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Current Status of Diuretics in Management of Hypertension

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Hypertension is now recognized as a major public health problem which contributes to increased morbidity and mortality due to cardiovascular disease. Studies from our country have revealed that it is a major problem with prevalence rates of 25% in urban areas and 20% in the rural areas[1]. It is a chronic disease which many a times remains undetected and manifests with complications. Those who are detected also may not receive appropriate or optimal therapy.

The relationship between BP and risk of cardiovascular disease (CVD) events is continuous, consistent, and independent of other risk factors. The higher the BP, the greater the chance of myocardial infarction, heart failure (HF), stroke, and kidney disease. For individuals aged 40 to 70 years, each increment of 20 mmHg in systolic BP or 10 mmHg in diastolic BP doubles the risk of CVD across the entire BP range from 115/75 to 185/115 mmHg[2].

Antihypertensive therapy substantially reduces the risk of hypertension related morbidity and mortality. In clinical trials, antihypertensive therapy has been associated with 35 to 40% mean reductions in stroke incidence; 20 to 25% in myocardial infarction; and more than 50% in heart failure[3].

Recent clinical trials have demonstrated that effective BP control can be achieved in most patients with hypertension, but the majority will require two or more antihypertensive drugs, when physicians fail to prescribe lifestyle modifications, adequate antihypertensive drug doses, or appropriate drug combinations, inadequate BP control may result.

However, the optimal choice for initial therapy of hypertension is uncertain. Therapy of hypertension has become a complicated and challenging task for the clinician. There are a number of newer drugs being introduced, there are new classes of agents and combination products flooding the market. A clinician should know the details of various classes of antihypertensive agents, regarding their efficacy and adverse events as well as the benefits and compelling reasons to use a particular drug. The impact of the drug on co-morbid conditions is one of the major criteria in the decision making.

Initial evaluation of the patient is an important exercise to be carried out by the physician. There are three main objectives of evaluation: i) To identify known causes of hypertension i.e., secondary hypertension (the treatment of this group is focused as well as rewarding), ii) Assess the presence or absence of target organ damage, iii) Identify other concomitant disorders or risk factors that may determine the prognosis and guide treatment approaches. Such data is acquired through a detailed history, physical examination, laboratory tests and other special diagnostic procedures.

Goals of Therapy

The ultimate goal of antihypertensive therapy is the reduction of cardiovascular and renal morbidity and mortality. Because most patients with hypertension, especially those aged at least 50 years, will reach the diastolic BP goal once systolic BP is at goal, the primary focus should be on achieving the systolic BP goal. Treating systolic BP and diastolic BP to targets that are less than 140/90 mmHg is associated with a decrease in CVD complications. In patients with hypertension with diabetes or renal disease, the BP goal should be less than 130/80 mmHg.

In the 1950's the drugs used in the management of hypertension were methyldopa, reserpine, hydrallazine. Though effective, these agents were observed to loose their efficacy in the long term when used as monotherapy. With the introduction of diuretics, they were used as add on therapy to overcome the problems of pseudo-resistance.. Soon diuretics were shown to be equally effective when used alone and they became the cornerstone of therapy. They figured as first line agents in every large trial from 1967 to 1990. During the period from 1977-87, the Joint National Committee on Hypertension recommended diuretics and beta-blockers as the first line agents. The JNC IV reversed this, since the doses in which diuretics were used during this period were found to adversely affect the diabetic status, produced hypokalemia and increased the uric acid levels[4].

The advent of newer drugs for the treatment of hypertension like the calcium channel blockers and ACEI resulted in a decreased use of diuretics. The steady introduction of newer agents and their heavy promotion by the industry made the physicians to switch away from use of diuretics as first line agents in the treatment of mild to moderate hypertension.

Earlier clinical trials have documented the benefit of lowering blood pressure using primarily thiazide diuretics or beta-blockers. After these studies several newer classes of antihypertensive agents–ACE inhibitors calcium channel blockers, alpha adrenergic blockers and more recently angiotensin receptor blockers have become available.

During the past decade, major randomized placebo controlled trials have documented that ACE inhibitors and calcium channel blockers reduce cardiovascular events in individuals with hypertension. However their relative value compared with older less expensive agents remains unclear. There has been considerable uncertainty regarding the effects of some classes of antihypertensive drugs on risk of coronary artery disease. The relative benefit of these agents in high risk hypertensive subgroups such as the elderly and those with hypertension was not clearly established.

Data from several studies such as SHEP[6] and TOMHS[7] which assessed low dose diuretics and studied mortality as their end points—resulted in revival of diuretics in the management of hypertension with the JNC V and then JNC VI endorsing the diuretics as the first line management tools.

TOMHS study showed that the blood pressure lowering was as good as with other agents, effect on LVH regression was equivalent to that of ACEI. Low dose diuretic therapy does not adversely affect lipid or blood glucose—has lowest rates of intolerance with fewer withdrawals due to adverse events. Low dose diuretic therapy significantly reduces cardiovascular events in hypertensive subjects[7].

In 1999 the WHO/ISH hypertensions guidelines mentioned that all antihypertensive drugs are suitable to control blood pressure[8]. The JNC VII report in 2003 has stated that thiazide type diuretics should be used for most patients with uncomplicated hypertension, either alone or in combination with drugs from other classes (Table 1). Certain high risk conditions are compelling indications for the initial use of other antihypertensive drugs classes such as ACE inhibitors, ARBs, Calcium channel blockers, β-blockers etc[4].

Various classes of diuretics and their sites of action are depicted in Table 2. Figure 1 displays the sites at which the diuretic subclasses have their major effects on electrolyte and water resorption in the nephron after glomerular filtration has occurred.

Thiazide-Type Diuretics

Hydrocholorthiazide and its many variants are effective in lowering blood pressure either as monotherapy and in combination with β-blockers, ACE inhibitors, or angiotensin receptor blockers. There remains some controversy as to whether a thiazide-type diuretic should be the initial treatment for all hypertensives. The evidence from the SHEP study emphasizes the value of a low-dose thiazide-type drug as initial therapy for isolated systolic hypertension in older patients[8], and ALLHAT strongly supports that choice for African-American hypertensives[9]. For others, who are started on a β-blocker, ACE inhibitor, or angiotensin receptor blocker and whose pressure remains above goal, there is a convincing argument that a diuretic should be the next step[10]. Either way, most hypertensives placed on one of these two drug combinations can be well controlled. Using a thiazidetype drug requires baseline serum electrolyte measurement and monitoring of serum potassium. Gout remains an occasional adverse reaction as a consequence of diuretic-induced hyperuricemia, and infrequently, hypercalcemia may occur. These effects are the result of thiazide-related reductions in urinary urate or calcium excretion. Type 2 diabetes may develop during the course of thiazide-type diuretic treatment, yet in elderly patients, there seems to be little added risk for cardiovascular events compared with preexisting diabetes[8]. For those patients who develop hypokalemia on low-dose thiazidetype diuretics, a diagnosis of primary aldosteronism may be considered. Addition of potassium-sparing drugs, spironolactone,

Table 1: JNC 7

BP Classification	*Systolic BP*	*Diastolic BP*	*Without compelling indication*	*With compelling indication*
Normal	<120	<80		
Pre-hypertension	120-139	80-89	No antihypertensive drug indicated	Drug(s) for compelling indication
Stage 1 hypertension	140-159	90-99	Thiazide type diuretics for most, may consider ACEI, ARB, β-blocker, CCB or combination	Drug(s) for compelling indication Other antihypertensive drugs (diuretics, ACEI, ARB, CCB, β blockers) as indicated
Stage 2 hypertension	≥ 160	≥ 100	2 drug combination for most (usually thiazide type diuretic and ACEI or ARB or β-blocker or CCB)	Drug(s) for compelling indication Other antihypertensive drugs (diuretics, ACEI, ARB, CCB, β blockers) as indicated

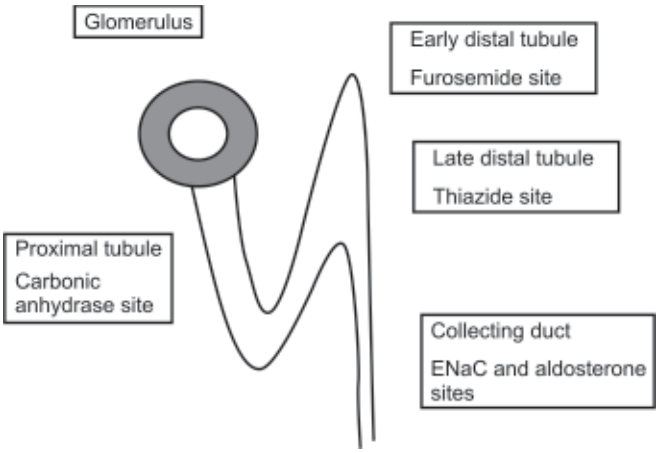

Fig. 1: Sites of action of different classes of diuretics

eplerenone, or amiloride, may achieve effective control of hypertension and correct hypokalemia without the need for extensive diagnostic assessment or consideration of adrenalectomy, since no study has clearly shown that surgical treatment for primary aldosteronism is superior to effective medical management.

Other Thiazides

Metalazone is powerful diuretic within the overall thiazide family. It is effective even in patients with reduced renal function. The standard dose is 5-20 mg once daily for CCF, renal edema and 2.5-5 mg for hypertension. In combination with furosemide, metazolone may provoke a profound diuresis, with risk of excessive volume and potassium depletion. Mykrox is a rapidly acting formulation of metazolone with high bioavailability. It is used for hypertension in the doses of 0.5-1 mg once daily.

Indapamide

It has a structural similarity to the thiazides, it was developed to produce a sulphonamide derivative with a 2 methyl indoline moiety that would dissociate thiazide antihypertensive effects from diuretic effects. Indapamide, therefore, has direct vascular effects causing vasodilation and at high concentrations has class I and II antiarrhythmic effect. It has a terminal half life of 14-16 hours and effectively reduces blood pressure over 24 hours. It is lipid neutral and other metabolic problems associated with thiazides are also not significant with this drug. Indapamide has also been shown to possess additional benefits in terms of regression of LVH[11] and reduction of microalbuminuria in diabetic patients[12].

Loop Diuretics

Furosemide and its analogs (bumetanide or torsemide) interrupt resorption of sodium, calcium, and potassium in the distal renal tubule at the ascending limb of the loop of Henle at sites distinct from the thiazide-sensitive loci. These loop-active agents have a short duration of action and, for treatment of hypertension, must be given twice daily. Renal insufficiency reflected by reduced creatinine clearance limits the effectiveness of thiazide-type diuretics. In contrast, furosemide is highly effective despite renal impairment, although high doses are often needed when serum creatinine increases. The loop-active diuretics may cause hypokalemia, which can be countered by potassium supplementation or potassium-sparing diuretics. Close monitoring of serum potassium is necessary in these circumstances. Unlike the thiazide-type agents, the loop-active diuretics increase calcium excretion and can reduce serum calcium as a treatment for hypercalcemia

Table 2: Classification and sites of action of diuretics

Diuretic class	*Site of action*	*Comment*
Thiazides		
Bendrofluazide Hydrochlorothiazide Chlorthalidone	Proximal part of the distal tubule	All have antihypertensive efficacy. Minor doubts regarding optimal dose range
Thiazide-Type Diuretics		
Indapamide	Proximal part of the distal tubule and direct vascular effects	Indapamide was developed to produce a sulphonamide derivative with a 2 methyl indoline moiety that would dissociate thiazide antihypertensive effects from diuretic effects
Loop Diuretics		
Frusemide Bumetamide	Ascending limb of the loop of Henle	Potent diuretic and saliuretic, but less useful for treating hypertension
Potassium Sparing Diuretics		
Spironolactone Amiloride	Distal tubule – aldosterone antagonist Distal tubule – sodium potassium exchange	May be particularly useful/effective when hyperaldosteronism is implicated. May cause hyperkalemia in renal failure and the elderly

Potassium Sparing Diuretics

Spironolactone, an inhibitor of the mineralocorticoid receptor, has been used for many years. Although once quite popular, especially in combination with a thiazide diuretic, spironolactone nearly fell out of view (except for its use as a medical treatment for primary aldosteronism) until it was resurrected for its value in the treatment of congestive heart failure. Spironolactone can be highly effective in many patients with refractory hypertension in combination with a thiazide-type diuretic and can correct hypokalemia as well. However, gynecomastia is a limiting adverse reaction for men treated with spironolactone because of the antiandrogen effect of this drug. Premenopausal women treated with spironolactone may develop menstrual irregularities, so that spironolactone is most likely to have sustained acceptance only by postmenopausal women. Eplerenone has recently been developed as a selective mineralocorticoid antagonist whose adverse effect profile is far more acceptable to a broader range of patients compared with spironolactone[13]. Eplerenone should be considered an alternative for those who have a good clinical response to spironolactone but who develop unacceptable adverse reactions.

