Why Are We Still Using Hydrochlorothiazide?

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"That monster, custom, who all sense doth eat…"—Shakespeare, Hamlet; Act III, Scene 4.

Was there ever a greater misunderstanding of reality than the suggestion, in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7), that thiazide diuretics were the first drugs of choice for the treatment of hypertension, an opinion based largely on tradition, but also based on the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which did not use a thiazide at all? The ceremonial repetition of the statement that thiazide diuretics should be used as first-line therapy in patients with hypertension has become so common that it appears, in one form or another, in every guideline writer's lexicon of unassailable truth.

Hydrochlorothiazide (HCTZ) has been available and used for the treatment of hypertension for more than 50 years, and is the most commonly prescribed antihypertensive drug worldwide. In 2007, more than 130 million prescriptions for HCTZ, either alone or in combination, were written in the United States.[1] During the lifetime of the JNC, starting in 1976, thiazide diuretics have been recommended as first-line or preferred therapy for hypertension. The use of thiazide diuretics was actively, even aggressively, promoted by the National Heart, Lung and Blood Institute ALLHAT/JNC 7 "dissemination project,"[2] which reached more than 18,000 physicians. In spite of this aggressive advocacy and the continuing extensive use of HCTZ, there is little evidence that supports the JNC 7 recommendation[3] for first-line therapy of hypertension with a thiazide diuretic, such as HCTZ, bearing in mind that the diuretic shown to be equipotent with amlodipine and lisinopril in preventing cardiovascular (CV) events in ALLHAT, was not HCTZ but chlorthalidone,[4] which is not a thiazide diuretic.[5] Monotherapy with HCTZ in the lower doses used today has never been shown to reduce CV morbidity or mortality.

In addition, HCTZ has a number of side effects that detract from its status as the drug of first choice in the treatment of hypertension.

DIABETES

In a network meta-analysis of 22 clinical trials with 141,153 participants who did not have diabetes at randomization, Elliott and Meyer (2007)[6] reported that there is a 30% greater risk with diuretics compared with placebo (odds ratio, 1.30; 95% confidence interval [CI], 1.07–1.58, *P*=.009) of developing diabetes during the relatively few years' duration of each of these clinical trials. Diuretics were the only drugs to cause a statistically significant increase in incident diabetes. Another network meta-analysis, by Messerli and colleagues in 2008,[7] reported the same result: "In the analysis of six trials enrolling 30,842 patients with hypertension, diuretics resulted in a 32% increased risk of new-onset diabetes compared with placebo or non–β-blocker antihypertensive agents. Compared with placebo, diuretics resulted in a strong trend toward a 22% increased risk of new-onset diabetes, suggesting that the risk is due to the medication itself. When compared with antihypertensive agents other than β-blockers, diuretics conferred a 35% increased risk of new-onset diabetes."

An important question is: does thiazide diuretic–induced diabetes mellitus increase morbidity and mortality? Several studies have addressed this issue with consistent results. In 2004, Verdeccia and colleagues[8] reported a 16-year follow-up of almost 800 initially untreated hypertensive patients, and found that patients with new-onset diabetes and those with a previous diagnosis of diabetes were almost 3-fold more likely to develop subsequent CV disease than those who remained free of diabetes. Alderman and colleagues[9] studied almost 7000 patients and reported that "Cardiovascular disease incidence has a direct dose response relation with diuretic used with frequent users having the highest rate." Similar results have been reported in the 11,645-patient Multiple Risk Factor Intervention Trial (MRFIT)[10] and the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study.[11]

The conclusion is that thiazide diuretics impair glucose tolerance and cause incident diabetes. Diabetes increases the risk of CV events.

HYPOKALEMIA

It is well accepted that a low to medium dose of a diuretic such as HCTZ (12.5–25 mg/d) is effective in lowering blood pressure (BP) with considerably fewer metabolic side effects than were seen in the days when HCTZ was prescribed in doses of 50 mg/d or even 100 mg/d. At these higher doses, there was a considerable rate of serious metabolic side effects such as low serum potassium, low serum sodium, and elevated uric acid and cholesterol.

A low serum potassium level is particularly dangerous, especially in a high-risk patient with coronary artery disease, since it can precipitate a fatal arrhythmia and cardiac arrest. This has been documented as a risk of thiazide diuretic therapy.[12]

Most risk factors are graded, rather than having a cut-off or threshold value, so a patient with significant

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coronary artery disease, already at risk for a life-threatening arrhythmia, with a serum potassium level in the low-normal range would be expected to have a greater risk of sudden cardiac death than if the potassium were comfortably in the middle of the normal range. This could at least partly explain, in the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial,[13] the excess number of trial participants in the benazepril-HCTZ group, compared with the benazepril-amlodipine group, who died from CV causes (134 vs 107) or who had a fatal or nonfatal myocardial infarction (159 vs 125).

