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Hydrochlorothiazide (HCTZ) is not the most useful nor versatile thiazide diuretic

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Abstract

Purpose of review—To determine usefulness and versatility of hydrochlorothiazide (HCTZ) relative to other thiazide diuretics in the treatment of hypertension.

Recent findings—Hydrochlorothiazide (HCTZ) was found to be less potent in lowering BP than other thiazide diuretics, including chlorthalidone (CTD) and bendroflumethiazide. A recent meta-analysis also suggested HCTZ (12.5–25 mg daily) to be less potent than antihypertensive agents from several other classes, including angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and calcium antagonists. The risk of hyponatremia, hypokalemia, and hyperuricemia associated with HCTZ was lower than CTD while the risk of gouty arthritis was similar. Despite lower risks of metabolic side effects, meta-analysis of clinical trials showed that, for any given difference in achieved clinic systolic BP, HCTZ therapy was associated with 18% higher adverse cardiovascular events when compared to CTD.

Summary—Increasing evidence suggested inferiority of HCTZ in lowering BP and cardiovascular outcomes in hypertensive patients when compared to other drugs in the same class, particularly chlorthalidone and Indapamide. Thus, HCTZ is neither more useful nor versatile than other thiazide diuretics. CTD and indapamide should be preferred over HCTZ in most hypertensive patients when diuretics are required for treatment of hypertension.

Keywords

hypertension; thiazide diuretics; hydrochlorothiazide; chlorthalidone

Introduction

Hydrochlorothiazide is a thiazide-type diuretic which has been available for clinical use for more than 5 decades. Although hydrochlorothiazide (HCTZ) is the most commonly prescribed thiazide diuretics in the U.S., HCTZ differs markedly from other drugs in this class in regards to pharmacokinetic property, antihypertensive efficacy, and cardiovascular risk reduction. The scope of the article includes current review of literature with the

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emphasis on safety and efficacy of HCTZ in treatment of hypertension compared to other thiazide diuretics and classes of antihypertensive drugs.

Thiazide diuretics comprise of two major classes, the thiazide-type and thiazide-like diuretics. All thiazide-type diuretics, including HCTZ, chlorothiazide, and bendroflumethiazide, share the common structure of benzothiadiazine dioxide scaffold (1). Thiazide-like diuretics, chlorthalidone (CTD), metolazone, and indapamide, lack the characteristic benzene ring but still possess ability to inhibit sodium chloride co-transporter in the distal convoluted tubule (2). In vitro studies indicated the highest binding affinity to distal convoluted tubule of bendroflumethiazide followed by indapamide and CTD with the lowest value in HCTZ (2). Both thiazide-like and thiazide-type diuretics exhibit ability to inhibit carbonic anhydrase enzymatic activity (1). However, CTD is preferentially taken up by the red blood cells to inhibit carbonic anhydrase enzyme, which may explain exceedingly long half-life of chlorthalidone of 30–72 hours (3–5). In contrast, half-life of HCTZ and other thiazide diuretics are only in the range between 5–15 hours (6–8).

Antihypertensive efficacy

At the dose commonly prescribed in clinical practice of 12.5–25 mg/day, HCTZ was shown to modest effect on 24-hr ambulatory BP by 6.5/4.5 mmHg (9). This magnitude of reduction in BP was inferior to other drug classes, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs) (9). The antihypertensive efficacy of HCTZ was found to be similar to other drug classes only at the higher daily dose of 50 mg. In a recent meta-analysis HCTZ, at the daily dose between 12.5–25 mg, caused a smaller reduction in clinic BP when compared to low dose CTD and bendroflumethiazide (10). The estimated doses of bendroflumethiazide, CTD, and HCTZ predicted to lower clinic systolic BP by 10 mmHg was 1.4, 8.6, and 26.4 mg, respectively (10). At the higher dose range, however, all three thiazide diuretics were shown to cause similar reduction in BP, suggesting difference in potency but not maximal efficacy. Another meta-analysis conducted by the British National Institute for Health and Clinical Excellence (NICE) group showed that indapamide was more potent than HCTZ in lowering BP (11). Accordingly, the thiazide-like diuretics are preferred over HCTZ and other thiazide-type diuretics by the NICE guidelines (11).

