DRUGS FOR HYPERTENSION

(HIGH BLOOD PRESSURE)

Hypertension

- <20% of cases are due to SECONDARY factors
  - ✓ factors that can be clearly defined and corrected
    - ✧ Pheochromocytoma
    - ✧ Coarctation of the aorta
    - ✧ Renal vascular disease
    - ✧ Adrenal cortical tumors

Hypertension

- Unfortunately, the BARORECEPTOR REFLEX and the RENIN RESPONSE in primary hypertension are reset to maintain the higher blood pressure.
- As a result, they respond to lower blood pressure with compensatory homeostatic responses which may be significant.
- Compensatory mechanisms can be counteracted with:
  - Beta blockers (for tachycardia)
  - Diuretics or angiotensin antagonists (for salt and water retention)

Diuretics – Mechanisms of Action

- Drugs that lower blood pressure by:
  - ✧ reduction of blood volume
  - ✧ depleting the body of sodium

- Some have direct vasodilating effects
- Effective at lowering BP by 10-15 mm Hg
- Provide adequate treatment for MILD or MODERATE essential hypertension

Diuretics - Thiazides

- Thiazides
  - Adequate in mild hypertension
  - When given, the maximum antihypertensive effect is often achieved with doses lower than those required for the maximum diuretic effect.

Diuretics - Thiazides

❑MECHANISM OF ACTION

- ✧ Act mainly on proximal part of convoluted tubule
- ✧ Sodium excretion and urine volume are increased by interference with transfer across cell membranes which results on reduced in blood volume
- ✧ However, changes in cardiac output and extracellular fluid volume are transient and, in the long-term, the major haemodynamic effect is a reduction in peripheral resistance due to subtle alterations in the contractile responses of vascular smooth muscle.

Diuretics - Thiazides

- PHARMACOKINETICS
  - Well-absorbed orally
  - Widely distributed
  - subject to a variable degree of hepatic metabolism
  - The effect on the kidney depends upon excretion into the renal tubule; efficacy falls with increasing renal impairment.

ADVERSE EFFECTS OF THIAZIDES-1

Initially, they were used at high doses which caused a high incidence of adverse effects. Lower doses now used cause fewer adverse effects. Among them are:

- **HYPOKALEMIA**
- **DEHYDRATION** (particularly in the elderly) leading to POSTURAL HYPOTENSION
- **HYPERGLYCEMIA** possibly because of impaired insulin release secondary to hypokalemia
- **HYPERURICEMIA** because thiazides compete with urate for tubular secretion

ADVERSE EFFECTS OF THIAZIDES-3

Less common problems

- **HYPERSENSITIVITY** - may manifest as interstitial nephritis, pancreatitis, rashes, blood dyscrasias (all very rare)
- **METABOLIC ALKALOSIS** due to increased sodium load at the distal convoluted tubule which stimulates the sodium/hydrogen exchanger to reabsorb sodium and excrete hydrogen
- **HYPERCALCEMIA**

Sympathoplegics-Mechanisms of Action

- Drugs that interfere with sympathetic (SANS) control of cardiovascular function
- Reduces:
  - Venous tone
  - Heart rate
  - Contractile force of the heart
  - Cardiac output
  - Total peripheral resistance

Sympathoplegics-Mechanisms of Action

1. Centrally acting Sympathoplegic Drugs
2. Ganglion-blocking agents
3. Adrenergic Neuron-Blocking Agents
4. Andrenoreceptor Antagonists
    a. Alpha
    b. Beta
5. Inhibitors of Angiotensin

Sympathoplegics-
Centrally acting Sympathoplegic Drugs

❑Mechanism of Action

✧These agents reduce sympathetic outflow from vasopressor centers in the brainstem but allow these centers retain or even increase their sensitivity to baroreceptor control

✧Antihypertensive and toxic actions of these drug are generally less dependent on posture than are the effects of drugs that act directly on peripheral sympathetic neurons

Sympathoplegics-
Centrally acting Sympathoplegic Drugs

- **METHYLDOPA**
  - Useful in treatment of mild to moderately severe hypertension
  - Lowers blood pressure chiefly by reducing peripheral vascular resistance with a variable reduction in heart rate and cardiac output

Sympathoplegics-
Centrally acting Sympathoplegic Drugs

❑METHYLDOPA- Pharmacokinetics

- ✧Enters the brain via an aromatic amino acid transporter
- ✧Usual oral dose produces its maximal antihypertensive effect in 4-6 hours, effect can persist for up to 24 hours
- ✧Because effect depends on accumulation and storage of a metabolite (alpha-methylnorepinephrine) in the vesicles of nerve endings, the action persists after the parent drug has disappeared from the circulation

Sympathoplegics-
Centrally acting Sympathoplegic Drugs

- **METHYLDOPA**- Adverse Effect/Toxicity
  - ✧Overt sedation = most frequent undesirable effect
  - ✧Persistent mental lassitude and impaired mental concentration (long-term therapy)
  - ✧Nightmares,mental depression,vertigo and extra pyramidal signs (occur relatively infrequent)
  - ✧Lactation (increased prolactin secretion) both in men and women

