Antihypertensive Drugs

Lecture-Pharm D
Medicinal Chemistry
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HYPERTENSION

- Hypertension is not a disease
- It is an arbitrarily defined disorder to which both environmental and genetic factors contribute
- Hypertension - An inc. in BP such that systolic is > 140 mm/Hg & diastolic > 90 mm/Hg on 2 or more occasions after initial screening
Essential Hypertension = most common. About 90% of clients.

* Exact Origin unknown. Contributing Factors - family hx, hyperlipidemia, diabetes, obesity, aging, stress, excessive ETOH & smoking.

Secondary Hypertension is about 10%, related to endocrine or renal disorders.
# Stages Of Hypertension

<table>
<thead>
<tr>
<th>Stage</th>
<th>Systolic Range (mm/Hg)</th>
<th>Diastolic 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>
</tr>
</tbody>
</table>
Response mediated by the sympathetic nervous system

- Activation of $\beta_1$ adrenoceptors on heart → Cardiac output
- Activation of $\alpha_1$ adrenoceptors on smooth muscle → Peripheral resistance

Decrease in blood pressure

- Renal blood flow ↓ → Renin ↑ → Angiotensin II ↑
- Glomerular filtration rate ↓ → Sodium, water retention ↑ → Blood volume ↑

Increase in blood pressure

Response mediated by the renin-angiotensin-aldosterone system
CLASSIFICATION

1) Sympatholytic drugs
- Centrally acting antiadrenergic agents.
- Adrenergic neuron blocking agents.
- Alpha adrenergic blockers.
- Beta adrenergic blockers.
- Alpha-beta adrenergic blockers.

2) Vasodilators
- Nitric oxide releasers.
- Potassium channel openers.
- Calcium channel blockers.

3) Diuretics
- Thiazides and congeners.
- Loop diuretics.
- Potassium-sparing diuretics

4) Angiotensin inhibitors and antagonists.
- Angiotensin Converting Enzyme (ACE) inhibitors.
- Angiotensin receptor antagonists.
Central Sympatholytics (α-2 Agonists)
Drugs: clonidine (Catapres), methyldopa (Aldomet)

1. Site of Action
   CNS medullary cardiovascular centers
   clonidine; direct α-2 agonist
   methyldopa: “false neurotrans.”

2. Mechanism of Action
   Stimulate Alpha-2 receptors \(\rightarrow\) dec. sympathetic activity \(\rightarrow\) dec. epi., norepi. & dec.renin release \(\rightarrow\) dec. peripheral vascular resistance
Clonidine is an example of phenyl imino imidazoline derivative that possesses selective $\alpha_2$-adrenergic receptor.
ADR: Dry mouth, drowsiness, headache and constipation.
Dose: 50-100 μg tid.
Use: Selective α₂ - adrenergic receptor. It is used as antihypertensive agent. It possess sedative property and used for withdrawal syndrome of opioid analgesic.
Methyldopa (Aldomet)

ADR: Peripheral oedema, mental depression, anxiety and nightmares.

Dose: 250mg bid - tid for 2 days. Maximum dose is 3g daily.

Use: It is drug of choice for treating hypertension during pregnancy.

L – a – methyl – 3, 4 - dihydroxy phenyl alanine.
All these agents block the effects of endogenous and exogenous catecholamine. These drugs slow the heart rate and decrease the force of contraction.

β-Blockers are classified into two main types:


Therapeutic uses of β-blockers: Used in the treatment of hypertension, coronary artery disease, arrhythmiasis and open angle glaucoma.
β - blockers are structurally similar to β - agonist. The catechol ring can be replaced by a variety of ring system without loss of antagonistic activity.

Replacement of catechol hydroxyl group with chlorine or phenyl ring system retains β-blocking activity. eg. Pronethalol, Dichloro isoproterenol.

