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ANTIHYPERTENSIIVES: A REVIEW

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Keywords:

Hypertension, Myocardial infarction, peripheral arterial disease, systolic and diastolic

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ABSTRACT

Systemic hypertension is major risk factor for cardiovascular disease and is present in 69% patients with first myocardial infarction. In 77% of patients with a first stroke, in 74% of patients with chronic heart failure and in 60% of patients with peripheral arterial disease. Blood pressure is summarized by two measurements, systolic and diastolic, which depend on whether the heart muscle is contracting(systole) or relaxed between beats(diastole).This equals the maximum and minimum respectively. Normal blood pressure at rest is within the range of 100-140 mm Hg systolic and 60-90 mm Hg diastolic. Dietary and lifestyle changes can improve blood pressure control and decrease the risk of health complications, although drug treatment is still often necessary in people for whom lifestyle changes are not enough or not effective.

INTRODUCTION:

Blood pressure is the pressure exerted by the blood on the walls of blood vessels. When the left ventricle of the heart pushes the blood into aorta the pressure produced is called systolic blood pressure and when the heart is resting after the ejection of blood then pressure within the arteries is called diastolic blood pressure. Hypertension has been divided into two categories i.e. primary or essential hypertension in which the cause of hypertension is not know and secondary hypertension in which cause is known. Hypertension is often called "the silent killer" because it generally has no symptoms until serious complications develop, Hypertension

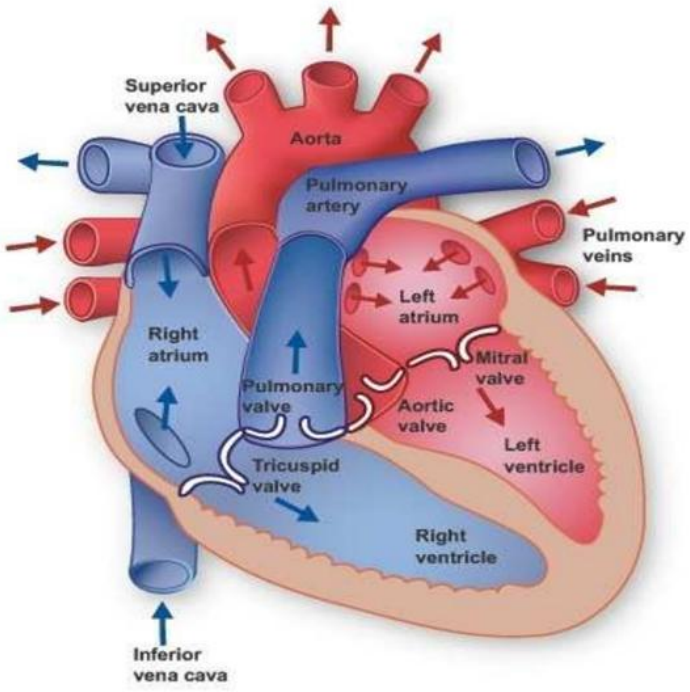

Fig. 1: Diagram of the Heart

May also be a side effect of certain medications, such as over the counter cold medications and oral contraceptive and other hormone drugs. Obesity, heredity and life style also play a role in the developments of hypertension. Antihypertensive drugs are used in the treatment of hypertension. Hypertension or high blood pressure is a very common and serious condition that can lead to or complicate many health problems. The risk of cardiovascular morbidity and mortality is directly correlated with blood pressure. Risks of stroke, MI, angina, heart failure, kidney failure or early death from a cardiovascular cause are directly correlated with BP. Hypertension is often called "the silent killer" because it generally has

no symptoms until serious complications develop. There are three general types of hypertension. Essential or primary hypertension occurs when the condition has no known cause. This form of hypertension cannot be cured, but it can be controlled. More than 90% of individuals with hypertension have essential hypertension. Genetic factor may play an important role in the development of essential hypertension. When hypertension is caused by another condition or disease process, it is called secondary hypertension. Fewer than 10% of patients have secondary hypertension; where either a co-morbid disease or drug is responsible for elevating BP. In most of these cases renal dysfunction resulting from sever chronic kidney disease or renovascular disease is the most common secondary cause. Hypertension has a variety of causes. Blood pressure generally tends to rise with age. Hypertension can also be caused by other medical conditions, such as thyroid disease or chronic kidney disease. Hypertension may also be a side effect of certain traceptives and other hormone drugs.

