Thiazide and Loop Diuretics

Domenic A. Sica, MD;[1] Barry Carter, PharmD;[2] William Cushman, MD;[3] Lee Hamm, MD[4]

From the Department of Medicine, Section of Clinical Pharmacology and Hypertension, Virginia Commonwealth University Health System, MCV Station, Richmond, VA;[1] Department of Pharmacy Practice and Science, College of Pharmacy and Department of Family Medicine, Carver College of Medicine, University of Iowa, Iowa City, IA;[2] Department of Preventive Medicine, University of Tennessee College of Medicine, Memphis, TN;[3] and Professor and Greenberg Chair of Medicine, Department of Medicine, Tulane University School of Medicine, New Orleans, LA[4]

Key Points and Practical Recommendations

- Although chlorthalidone and hydrochlorothiazide are structurally similar, they are very different pharmacokinetically, with chlorthalidone having both an extremely long half-life (approximately 40 to 60 hours) and a large volume of distribution, with gradual elimination from the plasma compartment by tubular secretion.
- Furosemide usage, the most widely used diuretic in the loop diuretic class, can be complicated by extremely erratic absorption, with a bioavailability range of 12% to 112%.
- Chlorthalidone, at a dose of 25 mg, is comparatively more potent than 50 mg of hydrochlorothiazide, particularly as related to overnight blood pressure reduction.
- In ALLHAT, there was no difference among chlorthalidone, amlodipine, lisinopril, and doxazosin for the primary outcome or mortality.
- Secondary outcomes were similar except for a 38% higher rate of heart failure with amlodipine; a 10% higher rate of combined cardiovascular disease, a 15% higher rate of stroke, and a 19% higher rate of heart failure with lisinopril; and a 20% higher rate of cardiovascular disease, a 20% higher rate of stroke (40% higher rate in blacks), and an 80% higher rate of heart failure with doxazosin, compared with chlorthalidone.
- The ACCOMPLISH study may affect future practice guidelines as a result of its findings favoring the amlodipine/benazepril combination; however, the generalizability to patient populations with a lesser cardiovascular risk profile remains in question and the dose of hydrochlorothiazide was only 12.5 mg to 25 mg daily, which was a dose lower than that used in placebo-controlled trials using hydrochlorothiazide.
- Certain low-renin patient groups (eg, blacks, the elderly, and diabetics) as well as those who manifest the metabolic syndrome are commonly more responsive to thiazide-type diuretic therapy.
- Diuretics can be successfully combined with β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, centrally acting agents, and even calcium channel blockers.
- Although thiazide-type diuretics are among the best-tolerated antihypertensive agents in terms of symptomatic adverse effects, diuretic-related adverse side effects include those with established mechanisms (eg, such as electrolyte changes and/or metabolic abnormalities) and other side effects, which are less well understood mechanistically (eg, impotence), although the latter is not universally accepted as a diuretic-related side effect.
- Thiazide-induced hypokalemia is associated with increased blood glucose, and treatment of thiazide-induced hypokalemia may reverse glucose intolerance and possibly prevent diabetes.
- Thiazide-induced hyperuricemia occurs as a result of volume contraction and competition with uric acid for renal tubular secretion, but does not necessarily contraindicate using a thiazide, especially if a uric acid–lowering drug such as allopurinol is being used.
- Adverse interactions include the blunting of thiazide effects by nonsteroidal anti-inflammatory drugs and the potential to increase fatigue, lethargy, and increase in glucose when combined with β-blockers.
- Thiazide-type diuretics are useful first-line agents in the treatment of hypertension because they have been proven to reduce cardiovascular mortality and morbidity in systolic and diastolic forms of hypertension and do so at low cost.
- Loop diuretics should not be used as first-line therapy in hypertension since there are no outcome data with them. They should be reserved for conditions of clinically significant fluid overload (eg, heart failure and significant fluid retention with vasodilator drugs, such as minoxidil) or with advanced renal failure and can be combined with thiazide-type diuretics. *J Clin Hypertens (Greenwich).* 2011;13:639–643. ©2011 Wiley Periodicals, Inc.

