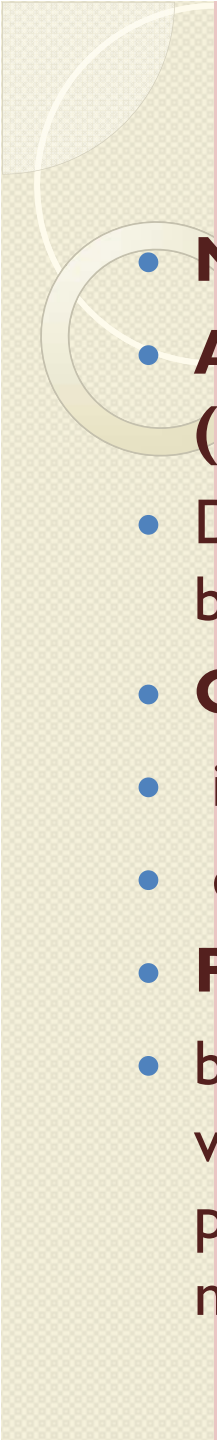




# DRUG THERAPY OF HYPERTENSION

- 
- **Most common cardiovascular disease.**
  - **Arterial Pressure** is the product of **cardiac output (C.O.)** and **peripheral vascular resistance (P.V.R.)**.
  - Drugs lower pressure by actions on either P.V.R or C.O. or both.
  - **C.O. may be reduced by –**
    - inhibiting myocardial contractility or
    - decreasing ventricular filling pressure
  - **P.V.R. may be reduced –**
    - by acting on smooth muscle to cause relaxation of resistance vessels or by interfering with the activity of systems that produce constriction of resistance vessels e.g. sympathetic nervous system.

# Blood Pressure Regulation

- At four levels-
  1. Resistance Arterioles
  2. Capacitance venules
  3. Heart
  4. Kidney

Baroreflexes , mediated by autonomic nerves, act in combination with humoral mechanisms ,including **Renin-angiotensin-aldosterone system** to coordinate functions at these four control sites & to maintain normal blood pressure.

Vasoactive substances – endothelin-1, Nitric oxide

Also involved.

# HYPERTENSION

## JNC 7 GUIDELINES & C/F

- **NORMAL** SYSTOLIC B.P. < 120mmHg,
- DIASTOLIC B.P. < 80mm
- **PREHYPERTENSION**        SBP 120-139, DBP 80-89
- **STAGE I HT**                    SBP 140-159 , DBP 90-99
- **STAGE II HT**                    SBP > 160 , DBP > 100
  
- **BP  $\geq$  140/90 - HYPERTENSION**

- 
- NO OBVIOUS CAUSATIVE FACTOR –  
**ESSENTIAL HYPERTENSION\***

- **SECONDARY HYPERTENSION –**  
PHEOCHROMOCYTOMA  
RENAL ARTERY STENOSIS  
COARCTATION OF AORTA  
CUSHING SYNDROME  
PRIMARY ALDOSTERONISM


- \* Based on a myth.

## **A COMBINATION OF ABNORMALITIES-**

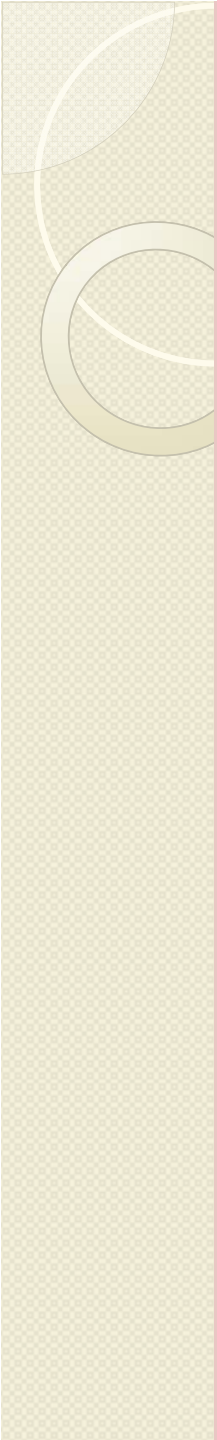
- GENETIC INHERITANCE
- PSYCHOLOGIC STRESS
- ENVIRONMENTAL & DIETARY FACTORS -
- INCREASED SALT
- DECREASED POTASSIUM ,CALCIUM

# WHY TO TREAT

- **CAN LEAD TO –**
- **STROKE**
- **DISEASES OF CORONARY ARTERIES WITH MYOCARDIAL INFARCTION AND SUDDEN CARDIAC DEATH**
- **CARDIAC FAILURE**
- **RENAL INSUFFICIENCY**
- **DISSECTING ANEURYSM OF AORTA**


- 
- Risk of damage to kidney, heart & brain directly related to the extent of blood pressure elevation.
  - Starting at 115/75 mm Hg ,CVS risk doubles at every 20/10mm increase.
  - Both Systolic & diastolic hypertension are associated with end organ damage.
  - Isolated systolic hypertension also risky.



- 
- **SBP  $\geq$  210 mm Hg**
  - **DBP  $\geq$  120 mm Hg**
  - **FULMINANT ARTERIOLOPATHY**
    - ENDOTHELIAL INJURY
    - INTIMAL THICKENING
    - ARTERIOLAR OCCLUSION
  - IT IS PATHOLOGICAL BASIS OF SYNDROME OF **MALIGNANT HYPERTENSION** A/W -
  - RAPIDLY PROGRESSIVE MICROVASCULAR OCCLUSIVE DISEASE IN THE KIDNEY (RENAL FAILURE)
  - BRAIN ( HYPERTENSIVE ENCEPHALOPATHY)
  - RETINA ( HAEMORRHAGES ,EXUDATES, DISCEDEMA)
  - MICROANGIOPATHIC HAEMOLYTIC ANEMIA

# MANAGEMENT

- **NON-PHARMACOLOGICAL MEASURES**
  - **LIFE-STYLE MODIFICATIONS --**
  - **RELIEF OF STRESS-** EMOTIONAL , ENVIRONMENTAL
  - **DIETARY MANAGEMENT-**
  - DECREASE SODIUM INTAKE- MILD SALT RESTRICTION ,UPTO 5 g .(In moderate to severe –salt restriction upto 2g)
  - INCREASE K<sup>+</sup> OR CALCIUM INTAKE
  - CALORIC RESTRICTION – DECREASE IN WEIGHT
  - DECREASE INTAKE OF CHOLESTEROL RICH DIET & SATURATED FATS – DECREASE INCIDENCE OF ARTERIAL SCLEROSIS
  - DECREASE ALCOHOL INTAKE
  - STOP SMOKING

- 
- **REGULAR EXERCISE WITHIN LIMITS**
  - **CONTROL OF OTHER RISK FACTORS  
OR DISEASES CONTRIBUTING TO  
DEVELOPMENT OF ARTERIOSCLEROSIS**  
e.g. **DIABETES**

# CLASSIFICATION

- Drugs that alter sodium & water balance
- **Diuretics** –
  - Thiazides : Hydrochlorothiazide  
Chlorthalidone  
Indapamide
  - High Ceiling : Frusemide
  - Potassium sparing : Spironolactone  
Triamterene  
Amiloride

## **C/F contd.**

### **Drugs that alter sympathetic nervous system function**

#### **Central Sympatholytics –**

Clonidine , Methyldopa

#### **Ganglionic blocking agents –**

Trimethaphan

#### **Adrenergic Neuron-blocking Agents –**

Guanethidine, Guanadrel

#### **Beta-Adrenergic Antagonists –**

Propranolol , Metoprolol

#### **Alpha adrenergic antagonists –**

Prazosin, Terazosin, Doxazosin, Phenoxybenzamine,  
Phentolamine

#### **Mixed Adrenergic Antagonists –**

Labetalol, Carvedilol



## C/F contd.

- **CALCIUM CHANNEL BLOCKERS -**

Dihydropyridines

Phenylalkylamines

Benzothiazepines

## C/F contd.

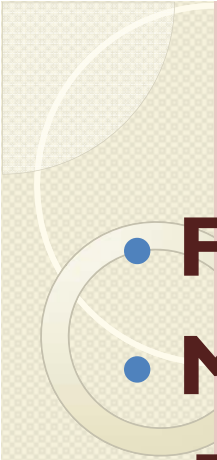
- **INHIBITORS OF ANGIOTENSIN**
- **Angiotensin Converting Enzyme Inhibitors**
- Captopril, Enalapril , Lisinopril, Ramipril  
Perindopril
- **Angiotensin Receptor Blocking Agents**
- Losartan, Valsartan, Irbesartan, Telmisartan  
Candesartan



# THIAZIDES

- Most commonly used diuretics in uncomplicated hypertension.
- Initially decrease in BP by decreasing blood volume and cardiac output.
- Compensatory mechanisms operate to almost regain sodium balance and plasma volume.
- C.O. is restored after 6-8 wks, P.R. decreases.

- **Slow reduction in t.p.r.**
- **Small persisting sodium & Volume deficit**
- **Decrease in intracellular sodium conc. in vascular smooth muscle**
- **Decrease in stiffness of vessel wall  
(Sod. Increases stiffness)**
- **Increased compliance**
- **Decreased responsiveness to constrictor stimuli (NA ,Angiotensin II)**
- **SALT RESTRICTION – SIMILAR EFFECT**
- **HIGH SALT INTAKE – ANTIHYPERTENSIVE ACTION OF DIURETIC LOST**

- 
- **FALL IN BP DEVELOPS GRADUALLY**
  - **MILD ANTI - HYPERTENSIVES, BUT POTENTIATE ALL OTHER ANTI-HT**
  - **PREVENT DEVELOPMENT OF TOLERANCE -**

**TO VASODILATORS BY NOT ALLOWING EXPANSION OF PLASMA VOLUME.**

- **GOOD FOR ELDERLY, FOR ISOLATED SYSTOLIC HYPERTENSION**

# **P/K**

- **GIVEN ORALLY**
- **LEAD TO DISTURBANCES IN ELECTROLYTE BALANCE**
- **DECREASED BLOOD LEVEL OF POTASSIUM AND MAGNESSIUM**
- **CALCIUM RETAINED , BLOOD LEVEL OF CALCIUM INCREASED**

# Low dose of thiazides

- 12.5 – 25 mg hydrochlorothiazide alone or with potassium sparing diuretic
- low dose thiazide is preferred because -
- **Problems with 50 mg –**
- Hypokalemia
- Carbohydrate intolerance
- Dyslipidemia
- Hyperuricemia
- Sudden cardiac death – torsades de pointes, ischemic ventricular fibrillation, pptd. by hypokalemia .



- **Low dose –**

- Little fall in serum potassium
- No incidence of arrhythmia
- No impairment of glucose tolerance
- No increase in serum cholesterol over long term.
- **HIGH DOSES OF THIAZIDE OR LOOP DIURETIC USED WHEN POTENT VASODILATORS / SYMPATHOLYTICS HAVE INDUCED FLUID RETENTION.**

# LOOP DIURETICS

- ACT FAST
- **INDICATED IN HT WHEN -**
- IT IS COMPLICATED BY POOR RENAL FUNCTION
- PATIENTS WHO HAVE NOT RESPONDED TO THIAZIDES
- CO-EXISTING REFRACTORY CHF

- CAUSE DECREASED RENAL VASCULAR RESISTANCE
- INCREASED RENAL BLOOD FLOW
- **DISADVANTAGES –**
- STRONG DIURETIC BUT WEAKER ANTI-HT THAN THIAZIDE.
- BRIEF DURATION OF ACTION ; 4-6 HRS.
- FALL IN BP DUE TO DECREASE IN PLASMA VOLUME.
- MAY NOT MAINTAIN SODIUM DEFICIENT STATE ROUND THE CLOCK.
- MORE FLUID AND ELECTROLYTE IMBALANCE, WEAKNESS AND OTHER SIDE EFFECTS.



# CENTRAL SYMATHOLYTICS

## CLONIDINE

- Stimulates-  $\alpha$ -2a receptors (autoreceptors) in the brainstem - Decreases sympathetic outflow.
- Leads to fall in B.P. & H.R.
- **Rapid i.v. clonidine** – stimulates peripheral  $\alpha$ -2b receptors at high conc.
- Transient increase in B.P.
- Given Orally, only decrease in BP

# Clonidine

- **Therapeutic Window Phenomenon-**
- 0.2 – 2.0 ng/ml – optimum lowering of BP.
- At higher conc, fall in BP is less marked.
- Useful in mild to moderate HT.
- Used in combination with a diuretic in patients who haven't responded to diuretic alone.

# USES

- **MODERATE HYPERTENSION** – COMBINED WITH A DIURETIC.
- **OPIOID WITHDRAWL-** OPIOID &  $\alpha$ -2 receptors CONVERGE ON THE SAME EFFECTOR SYSTEM.
- **FACILITATES ALCOHOL WITHDRAWL & SMOKING CESSATION.**
- **ANALGESIC ACTIVITY-** POST-OP ANALGESIA & INTRA-THECAL/EPIDURAL SURGICAL ANALGESIA.
- **DIARRHOEA DUE TO DIABETIC NEUROPATHY.**
- **PRE-OPERATIVELY-** INCREASES CVS STABILITY.

## S/Es

- Sedation
- Mental Depression
- Disturbed Sleep
- Dryness of mouth, nose, eyes
- Constipation
- Salt and water retention
- Bradycardia
- Postural HT
- **Alarming rise in BP-** A patient taking  $>300\mu\text{g}/\text{day}$  ,
- If Suddenly withdraws or misses one or two doses
- Restlessness , Tachycardia , anxiety , Sweating, Headache, Nausea & vomiting .

## Rise in BP due to

- Sudden removal of central sympathetic inhibition –
- release of large quantities of stored Catecholamines.
- Supersensitivity of peripheral adrenergic structures to catecholamines,  
(chronic reduction of sympathetic tone during clonidine therapy)

# **METHYL DOPA**

## **ALPHA- METHYL DOPA**

| aromatic L-aminoacid decarboxylase

## **ALPHA-METHYL DOPAMINE**

| dopamine beta-oxidase

## **ALPHA-METHYL NOREPINEPHRINE**

REPLACES NOR-EPINEPHRINE IN NEUROSECRETORY VESICLES

ACTS IN CNS TO INHIBIT ADRENERGIC NEURONAL OUTFLOW FROM BRAINSTEM

ACTS AS AN AGONIST AT PRESYNAPTIC ALPHA-2 RECEPTOR

DECREASES NE RELEASE

REDUCES OUTPUT OF VASOCONSTRICTOR ADREN. SIGNALS

DECREASES BP.

- SAFE IN PREGNANCY
- **S/Es** – Sedation on starting
- With long term – persistent lassitude & impaired mental conc.
- Nightmares , mental depression , vertigo , extra-pyramidal signs.
- Lactation
- Hemolytic anemia , hepatitis , drug fever