Comparative Antihypertensive Effects of Hydrochlorothiazide and Chlorthalidone on Ambulatory and Office Blood Pressure

Michael E. Ernst, Barry L. Carter, Chris J. Goerdt, Jennifer J.G. Steffensmeier, Beth Bryles Phillips, M. Bridget Zimmerman, George R. Bergus

Abstract—Low-dose thiazide-type diuretics are recommended as initial therapy for most hypertensive patients. Chlorthalidone has significantly reduced stroke and cardiovascular end points in several landmark trials; however, hydrochlorothiazide remains favored in practice. Most clinicians assume that the drugs are interchangeable, but their antihypertensive effects at lower doses have not been directly compared. We conducted a randomized, single-blinded, 8-week active treatment, crossover study comparing chlorthalidone 12.5 mg/day (force-titrated to 25 mg/day) and hydrochlorothiazide 25 mg/day (force-titrated to 50 mg/day) in untreated hypertensive patients. The main outcome, 24-hour ambulatory blood pressure (BP) monitoring, was assessed at baseline and week 8, along with standard office BP readings every 2 weeks. Thirty patients completed the first active treatment period, whereas 24 patients completed both. An order–drug–time interaction was observed with chlorthalidone; therefore, data from only the first active treatment period was considered. Week 8 ambulatory BPs indicated a greater reduction from baseline in systolic BP with chlorthalidone 25 mg/day compared with hydrochlorothiazide 50 mg/day (24-hour mean = −12.4±1.8 mm Hg versus −7.4±1.7 mm Hg; P=0.054; nighttime mean = −13.5±1.9 mm Hg versus −6.4±1.8 mm Hg; P=0.009). Office systolic BP reduction was lower at week 2 for chlorthalidone 12.5 mg/day versus hydrochlorothiazide 25 mg/day (−15.7±2.2 mm Hg versus −4.5±2.1 mm Hg; P=0.001); however, by week 8, reductions were statistically similar (−17.1±3.7 versus −10.8±3.5; P=0.84). Within recommended doses, chlorthalidone is more effective in lowering systolic BPs than hydrochlorothiazide, as evidenced by 24-hour ambulatory BPs. These differences were not apparent with office BP measurements. (Hypertension. 2006;47:352-358.)

Key Words: diuretics ■ blood pressure monitoring, ambulatory ■ antihypertensive agents ■ hypertension, essential ■ antihypertensive therapy

Evidence from the Antihypertensive and Lipid-Lowering to prevent Heart Attack Trial (ALLHAT) and other pivotal hypertension studies has established that thiazide-type diuretics confer significant reductions in stroke and cardiovascular events.1–7 Given their strong record of evidence, low cost, and favorable tolerability, low-dose thiazide-type diuretics are recommended as initial therapy in most hypertensive patients and are the foundation for multiple antihypertensive drug regimens, according to the Seventh Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.8

The Seventh Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure guidelines do not advocate a specific thiazide but list several acceptable options.8 The ALLHAT and numerous other historic hypertension trials preferentially used chlorthalidone.1,4–7 Chlorthalidone was once commonly prescribed; however, over the last 20 years, evidence from these trials has been largely neglected with the widespread adoption of hydrochlorothiazide (HCTZ) and HCTZ-triamterene combinations for use in clinical practice.9,10 Reasons for this prescribing shift are unclear but may result from concerns about hypokalemia with chlorthalidone,10–12 the relative lack of fixed-dose combination products containing chlorthalidone with other antihypertensive agents, as well as a generally held belief that HCTZ/HCTZ combinations also reduce stroke and cardiovascular events.13–15

Most clinicians assume that HCTZ and chlorthalidone are clinically interchangeable. Early, small dose-equivalence studies16–19 suggested similar antihypertensive efficacy; however, these studies used higher doses of the 2 drugs than are recommended today, and none evaluated responses based on 24-hour ambulatory blood pressure (BP) monitoring (ABPM), now an estab-

Received September 14, 2005; first decision October 3, 2005; revision accepted December 4, 2005.

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Hypertension is available at http://www.hypertensionaha.org

DOI: 10.1161/01.HYP.0000203309.07140.d3

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lished standard for antihypertensive comparisons. The recent ALLHAT study findings have resurrected the question of whether there may be specific benefits unique to chlorthalidone.\textsuperscript{10} Chlorthalidone possesses a distinct pharmacokinetic profile from that of HCTZ, and it has been suggested that its longer duration of action might provide greater antihypertensive effects, particularly throughout nighttime hours.\textsuperscript{10} The objective of our study was to compare the 24-hour antihypertensive efficacy profile of HCTZ and chlorthalidone using ABPM and standard office BP measurements.

Methods

Study Participants

Men and women aged 18 to 79 years were eligible if they had prehypertension or a new or established diagnosis of hypertension (stage 1 or 2), were not receiving antihypertensive medications, and had average office BP values in the last 6 months between 140 and 179 mm Hg systolic or 90 and 109 mm Hg diastolic.

Patients were excluded for the following reasons: (1) office BP \( \geq 180/110 \) mm Hg; (2) use of a thiazide-type diuretic or any other antihypertensive agent within the last 3 months; (3) type 1 or 2 diabetes; (4) chronic renal insufficiency (serum creatinine \( \geq 1.8 \) mg/dL); (5) pregnancy; (6) dementia or other cognitive impairment prohibiting informed consent; (7) history of ischemic stroke, unstable angina, or myocardial infarction within the past 6 months; (8) chronic use of decongestants, other sympathomimetic agents, or nonsteroidal antiinflammatory drugs; (9) documented alcoholism or current illicit drug use; (10) chronic atrial fibrillation; (11) history of gout or hyperuricemia; or, (12) known allergy to study medications.

Study Design

The study was a randomized, single-blinded, 8-week active treatment, crossover trial with a 4-week washout between treatments.

Setting and Locations

Patients were identified at a regular clinic visit from 2 primary care practices (1 internal medicine and 1 family medicine) within the University of Iowa Family Care Center. After informed consent was obtained, all of the study visits occurred in the University of Iowa General Clinical Research Center. All of the study procedures were approved by the University of Iowa Institutional Review Board, University of Iowa Hospitals and Clinics Pharmacy and Therapeutics Review Board, and University of Iowa Hospitals and Clinics General Clinical Research Center Review Board.

Intervention

Patients were randomized to receive either HCTZ (Qualitest Pharmaceuticals Inc) or chlorthalidone (Mylan Pharmaceuticals Inc). The initial dose of HCTZ was 25 mg (supplied as 50-mg tablets), and the initial dose of chlorthalidone was 12.5 mg (supplied as 25-mg tablets). All of the study medications were broken in half by the study investigators before dispensing to the patient, and patients were instructed to take 1 of the half tablets each morning immediately after arising for the day. Study medication was packaged by the investigators in identically labeled prescription bottles containing only the patient name, date, and directions for use.

At week 4, both medications were force-titrated to a full tablet (HCTZ 50 mg every morning and chlorthalidone 25 mg every morning) and maintained at this dose for the remainder of the active treatment period, unless BP was \(<110/60 \) mm Hg or symptomatic orthostatic hypotension occurred. No other antihypertensives were allowed during the study.

The doses of HCTZ and chlorthalidone that were selected for the study were based on our previous review of the literature, which suggested 25 mg of chlorthalidone would be approximately equivalent to 50 mg of HCTZ.\textsuperscript{10} The hypothesis for the study was that these 2 doses should have equivalent effects on BP. Therefore, to prove this hypothesis, it was necessary to force-titrate the dose of both drugs to these doses so that the final statistical analysis would be based on the prespecified target doses of both drugs.

Assessments and Follow-Up

Office BP. 24-hour ABPM, height, weight, serum potassium, and creatinine were obtained at baseline. Office BP measurement was performed by a study nurse blinded to treatment according to standard guidelines for measurement of BP by sphygmomanometry.\textsuperscript{20} The average of 2 readings taken \( \geq 30 \) seconds apart was recorded. Twenty-four-hour ABPM was performed according to usual clinic procedures (readings taken every 20 minutes from 6:00 AM to 6:00 PM and every 30 minutes from 6:00 PM to 6:00 AM).\textsuperscript{21}

After their baseline visit, patients were required to return biweekly during the active treatment phases of the study to have office BP, weight, laboratory assessment, and/or dosage titration. Office BP readings were performed at trough, \( \approx \) 23 to 26 hours after dose. ABPM was repeated at week 8.

Serum potassium was measured every 2 weeks during the active treatment phase, and supplemental potassium chloride extended-release tablets (Warrick Pharmaceuticals Corp) 20 meq QD were added and adjusted accordingly whenever serum potassium fell below 3.5 meq/L. All of the patients were advised to regularly eat foods high in potassium during the study.

Patients were asked to maintain a daily log of medication administration time. At each visit, medication adherence was assessed via tablet counts, and patients were queried about any adverse events. After completion of the first 8-week active treatment period, patients discontinued the study medication and underwent a 4-week washout before reentering the second active treatment period.

Main Outcome Measures

The primary outcome was a comparison of the change in 24-hour mean systolic (SBP) and diastolic (DBP) ambulatory BP from baseline to week 8 between chlorthalidone and HCTZ. Secondary outcomes analyzed included the comparison between chlorthalidone and HCTZ of changes in mean SBP and mean DBP for office BP at each visit and change in ambulatory daytime and nighttime mean SBP and DBP from baseline to week 8. The primary safety outcome, development of hypokalemia (defined as serum potassium \(< 3.5 \) meq/L), was compared between the drugs.

Sample Size

A priori calculation suggested that a sample size of 20 should give power of 0.80 to detect a difference in mean change of \( \geq 4 \) mm Hg in SBP between the 2 treatments using a paired \( t \) test at the 0.05 significance level, assuming a standard deviation of 6 mm Hg for mean SBP change. We planned to oversample by 20% and complete at least 24 patients in case dropouts occurred.

Statistical Analyses

Data were analyzed by intention-to-treat. Comparison of demographic variables between the 2 groups at baseline was performed using Student \( t \) test for continuous variables and Fisher’s exact test for nonparametric variables.

Because a crossover design was used, with approximately half of the subjects receiving chlorthalidone first and the other half receiving HCTZ first, a linear mixed model analysis was used to test for a possible carryover or drug order effect. The fixed effects in the model were drug order (chlorthalidone–HCTZ or HCTZ–chlorthalidone), drug, and time. The model also included all 2-factor interactions and the 3-factor interaction. A significant order–drug–time interaction was found, suggesting that the order that the 2 drugs were given had a significant effect on the difference of the magnitude of mean change in BP between the 2 drugs.

In the presence of the drug order effect, the alternative to testing for drug effect was to analyze the data using only the first active treatment period. For this analysis, a linear mixed model was used for repeated measures, with drug, time, and drug–time interaction as the fixed effects in the model. In this model, drug effect is a between-subject factor. A significant drug–time interaction would
indicate that the mean change over time differed significantly between the 2 drugs. Repeated-measures analysis was used to examine changes in potassium between the groups.

For mean comparisons involving multiple tests (ie, between drug comparison of office BP change at weeks 2, 4, 6, and 8), Bonferroni’s method was used to adjust the \( P \) value to account for the number of tests performed, where the Bonferroni-adjusted \( P \) value is the unadjusted \( P \) value multiplied by the number of tests. For analysis of the ABPM data, daytime hours were defined in a clock-time–dependent manner with daytime hours from 6:00 AM to 10:00 PM, and nighttime hours from 10:00 PM to 6:00 AM. These were selected as modified from recommended guidelines.\(^{22,23}\)

All of the statistical analyses were performed using SAS version 9.1 (SAS Institute, Inc). BP statistics are reported as mean±SEM. A \( P \) value of <0.05 was considered statistically significant.

### Results

#### Study Population

Thirty-two patients were originally consented and enrolled into the study. One person did not meet inclusion criteria after the baseline ABPM was performed and was subsequently dropped from the study. One person withdrew consent after the baseline visit, leaving a total of 30 patients who were randomized and received study medication (16 received HCTZ initially and 14 received chlorthalidone). All of the patients were naïve to antihypertensive treatment, with the exception of 1 patient who had been treated in the past but subsequently discontinued therapy >3 months before study enrollment.

Table displays the baseline characteristics of the 30 subjects who received study medication. Subjects were mostly white, middle-aged, with stage I hypertension. Patients randomized to HCTZ had slightly higher body mass index (\( P =0.029 \)). Adherence was >95% for all of the study participants for all of the visits. All of the patients in each group successfully achieved and maintained target doses of the drugs, and no dosage reductions were necessary during the study. No significant changes in body weight were observed between groups during the study.

#### Order–Drug–Time Interaction

After the planned sample of 24 patients completed both active treatments (11 receiving HCTZ first and 13 chlorthalidone first), we discovered a significant order–drug–time interaction. Figure 1 shows this interaction for the average 24-hour SBP. The antihypertensive efficacy of chlorthalidone appeared to be significantly greater compared with HCTZ when it was administered first but was not the case when given second (after HCTZ). This effect was noted for average 24-hour, daytime, and nighttime SBP (\( P =0.025 \) for average 24-hour SBP; \( P =0.032 \) for daytime SBP; \( P =0.055 \) for nighttime SBP). A similar pattern of response was noted for office BP, although it was not statistically significant (order–drug–time interaction \( P =0.180 \)). The mean change from baseline to week 8 in office SBP for the group where chlorthalidone was given first was \(-16.8 \pm 3.3 \text{ mm Hg}\) for chlorthalidone and \(-8.5 \pm 3.3 \text{ mm Hg}\) for HCTZ (order–drug–time interaction \( P =0.080 \)). In contrast, in the group where HCTZ was administered first, the mean change in office SBP was \(-7.6 \pm 3.6 \text{ mm Hg}\) for chlorthalidone compared with \(-8.5 \pm 3.5 \text{ mm Hg}\) for HCTZ (\( P =0.849 \)).

The order–drug–time interaction may be partly attributable to an inadequate washout period for chlorthalidone, where baseline ambulatory SBP for HCTZ when administered after chlorthalidone (132.8±2.2 mm Hg for 24-hour average; 137.9±2.2 mm Hg daytime; 122.3±3.2 mm Hg nighttime) was generally lower compared with the chlorthalidone baseline ambulatory SBP (137.2±2.2 mm Hg for 24-hour average; 142.9±2.2 mm Hg daytime; 126.4±3.2 mm Hg nighttime). However, it is not clear whether an inadequate washout contributed to the reduced mean change in SBP observed with chlorthalidone when it was preceded by HCTZ.

At the time that the order–drug–time interaction was discovered, study enrollment was halted. Six subjects were finishing the first active treatment period. They were allowed to finish the first active treatment period, bringing the total number of completers of the first active treatment period to 30. To insure statistical robustness of the data in the presence of a possible carryover effect, it was decided that only the data from completers of the first active treatment period would be analyzed (\( n =30 \)), thus essentially changing the study from a crossover to a parallel design. The order–drug–time interaction was strong, and it was determined that it would not likely diminish, even if the remaining 6 subjects were crossed over and completed the second arm of the study.

### Baseline Demographic Characteristics of Subjects Completing Study Period 1 (\( n =30 \))

<table>
<thead>
<tr>
<th>Variable</th>
<th>HCTZ (( n =16 ))</th>
<th>Chlorthalidone (( n =14 ))</th>
<th>( P ) Value</th>
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<tbody>
<tr>
<td>Sex (male)</td>
<td>9 (56%)</td>
<td>7 (50%)</td>
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<tr>
<td>Ethnicity (white)</td>
<td>13 (81%)</td>
<td>12 (86%)</td>
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<tr>
<td>Age</td>
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<td>46±15</td>
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<td>Weight, kg</td>
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</tr>
<tr>
<td>Height, cm</td>
<td>173.6±10.0</td>
<td>173.0±9.4</td>
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</tr>
<tr>
<td>Body mass index</td>
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<td>26.6±3.4</td>
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</tr>
<tr>
<td>Glomerular filtration rate, ml/min (MDRD method)</td>
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<td>87.5±15.4</td>
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</tr>
<tr>
<td>Office SBP, mm Hg</td>
<td>140.1±12.7</td>
<td>144.9±9.8</td>
<td>0.255</td>
</tr>
<tr>
<td>Office DBP, mm Hg</td>
<td>91.1±11.5</td>
<td>95.6±7.2</td>
<td>0.215</td>
</tr>
<tr>
<td>Serum potassium, meq/L</td>
<td>4.2±0.3</td>
<td>4.2±0.2</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Values reported as mean±SD. MDRD indicates Modification of Diet in Renal Disease Study Group.
Ambulatory BPs
Figure 2 displays changes from baseline to week 8 in mean 24-hour, daytime, and nighttime SBPs for ABPM for the first active treatment period. The data indicated a greater reduction in 24-hour mean SBP with chlorthalidone 25 mg/day compared with HCTZ 50 mg/day (−12.4±1.8 mm Hg versus −7.4±1.7 mm Hg; P=0.054). The greater reduction in 24-hour mean SBP with chlorthalidone appeared to be primarily because of its effect on reducing nighttime mean SBP. The reduction in SBP during nighttime hours was −13.5±1.9 mm Hg for chlorthalidone versus −6.4±1.7 mm Hg for HCTZ (P=0.009). The reduction in daytime mean SBP was not significantly different between chlorthalidone and HCTZ (−11.4±2.0 mm Hg versus −8.1±1.9 mm Hg, respectively; P=0.230). We also examined the effects of sex, age, and body mass index as covariates in our analysis and found no change in the results.

For DBP, although the changes from baseline to week 8 in the 24-hour, daytime, and nighttime mean values were greater with chlorthalidone, the differences were not statistically significant (24-hour mean DBP reduction = −7.1±1.4 mm Hg chlorthalidone versus −5.1±1.3 mm Hg HCTZ, P=0.297; daytime mean DBP reduction = −7.6±1.4 mm Hg chlorthalidone versus −6.5±1.3 mm Hg HCTZ, P=0.593; nighttime mean DBP reduction = −7.2±1.7 mm Hg chlorthalidone versus −4.6±1.6 mm Hg HCTZ, P=0.288).

Office Blood Pressures
Figure 4 displays office SBP means at each study visit for the first active treatment period. At week 2, chlorthalidone reduced SBP from baseline an average of −15.7±2.2 mm Hg compared with −4.5±2.1 mm Hg for HCTZ (P=0.001). Although the trend in favor of greater reduction in SBP was noted in office SBP for chlorthalidone at each study visit, the difference was statistically significant only at week 2. Mean reductions in DBP between the 2 drugs were also greater at each study visit for chlorthalidone; however, they were not statistically significant at any visit. Diastolic BP was reduced −2.9±1.7 mm Hg for HCTZ versus −6.1±1.9 mm Hg for chlorthalidone at week 2, −4.5±2.3 mm Hg for HCTZ versus −7.2±2.5 mm Hg for chlorthalidone at week 4, −6.8±2.7 mm Hg for HCTZ versus −7.4±2.8 mm Hg for chlorthalidone at week 6, and −6.9±2.9 mm Hg for HCTZ versus −8.1±3.1 mm Hg for chlorthalidone at week 8 (P>0.89 for all).

Adverse Effects
Changes in serum potassium were similar between the patients treated with HCTZ or chlorthalidone (drug–time inter-
action $P = 0.76$). At week 2, the mean change ($\pm SD$) in serum potassium from baseline was $-0.3 \pm 0.4$ meq/L for HCTZ and $-0.4 \pm 0.4$ meq/L for chlorthalidone. At week 6, the mean change from baseline was $-0.5 \pm 0.4$ meq/L for HCTZ and $-0.5 \pm 0.3$ meq/L for chlorthalidone. At week 8, the mean change from baseline was $-0.4 \pm 0.4$ meq/L for HCTZ and $-0.5 \pm 0.4$ meq/L for chlorthalidone.

Of the 24 subjects that completed the 2 active treatment phases of the study, the incidence of hypokalemia (serum potassium $< 3.5$ meq/L) with HCTZ was 50%, which was 45% (5 of 11) of those that were administered HCTZ first and 54% (7 of 13) of those that took HCTZ preceded by chlorthalidone (Fisher’s exact test $P = 1.0$). A similar incidence of hypokalemia (46%) was observed with chlorthalidone, with 38% (5 of 13) of those that were administered chlorthalidone first and 55% (6 of 13) of those that took chlorthalidone preceded by HCTZ (Fisher’s exact test $P = 0.682$). No patients experienced symptoms with hypokalemia, and no other serious adverse effects were reported by patients receiving either agent.

**Discussion**

For the dosing range evaluated, our study findings suggest that half the dose of chlorthalidone has greater antihypertensive efficacy than HCTZ. Although office BP did not readily detect this difference, week eight 24-hour ABPM indicated that chlorthalidone reduces SBP more effectively than HCTZ. Our results lend support to the recent findings that there may be differences in antihypertensive efficacy within the class of diuretics. In a small study of 19 patients with uncontrolled BP on stable doses of HCTZ for 6 months, substitution of chlorthalidone for HCTZ was found to reduce SBP an additional 4 to 7 mm Hg, which led to achieving goal BP in 6 of the 19 patients.²⁴

The trend observed with the 24-hour mean SBP in our study appeared to result from differences in the nighttime mean SBP, a finding which may have a pharmacokinetic basis. Chlorthalidone has a much longer elimination half-life (24 to 55 hours) than HCTZ (2.5 hours),¹⁰ a property suggested to result in more sustained BP reduction over 24 hours. This longer elimination half-life could help sustain a prolonged low level of diuresis, resulting in lower mean nighttime BP, a finding which would not be readily observed in office BP measurements routinely obtained during daytime hours.

Although differences in antihypertensive efficacy between HCTZ and chlorthalidone reached statistical significance only with nighttime ambulatory SBP in our study, it is a significant finding, because ABPM is known to correlate more closely with a prediction of cardiovascular outcomes than office BP.²⁵–²⁹ In particular, nighttime ambulatory BP readings have been found to be the most predictive of cardiovascular outcomes.²⁹ In the case of HCTZ, it has also been recently shown that office BP overestimates the antihypertensive response to HCTZ, with ABPM readings more reliably assessing antihypertensive response.³⁰

Lower nighttime BPs are physiologically important. In the Heart Outcomes Prevention Evaluation trial, ramipril-treated patients had significantly reduced cardiovascular morbidity and mortality compared with those not receiving ramipril.³¹ Interestingly, ramipril-treated patients were found to have significantly lower nighttime BP observed via ABPM, whereas the differences in BP between the 2 groups were not apparent when measured by daytime office BP.³² It is plausible that the lower BP observed with chlorthalidone during nighttime hours could provide additional protection from stroke and myocardial infarction in early morning hours when BP often surges. It is well-documented that diminished nocturnal decline in BP is associated with a higher risk for cardiovascular events.²⁶,³³–³⁵

Our ABPM findings suggest the intriguing prospect that a difference in cardiovascular outcomes is possible between chlorthalidone and HCTZ. A largely forgotten analysis of the Multiple Risk Factor Intervention Trial (MRFIT) indicated that these agents might not result in equivalent reductions in mortality.⁵ In 1980, after 5 years of study, the treatment protocol in MRFIT was changed to recommend chlorthalidone, not HCTZ, as the step 1 diuretic for the intervention group. The data leading to the protocol change indicated that
in clinics where HCTZ predominated, the mortality trend was unfavorable for the intervention group compared with usual care, whereas it was favorable in clinics primarily using chlorthalidone. Although the robustness of these findings has been questioned because of their post-hoc nature and lack of drug randomization (MRFIT participants were randomized to intervention versus usual care, with choice of diuretic in the intervention group being a local option), it is possible that differences in outcomes may have resulted from differences in BP control between the drugs. Unfortunately, study design limitations precluded separating this outcome from the effects of the MRFIT nutrition and smoking interventions, and, thus, BP differences were not reported.

We previously reviewed the literature that compared chlorthalidone to HCTZ. That analysis was based on older studies using higher doses of both drugs and suggested that chlorthalidone was 1.5 to 2.0 times as potent as HCTZ. None of the studies evaluated the antihypertensive efficacy of these drugs using ABPM end points, and ours is the first to directly compare chlorthalidone, in a dose <50 mg daily, to HCTZ. Our findings suggest that the differences in dose–response curves seen with these 2 drugs at higher doses is maintained at the lower doses and affirms that chlorthalidone is approximately twice as potent as HCTZ. Importantly, the higher potency of chlorthalidone does not seem to increase the risk of hypokalemia within the dose range studied.

The significance of the order–drug–time interaction with chlorthalidone is uncertain. Twenty-four–hour ABPM reveals that it may be partly attributable to an inadequate washout period for chlorthalidone, where baseline ambulatory SBP for HCTZ when administered after chlorthalidone was generally lower compared with chlorthalidone. However, an inadequate washout does not explain why chlorthalidone was less effective when administered after HCTZ. Of note, the final 24-hour results for chlorthalidone were performed 12 weeks after the last dose of HCTZ (4 weeks of washout followed by 8 weeks of chlorthalidone), which should have reduced the possibility of carryover. Furthermore, office BP values had returned to pretreatment levels in both groups during the washout. Perhaps this finding is related to differences in specific diuretic effects on plasma renin activity, genetic differences in α-adducin polymorphism, or cellular effects on the erythrocyte sodium concentrations or sodium–lithium countertransport mechanisms, requiring additional investigation.

Limitations
Several limitations are noted. First, the study was of short duration, and it is unclear whether differences observed in ABPM at week 8 between HCTZ and chlorthalidone would persist over longer follow-up. In addition, because ABPM was not performed at week 4, the week–8 responses do not fully represent response to forced-dose titration but are a response to 8 weeks of total therapy. However, our dosage titration schedule reflects what may be done commonly in clinical practice, and our data indicate a difference in efficacy at 8 weeks between the 2 agents.

Secondly, because an order–drug–time interaction was encountered, we chose the more robust analysis by including only data from the first active treatment period, but at the expense of potentially reducing the power. However, we were still able to observe greater antihypertensive efficacy with chlorthalidone compared with HCTZ, with a significant difference for nighttime SBP and a suggested difference for 24-hour SBP. Had we been able to use data from both active treatment periods with no carryover effect, it is likely that these tests for group differences would have resulted in smaller P values.

Third, we compared only 2 commonly used doses of each drug. Although often prescribed, we did not choose to study a 12.5-mg dose of HCTZ, because we felt that differences between the drugs would not likely surface with this dose given their suggested differences in potency. Likewise, we did not study doses of HCTZ >50 mg/day or 25 mg/day of chlorthalidone, because their additional antihypertensive effects are questionable and may pose an unnecessary increased risk of hypokalemia.

Fourth, our design was single-blind, which could be criticized as allowing bias to occur. Both patients and research nurses were not informed of which study medication the patient was currently receiving, but no additional action was taken to mask the treatments. However, bias was minimized through use of ABPM.

Lastly, our study examined only intermediate outcomes. Blood pressure is only a predictor of cardiovascular risk. Although use of ABPM has been shown to correlate more closely with prediction of cardiovascular events, at best, our findings can only suggest the potential for clinically significant differences in cardiovascular outcomes between these agents. In their network metaanalysis, Psaty and Furberg reported that the major health outcomes for chlorthalidone appeared similar to other thiazide-type diuretics; however, this was an indirect comparison, and others have called for randomized trials to directly compare the outcomes of chlorthalidone-based versus nonchlorthalidone-based diuretic regimens.

Perspectives
Our study compared the antihypertensive efficacy of usual recommended doses of HCTZ and chlorthalidone using both ABPM and conventional sphygmonanometry. It has important implications in evaluating whether these 2 agents are clinically interchangeable. We found that chlorthalidone, at half the dose, is more effective in lowering SBP than HCTZ, as evidenced by 24-hour ABPM. This difference is primarily because of additional antihypertensive efficacy observed throughout the nighttime hours. This significant difference is not appreciated when the assessment of antihypertensive efficacy is based on daytime office BP readings alone. When selecting thiazide-type diuretics for the treatment of hypertension, clinicians should consider the efficacy differences within the class. Future large-scale studies can help determine whether the antihypertensive differences between these agents result in clinically meaningful differences in morbidity and mortality.

Acknowledgments
Grant support was received from the American Association of Colleges of Pharmacy New Investigator’s Program, American Foundation for Pharmaceutical Education. This study sponsor did not participate in any of the following aspects of the study: collection, management, analysis, or interpretation of the data; and preparation, review, or approval of the article. Grant support was also received from M01-RR-59, National Center for Research Resources, General Clinical Research Centers Program, National Institutes of Health.
This study sponsor participated in collection, analysis, and interpretation of the data, and article preparation and review.

References


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*Hypertension*. 2006;47:352-358; originally published online January 23, 2006; doi: 10.1161/01.HYP.0000203309.07140.d3

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