Diuretics are tools of considerable therapeutic importance in hypertension. First, they effectively reduce blood pressure (BP), while at the same time decrease the morbidity and mortality associated with hypertension. Diuretics are currently recommended by the Seventh Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) as first-line therapy for the treatment of hypertension.[1] In addition, they remain an important component of therapy for volume-overload conditions, such as heart

Address for correspondence: Domenic Sica, MD, Section of Clinical Pharmacology and Hypertension, Virginia Commonwealth University Health System, Box 980160, MCV Stations, Richmond, VA 23298-0160
E-mail: dsica@mcvh-vcu.edu

DOI: 10.1111/j.1751-7176.2011.00512.x

failure (HF), nephrotic syndrome, and cirrhosis, in that they improve the symptoms of edema and congestion.[2]

MECHANISM OF ACTION

Pharmacology

Hydrochlorothiazide (HCTZ) is the most widely used thiazide-type diuretic. It has a bioavailability ranging from 60% to 80%, which is relatively dose proportional. Its absorption can be reduced (rapidity and extent of absorption) in HF and/or renal disease and its plasma half-life correlates with endogenous creatinine clearance values and ranges from 3.2 hours to 13.1 hours.[3] Chlorthalidone is another thiazide-type diuretic that has been proven effective in both BP reduction and improving cardiovascular (CV) outcomes. Chlorthalidone and HCTZ are very different pharmacokinetically.[4] Chlorthalidone is distinguished from HCTZ in having both an extremely long half-life, approximately 40 to 60 hours, and a large volume of distribution owing to its heavy partitioning into red blood cells. This latter feature creates a depot effect for chlorthalidone, allowing for a slow outward movement (red cell $\rightarrow$ plasma) and thereafter gradual elimination from the plasma compartment by tubular secretion.[5]

Furosemide is the most widely used diuretic in the loop diuretic class; however, its use can be complicated by extremely erratic absorption, with a bioavailability range of 12% to 112%.[6] The coefficient of variation for absorption varies from 25% to 43% for different generic furosemide products; thus, exchanging one furosemide formulation for another will not standardize patient absorption (and thus response) to oral furosemide.[6] Bumetanide and especially torsemide are more predictably absorbed than furosemide. The consistency of torsemide's absorption and its longer duration of action are distinguishing pharmacologic features among loop diuretics.[7]

INDICATIONS

Thiazide-type diuretics are indicated in the treatment of hypertension and they provide wide-ranging CV benefits. When used alone in the nonedematous patient, thiazide diuretics are as effective as most other antihypertensive drug classes, an observation that is independent of body mass index.[8] Head-to-head comparisons among the various thiazide-type diuretics have not shown significant differences for BP reduction when equivalent doses are used. The exception to this may be with chlorthalidone, which at a dose of 25 mg is comparatively more potent than 50 mg of HCTZ, particularly as related to overnight BP reduction.[9] Loop diuretics are less effective than thiazide-type drugs in reducing BP in the nonedematous patient;[10] however, as chronic kidney disease (CKD) transitions from stage 3 to 5, particularly with extracellular fluid (ECF) volume expansion, loop diuretics become the preferred diuretic therapy for management of hypertension.[11]

OUTCOMES STUDIES

Diuretics were key components of an additive regimen used by the Veterans Administration (VA) Cooperative Study Group started in the 1960s, a study that convincingly proved the benefits of BP control. Both the severe (diastolic, 115–129 mm Hg) and mild to moderate (diastolic, 90–104 mm Hg) subgroups demonstrated reduced CV morbidity and mortality with BP reduction.[11,13] In the VA Cooperative Study, only 2.7 patients needed to be treated to prevent a major CVD event in either BP stratum. Over the next 2 decades, subsequent trials primarily employed a variant of "stepped-care" therapy (diuretic followed by adrenergic inhibitor, followed by vasodilator) that later became the basis for advocating diuretic use in the several reports of the JNC. To date, there are no outcomes trials with loop diuretics in either hypertension or HF. In addition, thiazide-type diuretics have not been specifically studied in stage 4 or greater CKD as to CV benefits.

