Clinical Pharmacology of Antihypertensive

By
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Introduction

- **Hypertension** is a persistent elevation of blood pressure above 140 / 90 mmHg for more than three sitting.

- *(Optimal level <120 / 80 mmHg).*

- **Factors affecting blood pressure:**
  1. COP = HR × SV mainly affect SBP.
  2. TPR = diameter of arterioles × viscosity of blood affect DBP

- Each of these factors can be manipulated by **drug therapy**
Normal Regulation of Blood Pressure

A. **Short term regulation**: ANS (Sympathy, parasympath)

B. **Long term regulation**: RAS (kidney)

C. **Local chemical mediators** at the vascular endothelium: NP, PG, Bradykinin, NO, endothelin, adenosine
Types of hypertension

A. Primary hypertension:

1. Nearly 90% of patients have no specific cause.
2. Elevated blood pressure is usually caused by several abnormalities such as genetic inheritance, psychological stress, dietary factors.
3. Treatment: Such hypertension can be controlled by some combination of antihypertensive drugs and changes in daily habits.
4. LIFE LONG TTT
Pathophysiology of hypertension

1. Poly genetic factor
2. Environmental factors (diet, exercise, obesity, alcohol)
3. Activation of sympathetic nervous system
4. Activation of RAAS （renin-angiotensin-aldosterone system）→↓ Na excretion
5. ↑Na+ in diet
6. Dysfunction of vascular endothelium
B. Secondary hypertension (10% - 15%)

1. **Renal:** RAS, GN, IN, PCD, Ch.P

2. **Endocrine:** Conn’s, Cushing, Pheochromocytoma, Acromegaly

3. **Drugs:** Corticosteroids, estrogens, NSAIDs, cycolosporines

4. **Treatment:** Curative
# Hypertension Stages

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>Systolic BP measurement</th>
<th>Diastolic BP Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 120 mm Hg</td>
<td>AND &lt; 80 mm Hg</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120 – 139 mm Hg</td>
<td>OR 80 – 89 mm Hg</td>
</tr>
<tr>
<td>Stage I Hypertension</td>
<td>140 – 159 mm Hg</td>
<td>OR 90 – 99 mm Hg</td>
</tr>
<tr>
<td>Stage II Hypertension</td>
<td>160-179 mm Hg</td>
<td>OR 100-109 mm Hg</td>
</tr>
<tr>
<td>Emergency hypertension</td>
<td>180 mm Hg</td>
<td>OR 110 mm Hg</td>
</tr>
</tbody>
</table>
Hypertension

**TOD**
- LVH
- Angina or MI
- CHF
- Stroke or TIA
- Nephropathy
- Peripheral arterial disease
- Retinopathy

**Risk Factors**
- Smoking
- Dyslipidemia
- Diabetes
- Age >60 years
- Gender (men and postmenopausal women)
- Family Hx of CVD
Diagnosis

- Diagnosis is generally based on repeated, reproducible measurements of elevated blood pressure (more than 2) at fixed intervals,
- Do not rely on patient symptoms.
- White coat Hypertension
- Masked hypertension
- Emergency hypertension
- Isolated systolic HT in Elderly
Benefits of Lowering BP

Average Percent Reduction

35–40%  Stroke incidence

20–25%  Myocardial infarction

50%  Heart failure
The antihypertensive treatment strategies

1. To normalize blood pressure effectively.

2. Controlling hypertension is usually a lifelong treatment (patient compliance)

3. Long-term goal of antihypertensive therapy: **Reduce mortality** due to hypertension-induced disease To prevent target-organ damage to the heart, brain, kidneys and blood vessels, eye.
Strategy of treatment includes the following:

1- Evaluation of general condition of the patient.

2. Lifestyle Changes Recommended for all Patients
   1. Mental relaxation.
   2. Smoking cessation
   3. Regular exercise (mild) in mild and moderate cases.
   4. Weight reduction
   5. Salt (NaCl) restriction (reduce to 1.5g/day) and increase K in diet.
   6. Dietary Modifications: Decreases saturated fatty acid and cholesterol & Increase fruits & vegetables, fibers

111- Drug therapy:
   Start with monotherapy but if it is ineffective, combinations of two or more drugs can be used, based on age, sex, race, concomitant diseases and / or drugs.
Ways of Lowering Blood Pressure

- Reduce cardiac output (β-blockers, Ca^{2+} channel blockers)
- Reduce plasma volume (diuretics)
- Reduce peripheral vascular resistance (vasodilators)

\[ \text{MAP} = \text{CO} \times \text{TPR} \]
Drug Therapy for Hypertension

- **β Blockers**
- **Sympatholytics**
- **Centrally α-2 Agonist**
- **Ganglionic Blocker**
- **A.N.T. Inhibitors**
- **α₁-blockers**

Blood Pressure

- **Cardiac output**
- **P.V.R.**
- **Calcium Channel Blockers**
- **Direct Vasodilators**
- **Diuretics**
- **ARBs**
- **Renin inhibitors**
- **ACE**

Angiotensin II

- Vasospasm

NE

Direct Vasodilators

Calcium Channel Blockers

Diuretics
I. Diuretics

Mechanism of Action

- Initially, they act by reducing plasma volume and COP, followed by vasodilation and reduction in peripheral vascular resistance.

