REVIEW ON ANTIHYPERTENSIVE DRUGS

RESIST TO HYPERTENSION

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Abstract: Hypertension is the common disease of the world and which is the most important target to the world to oppose it. It can be resist by using some Antihypertensive drugs. It is the disease in which blood pressure pressure increases above the Normal level and leads to Hypertension. Now this review consists of the main Antihypertensive Drugs, their structures with Mechanism of Action and its Classification for managing the Hypertension.

Keywords: Antihypertensive Drugs, Hypertension, Clinical management, Losartan.

Introduction

Antihypertensive drugs are the class of drugs that are used to treat the Hypertension i.e. (high blood pressure). It prevent the complication of high blood pressure, such as Myocardial Infarction and Stroke. The Hypertension can be occur by reasons as follows:

- Stress
- Increase in blood pressure.

Evidence suggest that the reduction of blood pressure by 5 mmHg can decrease the risk of stroke by 34% and of ischaemic heart disese by 21% and also decrease the dementia, heart failure from cardiovascular disease. Normal range: 120/80 mmHg; below its level known as hypotension and above its level known to be hypertension.

CLASSIFICATION:

It can be classified as follows:

A) ACE Inhibitors: Captopril, Lisinopril, Ramipril
B) B-Blocker: Propranolol, Labetalol, Metoprolol
C) Alpha blocker: Prazosin, Chlorpromazine
D) Mixed Alpha + Beta Blocker: Carvedilol
E) Diuretics:
   1) Loop Diuretics: Furosemide
   2) Thiazide Diuretics: Hydrochlorothiazide, chlorothiazide.
   3) Thiazide like Diuretics: Clopamide
   4) K-sparing Diuretics: Spironolactone, Amiloride
F) Ca-channel blockers: Amlodipine, Nifedipine, Verapamil.
G) Angiotensin II receptor antagonists: Losartan, Telmisartan
H) Vasodilators: Sodium Nitroprusside, Hydralazine
1) Alpha-2 adrenergic receptor agonists: Clonidine, methyldopa.

History:
Chlorothiazide was discovered in 1957, but first known example is effective from 1947. To treat hypertension using Primaquine, an antimalarial.
Nowadays, CYT006-AngQb was only moderately useful successful in studies.
the fundamental goal of treatment should be the prevention of the important endpoints of hypertension, such as heart attack, stroke and Heart failure. Patient age and associated conditions and end organ damage also play a part in determining dosage and type of medication administered.

A) ACE INHIBITORS:
Captopril:
Is the Antihypertensive drug which sold under brand Capoten.
It was the first oral ACE inhibitor to treat Hypertension. It is not responsible for causing fatigue as associated with B-Blockers. Due to adverse drug event of causing hyperkalemia, as seen with most ACE inhibitors and medicine usually paired with diuretic.

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>70-75%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Liver</td>
</tr>
<tr>
<td>Elimination Half life</td>
<td>1.9 hrs</td>
</tr>
<tr>
<td>Excretion</td>
<td>Kidney</td>
</tr>
</tbody>
</table>

Formula: C9H15NO3S
SYNTHESIS:
Chemical synthesis of captopril by treatment of L-proline with (2S)-3-acetylthio-2-methylpropanoyl chloride under basic condition NaOH, aminolysis of the protective acetyl group.

Structure activity Relationship (SAR):
Captopril has an L-proline group which allows for it to be more bioavailable within oral formulations. The thiol moiety within the molecule has been associated with two significant adverse effects: the hapten or immune response. This immune response, also known as agranulocytosis, can explain the adverse drug events which may be seen in captopril with the allergic response, which would be: hives, severe stomach pain, difficulty breathing, swelling of the face, lips, tongue or throat.

The molecule's thiol moiety will attach to the binding site of the ACE enzyme. This will inhibit the port at which the angiotensin-1 molecule would normally bind, therefore inhibiting the downstream effects within the renin-angiotensin system.

Structure:
Mechanism of Action:

Captopril blocks the conversion of angiotensin I to angiotensin II and prostaglandins degradation inhibiting vasoconstriction and promotes vasodilation.

