Recently, there has been growing interest in the idea that chlorthalidone should be preferred over thiazides when it comes to selecting a nonloop diuretic for treatment of hypertension. Depending on how these drugs are dosed, it is believed that the nonthiazide diuretic chlorthalidone might provide greater cardiovascular protection than thiazide diuretics because of its more potent and prolonged effects on blood pressure. However, given that the chemical structure of chlorthalidone is clearly distinct from the basic chemical structure of the thiazides (Figure), it is possible that the nonthiazide chlorthalidone might also differ from thiazides with respect to effects on determinants of cardiovascular disease other than just blood pressure. Yet, few if any studies have ever directly compared the effects of the nonthiazide chlorthalidone versus thiazides on potential cellular or molecular mechanisms of cardiovascular morbidity and mortality independent of blood pressure.

Chlorthalidone Versus Thiazide Diuretics: Distinctly Different Impacts on Cellular and Molecular Mechanisms Relevant to Pathogenesis of Cardiovascular Disease

In this issue of Hypertension, Woodman et al report novel in vitro experiments in which chlorthalidone was found to reduce epinephrine-induced platelet aggregation and increase angiogenesis much more than bendroflumethiazide, a thiazide diuretic that is widely used in the United Kingdom. Given that Woodman et al performed their studies in cells incubated with chlorthalidone or bendroflumethiazide, rather than in cells obtained from patients treated with either drug, the observed effects on platelet aggregation and angiogenesis could not be secondary to differential effects of the 2 agents on blood pressure. If the greater effects of chlorthalidone on platelet aggregation and angiogenesis are also obtained in vivo, they could conceivably contribute to greater protection against stroke and myocardial infarction with chlorthalidone compared with bendroflumethiazide, and perhaps other thiazides as well.

In cultured vascular smooth muscle cells, Woodman et al also found that chlorthalidone reduced expression of mRNAs for vascular endothelial growth factor C and transforming growth factor-β3 much more than bendroflumethiazide. These proteins have potential to affect a variety of factors that could influence pathogenesis of cardiovascular disease, including interstitial fluid volume balance and cardiac fibrosis and remodeling. Thus, the results of Woodman et al raise the possibility that chlorthalidone differs from thiazides with respect to many mechanisms that could theoretically influence a host of cardiovascular outcomes in patients with hypertension.

Different Cellular and Molecular Effects of Chlorthalidone Versus Thiazides: Are Different Effects on Carbonic Anhydrase Isoenzyme Activity the Key?

What could explain the different cellular and molecular effects that Woodman et al observed between chlorthalidone and the thiazide diuretic they tested? One possible explanation put forth by the authors is that chlorthalidone has a greater ability to inhibit carbonic anhydrase (CA) activity than thiazides and that this could cause alterations in intracellular pH, cell volume regulation, and other biological processes of potential functional significance. CAs are widely distributed zinc metalloenzymes that catalyze the conversion of carbon dioxide and water to carbonic acid and ultimately bicarbonate ions and protons. It has long been recognized that CA inhibitors like acetazolamide and ethoxzolamide can have effects on cardiovascular and platelet functions of potential clinical significance. For example, acetazolamide was shown years ago to cause marked increases in cerebral blood flow, and ethoxzolamide was shown to significantly inhibit the velocity of thrombin-induced platelet aggregation.

Chlorthalidone and the thiazide diuretics inhibit CA activity through interaction of their sulfonamide moieties with the Zn(II) ion in the CA active site cleft and with specific amino acid residues in the enzyme as well. However, beyond the sulfonamide group, the scaffold structure of chlorthalidone is very different from that of the thiazides (Figure), and this can further influence CA activity by affecting molecular interactions with amino acids that line the active site cleft in the enzyme. When the sulfonamide diuretics became clinically available, only 1 CA isozyme was well known. However, beyond the sulfonamide group, the scaffold structure of chlorthalidone is now appreciated that 16 different CA isozymes or CA-related proteins exist and that the inhibitory profile of the nonthiazide chlorthalidone on these CA isozymes is markedly different from that of the thiazides because of chemical structural differences beyond the sulfonamide group (Table and Figure). The potential importance of these observations is highlighted by growing interest in the development of novel chemical modulators of many different CA isoforms for a variety of therapeutic purposes.

Chlorthalidone Is a Strong Inhibitor of Multiple Isoforms of CA

Chlorthalidone inhibits the activity of most CA isozymes much more potently than hydrochlorothiazide when tested at
For example, the inhibitory potency of indapamide against inhibition profile that is also very different from the thiazides. is a potent inhibitor of some isoforms of CA with an study. Indapamide, another nonthiazide sulfonamide diuretic, although its effects on various isozymes of CA require further said to be relatively devoid of inhibitory activity on CA,

long been suspected that vasodilator effects of nonthiazide action on plasma volume and cardiac output induced by other mechanisms, as well as the diverse nature and distribution of CA isoforms, one can readily imagine how the contrasting actions of nonthiazide versus thiazide diuretics on CA isoyme activity might give rise to different effects on a variety of mechanisms relevant to the pathogenesis of cardiovascular disease, including those that regulate blood pressure. For example, the antihypertensive effects of nonthiazide diuretics like chlorthalidone and thiazide diuretics might also contribute to their antihypertensive effects in the long term. It has been proposed that vasodilator effects of these drugs may be related to inhibition of vascular CA activity or to direct effects on vascular ion channels or both.

Could Effects on NO Production Also Be Involved?

Recently, it has been found that CA can generate NO from nitrite at high rates. Surprisingly, it appears that some CA inhibitors, including acetazolamide, can increase CA-mediated production of vasoactive NO despite inhibiting CA-mediated interconversion of carbon dioxide and bicarbonate. Thus, the ability of CA inhibitors to increase production of vasoactive NO might also help to explain the known vasodilatory effects of these drugs. This raises the possibility that a special effect of chlorthalidone on CA isoenzymatic profiles might be contributing to its presumed cardioprotective superiority not only by affecting the cellular and molecular pathways identified by Woodman et al., but perhaps by influencing NO activity in certain organs as well.

Perspectives

Although chlorthalidone is not a thiazide, it is frequently referred to as “thiazide-like” because chlorthalidone and the thiazide diuretics all inhibit the Na⁺-Cl⁻ cotransporter in the distal tubule. Referring to chlorthalidone in this imprecise fashion makes about as much sense as referring to amlodipine as a “benzothiazepine-like” or a “diltiazem-like” calcium antagonist simply because amlodipine and the benzothiazepines including diltiazem block L-type calcium channels in the vasculature (although amlodipine is a dihydropyridine and not a benzothiazepine).

Unfortunately, the imprecise description of chlorthalidone as “thiazide like” has led many to assume that chlorthalidone and the thiazides are alike with respect to all actions that might possibly influence cardiovascular outcomes in patients and thiazide diuretics might also contribute to their antihypertensive effects in the long term.
with hypertension. In fact many writers, including the authors of the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, lapse into dropping the qualifier “thiazide like” or “thiazide type” and on occasion simply call or classify chlorthalidone as a “thiazide diuretic” although it is clearly not a thiazide (eg, Table 10 in the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure).16

By placing nonthiazide molecules including chlorthalidone in a class labeled “thiazide diuretics,”16 the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure tacitly encouraged the belief that nonthiazide diuretics such as chlorthalidone and thiazide diuretics such as hydrochlorothiazide are equivalent with respect to their therapeutic effects on all of the important mechanisms of hypertension-related cardiovascular disease. From both a clinical perspective1–4 and now a mechanistic perspective,5 it would appear that lumping all of these heterogeneous molecules into a single therapeutic class may have been misguided.

The novel studies of Woodman et al,5 together with evolving research on inhibitors of CA isozyme activity,8,11,12 highlight distinct cellular, biochemical, and molecular effects of chlorthalidone that are of potential cardiovascular significance and that clearly distinguish chlorthalidone from at least some of the thiazides. Such observations suggest that when evaluating the relative benefit of antihypertensive agents, the results with chlorthalidone in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial should not be extrapolated to hydrochlorothiazide, nor should the results with hydrochlorothiazide in the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension Trial be extrapolated to chlorthalidone. The findings of Woodman et al5 raise the possibility that, even if one happens to achieve the same degree of blood pressure control by using a thiazide diuretic instead of chlorthalidone, one may not achieve the same degree of cardiovascular protection with these 2 different types of agents. As emphasized by Woodman et al,5 it is time to abandon use of the term “thiazide like” when referring to chlorthalidone.

Disclosures
T.W.K. has received speaker honoraria and consulting fees from, and is a stockholder in, companies with financial interests in the use of thiazide diuretics, nonthiazide diuretics, and/or other antihypertensive agents in the treatment of hypertension.

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