Advantages

- Reduce mortality, stroke and cardiovascular complications of hypertension.
- The least expensive antihypertensives.
Thiazide diuretics

Long-term

- Na⁺ in vessel wall
  - Na⁺-Ca²⁺ exchange
    - Ca²⁺ in smooth muscle cell
      - Peripheral resistance

Initial

- sodium, water retention
  - blood volume
    - Cardiac output

Decrease in BP

The mechanism for reduction of BP of thiazide Diuretics
Clinical uses

- 1st choice in uncomplicated hypertension.
- Systolic hypertension.
- Hypertension in elderly, black and obese patients
- Heart failure and renal failure.

Combined with other antihypertensives to potentiate their effect:
1. vasodilators.
2. ACEIs and β blockers.
1. Metabolic Side Effects
   - Hyperuricemia - hyperglycemia - hyperlipidemia.

2. Electrolyte Disturbances
   - Hypokalemia - hyponatremia - hypomagnesemia.

The Renin-Angiotensin System

1. ↓ Renal Perfusion Pressure
2. ↓ Na at Macula Densa cells
3. ↑ Sympathetic nerve activity (β-1)

Angiotensinogen

+ → Renin

Renin inhibitors

ACE

ACEI

Non-ACE (eg. Chymase in heart)

AT IV
AT III
AT II
AT I

ARBs
ACE Inhibitors

- **Mechanism of Action in hypertension**

1. Vasodilation due to
   - ↓ angiotensin II
   - ↑ vasodilator BK.

2. Anti-adrenergic effect by blocking central & peripheral adrenergic activity of angiotensin II (thus ACEIs decrease BP without reflex tachycardia).

3. Inhibition of aldosterone → Na+ loss.
A. **Captopril: Active**
given orally, well absorbed in fasting state, metabolized in liver by conjugation and less than half the dose is excreted unchanged in the urine. The half-life is 3 h.

B. **Enalapril: Prodrug**
is converted to enalaprilate with a half-life 11 h.

C. **Lisinopril: Active**
1. slowly absorbed with a half-life 12 h.
2. Primarily the kidney eliminates all ACEI except fosinopril and moexipril.

D. **Dosage:**
1. **Captopril:** start with 25 mg 2-3 times/day before meals; increase the dose at 1-2 week's intervals to control B.P.
2. **Enalapril:** oral dose 10-20 mg once or twice/day
3. **Lisinopril:** oral dose 10-80 mg/day.
Advantages

1. ↓ Cardiovascular mortality and morbidity.
2. Protect renal function especially in diabetics.
3. No metabolic side effects (no effect on glucose, lipid or uric acid).
4. May improve glucose intolerance in insulin resistance.
5. No changes in heart rate.

Indications

1. Diabetic hypertensives.
2. Hypertension with nephropathy in diabetics or nondiabetics.
3. Hypertension in HF or after myocardial infarction.
ADVERSE EFFECTS

1. **Dry cough** (5-20%). with or without wheezing, angioedema. thiazide Hypotension → In hypovolaemic patient. (2%).


3. **Hyperkalemia**

4. They are **contraindicated** with 2nd or 3rd trimester of pregnancy (to avoid fetal hypotension, anurea or renal failure associated with fetal malformation or death).
Advantages over ACEI:

1. They have no effect on bradykinin system so, no cough, wheezing, angioedema.

2. Complete inhibition of angiotensin action compared with ACEI. Explain?

3. Indirect activation of AT2. Explain?

ADRs: Same as ACEI except no cough, wheezing, angioedema.

