Course: Integrated Therapeutics 1

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Materials on: Exam #3

Required reading: Katzung, Chapter 11
HYPERTENSION

- 1 in 3 adults
- 64% of men and 75% women over the age of 75
- 55,000 related deaths, yearly
- >40 million office visits
- Despite clear improvements in survival with drug therapy, there are more than 61% hypertension patients whose BP is uncontrolled
- 33% are not aware they have high blood pressure
HYPERTENSION

Aside from blood pressure, hypertension is usually ASYMPTOMATIC until overt end organ damage is imminent or has occurred

– Kidney failure
– Coronary heart disease
– Heart failure
– Stroke
HYPERTENSION

2 Categories:

- **Secondary Hypertension**: secondary to a specific disorder:
  - Tumors
  - Kidney disorders
  - Pregnancy
  - Cushing’s syndrome
  - Use of medications

- **Essential Hypertension**: no clearly identifiable cause (95% of all cases); often multi-factorial
2 Categories:

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REGULATION OF BLOOD PRESSURE

Blood volume:
- Renin-Angiotensin System
- Angiotensin AT1 receptors
- Diuresis/Natriuresis

Diameter of arterioles (resistance vessels)
- Sympathetic N.S.
  - $\alpha_1$ adrenergic receptors
  - $\beta_2$ adrenergic receptors
- Renin-Angiotensin System
  - Angiotensin AT1 receptors

Heart Rate
- Sympathetic N.S.
  - $\beta_1$ adrenergic receptors
- Parasympathetic N.S.
  - Muscarinic receptors

Force of Ventricular Contraction
- Sympathetic N.S.
  - $\beta_1$ adrenergic receptors

Diuretics
- Inhibitors of RAS

Sympatholytic agents
- Vasodilators
- Inhibitors of RAS

Sympatholytic agents
Categories Of Antihypertensive Agents:

- Diuretics
- Sympatholytic agents
- Direct vasodilators
- Inhibitors of renin-angiotensin system
ANTIHYPERTENSIVE DRUGS

• In hypertensive individuals, the “set point” at which blood pressure is maintained by baroreceptors and the renin-angiotensin system is elevated

• Most of the drugs act on factors maintaining blood pressure (blood volume, PVR), but do not reset the “set point”

• If the blood pressure is lowered with medications, body develops compensatory responses to bring it back into the elevated range
DIURETICS USE IN HYPERTENSION

- Act upon various segments of nephrons in the kidney to produce an increase in the volume of the urine secondary to an increase in renal sodium excretion (i.e., decrease sodium re-absorption)
- The increased elimination of sodium is the primary mechanism through which diuretics produce their long-term hypotensive effects
- **Initial effects:** reduction in blood volume resulting in decreased blood pressure due to decreases in amount of blood being pumped by the heart (decreased cardiac output)
- **Delayed effects:** after 6-8 weeks, blood volume and cardiac output are restored back to normal, but peripheral resistance declines. Sodium is believed to increase vessel stiffness and neural activity, possibly through sodium-calcium exchange with increased intracellular calcium
DIURETICS USED IN HYPERTENSION: SITES OF ACTION

A NEPHRON

BLOOD

Proximal Tubule

Glomerular Filtration

Na+

Na+

Na+

Na+

Na+

Na+

Cortex

Medulla

Distal Tubule

Thiazides
(hydrochlorothiazide)

Loop of Henle

Potassium Sparing Agents
(spironolactone, triamterene)

High Efficacy Loop Diuretics
(furosemide)

Collecting Duct

K+

Na+

Na+

K+

Na+

Na+

Na+

Na+

Na+

BLOOD

URINE
DIURETIC DRUGS USED IN HYPERTENSION

• Loop diuretics
  – Bumetanide
  – Furosemide
  – Torsemide
  – Ethacrynic acid

• Thiazide diuretics
  – Chlorothiazide
  – Hydrochlorothiazide
  – Chlorthalidone
  – Indapamide
  – Metolazone

• Potassium-sparing diuretics
  – Spironolactone
  – Eplerenone
  – Triamterene
  – Amiloride
15-25% of filtered $\text{Na}^+$ is reabsorbed in the thick ascending limb of the loop of Henle.

