Chapter 6. Anti-Hypertensive Agents

Syllabus

- Beta blocker: Timolol,
- ACE inhibitors: Captopril, Lisinopril, Enalapril, Benazepril hydrochloride, Quinapril hydrochloride,
- Centrally Acting Adrenergic drugs: Methyldopate hydrochloride,* Clonidine hydrochloride, Guanabenz acetate
- Vasodilators: Sodium nitroprusside, Diazoxide, Minoxidil, Hydralazine hydrochloride
- Others: Guanethidine monosulphate, Reserpine

Hypertension Basics and Pharmacology:

- Hypertension: [https://youtu.be/hnh6TEWTi5Y](https://youtu.be/hnh6TEWTi5Y)
- Pathways: [https://youtu.be/M-bcWr-TRcM](https://youtu.be/M-bcWr-TRcM)
- Drug Classification: [https://youtu.be/MGC67FgBdns](https://youtu.be/MGC67FgBdns)

6.1. Antihypertensive Drugs

These drugs are used to lower blood pressure (BP) in high blood pressure (hypertension).

1. Sympathetic Inhibitors -
   (a) Centrally acting: Clonidine, Methyldopa.
   (b) Ganglion blocking: Pentolinium, Trimethaphan.
   (c) Adrenergic neurone blocking:
      (i) Inhibit NA storage: Reserpine
      (ii) Inhibit NA release: Guanethidine, Bethanidine.
   (d) Adrenergic receptor antagonists:
      (i) $\alpha$ blockers: Prazocin, Phentolamine, Phenoxybenzamine.
      (ii) $\beta$-blockers: Propranolol, Metaprolol, Atenolol etc.
      (iii) $\alpha + \beta$: Labetalol.

2. Direct Vasodilators: Hydralazine, Minoxidil, Diazoxide etc.

3. Diuretics: Thiazides, Furosemide, spironolactone.


5. Angiotensin Receptor Blockers: Losartan, Olmesartan, Telmisartan

6. Calcium channel blockers: Nifedipine, Diltiazem.
6.2. Medicinal Chemistry

1) Beta Blocker

Selective beta blockers (Atenolol, Metoprolol, Acebutolol, etc.) mainly block the beta-1 receptor at heart and further inhibit the cardiac activity resulting in decrease the force of contraction, heart rate and myocardial oxygen demands.

Non selective beta blockers like Propranolol, Pindolol, Timolol block the beta-1 receptor as well beta-2 receptor thus it may slightly increase the vascular resistance but overall, they decrease the blood pressure in long term usage due to potentially inhibit the cardiac activity.

Beta blockers mainly used in hypertension and angina pectoris.

A. Timolol

1-tert-butylamino-3-(4-morpholino-1,2,5-thiadiazol-3-yl-oxy)-propan-2-ol

MOA: Non-selective beta blocker, reduce the cardiac activity, blood pressure, and increase the vascular resistance.

Uses: Hypertension, Angina, Migraine, Eye drops for glaucoma.

2) Angiotensin Converting Enzyme inhibitors

MOA of ACEIs & ARBs
ACEIs are the RAAS modulators which inhibit the angiotensin converting enzyme which responsible for the conversion of Angiotensin I to Angiotensin II.

ACEIs reduce the blood pressure by inhibiting the Ang-II production, Bradykinin (vasodilator) metabolism, and in later enhance the production of Ang (1-7) (cause the vasodilation by Mas receptor).

**Uses:** ACEIs and ARBs are frequently used in the treatment of hypertension, heart failure, angina pectoris, diabetic nephropathy, and chronic renal failure.

**Drugs:** Captopril, Lisinopril, Enalapril, Benazepril hydrochloride, Quinapril hydrochloride

**MOA:** [https://youtu.be/2i913sF5NPY](https://youtu.be/2i913sF5NPY)

**RAAS System Physiology:** [https://youtu.be/WQswguFG_B4](https://youtu.be/WQswguFG_B4)

**Pharmacology:** [https://youtu.be/NalAGo5y6v0](https://youtu.be/NalAGo5y6v0)

**Sulphydryl Containing ACEIs**

**A) Captopril**

1-[(2S)-3-Mercapto-2-methyl-propionyl]-L-proline

**Dicarboxylate Containing ACEIs**

**B) Lisinopril**

6-amino-2-[[1S]-1-carboxy-3-phenyl propyl] amino[ hexanoyl] pyrrolidine-2-carboxylic acid
C) Enalapril

![Enalapril Structure]

1-ethoxy-1-oxo-4-phenyl butan-2-yl [ amino] propanoyl] pyrrolidine-2-carboxylic acid

D) Quinapril

![Quinapril Structure]

1-ethoxy-1-oxo-4-phenyl butan-2-yl [ amino] propanoyl]-3,4-dihydro-1H-isoquinoline-3-carboxylic acid

E) Benazepril

![Benazepril Structure]

1-ethoxy-1-oxo-4-phenyl butan-2-yl [ amino]-2-oxo-4,5-dihydro-3H-1-benzazepin-1-yl] acetic acid

3) Centrally Acting Adrenergic drugs

**Drugs:** Methyldopate hydrochloride*, Clonidine hydrochloride, Guanabenz acetate

These are the centrally acting adrenergic drugs which inhibit the adrenergic action on CVS by inhibiting the release of nor-adrenalin/adrenalin.

**MOA:** They act on Alfa-2 adrenoreceptor (auto receptor) in CNS and reduce the sympathetic outflow to the cardiovascular system resulted in decrease cardiac activity and blood pressure.

Apart from the Alfa-2 adrenoreceptor agonistic activity, Clonidine, guanabenz and guanfacine also act on imidazoline I₁ receptor on CNS and produce inhibitory action CVS similar as Alfa-2 adrenoreceptor.

Currently monoxidine and rilmenidine were developed as selective imidazoline I₁ receptor agonist and have lesser side effects as bradycardia, sedation and depression.

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www.youtube.com/pharmacologyconceptsbyrajeshchoudhary
www.pharmacyconcepts.in
A) Methyldopa

### Chemical Structure

![Methyldopa Structure](image)

**Methyldopa**

- **Formula**: \((L)-3-(3,4\text{-Dihydroxyphenyl})-2\text{-methylalanine}\)
- **Synthesis**:
  1. Resolution of \(L\)-isomer with camphorsulfonic acid salt
  2. Conc. sulfuric acid

**MOA**: Methyldopa converts into methyl noradrenaline which is potent \(\alpha_2\) receptor agonist and reduces the sympathetic outflow to the cardiovascular system resulting in decreased cardiac activity and blood pressure.

**Uses**: Preferred antihypertensive agent in pregnancy.

B) Clonidine

### Chemical Structure

![Clonidine Structure](image)

**Clonidine**

- **Formula**: \(N-(2,6\text{-dichlorophenyl})-4,5\text{-dihydro-1H-imidazol-2-amine}\)

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**Resources**:
- [www.youtube.com/pharmacologyconceptsbyrajeschoudhary](http://www.youtube.com/pharmacologyconceptsbyrajeschoudhary)
- [www.pharmacyconcepts.in](http://www.pharmacyconcepts.in)
MOA: activates the alfa 2 receptor and imidazoline I₁ receptor and reduce the sympathetic outflow to the cardiovascular system resulted in decrease cardiac activity and blood pressure

Uses:

✓ Hypertension.

✓ Also used in post-menopausal vasomotor instability, prophylaxis treatment of migraine, dysmenorrhoea, and cluster headache.

C) Guanabenz

MOA: activates the alfa 2 receptor and imidazoline I₁ receptor and reduce the sympathetic outflow to the cardiovascular system resulted in decrease cardiac activity and blood pressure

Uses:

✓ Hypertension.

4) Vasodilators

Drugs: Sodium nitroprusside, Diazoxide, Minoxidil, Hydralazine hydrochloride

These are the vasodilators which reduce the vascular resistance and cause the reduction of blood pressure.

A) Sodium nitroprusside

Na₂[Fe (CN)₃NO]. 2H₂O

Sodium penta cyano nitrosyl ferret (III) dihydrate

MOA: It metabolized to NO (nitric oxide) which activates the guanylyl cyclase enzyme and enhance the cGMP dependent vasodilation.

Uses: t is effective in treating hypertensive emergencies, but must be given by continuous intravenous infusion. Side effects of this drug include significant hypotension and cyanide or thiocyanate toxicity
Potassium channel openers

B) Diazoxide

\[
\text{7-Chloro-3-methyl-2H-1, 2,4-benzothiadiazine 1, 1-dioxide}
\]

**MOA:** it opens the voltage gated potassium channel further causes the vasodilation.

**Uses:** in hypertension and counter hypoglycemia in the disease state like insulinomea.

C) Minoxidil

\[
\text{2,4-diamino-6-piperidino-pyrimidine-3-oxide}
\]

**MOA:** it opens the voltage gated potassium channel further causes the vasodilation.

**Uses:**
- Topically used in alopecia to increase hair growth
- And in hypertension.

D) Hydralazine Hydrochloride

\[
\text{1-Hydrazinophthalazine monohydrochloride; or Phthalazine, 1-hyrazino-, monohydrochloride}
\]
**MOA:** It inhibit the IP3 mediated calcium signaling and relax the blood vessels  
**Use:** Hypertension, heart failure (but not in used presently).

5) **Others**  
**Drugs:** Guanethidine monosulphate, Reserpine  

A) **Guanethidine**

![Image of Guanethidine molecule]

2-[2-(azocan-1-yl) ethyl] guanidine

**MOA:** It reduces the release of catecholamines, such as norepinephrine. Guanethidine is transported across the sympathetic nerve membrane by the same mechanism that transports norepinephrine itself (NET, uptake 1), and uptake is essential for the drug's action. Once guanethidine has entered the nerve, it is concentrated in transmitter vesicles, where it replaces norepinephrine. It may also inhibit the release of granules by decreasing norepinephrine.

**Uses:**  
✓ Used in hypertension  
✓ Topically used in open angle glaucoma

B) **Reserpine**

![Image of Reserpine molecule]

methyl (1R,15S,17R,18R,19S,20S)-6,18-dimethoxy-17-(3,4,5-trimethoxybenzoyl)oxy-1,3,11,12,14,15,16,17,18,19,20,21-dodecahydroyohimban-19-carboxylate

**MOA:** It modulate the adrenergic neurotransmission by interfering with the vesicle transport and storage of the noradrenaline.

**Uses:** Used in hypertension and psychosis

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