Modern diuretic therapy evolved from 2 seemingly unrelated events in the 1930s: the development of sulfanilamide, the first truly effective antibacterial agent, and the description of the enzyme carbonic anhydrase. Sulfanilamide was observed to increase sodium (Na+)/potassium and water excretion by inhibition of carbonic anhydrase activity. Recognition of this action proved the impetus for synthesis of compounds, such as acetazolamide, that could more specifically inhibit carbonic anhydrase; however, acetazolamide was a short-acting compound, and diuretics with greater potency and/or duration of action were quickly sought. Chlorthalidone was the first of these new-generation diuretics, and its introduction in 1957 set the modern era of diuretic therapy in motion. Shortly thereafter several loop diuretics and a host of thiazide-type diuretics found their way to the marketplace as the result of active development programs.

As diuretics began to proliferate in numbers, loop diuretics were promptly distinguished from thiazide-type diuretics on the basis of potency and were quickly slotted as the more important diuretic class for volume overload states. Thiazide-type diuretics were early on seen as agents with greater effectiveness in reducing blood pressure (BP), but with a lesser ability to impact volume overload states. In the early days of thiazide-type diuretic use there was little effort expended to seriously distinguish one from the other in their BP-lowering effect even if there were major intraclass pharmacokinetic differences. Inexorably, the term “class effect” crept in to describe the actions of thiazide-type diuretics, applied both to BP reduction and ultimately outcomes.

Much of the recent debate on diuretic class effect has centered on the similarities and differences between chlorthalidone and hydrochlorothiazide (HCTZ).\(^1\) The concept of class effect with thiazide-type diuretics should be considered in 2 ways: effect on BP fall and event-rate reduction.\(^2\) The former is addressed by Ernst et al\(^3\) in this issue of *Hypertension*; the latter remains an issue that can at best be speculated on.

Although chlorthalidone and HCTZ are structurally similar compounds they are very dissimilar pharmacokinetically. Intraclass pharmacokinetic differences for various drug classes are often touted as relevant but oftentimes are little more than ways to capture a marketing edge. However, intraclass pharmacokinetic differences among the thiazide-type diuretics are genuine and likely to influence the results of their use. Chlorthalidone is distinguished from HCTZ in having an extremely long half-life and a very large volume of distribution owing to its extensive partitioning into red blood cells. This latter feature creates a hefty depot for chlorthalidone, allowing for a slow streaming effect (red cell → plasma) with subsequent gradual elimination from the plasma compartment by tubular secretion.\(^4\)

The extremely long half-life of 40 to 60 hours for chlorthalidone differentiates it from HCTZ, which has a much shorter but wider variation in half-life, from 3.2 to 13.1 hours.\(^5\) This plasma half-life difference can be expected to correlate with a more extended effect of chlorthalidone on diuresis and possibly BP. Moreover, the postdiuretic period of antinatriuresis, otherwise termed the “braking phenomenon”, is less apt to interfere with net Na⁺ loss when a long-acting diuretic, such as chlorthalidone, is being given. Second, chlorthalidone being present in the blood for a longer period of time might permit more drug exposure in tissue compartments where the drug has its effects.\(^6\) Diuretic blood levels needed to effect vessel dilation per se are typically several times higher than what is achieved therapeutically; therefore, it is unclear how the blood level of a diuretic relates to a direct vascular mechanism of action.\(^7\)

Differentiating these compounds pharmacokinetically begs the question of whether they are different from a BP lowering point-of-view. The studies by Ernst et al, irrespective of some methodological constraints in interpreting their data, argue rather convincingly for better BP reduction with chlorthalidone than with HCTZ at a fixed dose ratio of 2:1 (HCTZ, 50 mg; chlorthalidone, 25 mg). This BP difference was particularly impressive in the evening hours. The reduction in systolic BP during nighttime hours was −13.5±1.9 mm Hg for chlorthalidone versus −6.4±1.7 mm Hg for HCTZ and was highly significant. The reduction in daytime mean systolic BP was not significantly different between chlorthalidone and HCTZ (−11.4±2.0 mm Hg versus −8.1±1.9 mm Hg, respectively; \(P=0.230\)). These studies are all the more noteworthy in that BP changes were identified by ambulatory blood pressure monitoring, a methodology heretofore not applied in any of the past direct comparisons of chlorthalidone to HCTZ.\(^3\)

Is there a mechanistic basis for these BP differences? This is a difficult question to answer and one not addressed in the studies of Ernst et al.\(^3\) Although not apparent from these studies it is very likely that the plasma or interstitial volume changes with chlorthalidone were more so than was the case for HCTZ. Such volume changes might then have provided a permissive cue for a more significant BP reduction.\(^8\) An

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The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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**Editorial Commentary**

**Chlorthalidone Has It Always Been the Best Thiazide-Type Diuretic?**

Domenic A. Sica
additional consideration in these studies is the degree to which BP fell with a 25-mg dose of chlorthalidone. The reduction in office readings of $\approx 16/8$ mm Hg with chlorthalidone is on the high side for this drug and suggests that there had not been undue counterregulatory activation of the renin–angiotensin–aldosterone system (RAAS).\textsuperscript{9}

The question of defining dose equivalence between 2 compounds in a drug class is complex. Defining doses of HCTZ and chlorthalidone as being equipotent at 50:25 mg (2:1 ratio) in these studies was at best an a priori approximation and one based on expected BP reduction and not diuresis.\textsuperscript{1} In these studies the 2:1 ratio fell in favor of chlorthalidone being more potent, so this ratio ultimately did not apply. Of note, doses of chlorthalidone greater than 25 mg cannot be presumed to automatically provide an incremental benefit for BP reduction. If higher doses of chlorthalidone are given, a very much lengthier diuretic effect, greater volume losses, and significant RAAS activation may result. The latter can attenuate the BP-reducing effects of this compound and may be the basis for the flattening of the dose-response relationship for chlorthalidone and BP at doses above 25 mg/d.\textsuperscript{9} This sequence of events also impacts the dose equivalence relationship for these 2 compounds.

How does one then carry data such as these into clinical practice? If one believes that the degree to which BP is reduced is the most important variable in defining outcome then there is now better support for chlorthalidone as the preferred thiazide-type diuretic. The studies of Ernst et al show chlorthalidone 25 mg/d to be more potent than HCTZ 50 mg/d when therapy is begun straight-off with chlorthalidone. Interestingly, when chlorthalidone is substituted for HCTZ its BP reducing effect seems to be lessened by the preceding diuretic therapy.

Appreciating the difficulties in achieving goal BP in many patients, a sensible approach to a therapy decision, if a diuretic is being considered for first-step therapy, is to start with chlorthalidone; thereafter, other drugs can be added as needed for BP control. However, despite strong outcomes, data for chlorthalidone, and a very real difference in BP lowering efficacy, resistance to change will be the final arbiter of its broader acceptance as a therapy option for the hypertensive patient.

Such physician opposition to change can be viewed as a function of perception and secondarily as a byproduct of the limited availability of chlorthalidone. The belief that low-dose chlorthalidone is associated with excessive degrees of hypokalemia remains; thus, although chlorthalidone is a better antihypertensive compound its benefits are often believed to be exceeded by the risk of electrolyte abnormalities. Also, chlorthalidone simply is not as readily available as HCTZ; whereas, there are only a few fixed-dose antihypertensive combinations that contain chlorthalidone, the numbers of fixed-dose antihypertensive combinations that contain HCTZ are almost too many to count. At the end of the day, chlorthalidone will likely remain an underutilized yet very effective antihypertensive compound.

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Chlorthalidone: Has It Always Been the Best Thiazide-Type Diuretic?
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