Angiotensin I ────X───────→ Angiotensin II
Captopril blocks Conversion degradation prostaglandins & inhibits

Vasoconstriction.

/ / /

Vasodilation

1

1

1

Lowers blood pressure.

Uses:
1) To treat hypertension, congestive heart failure.
2) To preserve kidney function in diabetic nephropathy.
3) To elevate mood.

Adverse effect:
Cough, Headache, Hyperkalemia, Tachycardia.

Contraindication:
Tachycardia.

B) B-BLOCKERS:

Propranolol
Is the Antihypertensive drug effective in hypertension and ischemic heart disease.
It was the B-Blocker used in lowering blood pressure in mild to moderate hypertension. Usually B-Blockers are used in preventing reflex tachycardia, to reduce mortality in patients after myocardial infarction and heart failure in some patients.

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Oral, Rectal, Intravenous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>26 %</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Liver</td>
</tr>
<tr>
<td>Elimination Half life</td>
<td>4-5 hrs</td>
</tr>
<tr>
<td>Excretion</td>
<td>Kidney (&lt; 1 %)</td>
</tr>
</tbody>
</table>
Structure:

Propranolol:  
Formula: C₁₆H₂₁NO₂  
Synthesis:

Propranolol was synthesized from reaction between 1-naphthol and isopropylamine. Typically, 1.25 g of 1-naphthol (8.67 mM) was dissolved in 10 mL of ethanol : water (9:1), followed by adding 0.5 g of KOH into the above mixture under stirring for 30 min.

Mechanism of action:

It inhibits sympathetetic stimulation of heart which inhibits cAMP synthesis as a result reducing protein kinase activation. Less Ca influx to voltage gated L-type calcium channels and decrease sympathetic effect on heart and blood pressure reduced.

Uses:
1) Treats hypertension.  
2) To treat Angina pectoris, Myocardial infarction.  
3) Used in treating portal hypertension to lower portal vein pressure.  
4) In anxiety.

Adverse effects:
1) Myasthenia gravis  
2) Hyperthyroidism

Contraindication:
1) Bradycardia  
2) Sick sinus syndrome.
Prazosin:

Prazosin, sold under the brand name Minipress among others, is a medication used to treat high blood pressure, symptoms of an enlarged prostate, and nightmares. It is a less preferred treatment of high blood pressure. Prazosin was patented in 1965 and came into medical use in 1974. Prazosin has an onset of action of 30 to 90 minutes.

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Oral</th>
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<tbody>
<tr>
<td>Bioavailability</td>
<td>60%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Liver</td>
</tr>
<tr>
<td>Elimination Half life</td>
<td>2-3 hrs</td>
</tr>
<tr>
<td>Excretion</td>
<td>Kidney (&lt; 1 %)</td>
</tr>
</tbody>
</table>

Structure:

![Prazosin structure](image)

Formula: C19H21N5O4.

Synthesis:

Prazosin is synthesized using 2-furoic acid, from which compound 2 is obtained, and this acid can be readily replaced with numerous commercially available carboxylic acids.

Mechanism of Action:

Prazosin inhibits the postsynaptic alpha-1 adrenoceptors. This inhibition blocks the vasoconstricting effect of catecholamines (epinephrine and norepinephrine) on the vessels, leading to peripheral blood vessel dilation.

Prazosin --------> blocks alpha-1 receptor in arterioles -------> decrease sympathetic outflow

```
Peripheral resistance          <-------- Vasodilation
                          Decrease blood pressure
```
Uses:
1) Second-line choice for the treatment of high blood pressure.
2) Prazosin is also useful in treating urinary hesitancy associated with benign prostatic hyperplasia.
3) The drug is usually recommended for severe stings from the Indian red scorpion.

Adverse effects:
1) Dizziness, headache, drowsiness, lack of energy, weakness, palpitations, and nausea.
2) Vomiting, diarrhea, constipation, edema, orthostatic hypotension, dyspnea, syncope.
3) Depression, nervousness.

