CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will summarize the similarities and differences between hydrochlorothiazide and chlorthalidone

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Diuretics for hypertension: Hydrochlorothiazide or chlorthalidone?

ABSTRACT

Thiazide diuretics are the cornerstone of treatment of hypertension in most patients. Hydrochlorothiazide is the most commonly used thiazide diuretic in the United States, but interest in chlorthalidone is increasing. The authors summarize the literature comparing these two agents.

KEY POINTS

Chlorthalidone has a longer duration of action and a longer half-life than hydrochlorothiazide.

Chlorthalidone may be more potent than hydrochlorothiazide in lowering blood pressure, but it also may be associated with more metabolic adverse effects, such as hypokalemia.

No study has conclusively shown either drug to be better in preventing adverse clinical outcomes.

These differences should be considered when making choices about thiazide diuretic therapy for hypertension.

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THE THIAZIDE DIURETIC hydrochlorothiazide and the thiazidelike diuretic chlorthalidone are two old drugs that are still useful. Although similar, they differ in important ways still not fully appreciated more than a half century after they were introduced.

Most hypertension guidelines recommend thiazide diuretics as one of the classes of agents that can be used either as initial antihypertensive drug therapy or as part of combination therapy.[1–3]

In the United States, hydrochlorothiazide is used more often than chlorthalidone, but many clinical trials of antihypertensive therapy have used chlorthalidone.[4,5] In recent years, particularly after the publication of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), interest in chlorthalidone has been increasing, and new data are now available comparing these two diuretics.[6] While current US guidelines do not recommend one over the other, British guidelines prefer chlorthalidone.[7]

This review summarizes the data comparing the two drugs' pharmacology, antihypertensive effect, and impact on clinical outcomes to help guide clinicians in choosing antihypertensive drug therapy.

PHARMACOLOGY AND MECHANISM OF ACTION

Many of the differences in effectiveness and adverse effects of hydrochlorothiazide and chlorthalidone are thought to be due to their different pharmacodynamic and pharmacokinetic effects.

Pharmacodynamic effects

Hydrochlorothiazide and chlorthalidone differ significantly in chemical structure (**Figure 1**),

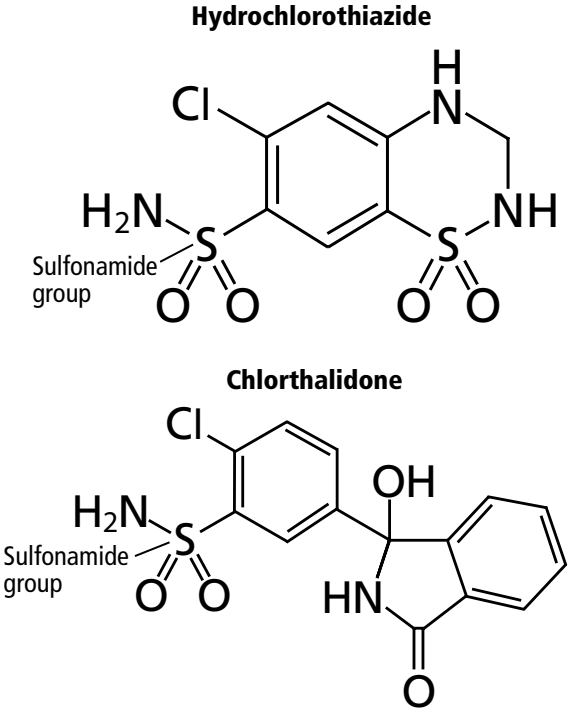

FIGURE 1. Although the chemical structures of hydrochlorothiazide (top) and chlorthalidone (bottom) differ, they both contain a sulfonamide group that inhibits carbonic anhydrase activity. This action may be associated with lower vascular contractility.

A pleiotropic effect of chlorthalidone: inhibition of platelet function

but both contain a sulfonamide group that inhibits carbonic anhydrase activity, which may be associated with lower vascular contractility. Both drugs are concentrated in the kidney and secreted into the tubular lumen[8]; therefore, their therapeutic diuretic effects are often achieved with relatively low plasma concentrations.

