Chlorthalidone Versus Hydrochlorothiazide
A Tale of Tortoises and a Hare

Norman M. Kaplan

Chlorthalidone (CTD) is the best diuretic for the treatment of hypertension, both in blood pressure–lowering efficacy and, most importantly, in prevention of hypertension-related morbidity and mortality. Despite this fact, hydrochlorothiazide (HCTZ) has been and continues to be by far the most frequently prescribed diuretic in the United States. Even among patients with resistant hypertension, where a more potent diuretic is especially needed, CTD is chosen in only 3% of patients. There are numerous possible reasons for this flagrant failure of evidence-based medicine. I will refer to the Aesop tale of “The Tortoise and the Hare” as my way of explaining the paradox. In this reference, physicians are the tortoises, whereas a pharmaceutical company is the hare; here, unlike in the original, the hare easily wins the race.

The 2 diuretics were approved for the treatment of hypertension within a year of each other, HCTZ in 1959 and CTD in 1960. Soon thereafter, small trails documented the equal efficacy of CTD in much smaller doses in lowering blood pressure compared with HCTZ or other thiazides. A few years later, the Multiple Risk Factor Intervention Trial (MRFIT) was begun, and the designers offered the 15 participating clinics the choice of using either HCTZ or CTD; 9 chose HCTZ and 6 chose CTD. After some 4 years, the MRFIT policy advisory board recommended that all of the participants be given CTD, because the trend of mortality was unfavorable in the HCTZ clinics compared with favorable trends in the CTD clinics.

The wisdom of this decision in favor of CTD was soon validated in 3 large controlled outcome trials, the Systolic Hypertension in the Elderly Program in 1991, the Verapamil in Hypertension and Atherosclerosis Study in 1997, and, most decisively, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial in 2002. In these 3 large outcome trials, CTD provided excellent protection against heart attacks and strokes. Meanwhile, no decreases in morbidity or mortality were seen in multiple trials using HCTZ.

Nonetheless, the machinations of the hare who owned the patent for HCTZ were immediately brought into play as soon as the drug had been approved. When the Veterans’ Administration Cooperative Studies on the Treatment of Hypertension were begun in 1964, HCTZ was made available and used in both the initial study on severe hypertension and the second one on less severe disease, along with reserpine and hydralazine. With this extra boost in awareness and the strengths of the largest pharmaceutical sales force in the world pushing its acceptance, HCTZ soon outsold CTD, then marketed by a smaller Swiss-based company. Moreover, HCTZ was quickly added in combination with antihypertensive drugs from every other class except calcium channel blockers, ending up in ≥28 combination tablets. Meanwhile, after its initial success, the use of CTD progressively fell, and it was combined with only 3 other antihypertensive agents.

The well-conditioned hare pushed its patented product as fast and as hard as possible. And the tortoises, US practitioners, soon accepted its superiority, and, by 2010, HCTZ was the choice in >95% of oral diuretic prescriptions.

Meanwhile, starting in 2004, investigators, most from the Carver College of Medicine at the University of Iowa, began publishing a series of careful comparisons of the antihypertensive effects of the 2 drugs, having noted that, even in prestigious textbooks of pharmacology, the 2 drugs were considered to be equivalent and interchangeable. They and others using 24-hour ambulatory monitoring have shown the longer and stronger efficacy of CTD over HCTZ.

Soon thereafter, using a retrospective cohort analysis of the MRFIT data, the clear proof of a greater reduction in heart attacks and strokes with CTD than with HCTZ was shown. Adding to this evidence, the Iowa group joined by other investigators presents, in this issue of this journal, further evidence for the superior antihypertensive efficacy of CTD over HCTZ using the greater regression of electrocardiographic left ventricular hypertrophy seen in those on CTD in the MRFIT. As they conclude, “Our findings on left ventricular hypertrophy support the idea that greater blood pressure reduction with CTD than HCTZ may have lead to differences in mortality observed in MRFIT.”

So what have the tortoises done in view of the conclusive evidence of the superiority of CTD over HCTZ, with the 2 now costing the same, 30 tablets for $4.00, and with no significant differences in adverse effects between the two? As expected from tortoises, they have moved exceedingly slow, as documented in references and. Now that pharmaceutical representatives are no longer promoting HCTZ, perhaps more publications and talks by nonbiased speakers will help, along with the likely impending intro-
duction of the first “modern” drug, an angiotensin receptor blocker, in combination with CTD. 19

Hopefully, we tortoises will overtake the hare, but, meanwhile, millions of hypertensive patients have been given a less effective drug that almost certainly did not protect them as well as CTD would have. The patients are neither tortoises nor hares, but they have been the unwitting recipients of a flagrant failure of evidence-based medicine.

It should be noted that the British National Institute for Health and Clinical Excellence has recently published new guidelines on preferred drugs for treatment of hypertension, in which diuretics have been demoted from first choice to third choice for the majority of patients. 20 One wonders, could awareness of the ability of CTD to reduce mortality as well as drugs from any other class have prevented the National Institute for Health and Clinical Excellence from denying the use of the correct diuretic from its preferred location? Surely, the British are now willing to accept hard evidence from their unruly and disloyal former colony.

One last issue: should the pharmaceutical company be faulted for its aggressive marketing of its patented HCTZ even if it was known to be an inferior drug? The answer would be “no” in keeping with the capitalistic economic model that Milton Friedman would have applauded. But what if, as has been repeatedly done, the larger pharmaceutical company bought the patent from the original patent holder soon after the evidence that CTD was the better drug became known and then marketed it as aggressively as they did HCTZ? Might their profits have been just as great and many millions more hypertensive patients provided better control of their hypertension?

Disclosures

None.

References