Since systolic hypertension carries a greater risk than diastolic hypertension for the large majority of hypertensive patients, the question has arisen as to whether diuretic therapy confers benefit in isolated systolic hypertension, the most common form of systolic hypertension. The Systolic Hypertension in the Elderly Program (SHEP) studied the impact of chlorthalidone-based therapy compared with placebo on the incidence of stroke and other CV events in 4736 participants with isolated systolic hypertension for 4.5 years. This chlorthalidone-based regimen reduced the incidence of stroke by 36%, myocardial infarction (MI) by 27%, HF by 54%, and overall CV morbidity by approximately 32%.[14]

A more recent outcome trial addressing diuretic use is the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[14] This trial randomized more than 42,000 individuals with hypertension and either known CVD or at least one other coronary heart disease (CHD) risk factor to initial therapy with chlorthalidone, doxazosin, lisinopril, or amlodipine. In ALLHAT, there was no difference among chlorthalidone, amlodipine, lisinopril, and doxazosin for the primary outcome or mortality. Secondary outcomes were similar except for a 38% higher rate of HF with amlodipine, a 10% higher rate of combined CVD, a 15% higher rate of stroke, and a 19% higher rate of HF with lisinopril; and a 20% higher rate of CVD, a 20% higher rate of stroke, and an 80% higher rate of HF with doxazosin, compared with chlorthalidone.[16] For stroke, there was a statistically significant race-by-treatment interaction. Chlorthalidone was superior to lisinopril in preventing incident stroke only in blacks (40% higher rate of stroke with lisinopril vs chlorthalidone in black patients but no difference in non-black patients).

A meta-analysis of 18 long-term trials and 48,220 patients has differentiated the effects of diuretics from β-blockers on health outcomes and found that low-dose diuretics were more effective than high-dose diuretics in decreasing CV events. High-dose diuretic therapy included studies that generally used starting doses greater than or equal to: chlorthalidone 50 mg, HCTZ 50 mg, chlorothiazide 500 mg, bendroflumethiazide 5 mg, methyclothiazide 5 mg, or trichlormethiazide 2 mg. Low doses in these trials were the equivalent of 25 mg to 50 mg of HCTZ or 12.5 mg to 25 mg of chlorthalidone. With low-dose diuretic therapy, the incidence of stroke was reduced by 34%, CHD by 28%, HF by 42%, and CV mortality by 24%. High-dose diuretics reduced strokes and HF by 51% and 83%, respectively; however, the risk reduction for HF was derived from fewer trials in that this outcome was not routinely reported in many of the high-dose trials.[17] This differentiation between low-dose and high-dose diuretics has been supported by a Cochrane Database Systematic Review on this topic.[18]

There are a limited number of studies that have shown diuretic therapy to be inferior to other drug classes in the treatment of patients with hypertension, but these trials usually used lower doses of HCTZ (12.5–25 mg) than what was used in placebo-controlled hypertension outcome trials. In one such study, the Avoiding Cardiovascular Events in Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial, 11,506 patients with hypertension who were at high risk for CV events received treatment with either benazepril plus amlodipine or benazepril plus HCTZ. The primary end point was a composite of death from CV causes, nonfatal MI, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization. There was a 20% relative risk reduction favoring the amlodipine and benazepril combination despite their being similar reductions in office and ambulatory BP values.[19] The ACCOMPLISH study may have an effect on how future practice guideline development occurs as a result of its findings favoring the amlodipine/benazepril combination; however, the generalizability of these study results to patient populations with a lesser CV risk profile remains in question and the dose of HCTZ was only 12.5 mg to 25 mg daily.

CLINICAL USAGE

Specific Recommendations by Indication

All thiazide-type diuretics can be administered once daily, which for convenience sake usually occurs in the morning. It is now clear that lower dosages of a thiazide diuretic, such as HCTZ (25–50 mg/d) are similarly efficacious as higher dosages (50–100 mg/d) in lowering BP;[20] thus, it is rarely necessary or desirable to use >50 mg/d of a thiazide diuretic. In the elderly, a beginning dose of 12.5 mg and a maximum dose of 50.0 mg HCTZ (or its equivalent) are recommended. This cautious dosing occurs, in part, because of the perception of there being a greater sensitivity to the volume-depleting effects of these compounds. In SHEP, 12.5 mg to 25.0 mg of chlorthalidone controlled more than 50% of patients for several years without significant untoward consequences.[14] However, chlorthalidone is a long-acting diuretic and should still be used cautiously if there is any concern about whether a patient can take in adequate replacement fluids if they are becoming dehydrated.

