Indian Health Service

IHS National Pharmacy and Therapeutics Committee

Formulary Brief: Chlorthalidone in Hypertension

May 2012

Background:

The IHS National Pharmacy and Therapeutics (NPTC) reviewed thiazide diuretics at their April 2012 meeting. This review primarily focused on two thiazides; hydrochlorothiazide and chlorthalidone. Hydrochlorothiazide is currently the single named agent in this class on the IHS National Core Formulary (NCF). After the review of evidence in guidelines and clinical trials involving the use of these two agents, chlorthalidone was **added** to the NCF. The committee is producing this formulary brief to review the evidence in favor of chlorthalidone use and to encourage its utilization as a first line option when initiating diuretic therapy in patients with essential hypertension.

Discussion:

Hypertension (HTN) affects approximately 76.4 million individuals in the United States. Currently, one in every three adults has HTN, a major risk factor for heart disease, stroke, congestive heart failure, and kidney disease. Hypertension is common in American Indian/Alaska Natives (AI/AN), affecting approximately 30% of individuals. AI/AN are 1.3 times more likely to have HTN than white adults.[1] Among American Indian men 45 to 75 years of age, the incidence of CVD ranges from 15 to 28 per 1000 population. Among women, it ranges from 9 to 15 per 1000.[2] Heart disease is the leading cause of mortality in AI/AN, reaching approximately 18.4% in 2007.[3] As such, life expectancy for AI/AN is 5.2 years less compared to all races in the United States (72.6 years to 77.8 years, respectively; 2003-2005 rates).[4]

Thiazide diuretics mechanism of action involves increasing the excretion of sodium and chloride by blocking their reabsorption in the distal tubule of the nephron, leading to reduced reabsorption of water and therefore diuresis. Both chlorthalidone (CTD) and hydrochlorothiazide (HCTZ) have FDA indications for the treatment of hypertension and edema. CTD has a significantly longer half-life compared to HCTZ (40-89 hours vs. 5.6-14.8 hours). It is recommended to be started at 25 mg daily and may be increased up to 100 mg daily for the treatment of hypertension. In treating edema, it can be started at 50-100 mg daily and increased up to 150-200 mg daily.[5, 6]

Guidelines

JNC 7 [7]

JNC 7 guidelines for the prevention, detection, evaluation, and treatment of HTN provided evidence-based recommendations based on scientific literature between 1997 to 2003. JNC 7 recommends initial therapy with lifestyle modifications. However, if blood pressure (BP) goals are not achieved (< 140/90 mmHg or < 130/80 mmHg with chronic kidney disease), thiazides or thiazide-like diuretics should be initiated for most patients with uncomplicated HTN, either alone or in combination with another class (ACE-Is, ARBs, BBs, CCBs). Selection of other agents as initial therapy should be utilized if thiazide diuretics cannot be used or if the patient has a compelling indication where a specific class is warranted. (i.e. heart failure, post myocardial infarction, high coronary disease risk, diabetes, chronic kidney disease, and recurrent stroke prevention).

NICE[8]

In August 2011, the National Institute for Health and Clinical Excellence (NICE) updated the clinical guidelines for managing hypertension in adults. They recommend using a thiazide-like diuretic (i.e. CTD) over a thiazide diuretic (i.e. HCTZ) when initiating or changing diuretic therapy. However, they also recommend that those patients currently stable and well controlled on HCTZ should continue treatment with HCTZ. These recommendations are based on the limited evidence available to support thiazides compared to the demonstrated benefits of thiazide-like diuretics. The Guideline Development Group (GDG) also comments that limited clinical outcomes data is available to support the use of thiazide diuretics including low dose. However, results comparing thiazide-like diuretics, including CTD, showed statistically significant clinical outcomes

including CV events, stroke, CHD event, but not significant outcomes in terms of mortality. Overall, the GDG emphasizes that the head to head comparison trials were underpowered to show a statistical difference in blood pressure lowering.

ACC/AHA[9]

In 2011, the American College of Cardiology and the American Heart Association (ACC/AHA) provided "expert consensus" for treating hypertension in the elderly. Thiazide diuretics including HCTZ and CTD are recommended for initial treatment of hypertension based on several studies, which demonstrated a reduction in cardiovascular, cerebrovascular, and renal adverse outcomes in the elderly. Overall, no studies looking at the comparative efficacy between HCTZ and CTD were mentioned. The author's commented that since CTD has a longer duration of action and increased potency, elderly patients may be at higher risk for metabolic adverse effects. There are no recommendations for which thiazide to initiate.

Clinical trials

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [10] studied the effects of CCBs or ACEIs versus diuretics (chlorthalidone was the *only* studied diuretic in the ALLHAT trial) on the incidence of combined fatal CHD and non-fatal MI. This multicenter randomized, double-blind, active controlled trial included 33,357 patients aged 55 years or older with hypertension and at least 1 other CHD risk. Mean follow-up was 4.9 years. Combined fatal and nonfatal MI and all-cause mortality did not differ between treatment groups. In contrast, blood pressures were significantly higher in the amlodipine (0.8 mm Hg, p=0.3) and lisinopril (2 mmHg, p<0.001) groups compared to the CTD group. Other secondary endpoints revealed a 38% higher risk of HF (p<0.001) with amlodipine compared with CTD. The lisinopril group had a 15% higher risk of stroke (p=0.02) and a 10% higher risk of combined CVD (p<0.001) compared with CTD.

The Multiple Risk Factor Intervention Trial (MRFIT)[11] was a randomized primary prevention trial using multiple interventions to determine the effect on mortality from CHD. Participants were men 35 to 57 years old (N=12,866) randomly assigned to either the special intervention (SI) program (N=6428) or usual care (UC) (N=6438) provided from health care facilities in their community. The SI program included smoking cessation counseling, dietary recommendations to decrease cholesterol, and treatment for hypertension. Subjects were defined as hypertensive based on a diastolic blood pressure of 90 mmHg or greater. Hypertension was managed in a stepwise procedure. Step 1 of the 4 total steps included the use of CTD or HCTZ 50-100 mg daily based on the physician's preference. Following Step 1, reserpine, hydralazine, guanethidine, or specific alternate drugs were added if goal BP was not reached. One-third of the SI subjects were on a diuretic alone. Overall, after 4 years, both CTD and HCTZ lowered blood pressure to a similar degree (systolic BP reduced 21.8 mmHg vs. 18.8, diastolic BP reduced 12.7 mmHg vs. 11.1). However, the overall intervention was multifactorial and it is unknown if there were true statistical differences among the 2 drugs after 4 years.

An extended follow up trial was conducted on all patients who were classified as hypertensive (N=8012)[12]. Significant increases in mortality due to all causes and CHD were seen in hypertensive patients with resting ECG abnormalities only through 1982, but were not seen following 1982. The authors hypothesized that these post-trial changes may be due to changes in diuretic therapy in the SI group 5 years after randomization. After 5 years, it was recommended that CTD be the only diuretic therapy for step 1 control of HTN. This change was based on favorable outcomes seen in clinics using CTD and unfavorable outcomes in other clinics using HCTZ. Therefore, beneficial mortality outcomes post-trial may have been due to this change in protocol. However, several other factors may have influenced these outcomes including the continued interventions targeting smoking cessation and cholesterol lowering.

Dorsch and colleagues performed a retrospective observational cohort analysis comparing the clinical effects of CTD and HCTZ using data from MRFIT.[13] The primary outcome measure was cardiovascular events (CVEs) that were adjudicated and pre-specified in MRFIT. Nonfatal events consisted of clinical MI, MI determined by annual ECG, stroke, coronary artery bypass surgery, ECG-defined left ventricular hypertrophy, heart failure, angina, and peripheral artery occlusive disease. Results revealed that patients on CTD had significantly fewer

CVEs compared with those on HCTZ (adjusted hazard ratio: 0.79 [95% CI: 0.68 to 0.92]; p=0.0016). The individual CVEs that contributed the most to this difference were clinical MI, ECG MI, coronary artery bypass, rose angina, and peripheral artery disease. Patients on CTD had a significantly lower SBP (p <0.0001), total cholesterol (p<0.0001), LDL (p=0.009), and serum potassium (p <0.0003), and higher uric acid over time (p<0.0001) compared to HCTZ. Glucose (p=0.1595) and triglyceride (p=0.2648) levels did not differ between groups.

Findings:

Based on the reviewed literature, CTD may be more beneficial in lowering SBP and preventing CVD events compared to HCTZ. Additionally, larger trials including ALLHAT and MRFIT show favorable outcomes with CTD when compared with other antihypertensive therapies. CTD's longer duration of action and higher potency may provide a greater antihypertensive effect, particularly throughout nighttime hours.[14] Moreover, the longer elimination half-life of CTD may result in more sustained BP reduction over 24 hours.[14] Conversely, CTD may have greater effects on lowering potassium and increasing uric acid versus HCTZ.[13] Overall, literature supports the safe and effective use of CTD in patients with HTN, and therefore, should be considered an alternative first line agent alongside HCTZ.

If you have any questions regarding this document, please contact the NPTC at nptc1@ihs.gov.

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