Same contraindications as ACEI
Mechanisms of Action

Reduce sympathetic activity to heart and/or blood vessels thereby decreasing cardiac output and/or total peripheral resistance

They include

- centrally-acting α-2 agonist
- Ganglionic Blocker
- Adrenergic Neural Terminal Inhibitors
- Adrenoceptor blockers.
Adrenergic Neural Terminal Inhibitors
Centrally Acting Agents

**Clonidine**

- $\alpha_2$ agonist at CNS; ↓ sympathetic outflow from CNS

**Side Effects:**

- Rebound hypertension
- Sedation
- Dry mouth
- Bradycardia
Methyldopa

Converted to methylnorepinephrine that acts on central alpha$_2$ receptors

Used in management of hypertension in pregnant women (first line agent)

**Side effects:**
- Sedation
- Nightmare
- Movement disorders
- Hyperprolactinemia
Ganglion blockers competitively block nicotinic cholinergic receptors on postganglionic neurons in both sympathetic and parasympathetic ganglia.

Most of these agents are no longer available clinically because of unacceptable adverse effects related to their primary action.
Adrenergic Neural Terminal Inhibitors

Reserpine

- Reserpine binds to noradrenergic storage vesicles → lose the ability to store (N.E.) → little transmitter is released upon nerve ending depolarization.

- Adverse Effect
  - CNS effects predominate, including sedation, inability to concentrate, and depression.
**α₁ -Adrenergic Blockers**

- Blocking the action of norepinephrine at \( \alpha_1 \) receptors in arteries and veins.
  - Reduces systemic vascular resistance without Causing reflex-mediated tachycardia
  - Improve lipid profile

- **Adverse effect**
  - Orthostatic hypotension
  - Fluid retention
  - Nasal congestion
Alpha 1–blockers: mechanism of action

- Reflexes
  - Renin release
    - Aldosterone secretion
    - Na retention by kidney
- Prazosin
  - Cardiac contractility and rate
  - Sympathoactivation
  - Venous tone
  - Arteriolar relaxation
  - Preload
  - TPR
β-Adrenergic Blockers

Mechanism of Action :-

- Initially, they decrease COP without effective drop in BP due to reflex vasospasm with early increase in TPR.
- Later, they decrease TPR and BP through↓ Renin release.
Advantages

- Decrease cardiovascular mortality & morbidity and protect against coronary heart disease.
- Relatively not expensive.

Indications

- Alternative to diuretics as 1st line treatment of uncomplicated hypertension.
- Used in young hypertensives where COP is high.
- Hypertension associated with coronary heart disease.
Side Effects (Less with B1-selective):
1. Bronchospasm, cold extremities.
4. Sense of fatigue.
Calcium Channel Blockers

Mechanism of Action

- Peripheral VD and ↓ TPR.
- Diuretic action secondary to ↑ renal blood flow.

Advantages

- No metabolic side effects (no changes in glucose, lipid or uric acid levels).
- May improve renal function.
Indications:

- 2nd Choice after diuretics in elderly hypertensives or in isolated systolic hypertension.
- 2nd Choice after β blockers in hypertensives with coronary heart disease.
- Hypertension with peripheral vascular disease (PVD).
- Hypertension with renal impairment.
Direct Vasodilators
Hydralazine

Mechanism of Action
- It is an arteriolar vasodilator that may act as a K+ channel opener with hyperpolarization of vascular membrane which prevents Ca2+ influx into the wall of blood vessels.

Pharmacokinetics
- It is rapidly absorbed from the gut.
- It is metabolized in the liver by acetylation. Fast acetylylators need large dose, while slow acetylylators may develop lupus syndrome.
- It is excreted by the kidney (↓the dose in renal disease).
Hydralazine & Hypertension

- IV hydralazine is the drug of choice in severe hypertension with pregnancy.
- The chronic use of hydralazine in hypertension is associated with rapid tolerance.

Adverse Effects

- Salt retention and edema.
- Reflex tachycardia.
- Lupus syndrome
Sodium Nitroprusside

Mechanism of Action
- It is a donor of nitric oxide (NO) that increases the level of cGMP which induces vasodilation by inhibiting Ca\textsuperscript{2+} influx into the wall of blood vessels.

Pharmacological Properties
- It has a potent direct vasodilator (arteriolar and venular) effect decreasing both preload and afterload.
- It has an immediate effect and very short duration of action (2 minutes).
- It is converted in the body into cyanomethemoglobin and free cyanide which is metabolized into thiocyanate in liver and excreted by the kidney.
**indication :-**

- It is useful in most hypertensive emergencies as hypertensive encephalopathy, severe hypertension with acute HF and dissecting aortic aneurysm.

**Side effects:-**

1. Hypotension
2. Reflex tachycardia
3. Cyanide toxicity
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<tr>
<th>Population</th>
<th>Goal BP, mmHg</th>
<th>Initial drug treatment options</th>
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<td>General ≥ 60y</td>
<td>&lt;150/90</td>
<td>Non-black: thiazide-type diuretic, ACEI, ARB, or CCB</td>
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<tr>
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Thank You