Brief Review

Hydrochlorothiazide Versus Chlorthalidone
Evidence Supporting Their Interchangeability

Barry L. Carter, Michael E. Ernst, Jerome D. Cohen

Abstract—Thiazide diuretics are one of the preferred pharmacologic treatments for hypertension. Hydrochlorothiazide and chlorthalidone have been the 2 most commonly used diuretics in major clinical trials. Treatment guidelines and compendia often consider these 2 drugs interchangeable agents within the class of thiazide or thiazide-like diuretics. Many sources list them as equipotent. Despite these beliefs, there is some suggestion that cardiovascular outcomes are not necessarily the same with these 2 drugs. We conducted a literature search from 1960 to 2003 to identify studies that evaluated the pharmacokinetic and blood pressure–lowering effects of these 2 agents. There are significant pharmacokinetic and pharmacodynamic differences between these diuretics. Chlorthalidone is ~1.5 to 2.0 times as potent as hydrochlorothiazide, and the former has a much longer duration of action. Whether these pharmacokinetic and pharmacodynamic features cause differences in outcomes is not known. (Hypertension. 2004;43:4-9.)

Key Words: clinical trials • diuretics • antihypertensive therapy • hypertension, detection and control

Thiazide diuretics have been the cornerstone in hypertension management for nearly 5 decades. Although diuretic use declined for 20 years, it has begun to increase. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) suggests thiazide diuretics for most patients with hypertension. The JNC guidelines, however, do not distinguish between the thiazide diuretics and actually list several acceptable options.

Most major clinical trials used either hydrochlorothiazide (HCTZ) or chlorthalidone. Trials sponsored by the National Heart, Lung, and Blood Institute used chlorthalidone, primarily because of the belief that it might have advantages related to its longer duration of action. In addition, intriguing findings from the Multiple Risk Factor Intervention Trial (MRFIT) suggested that chlorthalidone might confer mortality benefits over HCTZ, but these findings have never been investigated in a prospective study. Most experts generally consider HCTZ and chlorthalidone interchangeable, with little discussion about whether these drugs are truly equivalent.

Chlorthalidone (Hygroton) was commonly used in the 1970s, but its use has sharply declined in the past 20 years. The average physician has rarely prescribed chlorthalidone (it is often not listed on formularies), and most younger pharmacists have never dispensed the drug. It is not known why the drug has fallen out of favor. One theory is that clinicians observed more hypokalemia with chlorthalidone than with HCTZ.

The debate between possible differences between chlorthalidone and HCTZ has been reinvigorated by the seemingly disparate findings from the Antihypertensive and Lipid-Lowering to Prevent Heart Attack Trial (ALLHAT) and the Second Australian National Blood Pressure Study (ANBP2). ALLHAT found fewer events for all cardiovascular disease, stroke, and heart failure with chlorthalidone than with an angiotensin-converting enzyme (ACE) inhibitor and lower risk of heart failure with chlorthalidone than with amiodipine. In contrast, the ANBP2 used HCTZ as the diuretic but found an ACE inhibitor to be superior at reducing combined morbidity and mortality in men but not in women.

Possible explanations for these findings include differences in populations studied, sample sizes, numbers of outcomes, or the validity of outcome measures. It is not the purpose of this article to review these differences. However, these studies have fueled one of the most interesting therapeutic debates: namely, which, if any, diuretic is preferred for the treatment of hypertension. The purpose of this article is to (1) evaluate the scientific evidence to support whether chlorthalidone and HCTZ can be considered equivalent agents for hypertension, (2) propose equivalent doses of the 2 agents, and (3) suggest possible mechanisms for differences between these agents.

Literature Search
A literature search of Index Medicus from 1966 to 2003 was conducted by using the terms “hydrochlorothiazide” or “chlorthalidone.” References were reviewed for additional
citations, especially those before 1966. Each article was reviewed to determine whether either HCTZ or chlorthalidone had been used as a single agent or as initial therapy in clinical trials. Preference was given to studies that used single diuretic entities and studies that involved either fixed doses or randomized, crossover studies.