Side effects

Thiazide diuretics are known to cause a number of electrolyte abnormalities, including hyponatremia and hypokalemia. At the equivalent dose, CTD was shown to cause greater reduction in serum sodium than HCTZ, suggesting higher potency in inducing this side effect (12, 13). However, the risk of hyponatremia of CTD at the daily dose of 25 mg is similar to the risk associated with HCTZ at the daily dose of 50 mg (12). CTD and bendroflumethiazide were also shown to have higher potency in reducing serum potassium than HCTZ (10). Nevertheless, clinical significance of these findings appears to be trivial and outweighed by benefit from BP reduction of CTD. In one study, switching HCTZ to CTD at the same dose led to significant reduction in systolic BP by 16 mmHg but caused reduction in serum sodium by 1.1 mmol/L and potassium by 0.15 mmol/L (13).

Other than electrolyte abnormalities, HCTZ was shown to be associated with lower risk of hyperuricemia than CTD (10). However, the risk of symptomatic gouty arthritis was similar between HCTZ and CTD in one study (14). Both HCTZ and CTD were shown to induce insulin resistance and increase risk of diabetes mellitus (DM) (15, 16). Mechanisms underlying thiazide-induced dysglycemia is unknown but was postulated to be related to hypokalemia. In addition, overactivation sympathetic nervous system and renin-angiotensin-aldosterone system may contribute to thiazide-induced insulin resistance, independent of serum potassium (17, 18). Nevertheless, cardiovascular prognosis of patients with incident DM while on CTD appears to be benign. In the SHEP (Systolic Hypertension in Elderly Program) study, DM that developed during chlorthalidone therapy did not have a statistically significant impact on cardiovascular mortality or on all-cause mortality when compared to CTD treated patients without DM (19). In contrast, incident DM in the placebo-treated group carries a significant increase in cardiovascular mortality (19). Similarly, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) Diabetes Extension study indicated that incident diabetes during CTD treatment has less adverse long-term cardiovascular outcomes than incident diabetes that develops while on amlodipine or lisinopril (20).

Interestingly, a prospective observational study in middle-aged hypertensive men showed that incident diabetes during treatment with HCTZ 25–50 mg or bendroflumethiazide 2.5–5mg is not as benign as DM during CTD (21). In this study, the risk of stroke, myocardial infarction, and mortality was increased by 40–70% in individuals with incident DM compared to the control group who remained free of DM over period of follow up of 28 years (21).

Cardiovascular risk reduction

Although the net impact of antihypertensive benefit vs. metabolic risks of HCTZ vs. other thiazide diuretics on an individual patient may be difficult to discern, the most compelling evidence against usefulness of HCTZ is in the area of cardiovascular risk reduction. A retrospective observational cohort study from the Multiple Risk Factor Intervention Trial (MRFIT), a cardiovascular primary prevention trial where men 35 to 57 years of age, suggested superiority of CTD over HCTZ in lowering cardiovascular events (22). In this trial, hypertensive patients were randomized to a special intervention group consisting of treatment for hypertension, smoking cessation counseling, and dietary guidance to reduce sodium intake or to usual care. Investigators in the trial were allowed to choose to begin hypertension treatment with either HCTZ or CTD at 50 or 100 mg daily. Both HCTZ and CTD treatment was associated with lower cardiovascular events compared with untreated group but the relative risk reduction was greater with CTD than HCTZ despite lower serum potassium and higher uric acid levels in the CTD group (22). In the same trial, CTD was shown to induce greater reduction of left ventricular hypertrophy compared to HCTZ as evidenced by electrocardiography (23).

Treatment with HCTZ based regimen was also found to be inferior to calcium-channel blocker based regimen in another randomized clinical trial in hypertensive patients with high cardiovascular risks. The Avoiding Cardiovascular Events Through Combination Therapy in

Patients Living With Systolic Hypertension (ACCOMPLISH) Trial, which compared cardiovascular outcomes in patients treated with combination of HCTZ (12.5–25 mg daily) plus benazepril vs. combination of amlodipine (5–10 mg daily) plus benazepril at the identical dose, was terminated prematurely due to 20% higher event rates in the HCTZ arm (24). This difference in cardiovascular events was not explained by magnitude of BP reduction and was postulated to be related to vasoprotective effects of amlodipine (25). In contrast, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed that CTD (12.5–25 mg daily) was superior to both amlodipine arm and lisinopril arm in reducing new onset heart failure in the high-risk hypertensive patients (26). Although no clinical trial has been conducted to directly compare cardiovascular outcomes following treatment with HCTZ vs. CTD in hypertension, meta-analysis of randomized clinical trials of these 2 drugs has been conducted (27). In this meta-analysis by Rousch et al, HCTZ therapy was associated with 19% higher adverse cardiovascular events than CTD for any given reduction in clinic systolic BP (27). These findings provided important confirmation to MRFIT observational data, which was not included in the meta-analysis.