D) Mixed Alpha + Beta Blocker:

Carvedilol:
Carvedilol, sold under the brand name Coreg among others, is a medication used to treat high blood pressure, congestive heart failure (CHF). Carvedilol was patented in 1978 and approved for medical use in the United States in 1995.

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Oral</th>
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<tbody>
<tr>
<td>Bioavailability</td>
<td>25-35%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Liver</td>
</tr>
<tr>
<td>Elimination Half life</td>
<td>7-10 hrs</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urine, Feces</td>
</tr>
</tbody>
</table>

Structure:

Formula: C24H26N2O4

Synthesis:
Mixture of two enantiomers, R(+)-carvedilol and S(−)-carvedilol. Reaction of 4-oxiranyl-methoxy-9H-carbazole 8 with 2-(2-methoxy-phenoxy)-ethylamine 9 in monoglyme, and compound 8 was produced by the condensation of 4-hydroxy carbazole 6 with epichlorohydrin 7 in the presence of sodium hydroxide in dimethyl sulfoxide (DMSO) medium.

Mechanism of action:
It promotes vasoconstriction by action of b-receptor, as a result portal blood flow decreases. alpha receptor blocked and vascular tone of liver decreases.

Decrease hepatic       Non selective b-blocker ------- Decrease heart rate &
vascular tone <= Alpha-1 adrenergic blocker vasoconstriction

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<table>
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<tbody>
<tr>
<td>Decrease resistance</td>
</tr>
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</table>

Decrease portal blood flow / of liver

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Decrease portal pressure</td>
</tr>
</tbody>
</table>
Adverse effects:
1) Low blood pressure
2) Diarrhea
3) Weakness, Dizziness
4) Slowed heart rate.

Uses:
1) Management of congestive heart failure.
2) Carvedilol has been used in the treatment of uncomplicated hypertension.
3) Adjunct to angiotensin-converting-enzyme inhibitor (ACE inhibitors) and diuretics.

Contraindications:
1) Carvedilol should not be used in patients with bronchial asthma or bronchospastic conditions.
2) Second or third-degree atrioventricular block, sick sinus syndrome, severe bradycardia.

E) Diuretics:

Hydrochlorothiazide:
Hydrochlorothiazide is a diuretic medication often used to treat high blood pressure and swelling. Hydrochlorothiazide shows greater effect on systolic blood pressure than diastolic one which can reach 4 mmHg to 6 mmHg pressure reduction.

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Oral</th>
</tr>
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<tbody>
<tr>
<td>Bioavailability</td>
<td>70%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Non significant</td>
</tr>
<tr>
<td>Elimination</td>
<td>5.6—14.8 hrs</td>
</tr>
<tr>
<td>Excretion</td>
<td>Kidney</td>
</tr>
</tbody>
</table>

Structure:

Hydrochlorothiazide:
Formula: C7H8ClN3O4S2
Synthesis:
Hydrochlorothiazide is synthesized by either the reaction of para-formaldehyde with 5-chloro-2,4-disulfamoylaniline in nonaqueous media, or the reaction of formaldehyde with 6-chloro-7-sulfamoyl-2H-1,2,4-benzo thiadiazine-1,1-dioxide in aqueous alkaline solution.
Mechanism of action:

Hydrochlorothiazide inhibits sodium chloride cotransport in the distal convoluted tubule. More sodium is then excreted in the kidney with accompanying fluid. This action leads to a diuretic action that lowers blood pressure and cardiac output.

\[
\text{Hydrochlorothiazide inhibits} \rightarrow \text{Na}^+ / \text{Cl}^- \text{co transport} \\
\text{Decrease lower blood pressure} \leftarrow \text{Increase Sodium and Water excretion}
\]

Uses:
1) Hydrochlorothiazide is used for the treatment of hypertension, congestive heart failure, symptomatic edema, diabetes insipidus, renal tubular acidosis.
2) Hydrochlorothiazide is also sometimes used to prevent osteopenia and for treatment of hypoparathyroidism.
3) Prevention of kidney stones in those who have high levels of calcium in their urine.