Inhibition of NKCC2 transporter

The result is reduced $\text{Na}^+$ re-absorption and increased diuresis

Increased $\text{Na}^+$ in filtrate will exchange for $\text{K}^+$ at collecting duct, resulting in increased $\text{K}^+$ elimination and hypokalemia
LOOP DIURETICS

• More powerful than other two groups used in hypertension
• Used in following situations
  – More severe forms of hypertension
  – When multiple drugs are used that promote sodium retention
  – In conditions with marked sodium retention: heart failure, cirrhosis
• Adverse effects
  – Hypokalemia (proportional to the degree of natriuresis – more pronounced than with other types of diuretics)
  – Ototoxicity – hearing loss (usually reversible)
  – Hyperuricemia
  – Hypomagnesemia
**THIAZIDE DIURETICS**

- 4-8% of filtered Na\(^{+}\) is reabsorbed in the distal convoluted tubule
- Inhibition of NCC co-transporter
- By increasing the amount of sodium that reaches the distal tubule, thiazide diuretics also produce hypokalemia
- Thiazide diuretics have lower diuretic efficacy than loop diuretics
**THIAZIDE DIURETICS**

- First line of drugs in mild/moderate hypertension
- Low-cost but effective drugs: reduce morbidity and mortality
- Adverse effects
  - Hypokalemia
  - Hyperuricemia
  - Impaired carbohydrate tolerance – development of hyperglycemia in diabetics and patients with abnormal glucose tolerance tests – occurs due to impaired pancreatic release of insulin and diminished tissue utilization of glucose
  - Hyperlipidemia – increase in total serum cholesterol and LDL
POTASSIUM-SPARING DIURETICS

- Collecting tubule absorbs only 2-5% of filtered Na⁺.
- Principle cells in the collecting duct have channels on their apical membranes through which Na⁺ and K⁺ can pass.
- A Na⁺-K⁺ATPase on the basolateral membrane keeps the K⁺ concentration high and the Na⁺ concentration low in principal cells.
- Prevent Na⁺ - K⁺ exchange in the collecting duct, resulting in slight increases in Na⁺ elimination with increases in K⁺ reabsorption = POTASSIUM SPARING.

1. ANTAGONISTS at the mineralocorticoid receptor = reduced expression of the basolateral Na⁺-K⁺ATPase (Spironolactone, Eplerenone)
2. BLOCKERS of epithelial Na⁺ channels (ENaC) on the apical membrane (Triamterene, Amiloride)
POTASSIUM-SPARING DIURETICS

• The least efficient diuretic/natriuretic action
• May be used
  – In conjunction with loop diuretics/thiazides for correction of hypokalemia
  – In patients with concomitant heart failure, cirrhosis
• Adverse effects
  – Hyperkaliemia (may especially occur in patients who take other drugs that may cause hyperkalemia or inhibit renin-angiotensin system)
  – Triamterene may cause the formation of kidney stones, and cause acute kidney failure in combination with indomethacine
  – Spironolactone causes endocrine abnormalities (gynecomastia, impotence, prostate hyperplasia)
CATEGORIES OF SYMPATHOLYTIC AGENTS

• Sympathetic agents acting on adrenoceptors in CNS
• Acting on autonomic ganglia
• Inhibiting the release of NE from postganglionic sympathetic neurons
• Acting on postsynaptic adrenergic receptors
  – Alpha-antagonists
    • Non-selective alpha-antagonists
    • Selective alpha-1 antagonists
  – Beta-antagonists
    • Non-selective beta-antagonists
    • Selective beta-1 antagonists
SYMPATHETIC AGENTS ACTING ON CENTRAL NS

- Activate $\alpha_2$ receptors in the vasomotor center of the brain
- Reduce sympathetic nervous system activity in the body
- Reduce peripheral vascular resistance, decrease heart rate and cardiac output
SYMPATHETIC AGENTS ACTING ON CENTRAL NS

Methyldopa
Clonidine
Guanabenz
Guanfacine

• Cause CNS side effects but postural hypotension is less of an issue compared to direct sympatholytics
• Sudden withdrawal may cause rebound hypertension
SYMPATHETIC AGENTS ACTING ON CENTRAL NS

