The Choice of Thiazide Diuretics
Why Chlorthalidone May Replace Hydrochlorothiazide

Norman M. Kaplan

H thiazide diuretics were introduced in the United States for the treatment of hypertension in 1957. The first of these, chlorothiazide, was soon accompanied by a large number of other sulfonamide derivatives, including chlorthalidone. Hydrochlorothiazide (HCTZ) rapidly became the most commonly prescribed antihypertensive drug in the United States, whereas bendroflumethiazide was most popular in the United Kingdom. The initial popularity of HCTZ in the United States was abetted by its use in the first controlled trial of the treatment of nonmalignant hypertension, the Veterans’ Affairs Cooperative Study.1 The starting dose of HCTZ was 50 mg/d, and it was used along with reserpine and hydralazine. A number of other trials published in the 1970s all used higher doses of diuretic, for example, ≥50 mg of HCTZ per day.2

For reasons unknown to me, chlorthalidone was chosen to be the diuretic in the first large controlled trial of the treatment of hypertension, the Hypertension Detection and Follow-Up Program.3 In the Hypertension Detection and Follow-Up Program, all 10,940 patients were started on chlorthalidone from 25 to 100 mg/d. Other drugs were added to achieve control of the blood pressure. In addition, half were assigned to “referred” care and the other half to more closely monitored and intensively treated “stepped” care. The stepped care–treated half achieved a 4.4% further reduction in diastolic blood pressure and a 17.0% reduction in mortality.

In other large, placebo controlled trials published in the early 1980s, other diuretics were used: chlorothiazide in the Australian trial,4 HCTZ in the Oslo study,5 and bendroflumethiazide in the United Kingdom Medical Research Council Trial.6 In all of these trials, the diuretic was combined with other drugs to achieve the goal of therapy.

When the Multiple Risk Factor Intervention Trial was begun, either chlorthalidone or HCTZ, both at doses of 50 or 100 mg daily, could be used. In 6 clinics, chlorthalidone was chosen; in 9, HCTZ was used. After some 7 years, the Multiple Risk Factor Intervention Trial Policy Advisory Board recommended that all of the subjects be given chlorthalidone at a maximal dose of 50 mg/d, because the trend of mortality was unfavorable in the 9 clinics using HCTZ compared with the favorable trend in the 6 clinics using chlorothiazide.7

Nonetheless, HCTZ has been much more widely prescribed in the United States than chlorthalidone and, except for combination with a β-blocker (atenolol) and a central α agonist (clonidine), all of the many other available combinations with a diuretic contain HCTZ at doses ranging from 6.25 mg to 25.00 mg per day.2 Moreover, the multiple Joint National Committee reports only recommend a thiazide diuretic without choosing the specific agent.8

Overlooked Facts
These practices overlooked 2 facts. First, such low doses of HCTZ have never been shown to reduce cardiovascular morbidity or mortality, although they clearly increase the antihypertensive efficacy of whatever other drug with which they are combined. Second, chlorthalidone in doses from 12.5 to 25.0 mg/d has been shown repeatedly to reduce cardiovascular morbidity and mortality in randomized, controlled trials.3,7,9–11

As an example of the failure to recognize these facts, in a widely referenced analysis of the various antihypertensive therapies used as first-line agents, Psaty et al12 conclude that, “Low dose diuretics are the most effective first-line treatment for preventing the occurrence of cardiovascular disease morbidity and mortality,” but their analysis combined HCTZ, chlorthalidone, and other thiazides as either low dose or high dose. Moreover, the low-dose thiazides were often combined with other agents (Table).

Surprisingly, the first definite evidence for a significant difference in the antihypertensive efficacy of HCTZ and chlorthalidone was published just 5 years ago, in this journal.13 Their review concluded that, “chlorthalidone is about 1.5 to 2.0 times more potent as HCTZ, and the former has a much longer duration of action.” The authors called for a proper comparative trial of the 2 agents in lower doses but noted that, “a randomized trial to prove any differences in outcome will probably never be performed,” because the drugs are generic.

Even more surprisingly, the first published trial of the 24-hour ambulatory blood pressure monitoring comparing the 2 drugs appeared only 3 years ago, again in this journal and from the same investigators.14 They found a greater lowering of systolic blood pressure with 25 mg of chlorthalidone than with 50 mg of HCTZ in a crossover trial of stage 1 hypertensives (average baseline office blood pressure: 143/93 mm Hg) with 8-week periods of drug intake and a 4-week washout period between. The daytime ambulatory blood pressure monitoring was a statistically insignificant 3.3-mm Hg mean difference, but the nighttime mean difference was a highly significant 7.1-mm Hg...
lower blood pressure with chlorthalidone. Of further interest, the falls in serum potassium were similar during the 8-week periods of HCTZ or chlorthalidone intake, averaging 0.5 mEq/L.

**Meaning of the Facts**

A number of important facts pertinent to clinical practice can be concluded from currently available data, as described here. Chlorthalidone is the preferable diuretic for initial and subsequent therapy of hypertension, starting with 12.5 mg/d and increasing to ≤25.0 mg/d with or without other antihypertensive drugs.

Second, studies comparing other antihypertensive drugs in full doses against 12.5 to 25.0 mg of HCTZ15,16 are as likely to favor the other drug, as seen with comparisons against the inadequate doses of the β-blocker atenolol.17 As Messerli and Bangalore note, “Many pharmaceutical companies tend to go down the path of least resistance, ie, select an antihypertensive drug that can be eaten easily with regard to efficacy and safety.”17 Other reasons for the continued use of HCTZ may be involved.

Third, even in low doses, potent diuretics, such as chlorthalidone, can lower serum potassium enough to cause cardiac arrest.18 In view of the strong evidence that small doses of the aldosterone blockers spironolactone and eplerenone can protect vulnerable patients19,20 and significantly reduce blood pressures resistant to ≥3 drugs,21 a logical way to provide maximal antihypertensive efficacy and to prevent hypokalemia might be a combination of chlorthalidone and spironolactone 12.5/25.0 mg/d, although there are no trials in which the 2 drugs were given as combination. Both are inexpensive ($4 for a 30-day supply of each) but unfortunately not available in a single tablet. The 25-mg tablets of generic chlorthalidone can be halved with a pill cutter, and 25-mg doses of spironolactone are available.

**Conclusion**

There seems little reason to follow the advice of those who state that, “The risk/benefit of β-blockers and diuretics preclude their use for first-line therapy in hypertension.”22 β-Blockers without vasodilatory action have likely been proven to be inadequate,23 but appropriate use of diuretics can still be a safe and effective way to treat hypertension.

**Disclosures**

None.

**References**


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**Table. Outcome Trials of Assumed Low-Dose Thiazide for Initial Therapy of Hypertension Identified by Psaty et al12**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Diuretic Used, mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helgeland</td>
<td>HCTZ, 25 to 50 + triamterene, 50 to 100</td>
</tr>
<tr>
<td>Amery</td>
<td>Chlorthalidone, 12.5 to 25.0</td>
</tr>
<tr>
<td>SHEP Cooperative Research Group</td>
<td>Chlorthalidone, 12.5 to 25.0</td>
</tr>
<tr>
<td>Medical Research Council Working Party</td>
<td>HCTZ, 25 to 50 + amiloride, 2.5 to 5.0</td>
</tr>
<tr>
<td>PATS Collaborating Group</td>
<td>Indapamide, 2.5</td>
</tr>
<tr>
<td>Rosel EA et al</td>
<td>Chlorthalidone, 25</td>
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<tr>
<td>National Intervention Cooperative Study in Elderly Hypertension Study Group</td>
<td>Trichlormethiazide, 2</td>
</tr>
<tr>
<td>Brown MJ et al</td>
<td>HCTZ, 25 to 50 + amiloride, 2.5 to 5.0</td>
</tr>
<tr>
<td>ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group</td>
<td>Chlorthalidone, 12.5 to 25.0</td>
</tr>
<tr>
<td>Wing LMH et al</td>
<td>HCTZ, dosage unknown</td>
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