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 co-ordinate functions at these four control sites & to maintain normal blood pressure.

Vasoactive substances – endothelin-1,Nitic 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 ≥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≥ 210 mm Hg**
- **DBP≥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^+ 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 : Hydrochlorthiazide
  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, Terazocin, Doxazocin, 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 hydrochlorthiazide 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
- **DISADANTAGES –**
- 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- α-2a receptors (autoreceptors) in the brainstem - Decreases sympathetic outflow.
- Leads to fall in B.P. & H.R.
- **Rapid i.v. clonidine** – stimulates peripheral α-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 & α-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 >300µg/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