ETIOLOGY

Etiological factors correlated with hypertension in adults have also been associated with blood pressure elevations in youth. Hypertension and insulin resistance are also associated with the development of hypertension which leads to many problems. The elevated plasma insulin levels may cause sodium sensitivity. Adequate dietary potassium, calcium and magnesium intakes have been associated with lower blood pressure in youth. Potassium and calcium intakes are below recommended levels, particularly in adolescent females, while median intakes of phosphorus and protein, which promote calcium loss, are high. Lack of physical activity may increase the risk of developing hypertension by 20% -50%. A family history of hypertension is increase the likehood that an individual will develop hypertension disease. Essential hypertension occurs four times more frequently among blacks than whites, and it occur more often amoung middle- aged males and amoung middle-aged females.

CAUSES

1.Essential Hypertension

2.Renal

a) Acute nephritis

b) Interstitial nephritis and pyelonephritis

c) polycystic kidneys

3.Endocrine = Thyrotoxicosis, myxedema,pheochromocytoma,cushing’s syndrome.

4.Vascular = Arteriosclerosis, coaractition of aorta.

Table 1: Classification of Blood Pressure

Category pressure	Systolic pressure mm Hg	Diastolic pressure mm Hg
Normal.	90-119.	60-79
Pre-hypertension	120-139.	80-89
Stage 1.	140-159.	90-99
Stage 2.	> 160	> 100
Isolated systolic hypertension	>140.	<90

PRIMARY HYPERTENSION

It results when arterial blood pressure is increased due to increased peripheral resistance. It is further divided in to two types namely: benign and malignant hypertension

Benign hypertension

Here, there is a moderate increase in blood pressure with systolic pressure of 200 mm Hg and the diastolic pressure of above 100 mm Hg. However, in resting condition and sleep, the blood pressure returns to normal level. Later, if there is increase in blood pressure it will not come back to normal level in resting conditions.

Malignant hypertension

Here, the blood pressure elevated to a great extends of about 250 mm Hg of systolic pressure and 150 mm Hg of diastolic pressure. It produces severe symptoms like renal disease, retinal disease, and being a fatal disease, it causes death within few years. Some of the characteristics of primary or essential hypertension are,

1) The mean arterial pressure is increased 40-60 %.

2) The renal blood flow in the later stages is decreased about one half of normal.

3) The resistance to blood flow through the kidney is increased 2-4 fold.

4) The kidneys will not excrete adequate amounts of salt and water unless the arterial pressure is high.

SECONDARY HYPERTENSION

The different forms of secondary hypertension are

Cardiovascular hypertension

It is produced due to

a) Atherosclerosis- hardening and narrowing of blood vessels

b) Coarctation of aorta- narrowing of aorta.

Renal hypertension

It is produced due to

a) Stenosis renal arteries- narrowing of one or both renal arteries, so that the renal function is impaired.

b) Glomerulonephritis- nephritis with inflammation of the capillary loops in the renal glomeruli.

Endocrine hypertension

It occurs due to

a) Pheochromocytoma- tumer in adrenal medulla

b) Hyperaldosteronism- excess secretion of aldosterone from adrenal cortex Conn's syndrome.

c) Cushing's syndrome- excess secretion of cortisone.

d) Gigantism or Acromegaly- excess secretion of growth hormone.

Neurogenic hypertension

Acute hypertension can be caused by strong stimulation of the sympathetic nervous system.

a) Section of the baroreceptors nerves.

b) Lesions in tractus solitarius.

c) Increased intracranial pressure.