N, N - disubstitution decreases β-blocking activity. Activity is maintained when phenyl ethyl, hydroxy phenyl ethyl or methoxy phenyl ethyl groups are added to amine as a part of the molecule.
### Aryloxy Propanolamines

<table>
<thead>
<tr>
<th>Name</th>
<th>$\text{Ar}$</th>
<th>$\text{R}$</th>
</tr>
</thead>
</table>
| Metoprolol | \[
\begin{array}{c}
\text{CH}_3 - \text{O} \left(\text{CH}_2\right)_2 \\
\text{CH}_3 - \text{O} \left(\text{CH}_2\right)_2 \\
\end{array}
\] | - CH (CH$_3$)$_2$ |
| Atenolol   | \[
\begin{array}{c}
\text{NH}_2 - \text{CO} \cdot \text{CH}_2 \\
\end{array}
\] | - CH (CH$_3$)$_2$ |
| Acebutolol | \[
\begin{array}{c}
\text{NH}_2 - \text{CO} \cdot \text{CH}_2 \\
\end{array}
\] | - CH (CH$_3$)$_2$ |
| Propranolol| \[
\begin{array}{c}
\text{CH}_3 - \left(\text{CH}_2\right)_2 \cdot \text{CO} \cdot \text{NH} \\
\text{COCH}_3
\end{array}
\] | - CH (CH$_3$)$_2$ |

$\text{Ar} =$ aromatic ring structure  
$\text{R} =$ bulky alkyl group (isopropyl or tert-butyl)
General Method Of Preparation of Aryloxy propyl amine

Mechanism of action:

a) in heart (they reduce cardiac contractility and CO).

b) in kidney (they reduce renin release by sympathetic nerves)
   - Na loss by kidney (leading to BV reduction)
   - vascular relaxation in some vascular beds.

c) in the CNS (controversial)
Side-effects

- Bronchoconstriction (minimized by using beta-1 selective drug; bad for asthmatics)
- Increase in LDL/HDL ratio (bad for atherosclerosis)
- Depression, loss of energy (CNS effect)
- Increase AV node refractoriness (good for SVTs but could be bad if abnormal SA or AV nodes)
- Decreased cardiac contractility (good for angina, good or bad for CHF)
Propranolol (Betacap, Ciplar)

**Chemical Structure:**

![Chemical structure of propranolol](image)

**1-(Isopropyl amino)-3-(1-naphthyloxy)-2-propanol**

**ADR:** Cold extremities, insomnia, fatigue and dizziness.

**Dose:** Initially, 40-80 mg bid, usual range is 160-320mg daily.

**Use:** Effective antihypertensive agent. It is also used to treat arrhythmias, angina pectoris, post myocardial infarction, migraine prophylaxis and essential tremor.
**Atenolol (Hipres, Manoten)**

![Chemical Structure of Atenolol](image)

4-\{2-Hydroxy - 3 - [(1-methylethyl) amino] propoxy\} - benzeneacetamide.

**ADR:** Bronchospasm, cold extremities, fatigue and dizziness.
**Dose:** 25 - 100mg daily as a single dose.
**Use:** It is a $b_1$ - selective drug with low lipid solubility. Mainly used in the treatment of essential hypertension.
Mixed a and b - adrenergic blockers
A. Labetolol (Labesol, Normadate)

\[
\begin{align*}
\text{CONH}_2 & \quad \text{CH}_3 \\
\text{OH} & \quad \text{CH}_2 \cdot \text{NH} \cdot \text{CH} \cdot \text{CH}_2 \cdot \text{CH}_2 \\
\text{HO} & \quad \text{CH}_3
\end{align*}
\]

5-{1-Hydroxy -2- [(1-methyl -3-phenylpropyl) amino} ethyl] salicylamide

Competitive inhibitor of $\beta_1$, $\beta_2$ and $\alpha_1$ adrenergic receptor. It is optically active because it has two optically active centers. 1R, 1'R isomer possess $\beta$-antagonistic activity and 1S,1'R isomer possess $\alpha$-antagonistic activity

ADR: Orthostatic hypotension, dizziness and fatigue Dose: initially 100mg bid, increase gradually according to patient response to 200-400mg bid. Use: It is used to treat chronic hypertension of pheochromocytoma and hypertensive crisis.
B. Carvedilol (Carvil, Caslot)

1-(9H-Carbazol-4-yloxy) -3- [2-(2-methoxy phenoxy) ethyl amino] - 2 - propanol.