Adverse effects:
1) Hypokalemia, or low blood levels of potassium.
2) Hyperlipidemia, high cholesterol and triglycerides.
3) Headache.
4) Nausea/vomiting.

Contraindications:
1) Stage 4 CKD, Gout, Acute renal failure.
2) Hyponatremia.

F) Ca-channel blockers:

Verapamil:

It is a calcium channel blocker medication used for the treatment of high blood pressure, angina (chest pain from not enough blood flow to the heart), and supraventricular tachycardia. Verapamil was approved for medical use in the United States in 1981. It was the 151st most commonly prescribed medication in the United States, with more than 3 million prescriptions.

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Oral</th>
<th>Intravenous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>Metabolism</td>
<td>Liver</td>
<td></td>
</tr>
<tr>
<td>Elimination Half life</td>
<td>2.8—7.4 hours</td>
<td></td>
</tr>
<tr>
<td>Excretion</td>
<td>Kidney :11%</td>
<td></td>
</tr>
</tbody>
</table>

Structure:

\[
\text{Verapamil}
\]
Mechanism of Action:
Verapamil's mechanism in all cases is to block voltage-dependent calcium channels. Verapamil dilate the coronary blood vessels, which increases the supply of blood and oxygen to the heart. They also cause dilatation of systemic peripheral vessels as well, causing a reduction in the workload of the heart, hence the blood pressure decreases.

Verapamil ----> Block L-type Ca++ channels ----> Decrease Ca ++ and entry

Decreases heart rate & Vascular smooth muscles relaxed.

Uses:
1) For controlling ventricular rate in supraventricular tachycardia and migraine headache prevention.
2) Also used intra-arterially to treat cerebral vasospasm.

Adverse effects:
1) Dizziness (3.3%), nausea (2.7%), low blood pressure (2.5%), and headache.
2) Congestive heart failure, pulmonary edema, fatigue.

Contraindications:
1) Hypotension (systolic blood pressure less than 90 mm Hg), cardiogenic shock.
2) It is also contraindicated in people with atrial flutter or fibrillation and an existing accessory tract such as in Wolff-Parkinson-White syndrome.

I) Alpha-2 adrenergic receptor agonists:
Clonidine, sold under the brand name Catapres among others, is an α2-adrenergic agonist medication used to treat high blood pressure, ADHD. Clonidine was patented in 1961 and came into medical use in 1966. The reduction in circulating norepinephrine by clonidine was used in the past as an investigatory test for pheochromocytoma, which is a catecholamine-synthesizing tumor, usually found in the adrenal medulla. In a clonidine suppression test, plasma catecholamine levels are measured before and 3 hours after a 0.3 mg oral test dose has been given to the patient. A positive test occurs if there is no decrease in plasma levels.

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>70-80 %</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Liver</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urine</td>
</tr>
<tr>
<td>Elimination half life</td>
<td>5-13 hrs</td>
</tr>
</tbody>
</table>
Structure:

Clonidine

Mechanism of action:

Clonidine treats high blood pressure by stimulating α2 receptors in the brainstem, which decreases peripheral vascular resistance, lowering blood pressure. It has specificity towards the presynaptic α2 receptors in the vasomotor center in the brainstem. This binding has a sympatholytic effect, suppresses release of norepinephrine, ATP, renin, and neuropeptide Y which if released would increase vascular resistance.

Clonidine also acts as an agonist at imidazoline-1 (I1) receptors in the brain, and it is hypothesized that this effect may contribute to reducing blood pressure.

Clonidine ----> stimulates presynaptic α2 receptors ----> Inhibits release of NE

1
1
1
1

Lowers blood pressure.

Uses:

1) Resistant to hypertension.
2) Attention deficit hyperactivity disorder.
3) Drug withdrawal.

Adverse effects:

1) Sedation, dry mouth, and hypotension (low blood pressure).
2) Headache (dose-dependent), Fatigue.
3) Skin reactions (if given transdermally).

Contraindications:

1) In patient with hypersensitivity to clonidine.
2) In Diabetic patient with sulphonylurea.
3) In Angioedema.