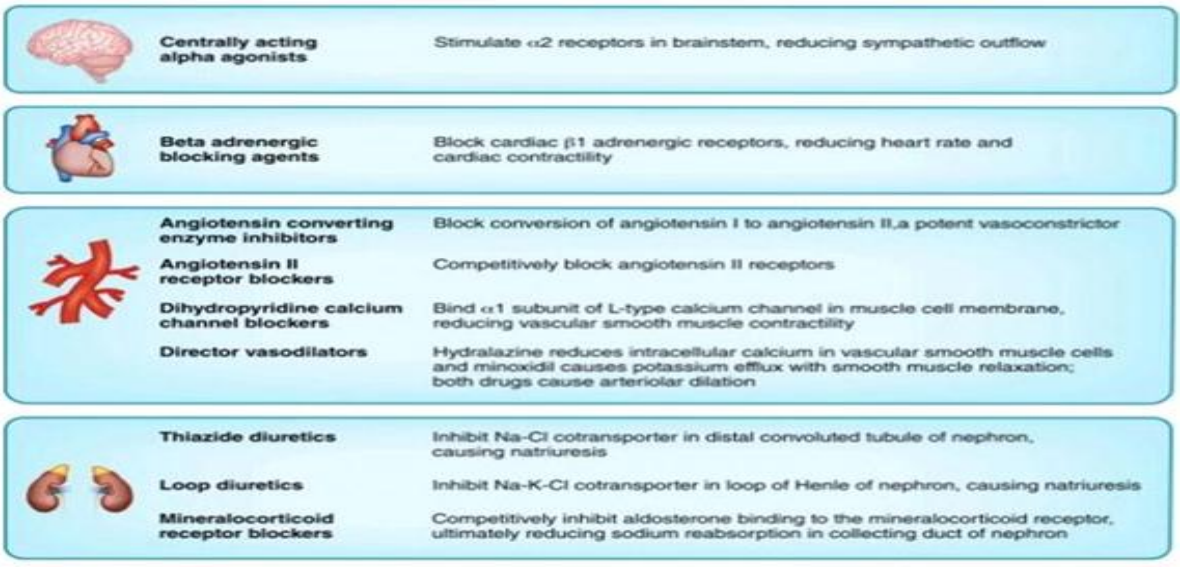

Fig.2: Major antihypertensive drug classes and their mechanisms

Table 2: Classification of antihypertensive drug

Class	Drug	Usual dose, range (mg per day)*	Daily frequency
Primary agents			
Thiazide or thiazide-like diuretics	Chlorthalidone	12.5-25	1
	Hydrochlorothiazide	25-50	1
	Indapamide	1.25-2.5	1
	Metolazone	2.5-10	1
ACE inhibitors	Benazepril	10-40	1 or 2
	Captopril	12.5-150	2 or 3
	Enalapril	5-40	1 or 2
	Fosinopril	10-40	1
	Lisinopril	10-40	1
	Moexipril	7.5-30	1 or 2
	Perindopril	4-16	1
	Quinapril	10-80	1 or 2
	Ramipril	2.5-10	1 or 2
	Trandolapril	1-4	1
ARBs	Azilsartan	40-80	1
	Candesartan	8-32	1
	Eprosartan	600-800	1 or 2
	Irbesartan	150-300	1
	Losartan	50-100	1 or 2
	Olmesartan	20-40	1
	Telmisartan	20-80	1
	Valsartan	80-320	1
CCB—dihydropyridines	Amlodipine	2.5-10	1
	Felodipine	5-10	1
	Isradipine	5-10	2
	Nicardipine SR	5-20	1
	Nifedipine LA	60-120	1
	Nisoldipine	30-90	1
CCB—nondihydropyridines	Diltiazem SR	180-360	2
	Diltiazem ER	120-480	1
	Verapamil IR	40-80	3
	Verapamil SR	120-480	1 or 2

