CHAPTER-IV

Pharmacology of Hypertension
Drugs and their dosage forms
Introduction

Hypertension means high blood pressure or systolic blood pressure which is consistently 140 mmHg (systolic is the "top" number of blood pressure measurement, which represents the pressure generated when the heart beats). Diastolic blood pressure is consistently 90 mmHg (diastolic is the "bottom" number of blood pressure measurement, which represents the pressure in the vessels when the heart is at rest). Either or both of these numbers may be too high.

Pre-hypertension is when your systolic blood pressure is between 120 and 139 mm or your diastolic blood pressure is between 80 and 89 mm on multiple readings. The reference norm is 140/90 mmHg. One has pre-hypertension, he is likely to develop high blood pressure at some point. Therefore, the doctor will recommend lifestyle changes to bring your blood pressure down to normal range. About 70 million Americans possess blood pressures above normal, which corresponds to a systolic blood pressure of 140 mmHg or a diastolic pressure of 90 mmHg. Two thirds of these individuals are aware of their diagnosis; however, somewhat less than half (45%) receive treatment and only about a third receive treatment sufficient to lower their blood pressure to at least the reference norm of 140/90 mmHg.1

Hypertension increases with age and appears more likely to occur in blacks compared to whites. Two of the major complications of hypertension, stroke and coronary vascular disease, can be lethal; however, these complications have, over the past 30 years, exhibited reduced frequency (about 50% less common).2 Unfortunately, this decline in frequency appears to have leveled off; by the increase in heart failure and end-stage renal disease, also complications of hypertension.2 Although the common focus on systolic and diastolic blood pressure remains important, for those individuals over 50 years old cardiovascular complications appear better predicted by systolic pressure and pulse
pressure compared to diastolic pressure. Generally, a single reading above the 140/90 mmHg threshold is not considered sufficient for a definitive diagnosis of hypertension.

However, there are exceptions to this rule. For example, sometimes patients present with hypertension with clear evidence of life-threatening, end-organ damage. In other cases, a blood pressure reading of >220/125 mmHg defines hypertensive urgency even if life-threatening end-organ damage is not apparent. Most of the times, hypertension is a diagnosis defined by repetitive blood pressure measurements, given that readings can be variable and patients exhibiting higher readings are the individuals most likely to exhibit blood pressure readings transitioning towards normal upon repetitive examinations.

Depending on the initial blood pressure value, excessive delay in establishing a diagnosis does carry some risk. In high-risk individuals even a three-month delay in initiating treatment may correspond to a 200% increase in cardiovascular morbidity/mortality.

Antihypertensive Drugs are classified into five types. They are diuretics, sympatholytics, vasodilatators, calcium channel blockers and angiotensin converting enzyme inhibitors.

Diuretics:

As noted above, there are three principal types of diuretics: the thiazide agents, examples of which include chlorthalidone and the prototypical agent chlorothiazide / hydrochlorothiazide; the loop diuretics such as furosemide, bumetanide, torsemide and ethacrynic acid. Finally the K⁺ sparing agents such as amiloride, triamterene and spiro lactone. At least as a premise, the use of diuretics represents an extension of the idea of hypertension management by limitation of sodium ingested in diet. The thiazides as a group are effective diuretics and also improve the action of other antihypertensive drugs. Clinical trials have demonstrated that diuretics continue to be central for management of
the hypertensive patient\textsuperscript{2,3}. Although the initial hypotensive effects of thiazide diuretics may be explained by the reduced extra cellular volume resulting in reduced cardiac output. Hypotensive effects, however, remains on following normalization of cardiac output. The mechanism is most likely a reduction in systemic vascular resistance\textsuperscript{1}. The diuretics are classified as thiazides and loop diuretics.

**Thiazides:**

Some important thiazide are hydrochlorothiazide, chlorothiazide, indapamide and metolazone. The thiazides act in the distal tubule to decrease sodium reabsorption (inhibits Na/Cl transporter). As a result of decreased sodium and chloride reabsorption, a hyperosmolar diuresis ensues. Delivery of more sodium to the distal tubule results in potassium loss by an exchange mechanism. Thiazides also promote calcium reabsorption, in contrast to loop diuretics. The initial decrease in blood volume followed by a longer-termed reduction in vascular resistance appear to account for the hypotensive effects of the thiazides.

**Loop diuretics:**

Bumetanide, Ethacrynic acid, Furosemide, bumetanide and ethacrynic acid are high-ceiling loop diuretics acting primarily at the ascending limb of the loop of Henle. The effectiveness of these agents is related to their site of action because reabsorption of about 30 - 40\% of the filtered sodium and chloride load occurs at the ascending loop. Distal sites are not able to compensate completely for this magnitude of reduction of NaCl reabsorption. Loop diuretics increase urinary Ca\textsuperscript{2+} in contrast to the action of thiazides. Loop diuretics also increase renal blood flow by decreasing renal vascular resistance. These drugs are rarely used in the management of hypertension because of their short duration of action and the availability of better drugs.
**Sympathetic:**

This category consists of three types of drugs namely centrally active drugs, adrenergic neuron blocker and adrenoceptor antagonists.

**Clonidine:** is an antihypertension drug which acts on the brain, inhibiting adrenergic outflow from the brainstem. Inhibition of sympathetic outflow results in a decrease in blood pressure.

**Mechanism of action:** Centrally acting selective $a_2$ adrenergic agonist is especially effective in management of severe hypertension or in renin-dependent hypertension. Transdermal clonidine patch is useful for surgical patients unable to take oral formulation. Clonidine reduces cardiac output (by reducing both stroke volume and heart rate) and peripheral resistance. Reduction in stroke volume occurs due to increased venous pooling (decreased preload). Clonidine does not interfere with cardiovascular responses to exercise. Renal blood flow and function is maintained during clonidine treatment. Clonidine has minimal or no effect on plasma lipids.

**Guanethidine:**

Guanethidine is an adrenergic neuron blocker which inhibits the function of postganglionic adrenergic neurons, thus inhibiting sympathetic function. Guanethidine uses the norepinephrine (N.E.) re-uptake transporter to reach its site of action, the neurosecretory vesicles. Guanethidine replaces norepinephrine in the vesicle and is released instead of the normal transmitter. Guanethidine is an inactive transmitter and the replacement of N.E. by an inactive agent is responsible for its antihypertensive effects (maintenance dosing). Adrenergic blockade by guanethidine results in post-synaptic supersensitivity. Sympathetic blockade by guanethidine produces, venodilatation
reduction in cardiac output due to inhibition of cardiac sympathetic innervation blockade of the sympathetic reflex arteriolar response to the reduction in cardiac output.

**Labetalol:**

Labetalol is a competitive antagonist at both $\alpha_1$ and $\beta_1$-adrenergic receptors. It also has an intrinsic sympathomimetic effect at $\beta_2$ receptors. Antihypertensive effects of labetalol results from actions at both $\alpha_1$ and $\beta_1$-adrenergic receptors. $\alpha_1$ receptor blockade results in vasodilatation which is further enhanced by $\beta_2$ receptor activation. A reduction in heart rate is mediated by $\beta_1$ receptor antagonism. Labetalol does not alter serum lipids.

**Vasodilators:**

Vasodilators used for treatment of management of hypertension. It is administered by a continuously variable rate i.v. infusion pump. It is a nitrovasodilator metabolized by smooth muscle cells to nitric oxide which dilates both arterioles and venules. The mechanism of action involves activation of ATP-sensitive potassium channels, hyperpolarization of arteriolar smooth muscle, relaxation and dilation. Adverse effects include salt and water retention and hyperglycemia. Diazoxide inhibits insulin release.

**Calcium channel blockers:**

Calcium channel blockers are effective in treating hypertension because they reduce peripheral resistance. These are two types. They are dihydropyridines and non dihydropyrimines.

**Amlodipine:**

Amlodipine has relatively little effect on reducing myocardial contractility compared to verapamil or diltiazem. Arteriolar vascular tone depends on free intracellular $\text{Ca}^{2+}$ concentration. Calcium channel blockers reduce transmembrane movement of $\text{Ca}^{2+}$ reducing the amount reaching intracellular sites and therefore reduce vascular smooth
muscle tone. All calcium channel blocks appear similarly effective for management of mild to moderate hypertension, for low-renin hypertensive patients (elderly and African-American groups). Ca$^{2+}$ channel blockers appear good choices for monotherapy (single drug) control.

**Angiotensin Converting Enzyme Inhibitors:**

Angiotensin II, a potent vasoconstrictor, is produced by the action of angiotensin converting enzyme (ACE) on the substrate angiotensin I. Angiotensin II activity produces a rapid pressor response a slow pressor response and vascular and cardiac hypertrophy and remodeling. Antihypertensive effects of ACE inhibitors are due to the reduction in the amount of angiotensin II produced.

ACE inhibitors are efficacious in management of hypertension and have a favorable side effect profile. ACE inhibitor are advantageous in management of diabetic patients by reducing the development of diabetic neuropathy and glomerulosclerosis. ACE inhibitor are probably the antihypertensive drug of choice in treatment of hypertensive patient who have hypertrophic left ventricles.

Hypertensive patients who have ischemic heart disease with impaired left ventricular function also benefit from ACE inhibitor treatment. ACE inhibitors reduce the normal aldosterone response to sodium loss (normally aldosterone opposes diuretic-induced sodium loss). Therefore, the use of ACE inhibitors enhance the efficacy of diuretic treatment, allowing the use of lower diuretic dosages and improving control of hypertension. If diuretics are administered at higher dosages in combination with ACE inhibitors significant and undesirable hypotensive reactions can occur with attendant excessive sodium loss. Reduction in aldosterone production by ACE inhibitors also affects potassium levels.
The tendency is for potassium retention, which may be serious in patients with renal disease or if the patient is also taking potassium sparing diuretics, nonsteroidal anti-inflammatory agents or potassium supplements.

**Angiotensin II: Effects**

- **Change in Peripheral Resistance**
  - Direct Vasoconstriction
  - Sympathetic Discharge
  - Adrenal Medullary Catecholamine Release
  - Noradrenergic Enhancement
    - (1) decreased reuptake
    - (2) increased release
    - (3) increased vascular responsiveness

- **Change in Renal Function**
  - Sodium Reabsorption (direct and aldosterone mediated)
  - Direct renin vasoconstriction
  - Noradrenergic transmission
  - Renal sympathetic tone

- **Rapid Pressor Response**
- **Slow Pressor Response**

- **Structural Changes Remodeling**
  - Proto-oncogene expression
  - Growth Factors
  - Afterload
  - Wall Tension

- **Vascular and Cardiac Hypertrophy & Remodeling**
References:

