

Antihypertensives

Approaches to Hypertension Treatment

- Inhibit Sympathetic impulses
 - Inhibit contractility
 - Inhibit heart rate
 - Inhibit vasoconstriction
- Inhibit smooth muscle function
- Inhibit RAAS
- Inhibit Renal retention of water

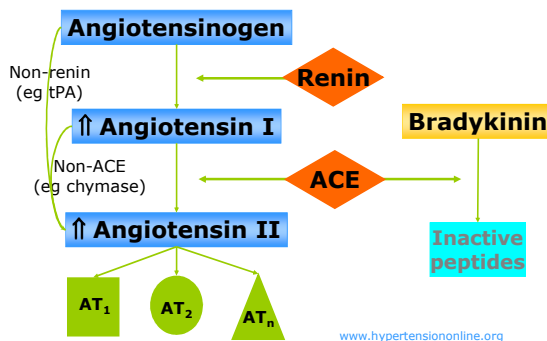
Antihypertensive Classes

- Diuretics – Inhibit Renal Retention
- ACE inhibitors – inhibit RAAS
- Calcium channel blockers – inhibit cardiac and/or arterial muscle constriction
- ARBs – inhibit RAAS
- Beta blockers – inhibit heart sympathetic
- Alpha-1 blockers – inhibit artery sympathet
- Alpha-2 agonist – inhibit both sympathetic
- Direct vasodilators – self explanatory

RAAS Inhibitors

- Renin inhibitors (DRAs)
- Angiotensin Converting Enzyme Inhibitors
- Angiotensin Receptor Blockers
- Aldosterone inhibitors

Renin-Angiotensin Cascade



Angiotensin Receptors

- Type I receptor (AT₁)
 - Vasoconstriction
 - Increased catecholamine release
 - Cardiac and smooth muscle cell proliferation
 - Sodium and fluid retention (through aldosterone)
- Type II receptor (AT₂)
 - Vasodilation
 - Inhibition of muscle cell proliferation
 - Apoptosis

Angiotensin II Receptor Blockers in Heart Failure, www.medscape.com, 2002

ACE Inhibitors

- Action
 - Inhibits Angiotensin II production
 - Inhibits Bradykinin breakdown
- Therapeutic Uses
 - Hypertension
 - Post MI, MI prevention
 - Nephropathy tx and prophylaxis
 - Heart Failure

Pass the Kleenex (Trivia)

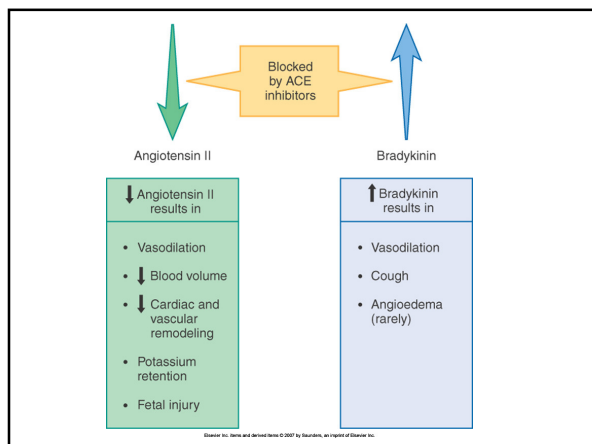
- What's the deal with "tissue ACE"?
 - 90% of ACE is found in or close to tissue
 - Vasculature
 - CNS
 - Adrenal
 - Heart
 - Kidney
 - Lung
 - Reproductive organs
 - Lipid soluble ACE inhibitors are distributed closer to the tissues than water soluble
 - Quinapril, Ramipril, Moexepiril, Benazepril

ACE inhibitor Agents

- Captopril – generic, shorter half-life, no food
- Enalapril – generic, can be given IV
- Lisinopril – generic, does not require activation
- Quinapril – generic
- Benazepril
- Ramipril
- Trandolopril
- Perindopril
- Fosinopril – does not require renal dosing
- Moexipril – no food