Mechanisms underlying superiority of CTD over HCTZ in lowering cardiovascular events beyond BP reduction are unknown. In vitro studies demonstrated ability of CTD in decreasing epinephrine-mediated platelet aggregation (28). Both chlorthalidone and bendroflumethiazide were found to reduce vascular permeability to albumin, but only chlorthalidone was shown to promote angiogenesis (28). In vivo studies in hypertensive patients demonstrated that CTD improved acetylcholine-mediated vasodilation in the forearm (29). Alternatively, long half-life of CTD may result in a sustained reduction in BP beyond period of clinic visit. Ernst et al demonstrated superiority of CTD over HCTZ in lowering nighttime BP in a randomized crossover study in hypertensive patients (30). This property of CTD may have long-term cardiovascular implication as nighttime BP was found to more predictive of cardiovascular events than daytime BP and office BP in many previous epidemiological studies (31, 32).

Versatility

HCTZ is widely used in the form of combination pill with other antihypertensive agents, which, at first glance, may represent an advantage over CTD or other thiazide diuretics in terms of ease of use. However, HCTZ is strictly present at the lower dose range (12.5–25 mg) in the form of combination pill, which in turn minimizes this potential advantage. A randomized double-blinded multicenter trial showed that smaller proportion of hypertensive patients treated with combination of low dose HCTZ plus azilsartan in the single combination pill achieved target BP goal compared with low dose CTD plus azilsartan (64 vs. 46%, respectively, $p < .001$) (33). Interestingly, in this trial, incidence of hypokalemia and drug adverse events requiring discontinuation was not different between the two groups (33). Furthermore, randomized clinical trials suggested that cardiovascular risk reduction associated with HCTZ is less evident in normal weight patients than in overweight or obese patients (34). In contrast, cardiovascular benefit of CTD was found to be uniformly present in each category of body mass index in the ALLHAT trial (35).

Conclusion

Summary of efficacy and safety of HCTZ is summarized in table 1. HCTZ is not proven to be more useful nor versatile than other thiazide diuretics. Increasing number of evidence suggested superiority of thiazide-like diuretics, particularly chlorthalidone and indapamide, in reducing both BP and cardiovascular events independent of BP reduction. Accordingly, CTD and indapamide are preferred over HCTZ in treatment of hypertension based on the 2011 NICE consensus statement (11). CTD is also preferred over all other thiazide diuretics by the 2008 American Heart Association Professional Education Committee of the Council for High Blood Pressure Research in patients with resistant hypertension (36). Unfortunately, HCTZ is prescribed 9–10 times more often than CTD and indapamide in combine in the United States (37, 38). In a recent national survey of office visits in the US, CTD was used in less than 3% of patients with resistant hypertension despite treatment with > 3 antihypertensive drugs (38). Replacing HCTZ with CTD in these patients could lead to more effective BP control and alleviate the need to add the fourth or fifth antihypertensive drugs, which will likely improve patients' acceptance and long-term compliance.

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* of special interest

** of outstanding interest

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Key points

- HCTZ is less potent than other thiazide diuretics, including CTD and bendroflumethiazide in lowering BP, at the lower dose range of 12.5–25 mg daily.
- Abnormalities in serum electrolytes and metabolic profile associated with low dose HCTZ are also less than CTD but the clinical significance of these findings are unknown.
- After accounting for difference in the magnitude of office BP reduction, HCTZ therapy is associated with higher cardiovascular event rate than CTD, suggesting potential pleomorphic effects of CTD or more sustained reduction in BP beyond clinic visit.

Table 1

Comparison of efficacy and safety of HCTZ vs. CTD.

Features	HCTZ	CTD
Half-life	Moderate (5–15 hrs)	Very long (30–72hrs)
Hypokalemia	↑	↑↑
Hyponatremia	↑	↑↑
Hyperuricemia	↑	↑↑
Reduction in office BP	↓	↓↓
Reduction in nighttime BP	↓	↓↓
Pleiotropic effects (antiplatelet effects and vascular effects)	None	Yes
Cardiovascular protection	↑	↑↑