Clinical Trials

Trials that used several diuretics and/or β-blockers in combination with diuretics as initial therapy or that did not separate results by type of diuretic or drug were difficult to interpret and are not discussed here. A few studies that included combinations with potassium-sparing diuretics were considered secondary sources of data, because several studies demonstrated that neither amiloride nor triamterene added to the antihypertensive effects of HCTZ or chlorthalidone. It is impossible to directly compare trials because of heterogeneous populations. However, on review of these articles, it is interesting to note that several trials reporting neutral or negative results in the diuretic groups often included HCTZ, whereas those with more favorable outcomes included chlorthalidone. Several trials of HCTZ, however, had favorable outcomes.

Some experts have begun to speculate whether there are true differences between HCTZ and chlorthalidone. One of the most intriguing findings was reported by MRFIT. Patients were randomized to either special intervention (SI) or usual care (UC). Initial therapy in the SI group was either HCTZ or chlorthalidone, and the choice was made locally by the clinic staff. The initial evaluation followed up 8012 men for 6.9 years, and there was a trend in favor of the SI group compared with the UC group, but the differences were not statistically significant. A follow-up analysis 3.8 years later found more favorable outcomes in the SI group compared with UC group, which is in contrast to the earlier observation. Six years into the trial, it was observed that in the 9 clinics that predominately used HCTZ, mortality was 44% higher in the SI group compared with the UC group. The opposite was true in the 6 clinics that predominately used chlorthalidone. The MRFIT Data Safety Monitoring Board changed the protocol near the end of the trial to exclusively use chlorthalidone. In the initial clinics that used HCTZ that had a 44% higher mortality in the SI group, the trend was reversed after the protocol was changed to chlorthalidone, and they then had a 28% lower risk of coronary heart disease mortality compared with the UC group. The investigators proposed several explanations, including a possible time delay in risk reduction that required longer follow-up to observe the effect or alternatively, that the change in the protocol to switch to chlorthalidone produced the more favorable effect observed toward the end of the trial. It is important to note that these findings were from a retrospective analysis of a design that was not randomized or blinded and must be interpreted with extreme caution. The findings do, however, raise interesting questions.

If chlorthalidone has more favorable effects on cardiovascular outcomes than does HCTZ, what are the possible mechanisms? The following discussion highlights some of the features of these 2 agents that might explain possible outcome differences.

Chemistry

HCTZ belongs to the benzothiadiazine class, referred to simply as thiazide diuretics. Benzothiadiazines were developed in an effort to find more potent carbonic anhydrase inhibitors. The prototype thiazide diuretic was chlorothiazide, but this drug is not commonly used today because of problems with bioavailability.

HCTZ has the chemical name 2H-1,2,4-benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro-, 1,1-dioxide (Figure 1). HCTZ has one additional hydrogen substituted on a nitrogen on the sulfonamide ring compared with chlorothiazide. All thiazides have a similar dual-ring structure. Though commonly considered a thiazide, chlorthalidone is not a benzothiadiazide and is more appropriately called a thiazide-like diuretic. Though chemically related to the sulfonamides, Figure 1 demonstrates that chlorthalidone is chemically unique. The chemical name for chlorthalidone is benzenesulfonamide, 2-chloro-5-(2,3-dihydro-1-hydroxy-3-oxo-1H-isooindol-1-yl).
with antihypertensive agents is that their pharmacodynamic response is generally much longer than their half-life would predict.27–29 For these reasons, most antihypertensive drugs can be given once or twice daily despite half-lives that would predict the need for more frequent dosing.