CHLORTHALIDONE IS A GOOD ANTIHYPERTENSIVE DRUG AND DIFFERS IN SIGNIFICANT RESPECTS FROM HCTZ

Chlorthalidone, not HCTZ, was the diuretic shown to be as good as amlodipine and lisinopril in ALLHAT. As stated, chlorthalidone is not a thiazide diuretic, so the reference to ALLHAT in all of the enthusiastic endorsements of thiazide diuretics for the treatment of hypertension is misplaced.

There are major differences between the archetypal thiazide diuretic, HCTZ, and chlorthalidone. First, chlorthalidone does not have the benzothiadiazine dioxide scaffold that defines a thiazide.[5] Also, there are significant pharmacokinetic and pharmacodynamic differences. HCTZ has a single-dose plasma half-life of 6 to 9 hours, chlorthalidone has a half-life of 40 hours. Equivalent figures for long-term dosing are HCTZ 8 to 15 hours and chlorthalidone 45 to 60 hours. It is therefore no surprise that, with 24-hour ambulatory BP monitoring, nighttime BP is lower with chlorthalidone than with HCTZ.[14,15]

There are also significant differences in pharmacodynamics between chlorthalidone and HCTZ. Chlorthalidone is 1.5 to 2.0 times more potent than HCTZ in reducing BP.[16] Chlorthalidone also compares favorably with bendroflumethiazide, a thiazide diuretic widely used in the United Kingdom, in the ability to decrease platelet aggregation and increase new vessel formation (angiogenesis), as well as to affect cell protein factors that are known to influence the development of CV disease.[17] There is also the possibility that chlorthalidone, like acetazolamide, another carbonic anhydrase inhibitor, can increase the production of nitric oxide,[18] which dilates blood vessels and is also vasculoprotective. These effects have never been reported for thiazide diuretics.

Do these differences of the effects on cellular function between chlorthalidone and HCTZ translate into better CV outcomes? There is good evidence that they do.

The debate concerning the differences between chlorthalidone and thiazide diuretics was intensified as a result of the disparate findings of ALLHAT[4] and the Second Australian National Blood Pressure Study (ANBP2).[19] ALLHAT reported fewer events for combined CV disease, stroke, and heart failure with chlorthalidone than with an angiotensin-converting enzyme (ACE) inhibitor. In contrast, ANBP2 used HCTZ as the diuretic but found an ACE inhibitor to be superior at reducing combined morbidity and mortality in men. This was indirect evidence that chlorthalidone and HCTZ may be substantially different, not only in their pharmacokinetic and pharmacodynamic effects, but also in their capacity to protect against CV morbidity and mortality.

In the long-term follow-up of the individuals who participated in the Multiple Risk Factor Intervention Trial (MRFIT) (MRFIT Research Group, 1990)[20] the authors reported: ''Two factors appear to have contributed to this more favorable mortality trend for the SI [special intervention] group: 1) a change in the diuretic treatment protocol for SI men about 5 years after randomization, which involved replacement of hydrochlorothiazide with chlorthalidone at a daily maximum dose of 50 mg; and 2) a favorable effect of intervention on nonfatal cardiovascular events during the trial years.'' A retrospective cohort analysis of the MRFIT data comparing chlorthalidone with HCTZ, conducted by Dorsch and colleagues,[21] showed that patients treated with chlorthalidone (more than 2300 patients) had a 21% lower risk of CV events than those taking HCTZ (more than 4000 patients). The adjusted hazard ratio was 0.79 (CI, 0.68–0.92; P=.006). Chlorthalidone also produced significantly lower mean systolic BP, total cholesterol, and low-density lipoprotein cholesterol than HCTZ. On the down side, the chlorthalidone group had lower potassium and higher uric acid levels than the HCTZ group. In an accompanying editorial, Flack and colleagues[22] stated: ''...the retrospective observational cohort analysis of the Multiple Risk Factor Intervention Trial by Dorsch and colleagues adds to the growing body of evidence supporting the superiority of chlorthalidone over HCTZ as the preferred diuretic in the treatment of hypertension.''

This is not to say that chlorthalidone does not affect glycemic control or lower serum potassium levels like thiazide diuretics. It does. The clinical trials data, however, particularly of ALLHAT, that support the use of chlorthalidone as the diuretic of choice are compelling. Clinicians may reasonably prescribe other medications as first-line treatment in patients with hypertension. However, if a diuretic is chosen, the best available evidence, from ALLHAT, favors chlorthalidone in most patients with uncomplicated hypertension. Also, chlorthalidone is a reasonable choice for use in combination with other agents for most patients who require more than one antihypertensive agent.

JNC 7 served a very useful purpose in collecting and codifying best practices for hypertension, but the one thing they got spectacularly wrong was to base their unrestrained zeal for ''thiazide-type diuretics'' on ALLHAT when the diuretic in ALLHAT was nothing of the sort. Since then, HCTZ has become something of a

habit, and old habits die hard. Aristotle put it best: ''All human actions have one or more of these seven causes: chance, nature, compulsion, habit, reason, passion, and desire.'' Let's have less habit and more reason.

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