Sympathoplegics-
Centrally acting Sympathoplegic Drugs

- **METHYLDOPA**- Adverse Effect/Toxicity
  - Sudden discontinuance causes REBOUND HYPERTENSION (may be severe)
  - Occasionally causes HEMATOLOGIC IMMUNOTOXICITY and in some patients HEMOLYTIC ANEMIA
  - May cause SEDATION
  - Toxicity is mediated by inhibition of dopaminergic mechanisms in the hypothalamus

Sympathoplegics-
Ganglion-Blocking Agents

❑Mechanism of Action

✧Competitively block nicotinic cholinoreceptors on postganglionic neurons in both sympathetic and parasympathetic ganglia

✧May directly block the nicotinic acetylcholine channel in the same fashion as neuromascular nicotinic blockers

Sympathoplegics-
Adrenergic Neuron-Blocking Agents

- **Guanethidine** - Mechanism and Sites of Action
  - ✧Inhibits the release of norepinephrine from sympathetic nerve endings
  - ✧Transported across the sympathetic nerve membrane by the same mechanism that transports norepinephrine itself (NET, uptake 1) and uptake is essential for drug's action
  - ✧Once it has entered the nerve, it replaces norepinephrine = gradual depletion of norepinephrine stores in nerve endings

Sympathoplegics-
Adrenergic Neuron-Blocking Agents

- **Guanethidine** - Mechanism and Sites of Action
  - Hypotensive action early in the course of therapy is associated with reduced cardiac output due to BRADYCARDIA and RELAXATION of CAPACITANCE VESSELS

Sympathoplegics-
Adrenergic Neuron-Blocking Agents

Guanethidine – Adverse effects

- Postural hypotension
- Hypotension following exercise
- Decreased blood flow to the heart and brain or OVERT SHOCK
- Delayed or retrograde ejaculation
- Diarrhea (increased GI motility due to parasympathetic predominance on controlling the activity of intestinal smooth muscle)

Sympathoplegics-
Adrenoreceptor Antagonists (BETA)

❑Propanolol

- ✧1st Beta blocker to be effective in hypertension and ischemic heart dsx
- ✧Used heavily in the treatment of hypertension

Sympathoplegics- Adrenoreceptor Antagonists

- **Propanolol** - Mechanism and Sites of Action
  - ✧Decreases BP as a result of a decrease cardiac output
  - ✧Inhibits stimulation of renin production by catecholamines
  - ✧It is likely that its effect is due in part to depression of the renin-angiotensin-aldosterone system

Sympathoplegics-
Adrenoreceptor Antagonists (ALPHA)

Prazosin – Mechanism of Action

- Selectively blocks alpha receptors in arterioles and venules
- Produce less reflex tachycardia when lowering BP than nonselective alpha-antagonists
- Alpha blockers reduce arterial pressure by dilating both resistance and capacitance vessels
- BP reduced more in upright than in supine position
- Salt and water retention occurs if administered without diuretics
- More effective in combination with other agents such as beta-blocker and a diuretic

Sympathoplegics-
Adrenoreceptor Antagonists (ALPHA)

- **Prazosin** - Adverse Effects
  - Dizziness
  - Palpitations
  - Headache
  - Lassitude
  - ORTHOSTATIC HYPOTENSION

Vasodilators

- Drugs that dilate blood vessels by acting directly on smooth muscle cells through nonautonomic mechanisms
- Compensatory responses: SALT RETENTION and TACHYCARDIA
- Four major mechanisms
    1. release of nitric oxide
    2. opening of Potassium channels (leads to hyperpolarization)
    3. blockade of calcium channels
    4. activation of D_1 dopamine receptors

Vasodilators

Mechanism of Smooth Muscle Relaxation	Examples
Release of nitric oxide from drug or endothelium	Nitroprusside
Hyperpolarization of vascular smooth muscle through opening of potassium channels	Diazoxide
Reduction of calcium influx via L-type channels	Verapamil
Activation of dopamine D_1 receptors	Fenoldopam

Vasodilators

Hydralazine

- Dilate arterioles but not veins
- Orally active
- suitable for chronic therapy
- Acts through the release of nitric oxide from endothelial cells
- Rarely used at high dosage because of its toxicity (limited efficacy)
- Uses: 1) Moderate hypertension when 1st line fails - with beta-blockers and diuretics
  2) Hypertension in Pregnancy

Vasodilators

Hydralazine -Pharmacokinetics&Dosage

- Well-absorbed and rapidly metabolized by the liver during first-pass metabolism so bioavailability is low (ave. 25%) variable among individuals
- Half-life ranges from 1.5 to 3 hours
- Vascular effect persist longer than do blood concentrations possible due to avid binding to vascular tissue
- Usual dosage ranges 40 mg/d to 200 mg/d
- Higher doses = greater vasodilation
- Dosing two to three times daily provides smooth control of blood pressure