Both drugs inhibit the sodium-chloride cotransporter in the luminal membrane of the distal convoluted tubule of the ascending loop of Henle, leading to a modest natriuresis and diuresis. The exact mechanism by which they lower blood pressure is not known: while the initial response is from diuresis and volume changes, long-term reduction in blood pressure is through uncertain mechanisms. In addition, chlorthalidone may have beneficial effects on endothelial function and oxidative stress.[9,10]

Both drugs also increase secretion of potassium and hydrogen ions and promote increased reabsorption of calcium through increased expression of a sodium-calcium exchange channel.[8] Chlorthalidone may cause more inhibition of carbonic anhydrase than hydrochlorothiazide, which can lead to lower intracellular pH and cell volume. This effect may in part explain a pleiotropic effect of chlorthalidone, ie, inhibition of platelet function, which in turn may contribute to this drug's beneficial effect on cardiovascular outcomes.[9]

Pharmacokinetic differences

Hydrochlorothiazide and chlorthalidone have important differences in their pharmacokinetic properties (**Table 1**).[11]

Hydrochlorothiazide has its onset of action in about 2 hours, and it reaches its peak in 4 to 6 hours. Though its duration of action is short—up to 12 hours—its pharmacodynamic response can be much longer than predicted by its kinetics, allowing once-daily dosing.[8]

Chlorthalidone has a longer duration of action than hydrochlorothiazide. This may be because it has a very high volume of distribution, since it is taken up into red blood cells and is bound to carbonic anhydrase.[12] This may result in a "drug reservoir" that keeps drug levels higher for a longer time.[13] Its long duration of action makes it a favorable choice for patients who have difficulty adhering to medication instructions. In addition, a missed dose is unlikely to have a "rebound" effect like that seen with some other antihypertensive agents. However, both chlorthalidone and hydrochlorothiazide are effective if taken once daily.

BLOOD PRESSURE-LOWERING

Both hydrochlorothiazide and chlorthalidone are effective antihypertensive agents. **Table 2** summarizes findings from studies that evaluated their blood pressure-lowering effect at various doses.[14–33] However, relatively few studies have directly compared these two agents' effects on blood pressure.

Ernst et al,[34] in a small study (but probably the best one to address this issue), compared chlorthalidone 12.5 mg/day (force-titrated to 25 mg/day) and hydrochlorothiazide 25 mg/day (force-titrated to 50 mg/day) in untreated hypertensive patients. After 8 weeks, ambulatory blood pressure monitoring indicated a greater reduction from baseline in systolic blood pressure with chlorthalidone 25 mg/day than with hydrochlorothiazide 50 mg/day (24-hour mean –12.4 vs –7.4 mm Hg, P = .05). Interestingly,

the change in nighttime blood pressure was greater in the chlorthalidone group (–13.5 mm Hg) than in the hydrochlorothiazide group (–6.4 mm Hg; P = .009). These data suggest that at the doses studied, chlorthalidone is more effective than hydrochlorothiazide in lowering systolic blood pressure.

Bakris et al,[35] using a different study design, compared the single-pill combination of azilsartan medoxomil and chlorthalidone vs coadministration of azilsartan medoxomil and hydrochlorothiazide in participants with stage 2 primary hypertension (≥ 160/100 mm Hg). Systolic blood pressure, as measured in the clinic, declined more with the chlorthalidone combination (–35.1 mm Hg) than with the hydrochlorothiazide combination (–29.5 mm Hg, mean difference –5.6 mm Hg, P < .001).

Meta-analyses also support the conclusion that chlorthalidone is more potent than hydrochlorothiazide in lowering blood pressure.[35,36] Several studies have shown that chlorthalidone at the same dose is 1.5 to 2 times as potent as hydrochlorothiazide.[33,36,37] Therefore, for clinical purposes, it is reasonable to consider chlorthalidone 12.5 mg daily as similar to 25 mg of hydrochlorothiazide daily.

TABLE 1

Pharmacokinetics and pharmacodynamics of hydrochlorothiazide and chlorthalidone

	Hydrochlorothiazide	Chlorthalidone
Onset	2 hours	2.6 hours
Peak effect	4–6 hours	1.5–6 hours
Absorption	Well absorbed [a]	65%
Duration	6–12 hours	48–72 hours
Protein binding	40%–68%	75%
Metabolism	Not metabolized	Hepatic
Elimination half-life	10–12 hours [b]	40–89 hours
Excretion pathway	Urine (as unchanged drug)	Urine [c]

[a] When taken with food, time to maximum concentration increases from 1.6 hours to 2.9 hours. Absorption is reduced in patients with chronic heart failure.
[b] Large variation due to biphasic elimination; may be much longer with renal impairment.
[c] Data not available on the percentage of dose as unchanged drug and metabolites, concentration of the drug in body fluids, degree of uptake by a particular organ or in the fetus, or passage across the blood-brain barrier.

