CHAPTER 8

ANTIHYPERTENSIVE DRUGS

Classification

1. Diuretics.
2. Beta adrenergic blockers.
3. Calcium channel blockers.
5. Angiotensin receptor blockers.
7. Direct arterial vasodilators.

1. Diuretics

Types

• Thiazides and related diuretics.
• Loop diuretics.
• Potassium sparing diuretics.

Mechanism of Action

• Initial effects: through reduction of plasma volume and cardiac output.
• Long term effect: through decrease in total peripheral vascular resistance.

Advantages

• Documented reduction in cardiovascular morbidity and mortality.
• Least expensive antihypertensive drugs.
• Best drug for treatment of systolic hypertension and for hypertension in the elderly.
• Can be combined with all other antihypertensive drugs to produce synergetic effect.

Side Effects

• Metabolic effects (uncommon with small doses): hypokalemia, hypomagnesemia, hyponatremia, hyperuricemia, dyslipidemia (increased total and LDL cholesterol), impaired glucose tolerance, and hypercalcemia (with thiazides).
• Postural hypotension.
• Impotence in up to 22% of patients.

Practical Considerations

• Moderate salt restriction is the key for effective antihypertensive effect of diuretics and for protection from diuretic-induced hypokalaemia.
• Thiazides are not effective in patients with renal failure (serum creatinine > 2mg /dl) because of reduced glomerular filtration rate.
• Frusemide needs frequent doses ( 2-3 /day ). Thiazides can be given once daily or every other day.
• Potassium supplements should not be routinely combined with thiazide or loop diuretics. They are indicated with hypokalemia (serum potassium < 3.5 mEq/L) especially with concomitant digitalis therapy or left ventricular hypertrophy.
• Nonsteroidal antiinflammatory drugs can antagonize diuretics effectiveness.

Special Indications

• Diuretics should be the primary choice in all hypertensives.
• They are indicated in:
  - Volume dependent forms of hypertension: blacks, elderly, diabetic, renal and obese hypertensives.
  - Hypertension complicated with heart failure.
  - Resistant hypertension: loop diuretics in large doses are recommended.
  - Renal impairment: loop diuretics.

Preparations and Dosage: see table 12.

2. Beta - Adrenergic Blocking Agents

Mechanisms of Action

• Initial decrease in cardiac output, followed by reduction in peripheral vascular resistance.
• Other actions include decrease plasma renin activity, resetting of baroreceptors, release of vasodilator prostaglandins, and blockade of pre-junctional beta-receptors.

Advantages

• Documented reduction in cardiovascular morbidity and mortality.
• Cardioprotection: primary and secondary prevention against coronary artery events (i.e. ischemia, infarction, arrhythmias, death).
• Relatively not expensive.

Practical Considerations

• Beta blockers are used with caution in patients with bronchospasm.
• Contraindicated in more than grade I AV, heart block.
• Do not discontinue abruptly.

Side Effects

• Bronchospasm and obstructive airway disease.
• Bradycardia
- Metabolic effects (raise triglycerides levels and decrease HDL cholesterol; may worsen insulin sensitivity and cause glucose intolerance). Increased incidence of diabetes mellitus.
- Coldness of extremities.
- Fatigue.
- Mask symptoms of hypoglycemia.
- Impotence.

Special Indications

- First line treatment for hypertension as an alternative to diuretics.
- Hypertension associated with coronary artery disease.
- Hyperkinetic circulation and high cardiac output hypertension (e.g., young hypertensives).
- Hypertension associated with supraventricular tachycardia, migraine, essential tremors, or hypertrophic cardiomyopathy.

Preparations and Dosages: see table 12

3. Calcium channel blockers

Types

- Dihydropyridine: nifedipine, amlodipine, felodipine, nicardipine, lacidipine.
- Non dihydropyridine:
  - Phenylalkylamine: verapamil.
  - Benzothiazepine: diltiazem.

Mechanisms of action

- Decrease in the concentration of free intracellular calcium ions results in decreased contraction and vasodilation.
- Diuretic effect through increase in renal blood flow and glomerular filtration rate.
- Inhibition of aldosterone secretion.

Advantages

- No metabolic disturbances: no change in blood glucose, potassium, uric acid and lipids.
- May improve renal function.
- Maintain optimal physical, mental, and sexual activities.

Special Indications

- Ischemic heart disease: when beta blockers are ineffective or contraindicated and in vasospastic angina.
- Elderly hypertensives: second agent of choice after diuretics.
- Peripheral vascular disease (e.g., Raynauld’s phenomenon).
- Side Effects
  - Dihydropyridine: flushing, headache, and lower limb oedema.
  - Non dihydropyridine: aggravation of heart failure and heart block. Verapamil may cause constipation.

Practical Considerations
Short acting dihydropyridine should be combined with beta blockers in coronary artery disease, and should be avoided in stroke, and hypertensive crisis.

Preparations and Dosages: see table 12.

4. Angiotensin Converting Enzyme Inhibitors

Types
- Class I: captopril
- Class II (prodrug): e.g., ramipril, enalapril, perindopril
- Class III (water soluble): lisinopril.

Mechanism of Action
- Inhibition of circulating and tissue angiotensin-converting enzyme.
- Increased formation of bradykinin and vasodilatory prostaglandins.
- Decreased secretion of aldosterone; help sodium excretion.

Advantages
- Reduction of cardiovascular morbidity and mortality in patients with atherosclerotic vascular disease, diabetes, and heart failure.
- Favorable metabolic profile.
- Improvement in glucose tolerance and insulin resistance.
- Renal glomerular protection effect especially in diabetes mellitus.
- Do not adversely affect quality of life.

Special Indications
- Diabetes mellitus, particularly with nephropathy.
- Congestive heart failure.
- Following myocardial infarction.

Side Effects
- Cough (10 - 30%): a dry irritant cough with tickling sensation in the throat.
- Skin rash (6%).
- Postural hypotension in salt depleted or blood volume depleted patients.
- Angioedema (0.2%): life threatening.
- Renal failure: rare, high risk with bilateral renal artery stenosis.
- Hyperkalaemia
- Teratogenicity.

Practical Considerations
- Contraindications include bilateral renal artery stenosis, pregnancy, known allergy, and hyperkalaemia.
- High serum creatinine (> 3 mg/dl) is an indication for careful monitoring of renal function, and potassium. Benefits can still be obtained in spite of renal insufficiency.
- A slight stable increase in serum creatinine after the introduction of ACE inhibitors does not limit use.
- ACE-I are more effective when combined with diuretics and moderate salt restriction.
Preparations and dosages: see table 12.

5. Angiotensin Receptor Blockers

Mechanism of action

They act by blocking type I angiotensin II receptors generally, producing more blockade of the renin - angiotensin - aldosterone axis.

Advantages

- Similar metabolic profile to that of ACE-I.
- Renal protection.
- They do not produce cough.

Practical Indications

Patients with a compelling indication for ACE-I and who can not tolerate them because of cough or allergic reactions.

Preparations and Dosages: see table 12.

6. Sympatholytics And Alpha Adrenergic Blockers

Types

1. Alpha 1-receptor blockers: prazocin, doxazocin.
2. Centrally acting alpha 2- agonists: methyldopa, clonidine.
4. Imidazoline receptor agonists: rilmenidine, moxonidine.

Advantages

- Alpha1- receptor blockers and imidazoline receptor agonists improve lipid profile and insulin sensitivity.
- Reserpine: neutral metabolic effects and cheap.

Special indications:

- Diabetes mellitus: alpha1- receptor blockers, imidazoline receptor agonists.
- Dyslipidemia: alpha 1- receptor blockers, imidazoline receptor agonists.
- Prostatic hypertrophy: alpha 1- receptor blockers.
- When there is a need for rapid reduction in blood pressure: clonidine.

Side Effects

- Prazocin: postural hypotension, diarrhea, occasional tachycardia, and tolerance (due to fluid retention).
- Methyldopa: sedation, hepatotoxicity, hemolytic anemia, and tolerance.
• Reserpine: depression, lethargy, weight loss, peptic ulcer, diarrhea, and impotence.
• Clonidine: dry mouth, sedation, bradycardia, impotence, and rebound hypertension if stopped suddenly.

Practical Considerations

• Prazocin, methyldopa, and reserpine should be combined with a diuretic because of fluid retention.
• In Egypt, reserpine is only available as combination pill with thiazide (Brenardine) which contains 0.1 mg of reserpine per tablet.

Preparations and Dosages: see table 12.

7. Direct Arterial Vasodilators

Types: hydralazine, diazoxide, nitroprusside, and minoxidil (see chapter 10).

Patients’ compliance to antihypertensive medications

Poor adherence to antihypertensive therapy remains a major therapeutic challenge contributing to the lack of adequate control of blood pressure in more than two thirds of patients with hypertension. One half of all patients discontinue antihypertensive medications within one year.

Causes of Poor Compliance

• Hypertension has no symptoms and treatment has to continue indefinitely.
• Poor communication with the patient. Very long intervals between follow-up visits, and frequent change of doctors impair the doctor-patient relationship.
• Logistic barriers e.g. expense of medications, inability to read instructions, complicated multi-dose regimens, etc....
• Adverse drug effects.

Strategies to Improve Compliance

• Educate patients about the disease and involve their families in the treatment.
• Stress that treatment is life-long.
• Consider cost while prescribing.
• Consider adverse effects at initial prescription and follow up visits.
• Prescribe simple once-daily regimens.
• Allow extra visits for blood pressure measurement at no extra charge to the patient.
• Arrange follow-up visits at intervals no more than three months apart, during the first year.
• Encourage life style modifications.
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<th>Class</th>
<th>Generic Name</th>
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<th>Common Brand Name(s)</th>
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* Combination with hydrochlorothiazide triamterene  
# Combination with spironolactone  
** Combination with triametrene  
*** Combination with ACE inhibitor  
“ Combination with thiazide & vasodilator