# Cardio-vascular system
# Antihypertensive agents

# BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

**Classification:**

1. **Sympatholytics/sympathoplegic agents/drugs that decrease sympathetic tonus:**

- central: alfa 2 presynaptic agonists and imidazoline I-1 pre-synaptic agonists: **clonidine**, guanfacine, guanabenz, monoxidine, rilmenidine
- pheripheral: guanetidine, reserpine
- alfa-blockers
- beta-blockers
- ganglioblockers

# BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

Classification:

1. Sympatholytics/sympathoplegic agents/drugs that decrease sympathetic tonus:

## 1.1 Central: Clonidine

-half life 8-12 hours; rapid soluble, rapid enters the brain from the circulation
Troches 0.1mg; 0.1-0.2mg/day→0.6mg/day in 2 administrations

**Side effects**: dry mouth, sedation-directly proportional to dose
-withdrawal→life threatening HTA crisis, due to increased sympathetic activity
-to be avoided in patients in treatment with trycyclic antidepressants, or at risk for depression

# BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

1.1 Central
*__Clonidine__
-Indications: all types of HTA, glaucoma and HTA

*__Guanabenz, guaiafacine__-similar to clonidine

*Rilmenidine-selectivity for I receptors-does not produce somnolence, sedation; longer duration→x1/day

# BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

*__Methyldopa__
-analog of L-dopa→alfa-methyldopamine and alfa methylnorepinephrine→replaces norepinephrine in storage vesicles→released by nerve stimulation→false neurotransmitter
-maximum effect in 4-6 hours, effects persists up to 24hours
-**Side effects**: sedation, impaired mental concentration, vertigo, extrapyramidal signs, increased PRL secretion and lactation
-haemolytic anemia, hepatic toxicity, lupus like syndrome
-troches 250mg→250x2/day→max 3g/day

**1.2: Pheripheral**

-**Guanethidine**: it substitutes NA in the storage vesicles and acts like a neurotransmitter, but being completely inactive

-used for HTA 10mgx3/day
-**Reserpine:** troches 0.25mg; inhibits the re uptake of NA in the storage vesicles

# BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

## 1.3 Ganglion blocking agents-trimethaphan

-block nicotinic receptors on postganglionic neurons in both S and PS ganglia
-increase potency, administered only in the hospital under careful supervising of blood pressure
-during surgical intervention, in order to induce hTA
-administered iv, infusion-trimethaphan

# BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

## 1.4 Alpha 1 adrenolytics:

-**non selective**: phentolamine, phenoxybenzamine
-**selective:** prazosin, doxazosin, terazosin-block alpha 1 receptors in arterioles and venules; produce less reflex tachycardia than nonselective ones
-selective-prefered; more efficient when used associated with other antihypertensive drugs
! Reduce arterial pressure by dilating both resistance and capacitance vessels
! Blood pressure is more reduced in the upright than in the supine position
**Prazosin:** troches 1;2 mg: 0.5mg/day, 1 week, increase slowly→3-30mg/day in 2 administrations
**Doxazosin:** half life 22 hours; 1mg/day→4mg/day or more
**Terazosin:** twice a day, 5-20mg; half life 12 hours

# BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

## 1.5 Beta-adrenolytic agents:

**CLASSIFICATION:**

-BETA 1: METOPROLOLUM, BETAXOLOLUM, BISOPROLOLUM, NEBIVOLOLUM, ESOMOLOLUM, ATENOLOLUM
-BETA 1 AND 2: PROPRANOLOLUM
-BETA1, 2 AND ALPHA ADRENOLYTICS: CARVEDILOLUM, LABETALOLUM
-QUINIDINE EFFECT-LOCAL ANESTHETIC: PROPRANOLOLUM, BISOPROLOLUM

**THERAPEUTIC USES:**

-hypertension: by lowering the cardiac output (beta 1 antagonist), low rennin secretion (beta 1 antagonist)

-angina pectoris: by inhibiting all cardiac functions with a lower oxygen necessary

--cardiac arrhythmias-by lowering the cardiac excitability

# BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

## 1.5 Beta-adrenolytic agents:

**PROPRANOLOLUM-troches 10;40mg; vials 1mg*
****METOPROLOLUM TROCHES 25;50;100MG***
****CARVEDILOLUM troches 6.25mg; 12.5; 25mg***
****BISOPROLUM troches 2.5; 5; 10mg***

# BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

2**. Vasodilators**

-direct/MUSCULOTROPIC

-BCCa

**TABLE 11–3 Mechanisms of action of vasodilators.**

| Mechanism | Examples |
|---|---|
| Release of nitric oxide from drug or endothelium | Nitroprusside, hydralazine, nitrates,[1] histamine, acetylcholine |
| Reduction of calcium influx | Verapamil, diltiazem, nifedipine |
| Hyperpolarization of smooth muscle membrane through opening of potassium channels | Minoxidil, diazoxide |
| Activation of dopamine receptors | Fenoldopam |

[1]See Chapter 12.

## BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

### 2.1 Vasodilators-direct (musculotropic)

→arteries: hydralazine, diazoxid, minoxidil
→veins and arteries: nitroprusside

**Hydralazine**
-small arteries vasodilation→ decrease PVR and hTA
-↑by a reflex mechanism renin secretion → disadvantage
-reflex tachycardia, ↑cardiac output
-half life 1.5-3 hours
**Side effects**: tachycardia, palpitations, angina, edema
-headache
-lupus like syndrome-high doses, peripheral neuropathy
-12.5x2/day initially→50-200mg/day in 2-4 administrations
-usually associated with a beta-blocker, in order to antagonize the side effects and prevent auto-limitation of anti-hypertensive effect

# BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

## 2.1 Vasodilators-musculotropic

***Sodium nitroprusside 100mg in 1000ml glucose pev**

-powerful parenteral administered vasodilator, used in hypertensive emergencies as well as severe heart failure

-dilates both arterial and venous vessels→ reduce PVR and venous return

-activates guanylyl-cyclase, either via release of NO or by direct stimulation→ increased intracellular cGMP→ relaxes smooth muscle

**Pharmacokinetics:** rapidly lowers blood pressure and its effects disappear in 1-10 minutes after administration

-iv infusion, in glucose 100mg in 1000mg of glucose-o.5mcg/kg/min→ up to 10mcg/kg/min;

**Toxicity**: accumulation of cyanide: weakness, disorientation, psychosis, muscle spasms, convulsions

-metabolic acidosis, arrhythmias, excessive hypotension and death

-administration of sodium thiosulfate, as a sulfur doner, or hydroxycobalamine

## BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

2.1 **Vasodilators-musculotropic**

***Diazoxid-vials 50mg**

-arterial dilation→ decrease both systolic and diastolic blood pressure
-reflex tachycardia→increase cardiac output
-increases activity of renin
-salt and water retention
-increases blood glucose, probably by diminishing the Insulin release and use of glucose
-relaxes visceral smooth muscles
-after rapid iv injection-low blood pressure in 5 minutes and lats for 4-12 hours

Vials 50mg: ½ vial repeated if needed

* **Nitroglycerine** (Trinitrosan 5/50mg)

# BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

2.2 **Calcium channels blockers**: block calcium influx into voltage dependant channels (slow L)

**Classification:**

*By the chemical structure:

→**dihydropyridine family:** amlodipine, felodipine, isradipine, nicrdipine, nifedipine, nisoldipine

→**benzotiazepines:** diltiazem

→**phenyl-alkyl amines**: verapamil

# BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

2.2 **Calcium channels blockers**: **By the effect:**

- -**mostly phripheral arterial dilators**: dihydropyridines-used for HTA
- -**mostly coronary vasodilators**: diltiazem-used to treat angina
- -**mostly cardiac depressants**: used in arythmias: verapamil

- !!**Affinity order**: Nifedipine: pheripheral arteries>coronaries>>contractile myocardic cells>conductor myocardic tissue
- D: coronaries>periperal arteries>>contractile m>>conductor m
- V: conductor m>contractile m>vessels

## BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

### 2.2 Calcium channels blockers:

***Nifedipine**

-good oral and sublingual absorption (about 90%)

-hepatic metabolisation

**Fd:**

-pheripheral arterial dilation→ decrease PVR and antihypertensive effect

-coronary dilation

-low cardiac depressant effect→low inotropic effect (does not depress sinusal node and AV node)

-reflex tachycardia, consecutive to hTA

**Side effects:**

-ortostatic hTA, cephalalgia, drowsiness, edema (due to vasodilation)

-tachycardia, palpitations

-depression, anxiety

-nausea

# BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

## 2.2 **Calcium channels blockers:**

***Nifedipine**

Indications:

-as antihypertensive drug, in all types of HTA; elective in HTA associated with asthma or coronary disease

-in coronary heart disease

-in heart failure

-troches 10mg; 1 troche x3-4/day

-sublingual 10mg, repeated after 30 minutes, if needed, in emergencies-HTA crisis

# BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

## 3. INHIBITORS OF ANGIOTENSIN

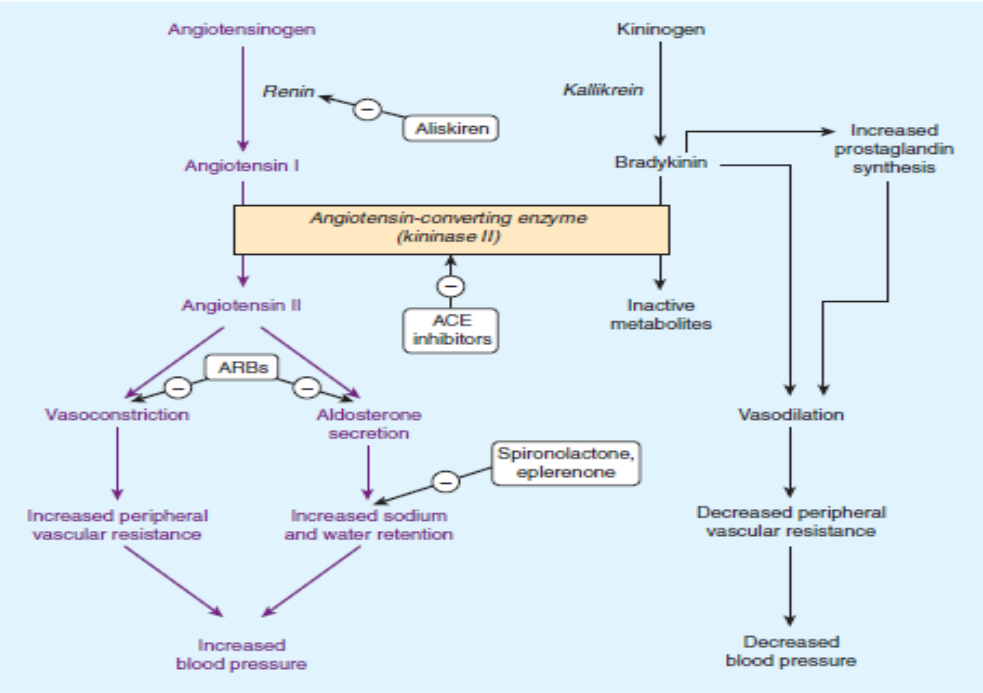


**FIGURE 11–5** Sites of action of drugs that interfere with the renin-angiotensin-aldosterone system. ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers.

# BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

3. **INHIBITORS OF ANGIOTENSIN**

**3.1 ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACE)**

-active drugs: captopril, lisinopril

-prodrug: benazepril, enalapril, fosinopril, moexipril, perindopril, ramipril, quinapril, trandolapril, zofenopril

3.2 **ANGIOTENSIN RECEPTOR-BLOCKING AGENTS**: sarlazina, candesartan, losartan, irbesartan

# BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

## 3. INHIBITORS OF ANGIOTENSIN

### 3.1 ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACE)

-↓ stimulation of angiotensin receptors AT-1,↓sympathetic stimulation and release of CA→arterial dilation with reduced PVR

-↓aldosterone secretion and ↓ water and salt retention

-↑renin secretion (positive feed-back, induced by decrease concentration of AGII), without consequences, due to inhibition of ACE

-ACE act not only on endocrine renin-angiotensin-aldosterone system, but also on paracrine systems from vessels and heart→ reduce hypertrophy of arterial walls and left ventricle

-increase bradikinine secretion, due to similarities between bradikinine and kinase II→stimulation of endogenous PG (PGE2 and PGI2)→vasodilation (flush), allergies

# BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

## 3.1 **ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACE)**

**Side effects:**

-dry mouth, nasal obstruction (due to PG and bradykinin excess)
-taste disturbances
-angioedema
-acute renal failure, especially in people with bilateral renal artery stenosis or stenosis of renal artery of a solitary kidney
-hyperkaliemia-in patients with renal insufficiency or diabetes
-hypotension
-contraindicated during second and third semester of pregnancy because of the risk of fetal hypotension, anuria and renal failure, sometimes associated with fetal malformations and death

**Indications:** especially in HTA with heart failure, chronic renal disease-diminish proteinuria and stabilize renal function (ex.diabetes), after myocardial infarction

# BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

## 3.1 ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACE)

DRUGS:

-Captopril troches 25; 50; 12.5 mg: 12.5-300mg/day

-Enalapril troches 5; 2.5; 10; 20 mg; vials 2.5mg/ml; 5-40mg/day(1-2 administrations)

-Fosinopril 10;20mg: 10-40mg/day (1-2 administrations)

-Perindopril 4; 8mg troches: 2-8mgx1/day

-Ramipril troches 2.5; 5; 10mg; 1.25-10mg/day, 1 administration

# BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

## 3.2 ANGIOTENSIN RECEPTOR-BLOCKING AGENTS

-block AT-1 receptors→block the effects of angiotensin II (cv)

-AT-2 →side effects

N: AT1: vascular smooth muscles, myocardium, brain, kidneys

AT2: medular suprarenalian gland, brain, kidneys, placenta

Activation of AT1 receptors: inhibit renin secretion, release of CA, arterial constriction, secretion of aldosterone, water and salt retention

Activation of AT2: anti-proliferation and reduce growth

**Side effects**: hTA, hiperkaliemia, decrease renal function, bilateral renal artery stenosis

-due to AT2 activation: contraindicated in pregnancy! Alter normal growth and development

# BASIC PHARMACOLOGY OF ANTIHYPERTENSIVE AGENTS

3.2 ANGIOTENSIN RECEPTOR-BLOCKING AGENTS

**DRUGS:**

Candesartan (Atacand): troches 8;16; 32 mg
Irbesartan (Aprovel) troches 150-300mg
Telmisartan=troches 20; 40mg; 80mg
Valsartan: troches 80mg