<table>
<thead>
<tr>
<th>Combination</th>
<th>Possible effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>An alpha or beta adrenergic blocker + Clonidine</td>
<td>Antagonism of clonidine action observed.</td>
</tr>
<tr>
<td>Hydralazine + Dihydropyridine</td>
<td>Haemodynamic action</td>
</tr>
<tr>
<td>Verapamil + B-blocker</td>
<td>Bradycardia</td>
</tr>
</tbody>
</table>

J) Angiotensin II receptor blocker:


Losartan:

Losartan, sold under the brand name Cozaar among others, is a medication used to treat high blood pressure (hypertension).

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>25-35 %</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Cytochrome P450</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urine</td>
</tr>
<tr>
<td>Elimination half life</td>
<td>2-3 hrs</td>
</tr>
</tbody>
</table>

Structure:

Losartan

Mechanism of action:

It is selective, competitive angiotensin II receptor type 1 (AT1) antagonist, reducing the end organ responses to angiotensin II. Losartan administration results in a decrease in total peripheral resistance (afterload) and cardiac venous return (preload). All of the physiological effects of angiotensin II, including release of aldosterone, are antagonized in the presence of losartan. Reduction in blood pressure occurs independently of the status of the renin–angiotensin system. As a result of losartan dosing, plasma renin activity increases due to removal of the angiotensin II feedback. Renin is released from the kidneys when there is reduced renal arterial pressure, sympathetic activation, or increased sodium delivery to the distal renal tubule. Renin then acts by converting angiotensinogen to angiotensin I; angiotensin converting enzyme (ACE) converts angiotensin I to angiotensin II; angiotensin II causes vasoconstriction and aldosterone release. Aldosterone serves to retain sodium from the distal renal tubule. Sodium retention ultimately results in increased blood pressure. Therefore, the use of angiotensin II receptor antagonists like losartan result in blocking the downstream effect of renin, angiotensin II, and ultimately decreasing blood pressure.

Angiotensinogen ---------> Angiotensin I -------------------------------> Angiotensin II

Renin         Angiotensin converting
Enzyme
(ACE)

I
I

I
I

I
Aldosterone release & Vasoconstriction

Antihypertensives & pregnancy

<table>
<thead>
<tr>
<th>Antihypertensives to be avoided during pregnancy</th>
<th>Anti hypertensives found safer during pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE inhibitors, ARBs:</strong> Risk of foetal damage, growth retardation.</td>
<td>Hydralazine, Methyldopa</td>
</tr>
<tr>
<td><strong>Diuretics:</strong> increase risk of foetal wastage, placental infarcts, miscarriage, stillbirth.</td>
<td>Dihydropyridine CCBs: if used, they should be discontinued before labour as they weaken uterine contractions.</td>
</tr>
<tr>
<td><strong>Nonselective β blockers:</strong> Propranolol cause low birth weight, decreased placental size, neonatal bradycardia and hypoglycaemia.</td>
<td>Cardioselective β blockers and those with ISA, e.g. atenolol, metoprolol, pindolol, acebutolol: may be used if no other choice.</td>
</tr>
<tr>
<td><strong>Sod. nitroprusside:</strong> Contraindicated in eclampsia.</td>
<td>Prazosin and clonidine—provided that postural hypotension can be avoided.</td>
</tr>
</tbody>
</table>

**Uses:**
1) Losartan is used for hypertension, including in people with left ventricular hypertrophy (enlarged heart muscle), and kidney dysfunction among type II diabetics. It may also delay progression of diabetic nephropathy. It is a suitable pharmacological agent for the reduction of renal disease progression in patients with type 2 diabetes, hypertension.

**Adverse effects:**
1) Losartan in adults: upper respiratory infections, dizziness, and back pain. People with type 2 diabetes and kidney disease may experience diarrhea, fatigue, low blood pressure, low blood glucose, elevated potassium, chest pain, or allergic reaction.
2) It injures liver.

**Contraindications:**
1) Hypertension.
2) Diabetic nephropathy patients.
References: