PHARMACOLOGY

Drugs acting on Cardiovascular System: Antihypertensive Drugs

Dr. Lalit Kumar Gupta
Dept. of Pharmacology
Lady Hardinge Medical College
Cannought Place
New Delhi-110 001

(6.12.2007)

CONTENTS

Keywords
Hypertension, Diuretics, thiazide diuretics, Vasodilators, angiotensin converting enzyme inhibitor,ACE inhibitor, angiotensin receptor blocker, ARB

Hypertension

Diagnosis is generally based on repeated, reproducible measurements of elevated blood pressure and not on patient symptoms.

Classification of High Blood Pressure for Adults Aged 18 Years and Older*

Category	Systolic	Diastolic
Optimal	<120	<80
Normal	< 130	< 85
High Normal	130 - 139	85 - 89
Hypertension - Stage 1	140 - 159	90 - 99
Stage 2	160 - 179	100 -109
Stage 3	≥ 180	≥ 110

*(*Adapted from* JNC-VI *)*

Drugs Used to Treat Hypertension

Classes of drugs used in the treatment of hypertension are listed below.

1. Diuretics

- thiazide diuretics (Hydrochlorothiazide)
- loop diuretics (Furosemide)
- potassium-sparing diuretics (Spironolactone)

2. Vasodilators

- alpha-adrenoceptor antagonists (alpha-blockers) [Prazosin]
- angiotensin converting enzyme inhibitors (ACE inhibitors) [Enalapril]
- angiotensin receptor blockers (ARBs) [Losartan]
- calcium-channel blockers (Nifedipine)
- direct acting arterial dilators (Hydralazine)
- ganglionic blockers
- nitrodilators
- potassium-channel openers

3. Cardioinhibitory drugs

- beta-blockers (Propranolol)
- calcium-channel blockers (Verapamil)

4. Centrally acting sympatholytics (Clonidine)

1. Diuretics

(i)Thiazides and Related Agents

Thiazides are one of the classes of antihypertensive that have been extensively tested in large clinical trials. In early trials, thiazides reduced the incidence of stroke by 40 per

cent, although the reduction in coronary heart disease was disappointing. This may have been due to the adverse metabolic effects of the large doses used. More recent trials, using lower doses, have demonstrated impressive reductions in both stroke and coronary heart disease, especially in the elderly (Lever and Brennan).

There is little to choose between the various thiazides, although it seems prudent to use agents, such as **hydrochlorothiazide** and **bendrofluazide**, that have been proved to be effective at low doses in clinical trials. Newer agents, such as indapamide, have fewer metabolic side effects, and may even regress hypertensive LVH on echocardiography.

Primary Mechanisms of Action: Thiazide diuretics reduce the reabsorption of sodium and chloride in the early part of the distal convoluted tubule of the kidney by inhibiting Na^+-Cl^- symport at the luminal membrane. This results in the delivery of increased amounts of sodium to the distal tubule, where some of it is exchanged for potassium. The net result is increased excretion of sodium, potassium and water. Circulating volume is diminished, reducing preload on the heart and, thus, cardiac output and blood pressure. With long-term therapy, autoregulation by the body's own compensatory mechanisms results in vasodilatation, reduction of peripheral vascular resistance and return of the cardiac output to normal. Thiazides also have some direct vasodilatory properties. They've efficacy of up to 10-15 mm Hg when administered alone and perhaps more when used in combination with other agents.

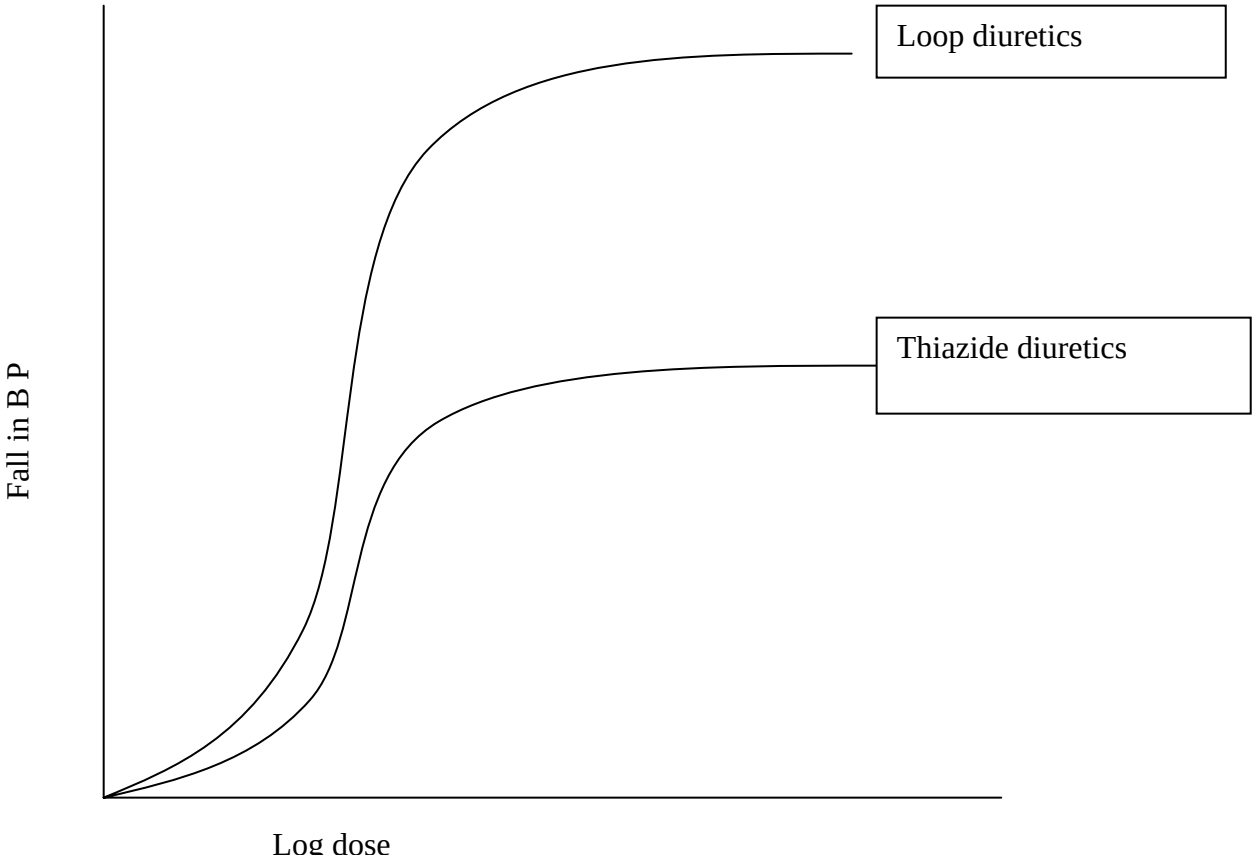


Fig. 1: Steep and flat dose response curves of Loop and Thiazide diuretics

Pharmacokinetics - Thiazides are rapidly absorbed orally and pro duce a prolonged diuresis. They tend to produce a maximal response at relatively low doses, such as 12.5mg hydro-chlorothiazide or 1.25mg bendrofluazide. Further increases in dose simply increase side effects with little further effect on blood pressure.

On the whole, standard doses of thiazides lower blood pressure as much as other first-line antihypertensives. In some patient groups, such as blacks and the elderly, the thiazides are particularly efficacious. However, they tend to be less effective in younger, white patients. Thiazides are used in patients with mild to moderate hypertension and normal cardiac/renal function.

Side effects: The main concerns about thiazide diuretics are their **metabolic side effects**. They may cause **hypokalaemia** due to renal potassium wasting. Hypokalaemia may give rise to **ventricular arrhythmias** and cause adverse drug effects in patients taking digoxin or drugs that prolong the QT interval on the ECG (eg, class I antiarrhythmics, tricyclic antidepressants, antihistamines). **Acute gout** is another common side effect of thiazides. **Impotence** may occasionally be a problem. Thiazides can **increase serum LDL-cholesterol and triglyceride levels**. There is also some evidence that diuretics **impair glucose tolerance and increase insulin resistance**. Rarer side effects include nausea, headache, rashes, photosensitivity and blood dyscrasias.

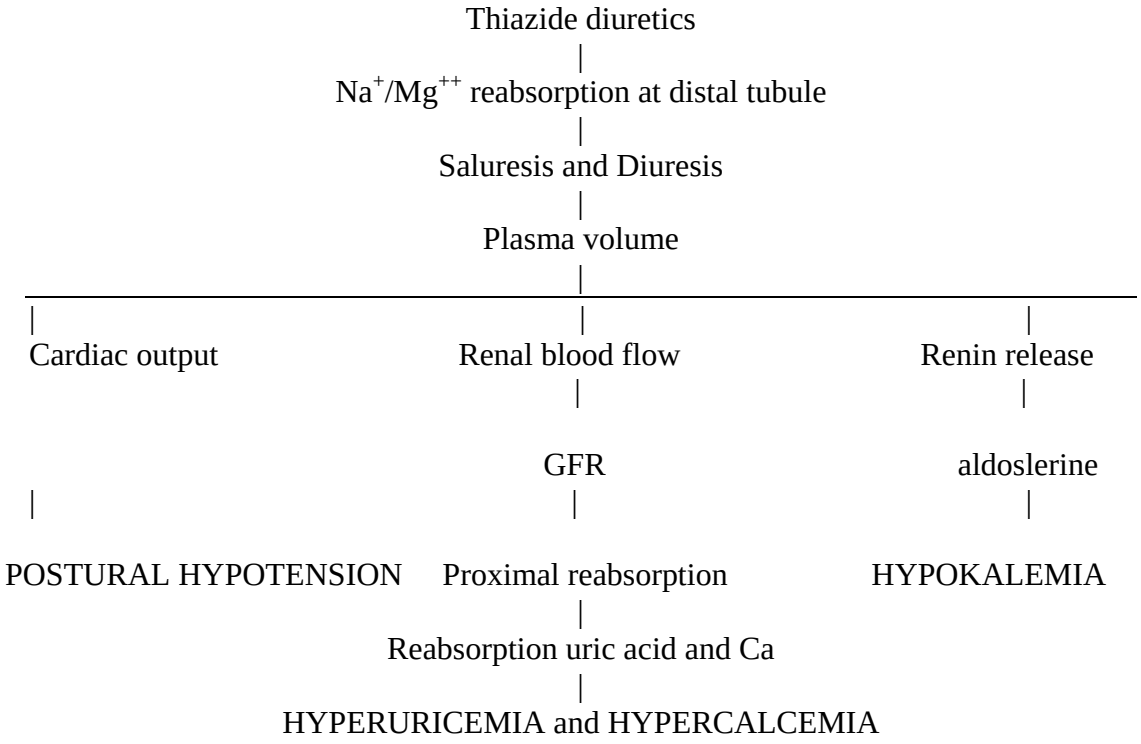


Fig.2: Pharmacological basis of Thiazide induced side effects

(ii)Loop Diuretics (High ceiling diuretics)

Loop diuretics act by inhibiting Na^+-K^+-$2Cl^-$ transporter in the thick ascending limb of the loop of Henle and inhibit the reabsorption of chloride, sodium and potassium. They produce a brisk but short-lived diuresis and are thus unsuitable as first-line agents for hypertension, as they do not provide 24-hour control. However, they do have a role in patients with impaired renal function in whom thiazides are ineffective, and in patients with hypertension resistant to multiple drug therapy, who are often fluid overloaded. Furthermore, they may be synergistic with agents such as the ACE inhibitors.

Furosemide

Side Effects: dehydration, most metabolic effects are same as in case of thiazides (i.e., hypokalemia, impaired diabetes control, increased LDL/HDL)

(iii)Potassium-Sparing Diuretics

Potassium-Sparing Diuretics are often used: 1) in combination with other diuretics (i.e., thiazides) to prevent or correct hypokalemia; 2) to avoid potassium depletion in patients taking digitalis.

Spironolactone

Spironolactone antagonizes effect of aldosterone, with a particular role in primary hyperaldosteronism or Conn's syndrome.

Side Effects: *hyperkalemia*, gynecomastia

Triamterene

Weak antihypertensive activity of its own.

Side Effects: *hyperkalemia*, gastrointestinal disturbances

Thiazide diuretics are available as fixed-dose combinations with potassium-sparing or other antihypertensive drugs. Thiazide diuretics Often used in combination with antihypertensive agents that impair vascular responsiveness (i.e., vasodilators) since blood pressure can become very sensitive to blood volume in the presence of these agents. Potassium supplements can be prescribed to compensate for hypokalemia. The thiazides are not useful in patients with renal insufficiency (glomerular filtration rate < 40 ml/min).

Vasodilators

(i) Alpha-blockers

Alpha 1 Blockers	Usual Dosage range
Prazosin	1-10 mg BID
Terazosin	1-20 mg daily
Doxazosin	1-16 mg daily

The α_1 adrenoceptor blockers produce vasodilatation by blocking the action of nor-adrenaline at post-synaptic α_1 receptors in both arteries and veins. This results in a fall in peripheral resistance, without a compensatory rise in cardiac output. The prototype α1-blocker — prazosin — is short acting and tends to produce precipitous falls in blood

pressure. Doxazosin combines the advantage of a more gentle reduction in blood pressure with the longer duration of action, permitting once daily dosing.

Side effects*: first dose produces precipitous fall in blood pressure*, dizziness (10% of patients), headaches (8% of patients), weakness (7% patients); decrease LDL/HDL. α_1-blockers are, on the whole, well tolerated. In women, α_1-blockers may cause urinary incontinence. In men, they may improve the symptoms of benign prostatic hypertrophy. Like most antihypertensive drugs, α_1-blockers can cause headache and fatigue. α_1-blockers do not impair exercise tolerance, improve carbohydrate metabolism, favourable effect on lipid profile, renal blood flow and g.f.r. maintained, and decrease blood pressure only to a certain extent, since fall is directly related to that component of vascular resistance maintained by sympathetic activation.

(ii) ACE inhibitors

ACE Inhibitors	Usual Dosage Range
Quinapril	5-40 mg daily
Ramipril	1.25-10 mg daily
Captopril	12.5-50 mg daily
Perindopril	2-8 mg daily
Benazepril	5-40 mg daily
Cilazapril	1-10 mg daily
Enalapril	5-40 mg daily -converted to metabolite enalaprilat
Lisinopril	5-40 mg daily - lysine derivative of enalaprilat
Fosinopril	10-40 mg daily

Angiotensin converting enzyme (ACE) inhibitors work by blocking the renin-angiotensin system, inhibiting the conversion of the inactive angiotensin I to the powerful vasoconstrictor and stimulator of aldosterone release, angiotensin II. This results in decreased peripheral vascular resistance and reduction in the levels of the sodium-retaining hormone — aldosterone.

ACE inhibitors may improve endothelial function and reduce central adrenergic tone. They also have beneficial effects on renal haemodynamics, reducing intraglomerular hypertension, resulting in improvements in proteinuric renal disease. ACE inhibitors are effective as single agents in hypertension. This class of drugs is one of the first choice drugs in all grades of essential as well as renovascular hypertension (except in bilateral renal artery stenosis). There is generally little to choose between the large number of ACE inhibitors available. Agents, such as fosinopril, have the advantage of hepatic as well as renal excretion and are less likely to accumulate in patients with renal failure. Perindopril, ramipril and trandolapril are agents with long half-lives, which provide good 24 -hour antihypertensive coverage.

There is useful synergism between the ACE inhibitors and diuretics and between ACE inhibitors and calcium channel blockers. The ACE inhibitors are particularly useful in diabetic hypertensives, in which they may be renoprotective, as they slow the progression of diabetic nephropathy. Furthermore, these agents have shown some benefits in improving diabetic retinopathy and even diabetic neuropathy.