Adverse events

- Bradykinin excess
 - Dry persistent cough
 - Angioedema
- First dose hypotension
- Hyperkalemia (suppression of aldosterone)
- Renal Failure (only with renal stenosis)
- Fetal injury

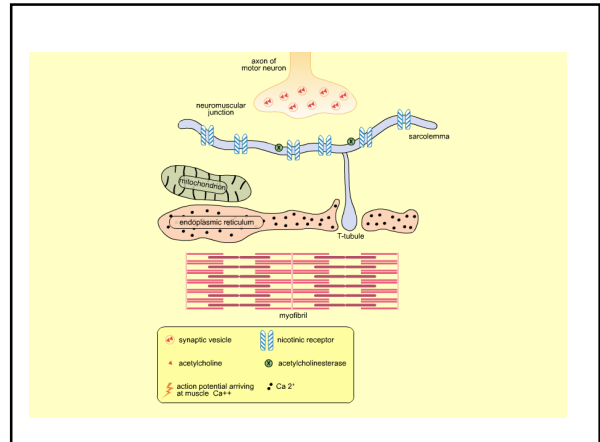


Angiotensin Receptor Blockers

- Instead of blocking Angiotensin production
- Blocks Angiotensin II type 1 (AT1) receptors
- Adverse effects
 - No cough but still may cause angioedema
 - Hyperkalemia (suppression of aldosterone)
 - Renal Failure

Aldosterone Receptor Blocker

- Eplerenone (more expensive, safer, more effective spironolactone)
- Approved for hypertension only
- Adverse events
 - hyperkalemia



Calcium Channel Blockers

- Inhibition of Calcium Channels
 - Arterial SMC: vasodilation
 - SA node: slowing of heart rate (chronotropic)
 - AV node: slowing of conduction (dromotropic)
 - Myocardium: reduction of contractility (inotropic)
- Calcium channels in heart are coupled to beta-1 receptors.

Calcium Channel Blockers

- Dihydropyridines act only on arterial SMC
 - Amlodipine – most popular in U.S.
 - Nifedipine – first (prototype)
- Nondihydropyridines act on arterial SMC and Cardiac calcium channels
 - Verapamil
 - Diltiazem

Nondihydropyridines

- Verapamil and Diltiazem
 - Dilation of arterioles
 - Reduction of heart rate
 - Reduction of AV conduction
 - Reduction of contractility
- Uses
 - Angina pectoris
 - Hypertension
 - Dysrhythmias

Nondihydropyridines

- Adverse Effects
 - Cardiac
 - Bradycardia
 - Partial or complete heart block
 - Non cardiac
 - Constipation
 - Dizziness
 - Edema of ankles and feet
 - Gingival Hyperplasia
- Drug interactions: digoxin and beta blockers

Dihydropyridines

- Effect only arteries at therapeutic doses
- May be used for angina pectoris and HTN
- Adverse effects
 - Hypotension
 - Ankle edema
 - Proteinuria
 - Gingival hyperplasia

Adrenergic Blockers

- Alpha-1 receptors
 - Arteries, bladder, urethra
 - Hypertension
 - BPH
 - Raynaud's Disease
- Adverse effects
 - Orthostatic hypotension
 - Reflex tachycardia
 - Nasal congestion
 - Impotence

Adrenergic Antagonists

- Alpha-1 blockers
 - Prazosin (minipress)
 - Terazosin (hytrin)
 - Doxazosin (cardura)
 - Tamsulosin (flomax)
- Give at night to reduce orthostatic hypotension
- Education Education Education

Beta Blockers

- Inhibition of Beta-1 receptors (heart)
 - Reduction in heart rate
 - Reduced force of contraction
 - Reduced velocity of impulse conduction
- Uses
 - Angina pectoris
 - Hypertension
 - Cardiac dysrhythmias
 - MI
 - Heart Failure
 - Performance anxiety

Beta blockers Adverse Effects

- Bradycardia
- Reduced CO
- Heart Failure
- AV heart block
- Rebound cardiac excitation
- Blunts effects of epinephrine (stress)
- Bronchoconstriction (beta-2 inhibition)
- Decreased glycogenolysis (beta-2 inhibition)

Beta Blocker agents

- Cardioselective vs nonselective
 - Propranolol – non selective
 - Metoprolol – cardioselective
- Fat soluble vs insoluble
 - Atenolol fat insoluble
- Precautions
 - Severe allergy
 - Diabetes

Vasodilators

- Arterial vasodilation
 - Decrease afterload: reducing workload
 - May increase perfusion esp of heart
- Venous (capacitance) vasodilation
 - Reduces venous return
 - Reduces preload → contractility, possibly CO
- Selectivity is important

Vasodilators

- Therapeutic uses
 - HTN
 - Angina pectoris
 - Heart failure
 - MI
 - Shock (Preserve renal perfusion)
- Adverse effects
 - Postural hypotension
 - Reflex tachycardia
 - Expansion of blood volume – combine with diuretic
 - Headache

Vasodilator agents

- Arterial vasodilators
 - Hydralazine
 - Minoxidil
 - Diazoxide
- Venous and arterial
 - Sodium nitroprusside
 - Organic Nitrates
 - Nitroglycerine (SL, IV, Transdermal)
 - Isosorbide dinitrate (PO)

Previously Studied Agents

- Alpha-1 Blockers
 - Prazosin, Terazosin, Doxazosin
- Beta Blockers
 - Propranolol, Metoprolol, Atenolol, Labetalol
- Indirect Adrenergic Antagonists
 - Clonidine, Reserpine

Hypertension Treatment

- Diagnosis
 - Confirm
 - Rule out secondary causes
 - Obtain baseline
 - Assess other risk factors
- Education
 - Disease, Diet, exercise, weightloss, smoking
- Drugs

Hypertension Treatment

- Treating HTN reduces
 - MI by 20 – 25%
 - Stroke 35 – 40%
 - Heart Failure >50%

Hypertension treatment

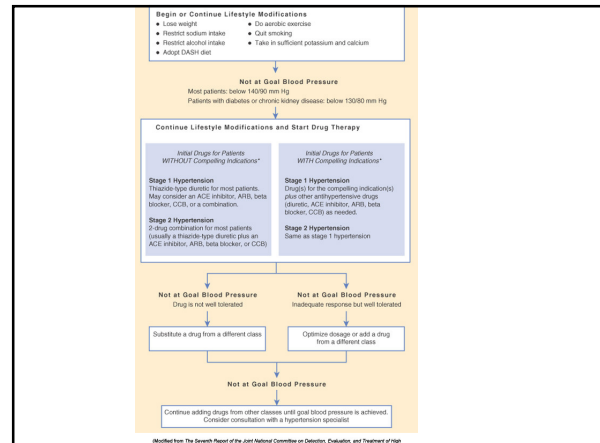
- Lifestyle Treatments
 - Weightloss
 - Sodium restriction
 - DASH Diet
 - Alcohol restriction
 - Exercise
 - Stop smoking
 - Potassium/Calcium intake

Medications

- Approach has changed
- Used to max one then switch or add
- Now use combinations early in lower doses
 - Reduces side effects
 - Attacks multiple pathophysiological mechanisms
- Particularly good combinations
 - Diuretics/beta blockers
 - ACE inhibitors/diuretics
 - ARB/diuretics
 - ACE inhibitors/calcium channel blockers

Special Considerations

- Renal disease: ACE inhibitor and/or ARB
- Diabetes: ACE inhibitor and/or ARB; caution with beta blockers and diuretics
- African Americans: ACE inhibitors less effective (BUT STILL WORK)
- Elderly: isolated systolic hypertension
 - Diuretics and vasodilators work best



Education

- Compliance/Adherence
 - Dizziness
 - Urination
 - Impotence
 - No magic pill
 - Self monitoring