Methyldopa

- Converted to active metabolites – same pathway as norepinephrine
  - \(\alpha\)-methylnorepinephrine
  - \(\alpha\)-methylidopamine
- Stored in adrenergic nerves vesicles
- Released when neuron stimulated
- Binds to \(\alpha_2\)-adrenoceptors in the vasopressor center of the brain to inhibit NE release and decrease sympathetic outflow to the vascular tissues
SYMPATHETIC AGENTS ACTING ON CENTRAL NS

Methyldopa

• Adverse effects
  – Sedation, impaired mental concentration
  – Nightmares, depression
  – Extrapyramidal signs
  – Lactation in men and women – increased prolactin secretion – via inhibitory action on dopaminergic mechanisms
SYMPATHETIC AGENTS ACTING ON CENTRAL NS

Clonidine

- Peripherally – partial $\alpha$-agonist and produces a pressor effect
- Central effect on brain medulla – inhibition of vasomotor center
  - Decreases sympathetic outflow
  - Increases parasympathetic outflow
  - Blood pressure lowering and bradycardia
  - Binds to non-adrenoceptor – imidazoline receptor
- Rarely induces postural hypotension
SYMPATHETIC AGENTS ACTING ON CENTRAL NS

Clonidine

• Adverse effects
  – Sedation
  – Dry mouth
  – Depression
  – Withdrawal may cause life-threatening hypertensive crisis

• Drug interaction
  – Drugs with alpha-AR blocking activity will inhibit the action of clonidine (tricyclic antidepressants and alpha-blockers)
SYMPATHOLYTICS ACTING ON PERIPHERAL NS

Baroreceptor in Carotid Sinus (detects stretch)

N. Tractus Solitarius

Vasomotor Center

Sympathetic Nerves

Arterial smooth muscle

Arterial blood pressure

Brain-stem

Spinal Cord

N. Tractus Solitarius

Sympathetic Nerves

Vasomotor Center

Baroreceptor in Carotid Sinus (detects stretch)

\( \alpha_1 \)-RECEPTOR ANTAGONISTS (PRAZOSIN; TERAZOSIN)

\( \alpha_1 \) receptor (vasoconstriction)

\( \beta_1 \) receptor (heart rate, contractile force)

GANGLION BLOCKERS (TRIMETHAPHAN)

RELEASE INHIBITORS (RESERPINE)

BETA BLOCKERS (PROPRANOLOL, ATENOLOL, NADOLOL)
**GANGLION BLOCKERS**

- These agents were first agents used for the pharmacotherapy of hypertension, but now their use is very limited
- These agents decrease the sympathetic outflow to blood vessels and cause vasodilation by blocking nicotinic receptors of the autonomic ganglia
- Trimethaphan
  - Used mainly for initial control of blood pressure in patients with acute dissecting aortic aneurysm, and to produce controlled hypotension and reduce hemorrhage during surgeries
  - Short duration of action – allows precise titration of blood pressure
  - Effect due to pooling of blood in capacitance vessels
GANGLION BLOCKERS

• High degree of clinical toxicities due to blockade of parasympathetic effects as well as blockade of nicotinic receptors at neuromuscular junctions

• Adverse effects
  – Sympatholytic – sexual dysfunction, postural hypotension, tachycardia
  – Parasympatholytic – urinary retention, constipation, dry mouth, blurred vision, precipitation of glaucoma
NOREPINEPHRINE RELEASE INHIBITORS

• Guanethidine
• Guanadrel
• Reserpine

• These agents deplete NE stores in pre-synaptic vesicles of post-ganglionic adrenergic neurons
• These agents have serious toxicities at higher doses, or with certain other drugs, or in conditions like pheochromocytoma
**NOREPINEPHRINE RELEASE INHIBITORS**

- Guanethidine, Guanadrel
- Too polar to enter the CNS
- Mechanism of action – inhibition of the release of norepinephrine from sympathetic nerve endings
  - Taken up by reuptake
  - Replace norepinephrine in vesicles
  - Cause a gradual depletion of norepinephrine stores
  - Inhibition of norepinephrine release via local anesthetic properties
- Long half life – 5 days
- Gradual sympathoplegia – maximal effect develops in about 2 weeks
- Initially cardiac output is reduced due to relaxation of capacitance vessels and bradycardia, with long-term therapy peripheral vascular resistance decreases
**NOREPINEPHRINE RELEASE INHIBITORS**