Table 3: Classification of antihypertensive drug

Class	Drug	Usual Dose, Range	Daily frequency
Diuretics—aldosterone antagonists	Eplerenone	50-100	2
β-Blockers cardioselective	Spironolactone	25-100	1
	Atenolol	25-100	2
	Betaxolol	5-20	1
	Bisoprolol	2.5-10	1
	Metoprolol tartrate	100-400	2
	Metoprolol succinate	50-200	1
β-Blockers cardioselective and vasodilatory	Nebivolol	5-40	1
β-Blocker- noncardioselective	Nadolol	40-120	1
	Propranolol IR	160-480	2
	Propranolol LA	80-320	1
β-Blockers—intrinsic sympathomimetic activity	Acebutolol	200-800	2
	Carteolol	2.5-10	1
	Penbutolol	10-40	1
	Pindolol	10-60	2
β-Blockers-combined α- and β-receptor	Carvedilol	12.5-50	2
	Carvedilol phosphate	20-80	1
	Labetalol	200-800	2
Direct renin inhibitor	Aliskiren	150-300	1
α_1-blockers	Doxazosin	1-8	1
	Prazosin	2-20	2 or 3
	Terazosin	1-20	1 or 2
Central α_1-agonist and other centrally acting drugs	Clonidine oral	0.1-0.8	2
	Clonidine patch	0.1-0.3	1 weekly
	Methyldopa	250-1000	2
	Guanfacine	0.5-2	1
Direct vasodilators	Hydralazine	50-200	2 or 3

TREATMENT FOR HYPERTENSION

Drug therapy

Diuretics

Low-dose diuretic therapy is effective and reduces the risk ofstroke, coronary heart disease, congestive heart failure, and totalmortality. Whilst thiazides are most commonly used, loop diur-etics are also used successfully and the association with a potassiumsparing diuretic reduces the risk of both hypokalaemia and hypo- magnesaemia. Even in small doses

diuretics potentiate other anti-hypertensive drugs. The risk of sudden death is reduced whenpotassium-sparing diuretics are used. In the long-term, spirono-lactones reduce morbidity and mortality in patients with heart fail-ure that is a typical complication of long-standing hypertension.

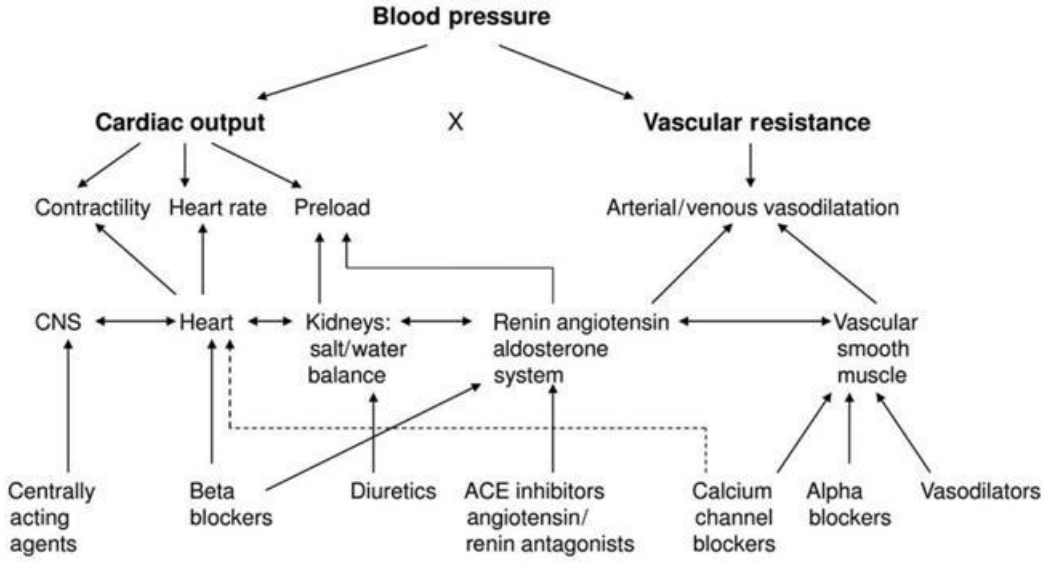

Fig. 3: Common classes of antihypertensive drug

Beta-blockers

High sympathetic tone, angina, and previous myocardial infarc-tion are good reasons for using b-blockers. As a low dose min-imizes the risk of fatigue (an unpleasant effect of b-blockade) addition of a diuretic or a calcium channel blocker is often bene-ficial. However, b-blockade therapy is associated with symptomsof depression, fatigue, and sexual dysfunction. These side-effectshave to be taken into consideration in the evaluation of the benefitsof treatment.Over the past few years b-blockers have been used increasinglyfrequently in the management of heart failure, a known complica-tion of arterial hypertension. They are effective but their introduc-tion in the presence of heart failure has to be very cautious, startingwith very low doses to avoid an initial worsening of heart failure.