Information from US National Library of Medicine. Dailymed. dailymed.nlm.nih.gov. Accessed May 31, 2015.

ADVERSE EFFECTS

Electrolyte disturbances are a common adverse effect of thiazide diuretics.

Hypokalemia. All thiazide diuretics cause potassium wasting. The frequency of hypokalemia depends on the dose, frequency of administration, diet, and other pharmacologic agents used.

Two large clinical trials, the Systolic Hypertension in the Elderly Program and ALLHAT, found that chlorthalidone caused hypokalemia requiring therapy in about 6% to 8% of patients.[38,39] Chlorthalidone therapy was associated with a lowering of serum potassium levels of 0.2 to 0.5 mmol/L.[36] In ALLHAT, chlorthalidone was associated with a reduction in potassium levels of approximately 0.2 mmol/L after 4 years.[38]

All diuretics require monitoring of electrolytes, especially during the first 2 weeks of therapy. Once a steady state is reached, patients are not usually at risk of hypokalemia unless the dose is increased, extrarenal losses of potassium increase, or dietary potassium is reduced.

Other electrolyte changes. Thiazide and thiazide-like diuretics can cause other metabolic and endocrine abnormalities such as hypochloremic alkalosis, hyponatremia, and hypercalcemia.[40,41] They can also cause photosensitivity and can precipitate gout.[42]

Observational studies have suggested that metabolic adverse effects such as hypokalemia and hyperuricemia are more common with chlorthalidone than with hydrochlorothiazide.[43] It is prudent to monitor laboratory values periodically in patients on diuretic therapy.

DRUG INTERACTIONS

The drug interaction profiles of hydrochlorothiazide and chlorthalidone are also similar. The most common interactions are pharmacodynamic interactions resulting from potassium depletion caused by the diuretics.

TABLE 2

Effect of different diuretic doses on systolic blood pressure

Diuretic and dose	Study	Mean difference in SBP vs placebo (mm Hg)
Hydrochlorothiazide 12.5 mg	Pool et al, 1997[14]	–4.40
	Pool et al, 2007[15]	–5.20
	Horie et al, 2007[16]	–7.80
	Chrysant, 1994[17]	–7.00
	Lacourcière and Arnott, 1994[18]	–10.2
	Villamil et al, 2007[19]	–6.40
	McGill and Reilly, 2001[20]	–5.30
	Weir et al, 1992[21]	–9.60
	Goldberg et al, 1989[22]	–7.10
	Papademetriou et al, 2006[23]	–7.10
	Chrysant and Chrysant, 2004[24]	–4.80
	Kochar et al, 1999[25]	–6.60
Hydrochlorothiazide 25 mg	Villlamil et al, 2007[19]	–6.80
	McGill and Reilly, 2001[20]	–15.10
	Benz et al, 1998[26]	–10.81
	Jounela et al, 1994[27]	–9.90
	Scholze et al, 1993[28]	–9.90
	Goldberg et al, 1989[22]	–10.30
	Canter et al, 1994[29]	–7.00
Chlorthalidone 25 mg	Vardan et al, 1987[30]	–12.40
	Materson et al, 1978[31]	–15.40
	Morledge et al, 1986[32]	–15.70
Chlorthalidone 50 mg	Morledge et al, 1986[32]	–16.70
	Materson et al, 1978[31]	–14.50

Information from Peterzan MA, Hardy R, Chaturvedi N, Hughes AD. Meta-analysis of dose-response relationships for hydrochlorothiazide, chlorthalidone, and bendroflumethiazide on blood pressure, serum potassium, and urate. Hypertension 2012; 59:1104–1109.

