DRUGS ACTING ON RENIN-ANGIOTENSIN SYSTEM

BY

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THE JUXTAGLOMERULAR APPARATUS
RENIN – ANGIOTENSIN SYSTEM

Angiotensinogen

\[ \text{Renin} \]

Angiotensin I

\( (\text{Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu}) \)

\[ \text{Angiotensin Converting Enzyme} \]

Angiotensin II

\( (\text{Asp-Arg-Val-Tyr-Ile-His-Pro-Phe}) \)

ACE-2

\[ \text{Angiotensin-(1-7)} \]

\( (\text{Asp-Arg-Val-Tyr-Ile-His-Pro}) \)

\[ \text{Angiotensin III} \]

\( (\text{Arg-Val-Tyr-Ile-His-Pro-Phe}) \)

AMP

\[ \text{Angiotensin IV} \]

\( (\text{Val-Tyr-Ile-His-Pro-Phe}) \)

\[ \text{AMP} \]
LOCAL RENIN ANGIOTENSIN SYSTEMS

**EXTRINSIC RAS** : Blood vessels capture the circulating angiotensinogen and renin and produce Ang II at the wall surface.

**INTRINSIC RAS** : Heart, blood vessels, brain, kidney, liver can synthesize all components of RAS according to the physiological need and pathological status.
PRORENNIN AND (PRO) RENIN RECEPTOR [PRR]
Angiotensin-2 Independent Pathway

Angiotensin-2 Dependent Pathway

PRR Intracellular Signalling

Non Enzymatic Activation/Augmentation

Activation of JAK-STAT, Protooncogenes, PAI-1

Cell Growth, Apoptosis, Fibrosis, Hyperplasia, Nephropathy

Prorenin

Renin

Angiotensinogen

Angiotensin-1

Angiotensin-2
OTHER ANGIOTENSIN PEPTIDES

- **ANGIOTENSIN-III**: Equipotent when it comes to action on adrenal gland.
- **ANGIOTENSIN-IV**: Inhibits IRAP, prevents neuropeptide degradation, improves the memory and cognition.
- **ANGIOTENSIN (1-7)**: From Angiotensin I or II by ACE-2. Actions opposite to ANG-II.
ANIOTENSIN RECEPTORS
ACTIONS

- **CVS**: Causes vasoconstriction by increasing Adr/NA release. Increases heart rate but can cause arrhythmia.
- **ADRENAL**: Increases the synthesis and secretion of aldosterone.
- **KIDNEY**: Increases the Na+ reabsorption in PCT.
- **CNS**: Stimulates ADH release and drinking behavior.
- Increases Adr/NA release from autonomic ganglia.
The Renin-Angiotensin-Aldosterone System, Anti-renin drugs, and the PRA Assay

Drawn from Laragh, JAMA, 1960
1. **Angiotensin converting enzyme (ACE) inhibitor** - Prevent generation of active Ang- II.

2. **Angiotensin Receptor Blockers (ARB)** - Antagonise the action of Ang- II in target cells.

3. **Direct Renin inhibitors** - Bind to renin and inhibit its action.

4. **Sympathetic blockers** - like α and β blockers etc.

5. **Aldosterone antagonists** - Block mineral corticoid receptor.
ACE Inhibitors

- These are the First line of drugs used in treatment of hypertension.
- Decreases BP gradually and is more marked if the Na+ level is low.
- Ang- I here is acted upon by ACE-2 and converted to Ang(1-7) that further reduces BP.
- Can be safely given in ischemic heart disease.
Ace Inhibitors: (Angiotensin Converting Enzyme) (Ends In April)

Action - ↓ Peripheral Vascular Resistance Without:

Ø • ↑ Cardiac Output
Ø • ↑ Cardiac Rate
Ø • ↑ Cardiac Contractility

Effects: Dizziness
Orthostatic Hypotension
GI Distress
Nonproductive Cough
Headache
<table>
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<tr>
<th>DRUGS</th>
<th>CAPTOPRIL</th>
<th>ENALAPRIL</th>
<th>FOSINOPRIL</th>
<th>PERINDOPRIL</th>
<th>RAMIPRIL</th>
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<tr>
<td>CHEMICAL NATURE</td>
<td>SULFHYDRYL</td>
<td>CARBOXYL</td>
<td>PHOSPHINATE</td>
<td>CARBOXYL</td>
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<td>ACTIVITY STATUS</td>
<td>ACTIVE</td>
<td>PRODRUG (ENALAPRILAT)</td>
<td>PRODRUG</td>
<td>PRODRUG (PERINDOPRILAT)</td>
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<td>PLASMA t 1/2</td>
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<td>11hr</td>
<td>12 hr</td>
<td>25-30 hr</td>
<td>8-48 hr</td>
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<td>RENAL</td>
<td>RENAL</td>
<td>RENAL / HEPATIC</td>
<td>RENAL</td>
<td>RENAL</td>
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</table>
USES

- **Hypertension** - 50% monotherapy. Free of postural hypertension, safe for asthmatics and diabetics. LVH reversed.

- **CHF** - Reduces preload and afterload. First line drugs in left ventricular inadequacy.

- **Myocardial infarction** - Reduces the recurrence of MI and need for angioplasty in non ST segment elevation MI.

- **Diabetic nephropathy** - Prevent or delay end-stage renal disease in both type I and II diabetes.

- Improves non-diabetic nephropathy.

- In post MI and other high cardiovascular risk patients, Ramipril reduced cardiac death and diabetes incidences.
Adverse Drugs Reactions

- **Hypotension** - in pts on diuretics or with CHF.
- **Hyperkalemia** - With usage of NSAIDs and β blockers.
- **Angioedema** - Swelling of lips, mouth, nose, larynx.
- **Cough**
- **Foetopathie** - Foetal growth retardation, hypoplasia of organs and IUD.
- **Rashes, headache, dysgeusia, proteinuria, acute renal failure.**
Ang- I to Ang- II

Vascular endothelium

ANGIOTENSINOGEN

Cathepsin D → Renin

Direct*

Chymase
Cathepsin G

ANGIOTENSIN I

Angiotensin Converting Enzyme (ACE)

ANGIOTENSIN II
ANGIOTENSIN RECEPTOR BLOCKERS (ARBs)

- Recent first line drugs used in hypertension treatment.
- Active AT1 receptor blockers.
- All overt actions of Ang- II are blocked.
- They don’t interfere with ACE actions.
- Result in indirect activation of AT2 receptor action.
Angiotensin II Receptor Blockers (ARBs)

- ARBs lower blood pressure and increase blood to heart.
- ARBs block angiotensin receptor.
DRUGS

- **Losartan**.
- **Candesartan**: Highest affinity for AT1 receptors due to -
  (i) Slow dissociation.
  (ii) Receptor desensitization.
- **Olmesartan**: Ester prodrug.
**USES**

- **Hypertension**: Produces same effect like ACE inhibitors without the adverse effects.
- **CHF**: Provides symptomatic relief.
- **MI**: Comparable to ACE inhibitors.

**ADR:**

- Hypotension and Hyperkalemia
- Headache, dizziness and weakness.
Combination of ACE inhibitors with ARB

- To obtain more complete inhibition of the RAS.
- To have a cardioprotective and nephroprotective action.
- Vasodilation by:
  1. Ang (1-7) production by ACE inhibitors
  2. Activation of AT2 receptors by ARBs.
Direct Renin Inhibitors

✓ Latest class of RAS inhibitory drugs – only one member Aliskiren is available.
✓ It is a non-peptide that binds to the catalytic site of Renin, thus inhibiting its...
Never used as a monotherapy.
Efficacy equal to ACE inhibitors and ARBs.
As an alternative to pts that don’t respond/ can’t tolerate 1st line drugs.
Reverses left ventricular hypertrophy and benefits CHF patients.
ADR: Dyspepsia, abdominal pain, headache and dizziness.
THANK YOU