Side effects: Dry cough, caused by the inhibition of bradykinin breakdown, is the most common side effect of ACE inhibitors. The far more serious, but rare, side effect of the ACE inhibitors is **angioedema**, which occurs in about 0.1 to 0.2 per cent of patients. Dramatic **deterioration in renal function can occur in patients with bilateral renal artery stenosis**. Serum urea and creatinine should, therefore, be checked before and a few weeks after starting an ACE inhibitor. This should not prevent the use of ACE inhibitors in those with other forms of renal disease. In these patients, ACE inhibitors are often agents of first choice, in view of data showing that they slow the progression of diabetic and non-diabetic nephropathy.

The ACE inhibitors can cause **hyperkalaemia** because they reduce aldosterone and, thus, potassium excretion. **First-dose hypotension** is probably an overstated side effect of ACE inhibitors but large doses of short acting captopril can cause sudden falls in blood pressure, especially in those with volume depletion, such as heart failure patients on large doses of diuretics**. Rarer side effects** include rash, taste disturbance, blood dyscrasias and a symptom complex that includes fever and vasculitis.
Note: contraindicated in second and third trimesters of pregnancy due to fetopathic potential.

(iii) Angiotensin II antagonists

Losartan 25-100 mg daily
Irbesartan
Candesartan
Valsartan
Telmisartan

This class of drugs is also called ARB (Angiotensin II Receptor Blockers). Like the ACE inhibitors, these drugs act on the renin-angiotensin system, blocking the action of angiotensin II at its peripheral receptors. Although binding of ARBs to angiotensin receptors is competitive, the inhibition by ARBs of biological responses to angiotensin II often is insurmountable. Candesartan exerts the maximum blockade to angiotensin II.

Possible advantages of ARBs could be:
ARBs do not inhibit the breakdown of bradykinin, therefore they do not cause cough. They have similar physiological effects to ACE inhibitors and produce similar falls in blood pressure. There is synergism of antihypertensive effect with thiazide diuretics. There is also evidence that they may regress LVH and improve proteinuria.

Possible disadvantages of ARBs could be:
ARBs stimulate renin release and this result in increased circulating levels of angiotensin II, which may act on some angiotensin receptors.

Side effects: The main advantage of the angiotensin II antagonists is their apparent lack of side effects. Like the ACE inhibitors, they may cause **hyperkalaemia, renal impairment and hypotension** but, otherwise, they are almost as well tolerated as placebo. Nevertheless, cases of **angioedema** have been reported with some of these agents. Like ACE inhibitors, ARBs also have teratogenic potential.

(iv) Calcium Channel Blockers

Nifedipine - relatively selective vasodilator and less cardiac depression than verapamil or diltiazem
Diltiazem - intermediate action on heart and blood vessels
Verapamil - greatest effect on heart

Primary Mechanisms of Action: inhibit Ca^{++} influx into vascular smooth muscle; relax peripheral arteriole smooth muscle and thereby decrease total peripheral resistance; interfere with both angiotensin II and $alpha_2$-mediated vasocontriction, and perhaps $alpha_1$-mediated vasoconstriction.

Calcium channel blockers may be divided into two classes — the dihydropyridines and the non-dihydropyridines. The dihydropyridines, such as nifedipine and amlodipine, act predominantly by causing peripheral vasodilatation. The non-dihydropyridines, such as verapamil and diltiazem, also slow the heart rate and atrio-ventricular node conduction. All calcium channel blockers are efficacious at reducing blood pressure as single agents. The older drugs, such as nifedipine, have short half-lives and may cause rapid vasodilatation, a reflex tachycardia and catecholamine surges. This may increase adverse effects and aggravate myocardial ischaemia. Longer-acting agents, such as amlodipine or slow-release preparations of nifedipine, partially overcome these problems.

Ca^{++} channel blockers are only rarely associated with abnormalities in electrolyte, carbohydrate, or lipid metabolism. The drugs do not alter plasma concentrations of uric acid. Ca^{++} channel blockers are useful in hypertensive patients with a wide variety of concomitant illnesses including ischemic heart disease, chronic pulmonary disease, diabetes mellitus and variant angina.

" In the mid-1990s, a series of pharmacosurveillance case-control studies suggested that the short-acting dihydropyridine drugs (such as nifedipine capsules) actually increased the risk of heart attacks. Other studies have found no increase in mortality or morbidity with short-acting calcium-channel blockers. More data from randomized controlled trials are needed to answer the questions that have been raised about the safety of calcium channel blockers. In the mean-time, **short-acting** calcium channel blockers, particularly nifedipine, should not be used for treatment of hypertension." (Massie)

Side effects: The main, and most troublesome, side effect of calcium channel blockers is **ankle oedema**. This is caused by vasodilatation, which also causes **headache, flushing and palpitation**, especially with short-acting dihydropyridines. Some of these side effects can be offset by combining a calcium channel blocker with a β-blocker. **Verapamil** reduces intestinal motility and, thus, can cause significant **constipation**. More seriously, it can cause **heart block**, especially in those with underlying conduction problems. **Diltiazem** can similarly cause **gastrointestinal and conduction problems**, although less frequently than verapamil. Verapamil, diltiazem and short-acting dihydropyridines are best avoided in patients with heart failure.

(v) Direct acting arterial dilators (Direct Vasodilators)

	Usual Dosage Range
Hydralazine	25-100 mg BID
Minoxidil	2.5-40 mg daily

These agents act directly to relax vascular smooth muscle, thereby reducing peripheral vascular resistance. The resulting activation of the sympathetic nervous system means that they can only successfully be used in combination with drugs that block sympathetic activity. Examples include hydralazine, whose main side effect is a lupus-like syndrome, and minoxidil. Minoxidil causes hair growth, a side effect welcomed by many middle aged men but not by their female counterparts.

Cardioinhibitory drugs

Beta-blockers

Beta-blockers act by blocking the action of noradrenaline at β adrenoceptors throughout the circulatory system and elsewhere. Their major effect is to slow the heart rate and reduce its force of contraction. Beta-blockers also cause some reduction in renin release and central sympathetic tone. Beta-blockers may be subdivided according to their ancillary properties. For example, **β_1 or cardioselective agents, such as atenolol**, have less action on β_2 receptors in the bronchi and peripheral vessels compared with **non-selective agents, such as propranolol**. This reduces (but does not abolish) β_2 receptor-mediated side effects. Lipid-soluble agents, such as propranolol and metoprolol, cross the blood-brain barrier more readily and are associated with a higher incidence of central side effects.

Labetalol and carvedilol have both α- and β_1-blocking properties, causing a reduction in peripheral vascular resistance, as well as slowing the heart rate. In addition to its β_1-blocking properties, carvedilol also has antioxidant effects, which give it theoretical advantages in reducing endothelial damage and lowering levels of highly atherogenic oxidised LDL-cholesterol. However, both labetalol and carvedilol have the disadvantage of possessing the side effects of both classes of drug.

Beta-blockers are useful as first-line antihypertensive agents, although they tend to be less effective in the elderly and in black hypertensives. For the treatment of hypertension it is best to choose a beta-blocker with high cardioselectivity and low lipid solubility to reduce side effects. A long half-life also allows once daily dosing.

Side effects: Most of the side effects of beta-blockers are predictable from their mode of action. For example, they **slow the rate of conduction** at the atrio-ventricular node and are thus contraindicated in patients with second- and third-degree heart block. Sinus bradycardia is common and is not a reason to stop beta-blockers unless the patient is symptomatic or the heart rate falls below 40 beats/minute.

Even small doses of β-blockers can cause bronchospasm due to blockade of pulmonary β_2 receptors, although the problem is less common with cardioselective agents. Even so, all beta-blockers are contraindicated in asthma. Blockade of b receptors in the peripheral circulation causes vasoconstriction, at least in the immediate term, and the drugs are, therefore, contraindicated in patients with rest ischaemia of the legs. Nevertheless, they are reasonably tolerated in those with lesser degrees of peripheral vascular disease. Lipid-soluble agents can cause central nervous system side effects of insomnia, nightmares and fatigue. Exercise capacity may be reduced by beta-blockers and patients may experience tiredness and fatigue. As with most antihypertensives, impotence has been reported, although rates are little higher than with placebo. Like diuretics, β-blockers can worsen glucose intolerance and hyperlipidaemia. In diabetic patients prone to hypoglycaemia, beta-blockers may, reduce the awareness of low blood glucose.

Central and Peripheral Sympatholytics

	Usual Dosage Range
Reserpine	0.0625-0.25 mg daily
Methyldopa	125 mg - 1 g daily
Clonidine	0.05-0.3 mg BID .

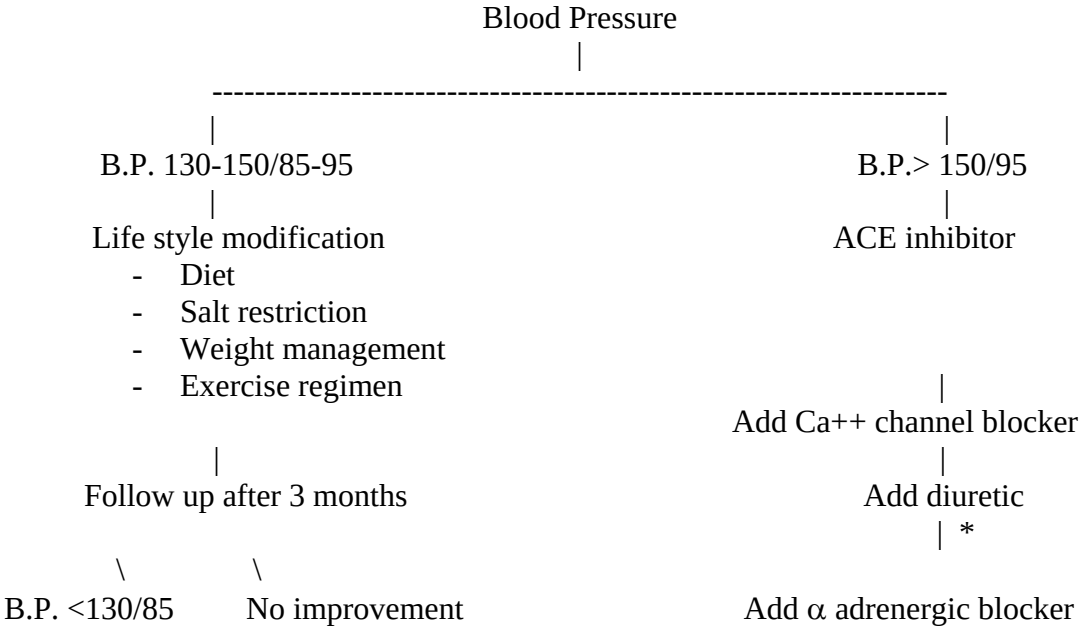
These drugs stimulate central α_2 adrenoceptors, resulting in a decrease in central sympathetic tone. This leads to a fall in both cardiac output and peripheral vascular resistance. Examples of such drugs include methyldopa and clonidine. The drugs cause **sedation, dry mouth and fluid retention**. Methyldopa can also cause autoimmune hepatic derangement and haemolytic anaemia. However, it is safe to use in hypertensive pregnant women and is commonly used in such patients. A new centrally acting drug, moxonidine, acts on central imidazoline receptors and is hoped to have the beneficial effects of centrally-acting drugs, without their side effects.

Adrenergic neurone blockers

Such agents are now rarely used. Reserpine and guanethidine inhibit the release of noradrenaline from peripheral nerves. This reduces sympathetic tone, peripheral vascular

resistance and cardiac output. They cause postural hypotension and central nervous system depression. Small doses of reserpine, combined with a diuretic, form an effective regimen and are used when cost of therapy needs to be reduced.

Clinical Management of Hypertension



* if controlled

Fig. 3: Strategies in management of hypertension

References

1. Lever AF, Brennan PJ. Clin Exp Hypertens. 1993 Nov;15(6):941-52 .
2. Massie BM. Clin Cardiol. 1998 Dec;21(12 Suppl 2):II12-7