Amiloride and triamterene are also customarily used drugs that inhibit the epithelial sodium transport channel (ENaC) of the collecting duct. The overall activity of this channel is controlled by the action of aldosterone. The ENaC inhibitors reduce potassium excretion as a consequence of their inhibition of the ENaC in preventing sodium resorption. The ENaC inhibitors have, in general, a minimal effect on blood pressure as monotherapy and are most effective for their potassium-sparing effects. The combination of a thiazide-type diuretic and amiloride (Co-amilizide) as initial treatment has been directly compared in a large randomized outcome trial (INSIGHT) with the long-acting calcium channel blocker, nifedipine GITS. The results of this trial found no statistically significant difference between the two treatments. However, a nonsignificant trend favored the diuretic combination[14]. It is likely that, in the United States, the combination of a thiazide-type diuretic and a potassium-sparing agent, such as amiloride (which is a very-well-tolerated, inexpensive, and generic drug), is underused.

Rarely, salt-sensitive hypertensives may have gain-of-function mutations of the ENaC, resulting in an autosomal recessive trait (Liddle's syndrome), which conveys a curative role for amiloride in this setting. It has been suggested that heterozygotic patterns may account for salt-sensitive and amiloride-responsive hypertension in some larger population groups[15].

Why Diuretics are Considered as First line of drugs for Hypertension?

The goal in hypertension management is reduction of morbidity and mortality due to cardiovascular disease by reducing high blood pressure as well as controlling the risk factors. Diuretics fulfill these goals of therapy.

The recent ALLHAT study demonstrated that thiazide type of diuretics are unsurpassed in lowering blood pressure and reducing the clinical events[16]. Evidence from this study proved that thiazide type of diuretics offer better reduction of blood pressure with lesser incidence of coronary revascularization and heart failure as compared to other drugs like CCB, ACEI or ARB[16]. Several other studies have also proved that thiazide type of diuretics offer significant reduction in the systolic blood pressure.

Diuretics prevent target organ damage. In the LIVE study[11] Indapamide offered superior cardioprotection by significantly reducing left ventricular wall thickness by 8.4gm/m^2. The Nestor study shows that Indapamide ensured nephroprotection significantly reducing micro-albuminuria by 35% in diabetic with hypertension[12].

In the PATS study indapamide has been shown to provide neuroprotection by significantly reducing the incidence of secondary strokes by 29%[17]. In the MRFIT study it was shown that patients with diastolic blood pressure of 75-79 mmHg and systolic blood pressure over 160 mmHg had a risk for death 25 times higher than subjects with a similar diastolic blood pressure but normal systolic blood pressure[18]. Studies have shown that it is the systolic blood pressure which is associated with higher risk of cardiovascular morbidity and mortality than the combined diastolic and systolic pressure. Patients with elevated systolic blood pressure are 5 times more likely to develop CHD than patients with normal systolic blood pressure. Controlling systolic blood pressure is considerably more difficult than controlling diastolic blood pressure. The systolic blood pressure target to below 140 mmHg can be achieved in only 34% of patients while the DBP target was achieved in 73% of hypertensive patients. Therefore, it seems that control of high SBP is extremely important in the effective control of hypertension. In a meta-analysis it was shown that indapamide SR was superior to all other antihypertensives in reducing the SBP.

The BHS/NICE recommendations of July 2006 have rationalized that it is appropriate to use ACEI/ARBs in younger patients since they have higher levels of renin compared to the elderly subjects in whom it is advisable to use diuretics and calcium channel blockers[20].

CONCLUSIONS

Contrary to the rumours of only a few years ago, diuretics have not fallen into disuse but have a highly important and multifaceted role to play in the treatment of hypertension. Identifiable but large subgroups within the hypertensive population (isolated systolic hypertension of the elderly) are those for whom diuretic treatment as initial management may achieve the most benefit. Combinations of the thiazide-type and potassium-sparing subclasses may be highly effective, providing nearly optimal therapy for some, and might be considered more often in the treatment of hypertension. Hypertensive subjects in whom other agents like ACE inhibitors and ARB or CCB are being used, diuretics can be combined to optimize blood pressure control. Diuretics are to be used as first line in uncomplicated hypertension, in the elderly, those who have systolic hypertension. The selection of a diuretic should be based on its efficacy and freedom from electrolyte and other metabolic disturbances.

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