Hydrochlorothiazide 25 mg is roughly equivalent to chlorthalidone 12.5 mg

Antiarrythymic drugs. Hypokalemia is a risk factor for arrhythmias such as torsades de pointes, and the risk is magnified with concomitant therapy with antiarrhythmic agents that prolong the QT interval independently of serum potassium concentration (eg, sotalol, dronedarone, ibutilide, propafenone). Therefore, combinations of drugs that can cause hypokalemia (eg, diuretics) and antiarrhythmic agents require vigilant monitoring of potassium and appropriate replenishment.[44]

Dofetilide is a class III antiarrhythmic agent and, like other antiarrhythmic drugs, carries a risk of QT prolongation and torsades de pointes, which is magnified by hypokalemia.[45] In addition, dofetilide undergoes active tubular secretion in the kidney via the cation transport system, which is inhibited by hydrochlorothiazide.[45] The resulting increase in plasma concentrations of dofetilide may magnify the risk of arrhythmias. Chlorthalidone has not been specifically studied in combination with dofetilide, but thiazide diuretics in general are thought to have a similar effect on tubular secretion and, therefore, should be considered similar to hydrochlorothiazide in this regard.

Digoxin. Similarly, digoxin toxicity may be enhanced in hypokalemia. As with antiarrhythmic agents, serum potassium should be carefully monitored and replenished appropriately when diuretics are used in combination with digoxin.

Lithium is reabsorbed in the proximal tubule along with sodium. Diuretics including hydrochlorothiazide and chlorthalidone that alter sodium reabsorption can also alter lithium absorption.[46] When sodium reabsorption is decreased, lithium ion reabsorption is increased and may result in lithium toxicity. Although this combination is not contraindicated, monitoring of serum lithium concentrations and clinical signs and symptoms of lithium toxicity is recommended during initiation and dose adjustments of thiazide diuretics.

Nonsteroidal anti-inflammatory drugs can decrease the natriuretic, diuretic, and antihypertensive effects of both hydrochlorothiazide and chlorthalidone.[47]

Renin-angiotensin-aldosterone system antagonists, ie, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and the renin inhibitor aliskiren, have potentially beneficial interactions with hydrochlorothiazide and chlorthalidone, producing additive decreases in blood pressure when coadministered with these diuretics. These effects may be particularly potent early in concomitant therapy and allow use of lower doses of diuretics, typically 12.5 mg of hydrochlorothiazide in combination therapy.

LONG-TERM EFFECTS ON CARDIOVASCULAR EVENTS

The long-term goal in treating hypertension is to lower the risk of cardiovascular disease. Therefore, the clinician needs to consider the effect of antihypertensive drug therapy on long-term clinical outcomes.

Antihypertensive drug therapy based on thiazide diuretics has been shown to lower cardiovascular risk when compared with placebo.[48] In addition, the effect of chlorthalidone-based antihypertensive therapy was similar to that of other antihypertensive drug classes in preventing most cardiovascular outcomes in ALLHAT.[4]

However, no study has directly compared hydrochlorothiazide and chlorthalidone with the primary outcome of reduction in long-term cardiovascular events. The data to date come from observational studies and meta-analyses. For example, in a retrospective analysis of the Multiple Risk Factor Intervention Trial, cardiovascular events were significantly fewer in those receiving chlorthalidone vs hydrochlorothiazide ($P = .0016$).[43]

Monitor potassium closely in patients on a thiazide plus an antiarrhythmic agent

In a systematic review and meta-analysis, chlorthalidone was associated with a 23% lower risk of heart failure and a 21% lower risk of all cardiovascular events.[49]

However, a Canadian observational study of 29,873 patients found no difference in the composite outcome of death or hospitalization for heart failure, stroke, or myocardial infarction between chlorthalidone recipients (3.2 events per 100 person-years) and hydrochlorothiazide recipients (3.4 events per 100 person-years; adjusted hazard ratio 0.93, 95% confidence interval 0.81–1.06).[50]

In summary, it is unclear whether chlorthalidone or hydrochlorothiazide is superior in preventing cardiovascular events.

SUMMARY

Thiazide and thiazidelike diuretics play an important role in managing hypertension in most patients. The eighth Joint National Committee guidelines do not recommend either hydrochlorothiazide or chlorthalidone over the other. The target dose recommendations are hydrochlorothiazide 25 to 50 mg or chlorthalidone 12.5 to 25 mg daily, with lower doses considered for the elderly.

There are important differences between hydrochlorothiazide and chlorthalidone in pharmacology, potency, and frequency of metabolic side effects. Clinicians should consider these factors to tailor the choice of thiazide diuretic therapy in hypertensive patients.

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