Chapter 19

Choosing a Diuretic in Hypertension: To Follow Instinct or Evidence

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THE LEGACY: ONE OF THE EARLIEST EFFECTIVE AND WELL TOLERATED TREATMENTS FOR HYPERTENSION

Thiazide diuretics have been in use for the management of hypertension since 1950s and are the first effective antihypertensive agents with an acceptable side effect profile. More than 60 years later, thiazide diuretics are still useful, as they reduce blood pressure (BP) in monotherapy, enhance the efficacy of other antihypertensive drugs and some of them also reduce the cardiovascular (CV) morbidity and mortality.

GUIDELINES: WHAT DO THEY SAY ABOUT DIURETICS?

Initially high doses of thiazide diuretics were used due to the belief that the efficacy was based on the amount of renal sodium excretion and reduction of plasma volume—higher the dose, greater the assumed BP reduction. However, The Sixth Report of the Joint National Committee (JNC-6) reasserted the use of low-dose thiazide diuretics as first-line therapy as the new evidence from Systolic Hypertension in the Elderly Program (SHEP), Swedish Trial in Old Patients with Hypertension-2 (STOP-2), Medical Research Council (MRC) and Treatment of Mild Hypertension Study (TOMHS) respectively assessed and confirmed the benefits of low dose diuretics, with mortality as their end-point. Using thiazide diuretics at low doses also reduce the incidence of electrolyte and metabolic side effects associated with their use at high doses.

The JNC-7 guidelines took-off from where JNC-6 had left, albeit, more specific in their recommendations for the use of thiazide type diuretics (and not thiazide diuretics) for most patients as a first line, after the much touted largest hypertension study Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) results showed no significant differences between the three arms comprising a thiazide type: (1) diuretic—chlorothalidone, (2) calcium channel blocker—amlodipine and (3) an angiotensin-converting enzyme inhibitor (ACEI)—lisinopril, on the outcomes of the trial. Thiazide type diuretics in combination with an ACE inhibitor, angiotensin II receptor blocker (ARB), beta-blocker or a calcium channel blocker were also recommended for patients with stage 2 hypertension in initiation.

Though the recommendation was for thiazide type diuretic, the diuretic to benefit most from them was hydro-chlorothiazide (HCTZ), as most of the fixed dose combinations (FDCs) available and launched later, contained it.

THE PURPOSE: OBJECTIVE OF HYPERTENSION MANAGEMENT

All the hypertension guidelines have been emphasizing that the prime objective of treating hypertension should be to reduce CV morbidity and mortality. Hence, the drug selected for a patient should be carefully weighed for evidence of CV events reduction available with it.

DIVERSITY IN UNITY: ARE ALL DIURETICS SAME?

Ever since JNC-1, diuretics have been at the forefront of their recommendations, but always as a class and never any discrimination has been made amongst them, except JNC-7 which said thiazide-type diuretic. Is it right to group all thiazide diuretics together, especially when so much of evidence is available with them? This will not do justice to some members of the class, which can be further subclassified as thiazide-type or thiazide-like diuretics, such as chlorothalidone or indapamide. Thiazide diuretics on the other hand, will mainly include HCTZ and bendroflumethiazide, out of which only HCTZ is available in India, mainly as part of fixed dose combinations (FDCs).

HARD TALK: LITERATURE REVIEW OF HYDROCHLOROTHIAZIDE

If we review the literature for evidence of morbidity—mortality reduction with diuretics, we find that with HCTZ, very few studies such as European Working Party on Hypertension in the Elderly (EWPHE), MRC (elderly), Veterans Administration (VA), etc. have shown some CV event reduction versus placebo or in International Nifedipine GITS (Gastro-Intestinal Therapeutic System) Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) where HCTZ was found to be equal to calcium antagonists. But, the dose used in these studies was 25–100 mg of HCTZ. At doses below 25 mg, there is no evidence of reduction in morbidity and mortality with HCTZ. Also, there are metabolic and electrolytic abnormalities associated with these high doses as seen by potassium supplements being added to HCTZ in 4 out of 9 studies.

Recently, a comprehensive review published in the Journal of American College of Cardiology has shown that not only is there no evidence of reduction in CV outcomes (heart attacks, stroke, death) with HCTZ at doses of 12.5–25 mg, even the 24-hour BP control (only 6.5/4.5 mm Hg) is much inferior to other antihypertensive classes. Note that at higher doses HCTZ has been shown to increase the risk of cardiac arrest dose-dependently. Compared to HCTZ 25 mg daily,
50 mg daily has been reported to increase the risk of primary cardiac arrest [odds ratio (OR) 1.7] and 100 mg was associated with an even larger increase in risk (OR 3.6). Professor Messerli, the author of this review, concluded by saying that whenever a diuretic is needed in hypertension, it should be chlorthalidone or indapamide.

The Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) study also showed that an ACEI in combination with HCTZ actually increased the risk of CV mortality, stroke and progression of chronic kidney disease by 25%, 18% and a significant 90% respectively, when compared to the same ACEI in combination with amlopidine. These effects could be due to the fact that at low dose, HCTZ is providing only the clinic BP reduction, with no reduction in night time BP. However, increasing the dose of HCTZ will inherently increase the incidence of hypokalemia and diabetogenicity which is seen with doses of 50 mg or higher. In the International Verapamil-Trandolapril Study (INVEST) study, the addition of HCTZ increased the incidence of new-onset diabetes (from 11–36%). Furthermore, in the Study of Tamoxifen and Raloxifene (STAR) trial the addition of a sartan did not make up for this diabetogenic effect.

In India, most of the FDCs contain HCTZ at even lesser dose of 6.25 mg or 12.5 mg. In view of the evidence discussed above, it is high time that physicians and cardiologists stop using such combinations as they only benefit the pharmaceutical companies promoting them.

LOOK ALIKE OR NEW CONTENDERS: THE THIAZIDE-LIKE DIURETICS

**Chlorthalidone**

On the other hand, the evidence of CV-events reduction in hypertensive patients is much superior and consistent with thiazide-like diuretics: indapamide and chlorthalidone. Chlorthalidone has shown significant CV events reduction versus HCTZ/placebo in trials like Multiple Risk Factor Intervention Trial (MRFIT), SHEP and Hypertension Detection and Follow-up Program (HDFP), whereas it was found to be equivalent to amlopidine and lisinopril in the largest hypertension trial ALLHAT. These benefits were proven at a dose of 12.5–25 mg per day with up to 100 mg per day in HDFP and were not without electrolytic and metabolic side effects. Around 8% patients needed potassium supplements and about 12% patients developed new onset diabetes in the group receiving chlorthalidone. Recently, it was also shown that chlorthalidone causes persistent activation of sympathetic nervous system and insulin resistance which could be the reason for increased new onset of diabetes. The other limitation to the use of chlorthalidone can be the incidence of erection problems in almost every alternate male patient as mentioned by Braunwald’s textbook of heart disease.

**Indapamide**

Indapamide, which is also a thiazide-like diuretic, has consistently shown not only superior BP control as compared to all drug classes including HCTZ in a meta-analysis, but also significant reduction in stroke, heart failure and all cause deaths, in studies like Hypertension in the Very Elderly Trial (HYVET), Perindopril Protection Against Recurrent Stroke Study (PROGRESS), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) and Post-stroke Antihypertensive Treatment Study (PATS). The HYVET study had to be prematurely stopped due to a phenomenal 21% reduction in all-cause mortality in patients receiving indapamide. HYVET also showed reduction in fatal strokes by 39% and heart failure by 64% in this fragile group, where there was no evidence earlier and hence the guidelines were not recommending any treatment for patients above 80 years. The 1 year extension of HYVET has shown that the continuation of indapamide treatment provides even better reduction of 52% in all-cause mortality. The implication of these results is such, that even guidelines have now started recommending, that patients who are 80 years and older, should receive the same antihypertensive treatment, as those above 55 years of age.