- Guanethidine, Guanadrel
- **Adverse effects**
  - Postural and exercise-induced hypotension
  - Diarrhea via increased parasympathetic activity
  - Inhibition of ejaculation in men
  - Significant sodium and water retention
- **Drug interactions**
  - Increases sensitivity to hypertensive effects of exogenous sympathomimetic amines
  - Hypertensive crisis in patients with pheochromocytoma
  - Antihypertensive action is inhibited by amphetamines, cocaine, tricyclic antidepressants
NOREPINEPHRINE RELEASE INHIBITORS

Reserpine

• One of the first drugs widely used for the treatment of hypertension – still used today
• Effective and relatively safe drug in mild to moderate hypertension
• Mechanism of action
  – Irreversibly blocks the synaptic vesicles from taking up and storing biogenic amines
  – Depletes both central and peripheral stores of NE, dopamine, and serotonin
  – Remains tightly bound to the transporter molecule for many days
  – Depletes chromaffin cells in adrenal medulla of CA stores
  – Penetrates into CNS and depletes neurotransmitters there
  – Lowers blood pressure by decreasing cardiac output and peripheral vascular resistance
NOREPINEPHRINE RELEASE INHIBITORS

Reserpine

- **Adverse effects**
  - Sedation
  - Mental depression
  - Nightmares
  - Parkinsonism syndrome
  - Mild diarrhea, cramps
  - Increase in gastric acid secretion
  - Nasal stuffiness

- **Contraindications**
  - Depression
  - Peptic ulcer
**ALPHA-RECEPTOR ANTAGONISTS**

- **Selective alpha-1 antagonists**
  - Doxazosin
  - Prazosin
  - Terazosin

- **Non-selective alpha antagonist**
  - Phentolamine

- **Mechanism of action**
  - These agents cause vasodilation and reduce peripheral resistance by blocking the post-synaptic $\alpha_1$-receptors that control the vascular tone of blood vessels
  - Dilation of resistance and capacitance vessels decreases blood pressure
ALPHA-RECEPTOR ANTAGONISTS

- Favorable effects on serum lipids
- The $\alpha_1$-selective antagonists produce less reflex tachycardia than non-selective $\alpha$-antagonists
- The non-selective $\alpha$-antagonists are used mainly in treatment of pheochromocytoma and other conditions with excessive release of CA
- Adverse effects
  - Retention of fluid and salt
  - Significant decreases in blood pressure after first dose (precipitous drop in blood pressure while standing) – low doses are given at bedtime to start therapy. Long-term treatment causes relatively little postural hypotension
**BETA-RECEPTOR ANTAGONISTS**

- **Mechanism of antihypertensive action**
  - Reduce blood pressure in hypertensive individuals after chronic use
  - Heart – decrease cardiac output
    - Negative inotropic effect
    - Negative chronotropic effect
  - Blood vessels
    - Initially – rise in PVR due to unopposed $\alpha$-AR action
    - Chronic use decreases PVR
  - Renin-angiotensin system – reduce the release of renin
    - Vasorelaxation (decrease in AT level)
    - Decreased blood volume (increased natriuresis/diuresis)
  - Blocking of presynaptic beta-receptors on adrenergic neurons in vascular smooth muscle
    - Reduction in sympathetic nerve activity
**BETA-RECEPTOR ANTAGONISTS**

- **Non-selective pure beta-antagonists**
  - Propranolol, Nadolol
- **Used in mild to moderate hypertension**
- **Significant decrease in BP without significant postural hypotension**
- **Used with vasodilators to prevent reflex tachycardia**
- **Adverse effects**
  - Reduced cardiac output
  - Bronchoconstriction
  - Impaired liver glucose mobilization
  - Produce an unfavorable blood lipoprotein profile (increase VLDL and decrease LDL)
  - Sedation, Depression
  - Withdrawal syndrome associated with sympathetic hyperresponsiveness
BETA-RECEPTOR ANTAGONISTS

Cardioselective (beta-1) blockers

- Metoprolol
- Atenolol
- Bisoprolol
- Betaxolol
- Esmolol

May have advantages in treating patients with

- Asthma
- Diabetes mellitus
- Peripheral vascular disease

- Atenolol, Bisoprolol, and Betaxolol have once-a-day dosing forms
- Esmolol has a short half-life, used intravenously for the treatment of hypertensive emergencies
BETA-RECEPTOR ANTAGONISTS

• Partial agonists (antagonists with ISA)
  – Acebutolol
  – Pindolol
  – Penbutolol

• Lower blood pressure due to decreased cardiac output and decreased PVR
  – May be due to a significant agonist effect on beta-2 receptors

• May have advantages in treating hypertensive patients with
  – Peripheral vascular disease
  – Bradyarrhythmias
  – Depressed cardiac function
DIRECT VASODILATORS

Vasodilators
– Arteriolar – relax arteries – resistance vessels
– Venular – relax veins – capacitance vessels

• **Vasodilators used in hypertension are arteriolar vasodilators**

• **Mechanism of action in hypertension**
  – Arteriolar vasodilation decreases peripheral vascular resistance and lowers blood pressure

• **Direct vasodilators**
  – Directly dilate arterial smooth muscle
  – Vasodilation is not mediated by their effect on adrenergic receptors
  – Because sympathetic nervous system remains intact, these drugs do not cause
    • Sexual dysfunction
    • Postural hypotension
DIRECT VASODILATORS

• Vasodilators used for long-term oral BP control
  – Hydralazine
  – Minoxidil
  – Calcium channel blockers (may be also used parenterally)

• Parenteral use for hypertensive emergencies
  – Nitroprusside
  – Diazoxide
  – Fenoldopam

• All relax smooth muscle in arterioles, by different mechanisms

• Nitroprusside dilates both arteries and veins
DIRECT VASODILATORS

Hydralazine
• Unknown mechanism of action
• Used in severe hypertension in combination with other antihypertensive drugs
• Metabolized by acetylation in liver
  – First pass effect – low (25%) bioavailability
  – Rapid and slow acetylators – variable bioavailability
• Adverse effects
  – Headache, nausea, anorexia, palpitations, sweating, flushing
  – Reflex tachycardia and sympathetic stimulation
  – Lupus-like symptoms - arthralgia, myalgia, and skin rashes
  – Peripheral neuropathy
DIRECT VASODILATORS

Minoxidil

• Mechanism of action
  – Opens potassium channels in smooth muscle cells
  – Increased potassium permeability hyperpolarizes cell membrane and makes depolarization and contraction of smooth muscle cells less likely

• More potent antihypertensive effect than with hydralazine

• Replacement for hydralazine when maximal dose does not work

• Causes more reflex sympathetic stimulation, sodium and fluid retention than hydralazine
DIRECT VASODILATORS

Minoxidil

• Adverse effects
  – Headache
  – Sweating
  – Tachycardia, palpitations
  – Hypertrichosis
  – Precipitation of angina (due to increased cardiac work)
  – Swelling (due to fluid retention)
CONSEQUENCES OF FEEDBACK REGULATION
INDIRECT EFFECTS OF VASODILATORS

EFFECTS OF DRUG-INDUCED VASODILATION ON HEART RATE

VASODILATOR ADMINISTRATION

\[ \downarrow \]

RELAXATION OF ARTERIAL SMOOTH MUSCLE

\[ \downarrow \]

DECREASE IN TOTAL PERIPHERAL RESISTANCE

\[ \downarrow \]

REDUCED BLOOD PRESSURE

\[ \downarrow \]

DETECTION BY BARORECEPTORS

INCREASED SYMPATHETIC N.S. ACTIVITY

DECREASED PARASYMPATHETIC N.S. ACTIVITY

BARORECEPTORS

REFLEX INCREASE IN HEART RATE
Consequences of Feedback Regulation = INDIRECT EFFECTS OF VASODILATORS

EFFECTS OF DRUG-INDUCED VASODILATION ON BLOOD VOLUME

VASODILATOR ADMINISTRATION

\[ \downarrow \]

RELAXATION OF ARTERIAL SMOOTH MUSCLE

\[ \downarrow \]

DECREASE IN TOTAL PERIPHERAL RESISTANCE

\[ \downarrow \]

REDUCED BLOOD PRESSURE

\[ \downarrow \]

DETECTION BY JUXTOGLOMERULAR APPARATUS IN THE KIDNEY

\[ \rightarrow \]

INCREASED RENIN SECRETION AND ANGIOTENSIN II PRODUCTION

\[ \rightarrow \]