Both β and α- adrenergic blocking agent. Only S isomer is β- blocking and both enantiomers have α- blocking activity.
Synthesis

4-(2,3-Epoxy-1-propoxy) carbazole + 2-(2-Methoxy phenoxy) ethylamine → Carvedilol
ADR: Bradycardia, atrioventricular block, angina pectoris and hypervolaemia.

Dose: Initially, 12.5mg once daily increased to 25mg once daily after 2 days. If necessary may increase to 50mg once daily or in divided dose.

Use: It is used to treat hypertension and congestive heart failure.
A– ADRENERGIC BLOCKING AGENTS

Mechanism of Action
Competitive antagonist at $\alpha$–1 receptors on vascular smooth muscle.

Site of Action- peripheral arterioles, smooth muscle

Blocking $\alpha$-receptors on vascular smooth muscle allows muscle relaxation, dilation of vessel, and reduced resistance
Quinazoline derivative and possesses quinazoline, piperazine and acyl moieties.
The presence of 4\textsuperscript{th} amino group and hetero moiety at 2\textsuperscript{nd} position is essential for \(\alpha_1\) receptor antagonistic activity
Prazosin (Minipress, Prazopress)

1-(4-Amino-6, 7 - dimethoxy-2-quinazolinyl)-4- (2-furanyl carbonyl) - piperazine.

ADR: Postural hypotension, syncope, palpitations and lack of energy.
Dose: Initially, 500 μg bid - tid for 3-7 days, increased to 1mg bid - tid for the next 3 - 7 days. Maximum dose is 20mg daily.
Use: It lowers blood pressure by blocking a₁ – adrenoreceptors.
Vasodilators

Drugs: hydralazine (Apresoline); minoxidil (Loniten); nitroprusside (Nipride); diazoxide (Hyperstat I.V.); fenoldopam (Corlopam)

1. Site of Action - vascular smooth muscle

2. Mechanism of action

- hydralazine: alters intracellular calcium, increases nitric oxide in arterioles
- minoxidil: increases nitric oxide in arterioles
- diazoxide: opens K+ channels on arteriolar membranes, stabilizes membrane
- fenoldopam: activates dopamine (D1) receptors on VSM (arterioles)
  - Low doses: dopamine stimulates primarily dopamine receptors - Vasodilation
  - Higher doses: stimulates B1 receptors - positive inotropic effect; Increases CO
  - Also releases NE from vascular nerve terminals - vasoconstriction

nitroprusside: induces nitric oxide from endothelial cells (arterioles and veins)
Classification
The vasodilators may be classified as follows.

- **Drugs with predominant venodilatory effect.**
  - Nitrates which reduces preload.

- **Drugs with predominant arteriolar dilating effect.**
  - Hydralazine, Minoxidil which reduces after-load.

- **Mixed arteriolar and venodilator:**
  - ACE inhibitors, Angiotensin antagonists, Sodium nitroprusside which reduces both preload and after-load.
Hydralazine (Apresoline)

Synthesis

2-Formyl benzoic acid + NH₂ - NH₂ Hydrazine → 1-Hydrazino phthalazine

→ Hydralazine

Hydralazine (Apresoline)
Angiotensin converting enzyme (ACE) inhibitors.