In the PROGRESS trial, indapamide in combination with perindopril has shown a significant reduction in stroke by 43%. ADVANCE, the largest trial done in diabetic patients where indapamide was routinely administered in combination with ACEI perindopril, showed a significant reduction in all-cause mortality by 14%, CV mortality by 18% and renal events by 21%. ADVANCE is also a proof metabolic safety of indapamide in the long-term as the hemoglobin A_{1c} (HbA_{1c}) was maintained over a period of 4.5 years. In PATS, indapamide showed a significant reduction in secondary strokes by 29%.

Importantly, these benefits of indapamide are proven at the therapeutic dosage of either 2.5 mg immediate release or the superior 1.5 mg sustained release. So, a treating physician can be certain that the benefits seen in clinical trials are being passed on to his/her patients, when he/she prescribes indapamide to their patients. The SR formulation avoids unnecessary peak in the plasma level of the drug and ensures that only a subclinical diuresis is there, while indapamide controls BP by its predominantly vascular effect. This minimizes the risk of diuretic related side effects like electrolytic or metabolic disturbances. The vascular mechanism of action of indapamide has been proven in hypertensive patients, as normalization of hyperreactivity of vasculature to noradrenalin.

This causes venorelaxation in hypertensive patients thereby reducing their BP. This action also causes venorelaxation, which explains why the risk of pedal edema is minimized when indapamide is added to amlopidine.

Furthermore, in a recent analysis of the X-CELLENT trial, a multicenter, multinational, randomized, double-blind, placebo-controlled study with 4 parallel treatment arms [placebo, candesartan, indapamide sustained-release (SR) and amlopidine] it was shown that 3-month treatment with indapamide SR or amlopidine, but not candesartan, is associated with a significant reduction in BP variability (BPV), an independent and strong predictor of CV events, such as stroke and coronary heart disease. The mechanism of BPV reduction was probably attributable to lowering BP or ameliorating the autonomic nervous system regulation or both.

Indapamide is also available as FDCs with perindopril 4 mg and amlopidine 5 mg, thereby offering more options to treating physicians.

Another point to consider while prescribing a drug with a modified-release formulation is that because of the variability between different SR formulations of the same drug, these should be prescribed by proprietary rather than generic name and substitution should be avoided.

**WHAT IS NEW: LATEST GUIDELINES AND THE IMPLICATIONS**

It was not surprising then, that the 2011 National Institute of Health and Clinical Excellence (NICE) guidelines for hypertension, released by the British Hypertensive Society, specifically recommend that whenever a diuretic is needed for hypertension, it should only be thiazide-like—such as indapamide or chlorthalidone; and that thiazides such as HCTZ or bendroflumethiazide, should be avoided. This clear recommendation should remove any ambiguity that all diuretics are same and clinicians can use the one that they like.

These latest NICE guidelines recommend the use of thiazide-like diuretics in patients above the age of 55 years who have evidence of, or are at risk of heart failure [post-myocardial infarction (MI) hypertensive patients] and those who are intolerant to calcium
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channel blockers. However, based on the recommendations of other guidelines like JNC 7, European Society of Cardiology (ESC) or World Health Organization (WHO), thiazide-like diuretics should be prescribed to most patients who are young and do not have any complications like diabetes or coronary artery disease that may warrant the use of renin angiotensin system blockers or beta-blockers. Since these patients are generally asymptomatic and would not like to take any medicine which may cause unwanted side-effects like tiredness, impotence or cough, use of safer thiazide-like diuretic can improve their compliance to treatment and hence improve their quality and quantity of life.

CONCLUSION

In the review above, it is clear that all diuretics are not the same and they are not interchangeable at all. Most clinicians use HCTZ based FDCs based on instinct as well as the noise level from the pharmaceutical industry. However, in this era of evidence-based medicine, we need to be using only those drugs which have the backing of morbidity—mortality studies.

In case of diuretics, the evidence of effective BP and mortality reduction exists only with two of them, i.e. chlorthalidone and indapamide. Indapamide might be having an edge due to better acceptability profile as also the benefit of study based dosage available for clinic use in 1.5 mg SR form. Indapamide is also available as FDCs with perindopril 4 mg and amlopidine 5 mg, thereby offering more options to treating physicians.

REFERENCES