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Efficacy of Low-Dose Chlorthalidone and Hydrochlorothiazide as Assessed by 24-h Ambulatory Blood Pressure Monitoring

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ABSTRACT

BACKGROUND Thiazide and thiazide-like diuretic agents are being increasingly used at lower doses. Hydrochlorothiazide (HCTZ) in the 12.5-mg dose remains the most commonly prescribed antihypertensive agent in the United States.

OBJECTIVES This study compared chlorthalidone, 6.25 mg daily, with HCTZ, 12.5 mg daily, by 24-h ambulatory blood pressure (ABP) monitoring and evaluated efficacy. Because HCTZ has been perceived as a short-acting drug, a third comparison with an extended-release formulation (HCTZ-controlled release [CR]) was added.

METHODS This 12-week comparative, double-blind, outpatient study randomized 54 patients with stage 1 hypertension to receive either chlorthalidone, 6.25 mg, (n = 16); HCTZ 12.5 mg (n = 18); or HCTZ-CR 12.5 mg (n = 20). ABP monitoring was performed at baseline and after 4 and 12 weeks of therapy.

RESULTS All 3 treatments significantly ($p < 0.01$) lowered office BP at weeks 4 and 12 from baseline. At weeks 4 and 12, significant reductions in systolic and diastolic 24-h ambulatory and nighttime BP ($p < 0.01$) were observed with chlorthalidone but not with HCTZ. At weeks 4 ($p = 0.015$) and 12 ($p = 0.020$), nighttime systolic ABP was significantly lower in the chlorthalidone group than in the the HCTZ group. With HCTZ therapy, sustained hypertension was converted into masked hypertension. In contrast to the HCTZ group, the HCTZ-CR group also showed a significant ($p < 0.01$) reduction in 24-h ABP. All 3 treatments were generally safe and well tolerated.

CONCLUSIONS Treatment with low-dose chlorthalidone, 6.25 mg daily, significantly reduced mean 24-h ABP as well as daytime and nighttime BP. Due to its short duration of action, no significant 24-h ABP reduction was seen with HCTZ, 12.5 mg daily, which merely converted sustained hypertension into masked hypertension. Thus, low-dose chlorthalidone, 6.25 mg, could be used as monotherapy for treatment of essential hypertension, whereas low-dose HCTZ monotherapy is not an appropriate antihypertensive drug. (Comparative Evaluation of Safety and Efficacy of Hydrochlorothiazide CR with Hydrochlorothiazide and Chlorthalidone in Patients With Stage I Essential Hypertension; CTRI/2013/07/003793) (J Am Coll Cardiol 2016;67:379–89) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ABPM = ambulatory blood pressure monitoring

BP = blood pressure

CR = controlled release

DBP = diastolic blood pressure

HCTZ = hydrochlorothiazide

SBP = systolic blood pressure

12.5 mg of hydrochlorothiazide per day has no significant antihypertensive effect
—P.F. Magee, E.D. Freis (1)

Hydrochlorothiazide (HCTZ) has been available for more than one-half a century and remains the most commonly prescribed antihypertensive drug worldwide. In the United States alone, >134.1 million prescriptions of HCTZ were written in 2008 (2). More than one third of HCTZ prescriptions (i.e., 48 million) were written for monotherapy. Over more than 3 decades, the prescription pattern of HCTZ has been heavily influenced by the 8 reports of the Joint National Committee (JNC) for Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, all of which recommended "thiazides" or "thiazide-like drugs" or "thiazide-type diuretics" as first-line or preferred therapy for hypertension. For most practicing physicians, the term "thiazide" simply means HCTZ (3). The more recent JNC reports also increasingly have recommended low-dose thiazide and thiazide-like diuretics as initial therapy in hypertensive patients. Although a clinical study 30 years ago showed that a dose of 12.5 mg of HCTZ per day had

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no significant antihypertensive effect (1), this dose remains the one most frequently prescribed in monotherapy, and hypertension remains, by far, its most common indication (2). However, despite its widespread use, and in contrast to chlorthalidone, little if any evidence is available regarding the efficacy and safety of HCTZ for the treatment of essential hypertension, particularly at the dose of 12.5 mg (4-6). Almost a decade ago, Carter et al. (7) found significant pharmacokinetic and pharmacodynamic differences between HCTZ and chlorthalidone. Chlorthalidone was found to be approximately 1.5× to 2.0× as potent as HCTZ and to have a much longer duration of action. Subsequently, Ernst et al. (8) compared effects of HCTZ with those of chlorthalidone in the daily doses of 25 mg (forced titrated to 50 mg) and 12.5 mg (force titrated to 25 mg), respectively, on ambulatory blood pressure (ABP) and office blood pressure (BP). In the present study, we scrutinized the antihypertensive efficacy of HCTZ, 12.5 mg daily, as assessed by 24-h ABP monitoring (ABPM), and compared it with low-dose (6.25 mg) chlorthalidone in patients with stage 1 essential hypertension. Because the antihypertensive efficacy of HCTZ may be hampered by its short half-life, a third arm, with an extended-release formulation (HCTZ-controlled release [CR]), was added.

METHODS

TRIAL DESIGN. This was a double-blind, double-dummy, randomized, parallel group, comparative, multicentric study conducted in Indian patients. The study was initially planned in 213 patients with stage 1 hypertension randomized in a 1:1:1 ratio to receive chlorthalidone, 6.25 mg tablets, or HCTZ-CR, 12.5 mg, tablets, or conventional HCTZ, 12.5-mg tablets. Between December 2012 and February 2015, only 54 patients were enrolled in the study. The reason for this slow recruitment was difficulty in getting patients with stage 1 hypertension at tertiary centers.

The study was carried out according to Good Clinical Practice guidelines and the Declaration of Helsinki. The study protocol was approved by the ethics committee at each of the participating centers, namely, KEM Hospital Research Centre, Ethic Committee (Pune, India); Institutional Clinical Ethics Committee at Rajiv Gandhi Medical College and Chhatrapati Shivaji Maharaj Hospital (Thane, India); Medilink Ethics Committee (Ahmadabad, India); Aadhya Independent Ethics Committee (Ahmadabad, India); Office of the Principal and Controller, Institutional Ethics Committee at Dr. S.N Medical College (Jodhpur, India); and Omega Ethical Committee (Mangalore, India). The Drug Controller General of India also approved the study protocol. All patients were provided with an oral explanation of the nature of the study and study drugs by the investigator at each center. The patient information sheet was provided in a language understood by the patient, and patients who provided written consent to participate were screened for the study.

SELECTION CRITERIA. Male and female patients between 18 and 65 years of age were eligible if they had stage 1 essential hypertension (office systolic blood pressure [SBP] between 140 and 159 mm Hg and diastolic blood pressure [DBP] between 90 and 99 mm Hg). As recommended in European Society of Hypertension/European Society of Cardiology hypertension guidelines (9) and 2 other guidelines (10,11), the hypertension was diagnosed on the basis of office BP and confirmed by 24-h ABPM measurements.

Exclusion criteria (among others) were secondary hypertension; diabetes; hyperuricemia; gout; chronic kidney disease; parathyroid diseases; recent cardiovascular disease or cardiovascular accident; abnormal renal function (serum creatinine: >1.5 mg/dl; blood urea nitrogen [BUN]: >20 mg/dl), abnormal liver function (aspartate aminotransferase [AST], alanine