Blood pressure

A-II blockers - block angiotensin II from receptors in blood vessels, adrenals, and all other tissues.
Angiotensin converting enzyme (ACE) inhibitors

- Sulfhydryl containing inhibitors. eg. Captopril
- Dicarboxylate containing inhibitors: eg. Enalapril, Lisinopril, Quinapril, Ramipril, Trandopril, Spirapril, Moxeipril, Benazepril
- Phosphonate containing inhibitor: eg. Fosinopril

Angiotensin antagonists

Losartan, Irbesartan, Candesartan, Telmisartan, Valsartan.
Angiotensin converting enzyme is a zinc containing glycoprotein. The important binding sites of ACE are cationic site to attract carboxylate ion. Zinc ion that can polarize the carbonyl group of amide function to make it more susceptible to hydrolysis.

Fig. 20.2. Active site of ACE inhibitors
Among the three zinc binding group, sulfhydryl group is superior, but they form disulfide which may result in shorter duration of action.
✓ N - ring must contain a carboxylic acid group to mimic the C-terminal carboxylate of ACE substrate.
✓ Larger hydrophilic heterocyclic in the N - ring increase the potency and alter pharmacokinetic properties.
✓ X - is usually a methyl group, which mimic the side chain alanine of the ACE substrate.
✓ When the stereochemistry of inhibitor is consistent optimum activity occurs with L-amino acid.
Sulfhydryl Containing Inhibitors

**Captopril (Aceten, Capotril)**

**Synthesis**

ADR: Hypotension, tachycardia, chest pain and palpitation.
Dose: Initially, 12.5 mg bid or 6.25mg bid in combination with diuretics.
Use: It is used in condition such as post myocardial infarction, congestive heart failure and preservation of kidney function in diabetic nephropathy.
Dicarboxylate containing ACE inhibitors

**Enalapril (Invoril, Enamate)**

Enalapril is a prodrug of Enalaprilate. It is devoid of side effects of rash and loss of taste seen in Captopril. It is hydrolyzed in the liver by esterase to active dicarboxylic acid Enalaprilate.
ADR: Initial hypotension may be severe and prolonged. Dizziness, headache and fatigue.
Dose: 5mg at bed time. Increased up to 40mg in divided doses.
Use: A prodrug of Enalaprilate, longer acting ACE inhibitor used in the treatment of reno vascular, essential and malignant hypertension and congestive heart failure.

Lisinopril (Dilace, Linvas)

1-[N2 - (S) -1-carboxy -3- phenyl propyl] -L- lysyl - L proline dihydrate

It is a lysine analogue of Enalaprilate.
ADR: Dizziness, headache, fatigue and cough.
Dose: 5 -10mg daily given at bed time
Use: It is an ACE inhibitor used in the treatment of reno vascular essential and malignant hypertension and also for ventricular congestive heart failure.
Phosphonate Containing ACE inhibitor
Fosinopril (Fovas)

It serve as a prodrug, it is hydrolyzed to active diacid Fosinoprilate.

ADR: Dizziness, orthostatic hypotension, palpitation and headache.

Dose: Initially, 10mg once daily at bedtime. Maintenance dose of 10-40mg.

Use: It is used for the treatment of hypertension and some types of chronic heart failure
**Angiotensin II receptor Antagonists (Blockers) - A-II Blockers**

Losartan (Cozaar)
- Newer drugs similar to ACE inhibitors + prevent release of aldosterone (Na+ retaining hormone)
- Act on renin - angiotensin system
- Diff between ACE & All is A-II blockers block angiotensin from angiotensin I receptors found in many tissues - blocks at receptor site.
- A-II blockers cause vasodilation & dec. peripheral resistance
Losartan (Resilo, Covance, Cosart)

It was the first non-peptide imidazole to be introduced as an orally active angiotensin-II antagonist. It inhibits competitively angiotensin-II to produce vasodilator effect.

ADR: Headache, dizziness, back pain and myalgia.

Dose: 50mg once daily, increased to 100mg daily as a single dose or in 2 divided doses if needed.

Use: It is used as antihypertensive agent and also in the treatment of heart failure.
Calcium Channel Blockers

- ↑Free calcium ↑muscle contractility, ↑peripheral resistance & BP.