Variations in Response and Use in Special Situations/Populations

Certain low-renin patient groups (eg, blacks, the elderly, and diabetics) as well as those who manifest the metabolic syndrome are commonly more responsive to thiazide-type diuretic therapy. The early action of diuretics to reduce ECF volume is best accomplished if dietary sodium (Na^+) is restricted at the beginning of therapy. The degree to which diuretics lower BP relates, in part, to the level of counterregulatory system activation, including an increase in heart rate and activation of the renin-angiotensin-aldosterone and sympathetic nervous systems. It is also generally recommended that diuretic-treated hypertensive individuals should increase their daily intake of potassium (K^+), although it is unclear that such an increase either fully compensates for the kaliuretic effect of thiazides or offers meaningful additional BP reduction.[21]

Combination Use With Other Agents

Diuretics can be successfully combined with β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), centrally acting agents, and even with calcium channel blockers. In the VA monotherapy study, the combination of a diuretic with drugs from any other class provided the best antihypertensive effect as compared with combinations without a diuretic.[22] Diuretics are combined with numerous other drug classes as fixed-dose combination products, with most such products utilizing HCTZ.[23]

DRUG INTERACTIONS AND ADVERSE EFFECTS

Thiazide-type diuretics are among the best-tolerated antihypertensive agents in terms of symptomatic adverse effects. Diuretic-related adverse side effects can be separated into several categories, including those with established mechanisms (eg, such as electrolyte defects and/or metabolic abnormalities) and other side effects, which are less well understood mechanistically (eg, impotence). Diuretic-related biochemical side effects are dose-dependent as well as more common and of greater intensity with loop diuretics. As practice patterns shifted to a low-dose strategy for thiazide-type diuretics, the frequency of metabolically negative side effects diminished. Thus, hypokalemia, hypomagnesemia, and glucose intolerance are much less common

with low-dose diuretics, and their development can be minimized by concurrent administration of an ACE inhibitor or an ARB. Thiazide-related biochemical side effects tend to be more common with longer-acting compounds such as chlorthalidone and metolazone, particularly when high doses are given.[24]

Volume depletion is more common with loop than thiazide-type diuretics and can be exacerbated by concurrent illness marked by excessive fluid losses, such as a gastrointestinal disorder or concomitant administration of a loop and a thiazide-type diuretic. Diuretic-related hyponatremia is uncommon but occurs more so with thiazide than loop diuretics in that thiazide diuretics do not interfere with the ability of the kidney to maximally concentrate urine. Reduction in the diuretic dose or discontinuation of the diuretic together with liberalization of Na^+ intake and, occasionally, restriction of water intake may correct this abnormality. Metabolic alkalosis is more common with loop diuretics, often associated with concurrent hypokalemia, and usually easily managed by provision of Cl^-, preferably as KCl. Thiazide-induced hypokalemia is associated with increased blood glucose values, and treatment of thiazide-induced hypokalemia may reverse glucose intolerance and possibly prevent the future development of diabetes.[25] Thiazide-induced hyperuricemia occurs as a result of volume contraction and competition of thiazides with uric acid for renal tubular secretion. In susceptible individuals, recurrent gouty arthritis can be precipitated but does not necessarily contraindicate using a thiazide, especially if a uric acid–lowering drug such as allopurinol is being used.[26]

In addition, various drug-drug interactions are recognized to occur with diuretics. Adverse interactions include the blunting of thiazide effects by nonsteroidal anti-inflammatory drugs and the potential to increase fatigue, lethargy, and an increase in glucose when combined with β-blockers. Lithium levels should be monitored closely in lithium-treated patients because thiazide and loop diuretics can reduce lithium excretion and precipitate lithium toxicity.[27]

CONCLUSIONS

Thiazide-type diuretics are useful first-line agents in the treatment of hypertension because they have been proven to reduce CV mortality and morbidity in systolic and diastolic forms of hypertension and do so at low cost. In outcomes trials, the benefits of thiazide diuretics are achieved at 12.5 mg to 25.0 mg of chlorthalidone or $\geq$50 mg of HCTZ. In combination with other classes of antihypertensive drugs, diuretics additively reduce BP. Biochemical abnormalities can occur in a dose-dependent manner with diuretic therapy (hypokalemia, hyperglycemia, and hyperuricemia). Loop diuretics should not be used as first-line therapy in hypertension since there are no outcome data with them. They should be reserved for conditions of clinically significant fluid overload (eg, HF and significant fluid retention with vasodilator drugs, such as minoxidil) or when renal failure is sufficiently advanced that thiazide diuretics have a limited effect except when used in combination with a loop diuretic.