Calcium channel blockers

Calcium channel blockers can be divided into dihydropyridines(e.g. nifedipine, nimodipine, amlodipine) and non-dihydropyridines(verapamil, diltiazem). Both groups decrease peripheral vascularresistance but verapamil and diltiazem have negative inotropicand chronotropic effects. Short-acting dihydropyridines such asnifedipine cause reflex

sympathetic activation and tachycardia,while long-acting drugs such as amlodipine and slow-releasepreparations of nifedipine cause less sympathetic activation.Short-acting dihydropyridines appear to increase the risk of sudden death. However, the systolic hypertension in Europe(SYST-EUR) trial which compared nitrendipine with placebo had to be stopped early because of significant benefits of active therapy.

Calcium channel blockers are effective in the elderly and may be selected as monotherapy for patients with Raynaud's phe- nomenon, peripheral vascular disease, or asthma, as such patients do not tolerate b-blockers. Diltiazem and verapamil are contra indicated in heart failure. Nifedipine is effective in severe hyper tension and can be used sublingually; there is need for caution because of the risk of excessive hypotension. Calcium channel blockers are often associated with b-blockers, diuretics and/or ACE inhibitors.

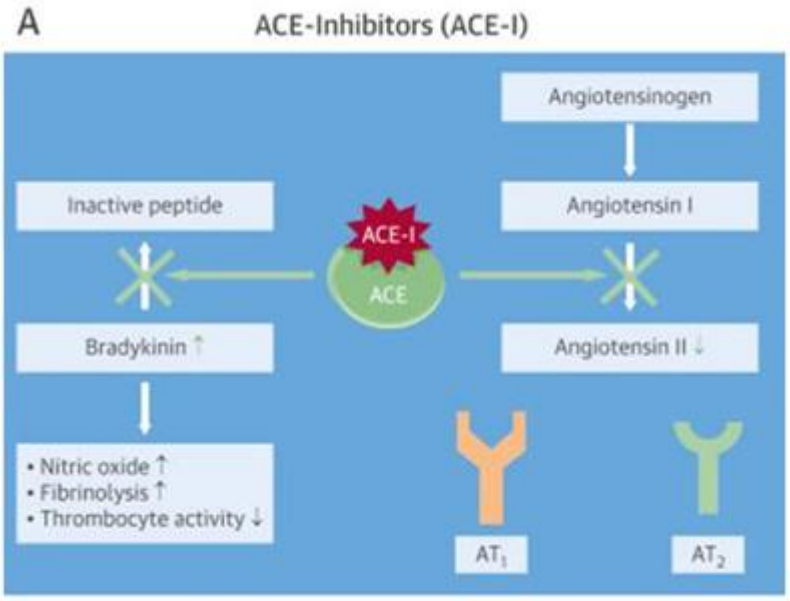

Fig. 4: MOA of ACE-I inhibitors

Angiotensin converting enzyme inhibitors

ACE inhibitors are increasingly being used as first line therapy. They have relatively few side-effects and contraindications except bilateral renal artery stenoses. Though ACE inhibitors are effect- live in unilateral renovascular hypertension, there is risk of isch aemic atrophy. Therefore, angioplasty or surgical renal artery reconstruction are preferable to long-term purely medical therapy. ACE inhibitors are first choice agents in diabetic hypertensive patients as they slow down the progression of renal dysfunction. In hypertension with heart failure, ACE inhibitors are also first choice drugs. The HOPE trial has shown that ramipril

reduced the risk of cardiovascular events even in the absence of hypertension. Thus, this ACE inhibitor may exert a protective effect by mechan- isms other than the reduction in blood pressure.

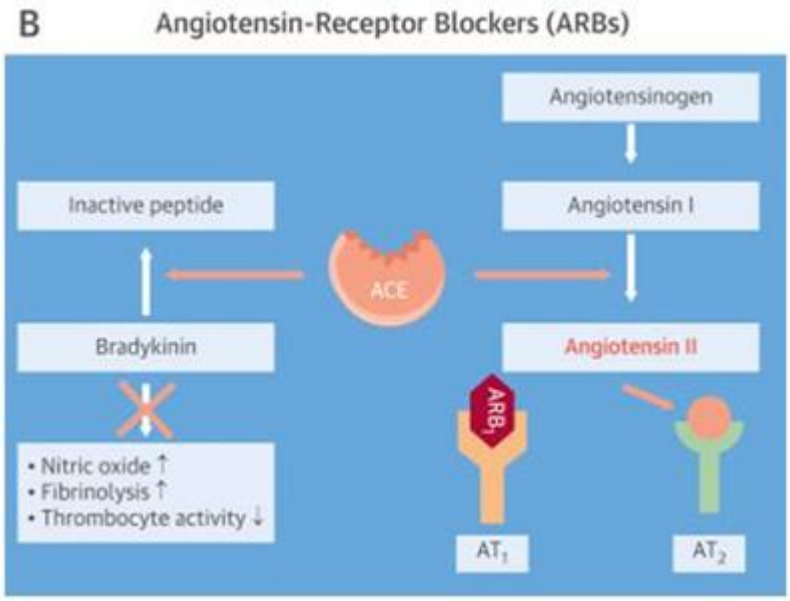

Fig. 5: MOA of Angiotensin- Receptor Blockers

Angiotensin II receptor blockers

As angiotensin II stimulates AT1-receptors that cause vasoconstriction, angiotensin AT1-receptor antagonists are effective antihypertensive drugs. Losartan, valsartan and candesartan are effective and cause less coughing than ACE inhibitors. The LIFE study is the most recent landmark trial in hypertension. More than 9000 patients were randomized to receive either the angiotensin receptor antagonist losartan or a b-blocker (atenolol). Patients in the losartan arm exhibited better reduction of mortality and morbidity, owing to greater reduction in strokes. Losartan was also more effective in reducing left ventricular hypertrophy, an independent powerful risk factor for adverse outcome. In patients with isolated systolic hypertension, the superiority of losartan over atenolol was even more pronounced than in those with systolic and diastolic hypertension. These favourable results led to an editorial entitled: 'Angiotensin blockade in hypertension: a promise fulfilled'. It must be noted that the comparator in the LIFE study was a b-blocker, and that, in the past, b-blockers were found to be no better than placebo in the elderly.

Alpha-Adrenergic blockers

Free from metabolic side-effects, these drugs reduce blood cho- lesterol and reduce peripheral vascular resistance. Prazosin is shorter acting than doxazosin, indoramin and terazosin. These drugs are highly selective for a1-adrenoceptors. Drowsiness, pos- tural hypotension, and occasionally tachycardia, can be trouble- some. Fluid retention may require the addition of a diuretic. Phenoxybenzamine is a non-competitive a-adrenoceptor agonist used (in association with a b-blocker) in the management of patients with phaeochromocytoma, though recently doxazosin has been used successfully.

Direct vasodilators

Hydralazine and minoxidil are directly acting vasodilators. Their usage has declined because of the potential for serious side-effects(lupus syndrome with hydralazine, hirsutism with minoxidil)

Central adrenergic inhibitors

Methyldopa is both a false neurotransmitter and a2-adrenoceptor agonist. Clonidine and dexmedetomidine are agonists at cent- rally located a2-adrenoceptors. The selectivity for a2- vs a1- adrenoceptors is greatest for dexmedetomidine followed by clonidine and least for a-methyldopa . Both clonidine and dexmedetomidine make the circulation more stable, reduce the release of catecholamines in response to stress, and cause sedation such that dexmedetomidine is now used for seda- tion in intensive care units. Moxonidine is representative of a new class of antihypertensive agents acting on imidazoline1 receptors (I1). Moxonidine reduces sympathetic activity by acting on centres in the rostral ventral lateral medulla, thereby reducing peripheral vascular resistance.

Natriuretic peptides

Natriuretic peptides play a role in the control of vascular tone and interact with the renin–angiotensin–aldosterone system. By inhib- iting their degradation, peptidase inhibitors make these naturally peptides more effective, thereby reducing vascular resist- ance. However, there are only small scale trials of their efficacy. Overall, recent studies have failed to demonstrate the superiority of modern agents over the more traditional drugs, except in special circumstances, as demonstrated in a meta-analysis based on 15 trials and 75 000 patients. In many patients, effective treatment is achieved by the association of two or more agents, with gain in efficacy and reduction of side-effects.

Reduction of Body Weight

Obesity and hypertension are closely associated,and the degree of obesity is positively correlated with the incidence of hypertension. Obese hypertensive may lower their blood pressure by losing weight regardless of a change in salt consumption. The mechanisms by which obesity causes hypertension in unclear, but increase the secretion of insulin in obesity could result in mediated enhancement of renal tubular reabsorption of Na+ and an expasion of extracellular volume.

Sodium Restriction

Severe restriction of salt will lower the blood pressure in most hospitalised hypertensive patients, this treatment methods was advocated prior to the development of effective antihypertensive drugs; However severe salt restriction isnot practical from a standpoint of compliance. Severe studies have shown moderate restriction of salt intakes to approximately 5g per day (2 g Na+) will on average, lower blood pressure by 12 mm Hg systolic and 6 mm Hg diastolic. An additional benefit of salt restriction is improved responsive to same antihypertensive drugs

Alcohol Restriction

Consumption pf alcohol can raise blood pressure, but it is unclear how much alcohol must be consumed to observe this effect. Heavy consumption of alcohol increase the risk of cerebrovascular accidents but not coronary heart disease. The mechanisms by which alcohol raises blood pressure is unknown, but it may involve increased transport of ca2+ alcohol also may result in poor compliance with antihypertensive regiments.

Physical Exercise

Increase physical activity lowers rates of cardiovascular disease in men. It is not known of this benefit effect is secondary to an antihypertensive response to exercise. Lake pf physical activity is associated with a higher incidence of hypertension. The beneficial effect of exercise can occur in subjects who demonstrate no change in body weight or salt intake during the training period.

Relaxation and Biofeedback therapy

The fact that long terms stressfull can cause sustained hypertension in animals has given credence to the possibility that relaxation therapy will blood pressure in some hypertensive patients.

Diet

Lacto vegetarian diet and high intake of polyunsaturated fish oils lower BP due to high content of potassium and vegetable diet high content of fiber.Natural Vegetables containing high levels of potassium, which lower the BP by:

1. Increased sodium excretion
2. Decreased sympathetic activity
3. Decreased renin angiotensin secretion and direct dilation of renal arteries.

Risk management

As well as pharmacological measures for the control of bloodn pressure, there should be active treatment of those factors known to increase the risk of hypertension. There are two distinctmeasures. First, those that lower blood pressure, for exampleweight reduction, reduced salt intake, limitation of alcohol consumption,physical exercise, increased fruit and vegetable consumption, and reduced total and saturated fat intake. Second, those that that reduce cardiovascular risk, for example stopping smoking; replacing saturated with polyunsaturated and monounsaturated fats; increased oily fish consumption; and reduced total fat intake. Because hypertensive patients are at very high risk of coronary artery disease, other therapeutic measures include aspirin and statin therapies. Lose-dose aspirin is effective in the preventionof thrombotic events such as stroke and myocardial infarction; this is also true in hypertensive patients whose blood pressure is well controlled. The risk of severe bleeding is very low provided blood pressure is reduced to below 150/90mmHg. The benefits of lipid-lowering drug treatment with statins are well established in coronary heart disease and in cerebrovascular disease, two conditions frequently associated with arterial hypertension.

CONCLUSION

Hypertension is a hemodynamic disorder, associated with a rise in peripheral vascular resistance, which can, in turn, lead to myocardial infarction, renal failure, stroke and death, if not identified early and treated effectively. Maintain a healthy weight, Exercise regularly. Avoid bush medicines as these could affect the treatment you are taking.

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