So, Calcium blockers
- Dec. calcium levels & promote vasodilation
- SE. Flushing, HA, dizziness, ankle edema, bradycardia, AV node block,

- 1, 4 - Dihydro pyridine
- Benzothiazepine derivatives
**1, 4 - Dihydro pyridine**

Following structural feature is important for activity

- A phenyl ring substitution at 4th position optimizes activity. Substitution at para or unsubstituted phenyl ring decreases the activity.
- 1, 4 - Dihydro pyridine ring is essential for activity. Substitution at N, or oxidation or reduction of the ring decreases or abolishes the activity.
- The 3rd and 5th position ester group optimizes activity. Any other electron withdrawing substitution results in agonist activity.
- When the ester at C3 and C5 are non - identical the C4 become chiral and stereoselectivity is observed. S- enantiomers have proved to be more effective.
<table>
<thead>
<tr>
<th>Compounds</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>$R_3$</th>
<th>$X$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>$\text{- CH}_2\text{O (CH}_2\text{)}_2\text{NH}_2$</td>
<td>$\text{- C}_2\text{H}_5$</td>
<td>$\text{- CH}_3$</td>
<td>2 - Cl</td>
</tr>
<tr>
<td>Felodipine</td>
<td>$\text{- CH}_3$</td>
<td>$\text{- C}_2\text{H}_5$</td>
<td>$\text{- CH}_3$</td>
<td>2,3 - Cl$_2$</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>$\text{- CH}_3$</td>
<td>$\text{- CH}_3$</td>
<td>$\text{- CH}_3$</td>
<td>2 - NO$_2$</td>
</tr>
<tr>
<td>Nitrendipine</td>
<td>$\text{- CH}_3$</td>
<td>$\text{- CH}_3$</td>
<td>$\text{- C}_2\text{H}_5$</td>
<td>3 - NO$_2$</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>$\text{- CH}_3$</td>
<td>$\text{- CH}_2\text{CH}_2\text{O CH}_3$</td>
<td>$\text{- CH (CH}_3\text{)}_2$</td>
<td>3 - NO$_2$</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>$\text{- CH}_3$</td>
<td>$\text{- CH}_2\text{CH (CH}_3\text{)}_2$</td>
<td>$\text{- CH}_3$</td>
<td>2 - NO$_2$</td>
</tr>
</tbody>
</table>
Amlodipine (Amlibon, Stamlo, Vamlo)

N,N' - Dibenzyl ethanol amine

Ethyl chloro acetoacetate

Keto form

Enol form

Methyl -2-amino -2-butoenoate

o-Chloro benzaldehyde

Debenzylation

HCl / Δ

-2 C₆H₅CH₂OH
**Nifedipine (Nifedine, Angiblock)**

**Step – I**

2-Nitro benzaldehyde + CH₃CO.CH₂COOCH₃ → Methyl acetoacetate

**Step – II**

CH₃COCH₂COOCH₃ → Ethyl acetoacetate

CH₃ - C = CH - COOCH₃ + NH₃ → Methyl -[2-acetyl - 3-(2-nitrophenyl)] -2-propenoate

**Step – III: Condensation of steps I and II products**

Methyl - [2-acetyl - 3-(2-nitrophenyl)] -2-propenoate + Methyl -3- amino -2- butenoate → Nifedipine

Cyclisation - H₂O
Phenyl Alkylamine Derivative
Verapamil (Calaptin, Vasopten)

5-(3,4-Dimethoxy phenethyl) methyl amino]-2-(3,4-diethoxyphenyl)-2-isopropylvaleronitrile

3,4-Dimethoxy -2-isopropyl valeronitrile

3,4-Dimethoxy phenyl ethyl - N-methyl-3-chloro propyl amine

Verapamil

- HCl
Benzothiazepine derivatives
Diltiazem (Coriem XL, Dilgard)

(+)-Cis-3-(acetyloxy)-5-[(2-dimethyl amino) ethyl]-2,3-dihydro-2-(4-methoxy phenyl) 1,5-benzothiazepin-4(5H)one.