uses of β-blockers

1. Mild to moderate hypertension
2. In **severe** HTN- in combination therapy with direct vasodilators to prevent compensatory tachycardia
3. In hypertensive emergencies (Labetalol, Esmolol)
4. Used in HTN with pheochromocytoma after α blocker.
5. Intraoperative & Postoperative hypertension (Esmolol)
6. Used in HTN with CHF (Carvedilol, Metoprolol, Bisoprolol)
7. Used in young patients
8. Coexisting anxiety or tachyca., exertional angina and post MI
9. Non-obese, high renin hypertensive
10. Pregnancy (cardioselective & β blocker with ISA)
Adverse effects of β–blockers

1. Bradycardia

2. Hypotension

3. Bronchoconstriction, so it is bad for asthmatic patients (minimized by using β₁ selective drug)

4. Insomnia, depression and nightmares

5. Hypoglycemia due to impaired ability of the liver for gluconeogenesis and glycogenolysis

6. Sexual dysfunction

7. ↑ AV node refractoriness (good for SVTs but could be bad if abnormal SA or AV nodes)
3. α-Blockers

Prazosin

It is $\alpha_1$-adrenergic antagonists

**MOA**

1. It antagonizes effect of sympathetic $\rightarrow \downarrow$ TPR and preload
2. It reduces baroreflex (thus it produces very little reflex tachycardia)

**Uses**

1. Can be used for monotherapy of mild hypertension
2. May improve LDL/HDL ratio
3. More effective in combination with β blocker & diuretic

**Side effects**

a) First-dose hypotension (specially with older patients)

b) Retention of salt and water
<table>
<thead>
<tr>
<th></th>
<th>β- Blockers (Propranolol)</th>
<th>α-and β-Blockers (Labetalol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>↓</td>
<td>unchanged</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>↓</td>
<td>unchanged or ↓</td>
</tr>
<tr>
<td>Venous tone</td>
<td>unchanged</td>
<td>↓</td>
</tr>
<tr>
<td>Postural hypotension</td>
<td>negligible</td>
<td>Evident</td>
</tr>
<tr>
<td>Renal blood flow</td>
<td>↓ (early) and normal (late)</td>
<td>unchanged</td>
</tr>
<tr>
<td>Efficacy of antihypertensive effect</td>
<td>good</td>
<td>High</td>
</tr>
<tr>
<td>Peripheral vascular resistance</td>
<td>↑ (early) and ↓ (late)</td>
<td>↓</td>
</tr>
</tbody>
</table>
4. Adrenergic Neuron Blockers

**MOA**

1. Drugs that prevent release of noradrenaline  
   (Guanethidine, Debrisoquin, Bethanidine, Guanoxan, Guanadrel)

2. Drugs that Inhibit Storage of Noradrenaline  
   (Reserpine and Deserpidine)

3. Drugs that Interfere with Synthesis of Norepinephrine  
   (Metyrosine (α Methyl tyrosine))

**Side effects**

1. Postural hypotension
2. Hypertensive crisis (with directly acting sympathomimetics)
3. Severe hypertensive reactions (Pheochromocytoma)
5. Ganglion blocking drugs (Ganglioplegic)

1. Inhibit postganglionic transmission

2. block the both sympathetic and parasympathetic nervous systems

Examples: hexamethonium, pentolium, mecamylamine, trimetaphan and pempidine

Uses

They are still used in some emerg. situations, such as aortic dissection
C. Calcium channel blockers

Dihydropyridines
   Nifedipine, Nicardipine, Nimodipine, Amlodipine, Nisoldipine, Nitrendipine, Isradipine

Benzothiazepines
   Diltiazem

Phenylalkylamines
   Verapamil, Gallopamil

Diphenylpiperazines
   Flunarizine, Trimetazidine, Ranolazine

Diarylaminopropylamine
   Bepridil

Misc
   Cinnarizine, Prenylamine
MOA of calcium channel blockers

In blood vessels

- Blocking of voltage gated-calcium channels
  - ↓ Ca^{++} in smooth muscle cells
  - Reduced formation of Ca^{++}/Calmodulin complex
  - No activation of myosin light chain kinase
  - No Phosphorylation of myosin light chain
  - Vasodilatation

On Heart

- ↓ Ca^{++} influx into cardiac cells
  - No breaking of troponin bridge
  - Less force & rate of contraction
  - ↓ BP

Decreased Peripheral Resistance
<table>
<thead>
<tr>
<th>Hemodynamic actions</th>
<th>Verapamil</th>
<th>Diltiazem</th>
<th>Nifedipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>↑</td>
<td>↓ unchanged</td>
<td>↓ or unchanged</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>↑</td>
<td>unchanged</td>
<td>unchanged</td>
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</tr>
<tr>
<td>Renal blood flow</td>
<td>↑ unchanged</td>
<td>↑ unchanged</td>
<td>↑ unchanged</td>
</tr>
<tr>
<td>Efficacy of antihyp. effect</td>
<td>moderate</td>
<td>moderate</td>
<td>moderate</td>
</tr>
<tr>
<td>PVR</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>t_{1/2}</td>
<td>2.8-7.4 hours</td>
<td>3-4.5 hours</td>
<td>2 hours</td>
</tr>
<tr>
<td>Metabolism/excretion</td>
<td>Hepatic/renal</td>
<td>Hepatic/renal</td>
<td>Hepatic/renal</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>35%</td>
<td>40%</td>
<td>45-56%</td>
</tr>
</tbody>
</table>
Uses of calcium channel blockers

1. Hypertension and Angina
2. Supraventricular arrhythmias
3. Migraine Prophylaxis
4. Atherosclerosis
5. Subarachnoid haemorrhage (Nimodipine)
6. Hypertensive emergencies (nicardipine)

Toxicity of calcium channel blockers

- Cardio-depression
- AV blocks
- Hypotension
- Bradycardia
- Cardiac failure
D. Drug acting on renin angiotensin system

1. Angiotensin Converting Enzyme Inhibitors (ACEI)

<table>
<thead>
<tr>
<th>Captopril</th>
<th>Trandolapril</th>
<th>Perindopril</th>
<th>Ramipril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril</td>
<td>Quinapril</td>
<td>Benzapril</td>
<td>Lisinopril</td>
</tr>
</tbody>
</table>

2. Angiotensin II type I (AT1) Receptor Blockers (Competitive antagonists)

<table>
<thead>
<tr>
<th>Losartan</th>
<th>Valsartan</th>
<th>Candesartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eprosartan</td>
<td>Irbesartan</td>
<td>Telmisartan</td>
</tr>
<tr>
<td>Saralasin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Renin inhibitor

| Aliskiren |
MOA of drug acting on renin angiotensin system

Sites of action of ACE inhibitors and angiotensin II receptor blockers

1. Site of angiotensin-converting enzyme blockade
2. Site of receptor blockade.
Uses of ACEi

1. Hypertension - with a thiazide diuretic or beta blockers
2. Congestive heart Failure
3. Diabetic Nephropathy
4. Myocardial Infarction
5. Hypertensive emergencies (Enalaprilat IV)
6. Primary or secondary hyperaldosteronism

Side effects of ACEi

1. Marked Hypotension ē First Dose in hypovolaemic patients
2. Acute Renal Failure In Renal Artery Stenosis
3. Proteinuria In Renal insufficiency ē High Doses of Captopril
4. Teratogenic effects in 2nd & 3rd Trimester
5. Dry and disturbing cough due to bradykinin and prostaglandin in the lung
6. Angioedema because of ↑ Bradykinin
Pharmacokinetics of ACEI

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, so dose should be ↓ in renal insufficiency

Prodrugs to active drugs by hydrolysis in Liver Enalapril, Deesterified → Enalaprilat, t½ 11 hrs

Half-lives: Variable (captopril, 2 hours: benazepril, 20 hours)

Drug interactions of ACEI

1. With K+ Supplements /K+ Sparing Diuretics (Marked hyperkalemia)

2. Non Steroidal Anti. Inflammatory Drugs may impair the hypotensive effect which is mediated through Bradykinin

Contraindication of ACEI

Pregnancy
Uses of Angiotensin II Receptor Blockers

HTN (first choice drugs) (thiazide diuretics can ↑ the antihypertensive effect)

Side effects of Angiotensin II Receptor Blockers

Like ACEIs except Dry cough & Angioedema

Effects of Angiotensin II Receptor Blockers

Effects like ACEIs, with following differences:

No Effect on Bradykinin, so no dry cough and no angioedema

More effective than ACEIs

Pharmacokinetics Angiotensin II Receptor Blockers

All compounds are administered by oral route only

Losartan: Oral bioavailability: 33%. Half-life: 2 hours
3. **Renin inhibitor** (Aliskiren)

**MOA**
Competitive inhibition of renin

**Pharmacokinetics**
- Oral bioavailability: 2.5%
- Mainly eliminated unmetabolized by biliary excretion
- Half-life: 24 hours

**Uses**
Hypertension (second choice drugs)

**Side effects**
- Hyperkalemia *(when given with ACEI or angiotensin antagonists)*
- Severe hypotension (rare)

**Contraindications**
- Pregnancy
E. Vasodilators

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

1. Arterial vasodilators  Hydralazine, Minoxidil, Diazoxide, Fenoldopam

2. Arterial & Venous vasodilator  Sodium Nitroprosside

3. Venous vasodilator

4. Calcium Channel Blockers

Arteriolar vasodilator

1. Hydralazine

MOA of hydralazine

Direct arteriolar dilator and do not dilate veins →↓PVR →↓BP

It probably acts through release of nitric oxide from endothelium
Pharmacokinetics of hydralazine

1. Well ab. from GIT
2. Rapid first pass metabolism in liver
3. low Bioavailability (25%)
4. Half Life : 2 - 4 hrs

Uses of hydralazine

Anti-hypertensive in pregnancy for short term Rx & in severe cases in combination

Toxicity of hydralazine

High dose causes

Reversible Systemic Lupus Erythematosis
Myalgia
2. Minoxidil

MOA of Minoxidil
It is a prodrug, converted to Minoxidil sulphate, an active metabolite which is $K^+$ channel opener $\rightarrow \downarrow$ PVR $\rightarrow \downarrow$ BP

Pharmacokinetics of Minoxidil
Only given orally, well absorbed from GIT and bioavailability (90%) Metabolized by conjugation DOA: 24 Hrs

Uses of Minoxidil
In severe HTN in comb. therapy Topically for baldness

Toxicity of Minoxidil
Tachycardia, palpitations, angina Hirsuitism (Topically used for baldness) Edema—When doses of beta blockers & diuretics are inadequate
Vasodilator of Arterioles & Veins (Nitroprusside)

MOA of Nitroprusside

Nitroprusside $\rightarrow$ NO $\rightarrow$ intracel. CGMP $\rightarrow$ Relaxation of S.M of Arterioles & Veins

$\downarrow$ B.P $\leftarrow$ $\downarrow$ P.R $\leftarrow$ Vasodilatation

Uses of Nitroprusside

1. Hypertensive emergencies
2. Severe heart failure
3. Controlled hypotension during surgery

Pharmacokinetics of Nitroprusside

Given IV infusion, OOA, few seconds and DOA, 1-10 minutes

Metabolized in RBC giving cyanide and thiocyanate

$\text{t}_{1/2}$ few minutes
Side effects of Nitroprusside

1. Excessive hypotension
2. Rebound hypertension
3. Palpitation

4. Metabolic Acidosis, arrhythmias and death due to cyanide toxicity and this can be prevented by Sodium Thiosulphate or Hydroxycobalamin.

5. Muscle spasm, convulsions and delayed hypothyroidism due to thiocyanate toxicity.

Contraindications of Nitroprusside

1. Impaired cerebral circulation
2. Compensatory hypertension (i.e., stenosis of aorta)

Long acting arteriolar vasodilator (Diazoxide)

MOA of Diazoxide

Opening ATPase sensitive K⁺ Channel → Stabilization of Memb. Potential

↓ B.P  ←  ↓ P.R  ←  Relaxation  ←  No Contraction
Pharmacokinetics of Diazoxide

Uses of Diazoxide
1. Hypertensive emergencies
2. Treatment of hypoglycemia secondary to insulinoma

Adverse effects of Diazoxide
1. Hyperglycemia - Secretion of insulin from β-cells is inhibited
2. Salt and water retention, edema
3. Excessive hypotension (may lead to stroke, angina and myocardial infarction)
4. Flushing and headache (all vasodilators cause this)
5. Hypertrichosis (Hair growth in 20% of patients).

Contraindications of Diazoxide
1. stenosis of aorta
2. Diabetes mellitus
3. Coronary disease
Prepheral Arteriolar Dilator (Fenoldopam)

MOA of Fenoldopam
It acts as agonist of D1 receptors

\[ \text{Dilatation of peripheral} \leftrightarrow \text{Natriuresis (inhibition of } NA^+ \text{ reabs. in the proximal tubule)} \]

Uses of Fenoldopam
Hypertensive emergencies and postoperative hypert. (given IV infus.)

Pharmacokinetics of Fenoldopam
1. Half-life: about 10 minutes  
2. Metabolism by conjugation

Side effects of Fenoldopam
1. Reflex tachycardia  
2. ↑ in IOP  
3. ↓ in serum K levels

Contraindications of Fenoldopam
1. Angina  
2. Glaucoma  
3. Hypokalemic states