REFLEX INCREASE IN SODIUM REABSORPTION = INCREASE BLOOD VOLUME/EDEMA

RENIN-ANGIOTENSIN SYSTEM
DIRECT VASODILATORS

Reflex compensatory responses to vasodilators

- Reflex tachycardia
  - Increases cardiac work – may precipitate angina or ischemic arrhythmias
  - Rationale for co-administration with beta blockers

- Reflex fluid retention
  - Increases cardiac work – may precipitate angina or ischemic arrhythmias
  - Rationale for co-administration of diuretics

- Vasodilators are almost always co-administered with a beta blocker and/or diuretic to prevent reflex responses
COMBINATION THERAPY WITH DIRECT VASODILATORS

1 – DIURETIC
2 – BETA-BLOCKER
Sodium nitroprusside

- Mechanism of action
  - Releases NO
- Rapidly lowers blood pressure; effects disappear within 1-10 minutes
- Administered by I.V. infusion in hypertension and heart failure emergencies
- Adverse effects
  - Accumulation of cyanide as a by-product of metabolism (mitochondrial enzyme rodanase – needs sulfate donor – sodium thiosulfate administered as a sulfate donor to facilitate the metabolism of CN)
  - Metabolic acidosis
  - Arrhythmias
  - Excessive hypotension
  - Methemoglobinemia
Diazoxide

- Opens potassium channels and stabilizes membrane potential at rest
- Effect is established within 5 min with I.V. infusion; lasts 4 to 12 hours
- Significant reflex sympathetic activation (tachycardia, increased cardiac output), sodium and water retention are rarely a problem because of short-term use
- Adverse effects
  - Excessive hypotension – may lead to stroke and MI
  - Inhibits insulin release from the pancreas – opens K+ channels in β cells
  - May precipitate hyperglycemia in diabetics
  - Used to treat hypoglycemia from insulinoma
DIRECT VASODILATORS

Fenoldopam

• Mechanism of action
  – Selective D$_1$ receptor agonist
  – Dilates peripheral and renal arteries
  – Increases natriuresis

• Administered by continuous I.V. infusion in hypertensive emergencies

• Has short half-life – 10 min

• Adverse effects
  – Flushing, headache
  – Reflex tachycardia
  – Increases intraocular pressure – should be avoided in patients with glaucoma
DIRECT VASODILATORS

• Calcium channel blockers (CCB)
• Block L-type voltage-gated calcium channels on cardiac and/or vascular smooth muscle
• Have antihypertensive, antianginal, and antiarrhythmic effects

• Cardioactive CCBs: relax vascular smooth muscle and reduce cardiac output (decrease heart rate, AV conduction, and force of contraction)
  – Verapamil
  – Diltiazem
• Non-cardioactive CCBs: relax vascular smooth muscle but have little effect on cardiac output
  – DIHYDROPYRIDINES (all end in “-dipine”)
    • Amlodipine
    • Felodipine
    • Isradipine
    • Nifedipine
**DIRECT VASODILATORS**

- **Dihydropyridines** are more selective vasodilators that cardioactive CCB, do not have cardiodepressant effect

- **Adverse effects of dihydropyridines**
  - Induce reflex sympathetic activation
  - Short-acting dihydropyridines CCBs increased the risk of myocardial infarction relative to patient taking diuretics or beta blockers
  - Use long-acting or sustained release formulations of dihydropyridines for the treatment of hypertension

<table>
<thead>
<tr>
<th>Dihydropyridine CCB</th>
<th>$T_{1/2}$</th>
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<tbody>
<tr>
<td>amlodipine</td>
<td>30-50 hours</td>
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<tr>
<td>felodipine</td>
<td>11-26 hours</td>
</tr>
<tr>
<td>isradipine</td>
<td>8 hours</td>
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<tr>
<td>nifedipine</td>
<td>4 hours</td>
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</table>
INHIBITORS OF RENIN-ANGIOTENSIN SYSTEM

RENIN INHIBITORS

Angiotensinogen \(\rightarrow\) Angiotensin I \(\rightarrow\) Angiotensin II

Blood \(\downarrow\) B.P.