**Hydrochlorothiazide**

Sources continue to list the half-life of HCTZ as short as 2.5 hours.30,31 Studies, however, have found that the half-life and duration of HCTZ are much longer. After single oral doses, HCTZ achieved peak concentrations in ~2 hours and had a half-life of ~6.5 to 9 hours (Table 1).32,33 Only one study found a half-life of 2.4 hours.34 The half-life of HCTZ is 8 to 15 hours with long-term dosing.33,35,36

The half-life of HCTZ would suggest that the drug should be given twice daily. Several studies, however, support once-daily dosing of HCTZ, demonstrating that the pharmacodynamic response is much longer than predicted by the half-life.38–41 One double-blind, randomized, crossover study in 24 patients administered HCTZ 100 mg once daily or 50 mg twice daily.31 Blood pressures (BPs) were measured 12 hours after twice-daily dosing and 24 hours after daily, single dosing. Mean sitting BP was 131/85 mm Hg with once-daily and 130/84 mm Hg with twice-daily therapy (P=0.22). These studies suggest that HCTZ can be given as a single, daily dose, which has been recommended in several of the last JNC guidelines.3

**Chlorthalidone**

Chlorthalidone serum concentrations peak ~2 to 6 hours after oral administration (Table 1).42–45 One randomized, crossover study in healthy volunteers found that peak serum concentrations after single doses of 50, 100, or 200 mg were 3.2, 5.6, and 7.9 µg/mL, respectively.42 The half-life of chlorthalidone in this single-dose study was ~42 hours (range, 29 to 55 hours). Interindividual variability in the half-life of chlorthalidone is large, with typical mean half-lives of 45 to 60 hours after long-term dosing.42–46 Chlorthalidone serum concentrations after 100 mg are only twice those of a 25-mg dose, indicating a flat dose–serum concentration curve (Table 2).42,45

Chlorthalidone rapidly enters (half-life, 15 minutes) and concentrates in erythrocytes.47 Studies have found 7 to 10 times greater concentrations of chlorthalidone in erythrocytes than in plasma.42,48 One possible explanation for the long half-life is that chlorthalidone concentrates in erythrocytes and is slowly released from this compartment.

The natriuretic effect of chlorthalidone was maximal at 18 hours and lasted >48 hours in one early study of the drug.49 One double-blind study found that thrice-weekly dosing of chlorthalidone did not completely control systolic BP (SBP), suggesting that every-other-day dosing might not be maximally effective.50

**Dose Response**

**Hydrochlorothiazide**

Doses of HCTZ often exceeded 100 mg daily, and the use of 200 to 450 mg daily was not unusual.51,52 Later studies revealed that 25 mg daily was nearly as effective as higher doses with less hypokalemia.22,53–55 Doses of HCTZ as low as 12.5 mg daily have significant antihypertensive effects in some patients but are not as effective as higher doses.56–58 In one study, 111 patients with hypertension were randomly assigned to placebo or 3, 6, 12.5, or 25 mg HCTZ for 6 weeks.58 SBP was reduced by 2.1, 3.8, 6.4, 6.5, and 12.0 mm Hg by these respective doses (Figure 2). Another study found reductions in SBP of 29, 21, 32, and 24 mm Hg in 51 elderly patients randomly assigned to 25 mg daily, 25 mg twice daily, 50 mg daily, and 50 mg twice daily, respectively.55

Five important principles are evident with HCTZ dosing: (1) some patients will respond to doses of 12.5 mg daily, (2) doses >25 mg daily often lower BP only slightly more than does 25 mg (ie, a relatively flat dose response), (3) hypokalemia is dose related, and the risk increases with dose,53,57,58 (4) there is a great deal of variability in response with some patients, requiring doses of 25 to 50 mg before substantial antihypertensive effects are observed,23,52,53 and the reduction in BP is greater when baseline BP is highest.

**Chlorthalidone**

Early studies with chlorthalidone used doses of 200 to 600 mg daily.49,59,60 In a study published in 1962, mean arterial pressure was reduced from 148 mm Hg at baseline to 128 mm Hg with chlorthalidone 50 mg daily and to 122 mm Hg with 100 mg daily.59 Tweeddale et al61 conducted

<p>| TABLE 1. Pharmacokinetic and Pharmacodynamic Comparisons of HCTZ and Chlorthalidone |
|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Drug</th>
<th>Onset, h</th>
<th>Peak, h</th>
<th>Half-Life, h</th>
<th>Duration, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCTZ</td>
<td>2</td>
<td>4–6</td>
<td>6–9 (Single dose)</td>
<td>12 (Single dose)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8–15 (Long-term dosing)</td>
<td>16–24 (Long-term dosing)</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>2–3</td>
<td>2–6</td>
<td>40 (Single dose)</td>
<td>24–48 (Single dose)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>45–60 (Long-term dosing)</td>
<td>48–72 (Long-term dosing)</td>
</tr>
</tbody>
</table>

| TABLE 2. Mean Chlorthalidone Serum Concentrations and BP Response (n=37) |
|-----------------|-----------------|-----------------|-----------------|
| Dose, mg/d      | Mean Serum Concentration, µg/mL | Mean Fall in Upright SBP, mm Hg | Mean Fall in Upright DBP, mm Hg |
| 25              | 6               | 18              | 8               |
| 50              | 9.3             | 23              | 11              |
| 100             | 11.2            | 24              | 10              |
| 200             | 13.3            | 28              | 10.5            |

Serum concentrations and BP responses were extrapolated from original figures by visual inspection.61
a randomized, double-blind trial and found that chlorthalidone serum concentrations and BP dose response were flat (Table 2 and Figure 2). Although there was an 8-fold increase in dose (25 to 200 mg), serum concentration increased only \( \approx 2 \)-fold. BP dropped 18/8 mm Hg with 25 mg daily but only 28/11 mm Hg with 200 mg daily.

Materson et al.\(^6^2\) randomly assigned 100 patients with hypertension to 12.5, 25, 50, or 75 mg daily or placebo for 12 weeks in a parallel design. Baseline BP differed between groups but was generally 144 to 148/97 to 98 mm Hg. After treatment, BP was 146/95, 140/91, 138/93, 135/91, and 135/91 mm Hg with placebo and with 12.5, 25, 50, and 75 mg, respectively. A standing diastolic BP (DBP) \( \approx 90 \) mm Hg and/or a decrease of 10 mm Hg or more was achieved in 0% of patients on placebo, in 45% with 12.5 mg, in 35% with 25 mg, in 41% with 50 mg, and in 42% with 75 mg daily. Thus, 12.5 mg did lower BP in many patients, though not statistically different from placebo. The higher doses achieved BP that was significantly lower than with placebo. Hypokalemia was clearly dose related: 5% with placebo and 30%, 40%, 58%, and 68% with 12.5, 25, 50, and 75 mg daily, respectively. The authors concluded that 25 mg daily was nearly as effective as higher doses and was associated with less hypokalemia.

Several other studies have confirmed that lower doses of chlorthalidone, especially 12.5 mg and 25 mg daily, offer the best efficacy-to-side effect ratio with respect to hypokalemia.\(^{50,63–66}\)

### Dose Equivalence

The studies cited earlier give some insight into dose equivalence between HCTZ and chlorthalidone, but none of these studies directly compared the 2 agents. Various compendia suggest that the 2 agents are equipotent (50 mg HCTZ is equivalent to 50 mg chlorthalidone).\(^{30,37}\) Interestingly, an article published in 1960, when chlorthalidone first became available, suggested that the dose equivalence of meralluride (a mercurial diuretic), HCTZ, and chlorthalidone had potency estimates of 1.0, 1.4, and 1.8, although the data for these estimates were not provided.\(^{60}\) If this estimate is accurate, then 50 mg HCTZ would be equivalent to \( \approx 39 \) mg chlorthalidone.

The earliest study of dose equivalence was a randomized, double-blind study of placebo, HCTZ 100 mg daily, and chlorthalidone 50 mg daily, each given for 6 weeks separated by a 2-week washout (Table 3).\(^{67}\) Pretreatment BPs were \( \approx 180/110 \) mm Hg. Chlorthalidone 50 mg reduced BP by 25/10 mm Hg, and HCTZ 100 mg reduced BP by 18/8 mm Hg. Although there was no statistically significant difference between the 2 drugs, the sample size was small and the power to detect a difference was low. Interestingly, potassium increased slightly with chlorthalidone (0.02 mEq/L) and decreased significantly with HCTZ (0.22 mEq/L, \( P = 0.009 \)). The fact that chlorthalidone appeared to be more than twice as potent as HCTZ might make it difficult to extrapolate to lower doses, because the flat dose-response curves for these 2 drugs likely differ in shape and slope.

Finnerty\(^{68}\) conducted a double-blind, randomized evaluation of HCTZ 50 mg twice daily (100 mg daily) compared with chlorthalidone 50 mg daily. After 4 weeks of treatment, chlorthalidone reduced mean BP by 18/15 mm Hg, whereas HCTZ reduced mean BP by 22/16 mm Hg (no significant difference between drugs). The percentage of patients with DBP \( \leq 90 \) mm Hg was 42% with chlorthalidone and 32% with HCTZ. Serum potassium decreased 0.38 mEq/L with HCTZ and only 0.03 mEq/L with chlorthalidone, but these differences were not statistically significant (\( P < 0.07 \)). Another study suggested that chlorthalidone is more potent than HCTZ (Table 3).\(^{69}\)

Inspection of the available studies suggests that 50 mg HCTZ is approximately equivalent to 25 to 37 mg chlorthalidone, similar to that proposed by Ford\(^{60}\) in 1960. The scientific basis for the more recent recommendations that the 2 drugs are equipotent is not clear. We suggest that equivalent doses of chlorthalidone should generally be 50% to 75% of typical HCTZ doses. There is, however, a gap in the data, because comparative doses of 12.5 to 25 mg have not been

### TABLE 3. Comparative Trials of HCTZ and Chlorthalidone

<table>
<thead>
<tr>
<th>Author, y (Sample Size)</th>
<th>Diuretic Doses</th>
<th>BP Reduction, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowlus et al, 1964(^{42}) (n=19)</td>
<td>HCTZ 100 mg daily</td>
<td>18/8</td>
</tr>
<tr>
<td></td>
<td>Chlorthalidone 50 mg daily</td>
<td>25/10</td>
</tr>
<tr>
<td>Clark et al, 1979(^{59}) (n=126)</td>
<td>HCTZ 25 mg + triamterene 50 mg daily</td>
<td>15/8</td>
</tr>
<tr>
<td></td>
<td>HCTZ 50 mg + triamterene 100 mg daily</td>
<td>18/12</td>
</tr>
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<tr>
<td></td>
<td>Chlorthalidone 50 mg daily</td>
<td>18/15</td>
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</table>
studied, and it is likely that these doses are on the steeper portions of the dose-response curves.

Discussion
Thiazide diuretics are often considered a class of drugs equivalent to thiazide-like agents, and HCTZ and chlorthalidone are often referred to interchangeably.1 It is, however, clear from this analysis that they are very different compounds. Whether these 2 drugs have different effects on clinical outcomes is unknown.10 Any such difference is probably not due to differences in duration of action, because HCTZ appears to effectively lower BP for 24 hours.

Should one diuretic be preferred on the basis of the scientific evidence? Both HCTZ and chlorthalidone have demonstrated risk reduction in clinical trials. However, the largest trials, including Hypertension Detection and Follow-up Program (HDFP), MRFT, Systolic Hypertension in the Elderly Program (SHEP), and ALLHAT, primarily used chlorthalidone as the initial therapy and more consistently showed reductions in cardiovascular events than did studies that primarily used HCTZ. Although it is possible that these differences are related to the population demographics, it is equally possible that cited differences account for the differences in outcome. Unfortunately, a randomized trial to prove any differences in outcome will probably never be performed.

At this time, we do not believe there is strong evidence to support the use of chlorthalidone over HCTZ. However, we are convinced that the weight of the scientific evidence suggests that clinicians should use one of these two agents as the preferred diuretic for treating hypertension. The typical starting doses of HCTZ should be 12.5 mg in the elderly and 25 mg in younger patients. Most patients will respond to 12.5 to 25 mg HCTZ, but maximum doses of 50 mg might be necessary for some patients. The typical starting dose of chlorthalidone should be 6.25 mg in the elderly and 12.5 mg in younger patients, with a maximum dose of 25 mg if necessary. Studies should be conducted that compare these 2 agents in lower doses to help elucidate whether one agent is clearly superior for the management of hypertension.

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References
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