Disclosure: The authors received no honoraria for their contribution to this issue.

References

1. Chobanian AV, Bakris GL, Black HR, et al. National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; 289:2560–2572.
2. Sica DA. Edema mechanisms in the heart failure patient and treatment options. *Heart Fail Clin*. 2008;4:511–518.
3. Beerman B, Groschinsky-Grind M. Pharmacokinetics of hydrochlorothiazide in patients with congestive heart failure. *Br J Clin Pharmacol*. 1979;7:579–583.
4. Sica DA. Chlorthalidone: has it always been the best thiazide-type diuretic? *Hypertension*. 2006;47:321–322.
5. Carter BL, Ernst ME, Cohen JD. Hydrochlorothiazide versus chlorthalidone: evidence supporting their interchangeability. *Hypertension*. 2004;43:4–9.
6. Murray MD, Haag KM, Black PK, et al. Variable furosemide absorption and poor predictability of response in elderly patients. *Pharmacotherapy*. 1997;17:98–106.
7. Vargo DL, Kramer WG, Black PK, et al. Bioavailability, pharmacokinetics, and pharmacodynamics of torsemide and furosemide in patients with congestive heart failure. *Clin Pharmacol Ther*. 1995; 57:601–609.
8. Materson BJ, Reda DJ, Cushman WC, et al. Single-drug therapy for hypertension in men. A comparison of six antihypertensive agents with placebo. *N Engl J Med*. 1993;328:914–921.
9. Ernst ME, Carter BL, Goerdt CJ, et al. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. *Hypertension*. 2006;47:352–358.
10. Holland OB, Gomez-Sanchez CE, Kuhnert LV, et al. Antihypertensive comparison of furosemide with hydrochlorothiazide for black patients. *Arch Intern Med*. 1979;139:1015–1021.
11. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis*. 2004; 43(supp 1):S1–290.
12. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressure averaging 115 through 129 mm Hg. *JAMA*. 1967;202:1028–1034.
13. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *JAMA*. 1970;213:1143–1152.
14. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the systolic hypertension in the elderly program (SHEP). SHEP cooperative research group. *JAMA*. 1991;265:3255–3264.
15. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA*. 2002;288:2981–2997.
16. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Diuretic versus alpha-blocker as first-step antihypertensive therapy. Final results from the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *Hypertension*. 2003;42:239–246.
17. Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. *JAMA*. 1997;277:739–745.
18. Wright JM, Musini VM. First-line drugs for hypertension. *Cochrane Database Syst Rev*. 2009;3:CD001841.
19. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med*. 2008;359:2417–2428.
20. Materson BJ, Cushman WC, Goldstein G, et al. for the Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Treatment of hypertension in the elderly. I. Blood pressure and clinical changes. Results of a department of veterans affairs cooperative study. *Hypertension*. 1990;15:348–360.

21. Kaplan NM, Carnegie A, Raskin P, et al. Potassium supplementation in hypertensive patients with diuretic-induced hypokalemia. *N Engl J Med*. 1985;312:746–749.
22. Materson BJ, Reda DJ, Cushman WC, et al. for the Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Results of combination antihypertensive therapy after failure of each of the components. *J Hum Hypertens*. 1995;9:791–796.
23. Sica DA. Rationale for fixed-dose combinations in the treatment of hypertension: the cycle repeats. *Drugs*. 2002;62:443–462.
24. Ernst ME, Carter BL, Zheng S, et al. Meta-analysis of dose-response characteristics of hydrochlorothiazide and chlorthalidone: effects on systolic blood pressure and potassium. *Am J Hypertens*. 2010; 23:440–446.
25. Zillich AJ, Garg J, Basu S, et al. Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. *Hypertension*. 2006;48:219–224.
26. Hunter DJ, York M, Chaisson CE, et al. Recent diuretic use and the risk of recurrent gout attacks: the online case-crossover gout study. *J Rheumatol*. 2006;33:1341–1345.
27. Juurlink DN, Mamdani MM, Kopp A. Drug-induced lithium toxicity in the elderly: a population-based study. *J Am Geriatr Soc*. 2004; 52:794–798.