Kidney

Stretch Receptor (Change Na⁺)

AT1 Angiotensin Receptors
- Direct vasoconstriction
- Aldosterone synthesis in adrenal cortex
- Vasopressin release

ANGIOTENSIN RECEPTOR ANTAGONISTS

ACE INHIBITORS

(Vasopressin)

Increased total peripheral resistance
Aldosterone: Increased sodium re-absorption in kidney
Vasopressin: Increase resistance and water retention
INHIBITORS OF RENIN-ANGIOTENSIN SYSTEM

• ACE inhibitors (all end in -pril)
  – Captopril
  – Enalapril
  – Lisinopril
  – Benazepril

• High- and low-renin hypertension – 20% of patients have high, and 20% have low renin activity – high-renin patients respond well to β-blockers and angiotensin inhibitors
INHIBITORS OF RENIN-ANGIOTENSIN SYSTEM

1 – ACE inhibitors
2 – AT1 antagonists
INHIBITORS OF RENIN-ANGIOTENSIN SYSTEM

ACE inhibitors

• **Mechanism of action**
  – Decrease BP by lowering peripheral vascular resistance
  – Inhibitory action on renin-angiotensin system
  – Stimulating action on kallikrein-kinin system

• **Unlike direct vasodilator – no reflex sympathetic activation**
  – Down resetting of baroreceptors
  – Increased parasympathetic activity
  – No effect on heart rate and cardiac output

• **Clinical indications**
  – Hypertension
  – Heart failure
  – Diabetic nephropathy
INHIBITORS OF RENIN-ANGIOTENSIN SYSTEM

ACE inhibitors

• Adverse effects
  – Dry cough, wheezing – most common, more in women than men
  – Angioedema
  – Severe hypotension after initial doses
  – Hyperkalemia in patients with renal insufficiency, diabetes, or those taking $K^+$-sparing diuretics or $K^+$-supplements, $\beta$ blockers or NSAIDS
  – Teratogenic effects – fetal hypotension, renal failure, malformations, and death
  – Acute renal failure – especially in patients with renal artery stenosis
ACE inhibitors

• Contraindications
  – Pregnancy
  – Renal artery stenosis

• Drug interaction
  – With NSAIDS – inhibition of antihypertensive action
  – With potassium-sparing diuretics – development of severe hyperkalemia
INHIBITORS OF RENIN-ANGIOTENSIN SYSTEM

Angiotensin II receptor antagonists (all end in – sartan)

• Losartan
• Valsartan
• Candesartan

• Mechanism of action

  – Angiotensin II exerts its effects through \( \text{AT}_1 \) and \( \text{AT}_2 \) subtypes
  – Smooth muscle contraction is mediated by the G protein-coupled \( \text{AT}_1 \) receptors
  – Activation of phospholipase C, formation of \( \text{IP}_3 \) and \( \text{DAG} \)
  – Antagonists in clinical use are competitive antagonists at the \( \text{AT}_1 \)
INHIBITORS OF RENIN-ANGIOTENSIN SYSTEM

AT1 receptor antagonists

- More selectively affect RAS than ACE inhibitors
  - Unlike ACE inhibitors, these agents do not affect bradykinin
  - Chronic use increases circulating levels of Angiotensin II and increase stimulation of AT2
  - Could be beneficial as evidence shows that AT2 activation causes dilation

- Effects
  - BP lowering similar to ACEI
  - Not as beneficial as ACE inhibitors for reversal of ventricular hypertrophy and remodeling
  - More complete inhibition of Angiotensin II activity compared to ACE inhibitors – enzymes other than ACE are capable of angiotensin II generation
INHIBITORS OF RENIN-ANGIOTENSIN SYSTEM

AT1 receptor antagonists

• **Adverse Effects**
  – Less risk of dry cough or angioedema
  – Otherwise similar to ACE inhibitors

• **Contraindications**
  – Renal artery stenosis
  – Pregnancy
INHIBITORS OF RENIN-ANGIOTENSIN SYSTEM

Renin inhibitors – The newest class of antihypertensives

Aliskiren (approved in 2007)

• Inhibit renin conversion of angiotensinogen to angiotensin I and therefore reduce angiotensin II levels

• Rationale for their use: ACE inhibitors and other drugs produce compensatory increases in renin synthesis and activity

• Advantages over other drug classes is unclear

• Side effect profile same as ACE inhibitors