FPIN's Help Desk Answers

Chlorthalidone vs. Hydrochlorothiazide for Treatment of Hypertension

KARYN SPRINGER, MD, *Utah Valley Family Medicine Residency, Provo, Utah*

Help Desk Answers provides answers to questions submitted by practicing family physicians to the Family Physicians Inquiries Network (FPIN). Members of the network select questions based on their relevance to family medicine. Answers are drawn from an approved set of evidence-based resources and undergo peer review.

This series is coordinated by John E. Delzell, Jr., MD, MSPH, Assistant Medical Editor.

Clinical Question

Is chlorthalidone more effective than hydrochlorothiazide for treatment of hypertension?

Evidence-Based Answer

Chlorthalidone produces slightly greater reductions in blood pressure compared with hydrochlorothiazide (HCTZ), but it is associated with greater declines in serum potassium levels. (Strength of Recommendation [SOR]: C, based on a meta-analysis of disease-oriented evidence.) Chlorthalidone lowers the risk of cardiovascular events about 18% more than HCTZ at the same achieved blood pressure. (SOR: B, based on a meta-analysis.)

In 2010, a meta-analysis of 137 randomized controlled trials (RCTs; N = 5,843) examined the effectiveness of chlorthalidone and HCTZ as monotherapy for hypertension.[1] A total of 29 trials of chlorthalidone (N = 2,995; dose range = 12.5 to 200 mg, median 25 mg) and 108 trials of HCTZ (N = 2,848; dose range = 3 to 450 mg, median 33 mg) were analyzed based on dose and study duration (all less than one year). When all study durations were pooled, 12.5 to 25 mg of chlorthalidone produced a statistically greater reduction in systolic blood pressure compared with HCTZ (–24 mm Hg vs. –14 mm Hg; $P < .05$). In studies of 12 to 52 weeks' duration, the use of chlorthalidone resulted in statistically greater reductions in serum potassium levels (–0.40 mEq per L [–0.40 mmol per L] vs. –0.24 mEq per L [–0.24 mmol per L]; $P = .008$). HCTZ and chlorthalidone were not directly compared in these RCTs.

A meta-analysis of nine RCTs (N = 78,350) examined the reduction in cardiovascular events in patients receiving chlorthalidone (six trials, N = 59,976; dose range = 12.5 to 100 mg) and HCTZ (three trials, N = 18,374; dose range = 12.5 to 50 mg).[2] Cardiovascular events were defined as myocardial infarction or new diagnosis of coronary heart disease, stroke, or congestive heart failure. When comparing patients with the same mean decrease in systolic blood pressure, the risk of cardiovascular events was lower in patients receiving chlorthalidone compared with those receiving HCTZ (risk ratio [RR] = 0.82; 95% confidence interval, 0.70 to 0.97). However, there were no head-to-head comparisons of chlorthalidone and HCTZ in these trials.

A 2006 randomized, single-blind crossover study (eight-week treatment plus a four-week washout) compared the effects of chlorthalidone (12.5 mg titrated to 25 mg) and HCTZ (25 mg titrated to 50 mg) on 24-hour ambulatory blood pressure.[3] The study included 30 patients who had stage 1 or 2 hypertension and were not currently taking antihypertensive medications. This trial was not included in the meta-analyses discussed previously because of its crossover design. At week 8, there was no statistical difference in reduction of 24-hour mean ambulatory systolic blood pressure between patients receiving 25 mg of chlorthalidone and those receiving 50 mg of HCTZ (–12 mm Hg vs. –7.4 mm Hg; $P = .054$). At week 2, office systolic blood pressure reduction was greater in patients receiving chlorthalidone (–16 mm Hg vs. –4.5 mm Hg; $P = .001$), but by week 8 the reductions were not statistically significant (–17 mm Hg vs. –11 mm Hg; $P = .84$). Only data from the first active treatment period were analyzed because there was a significant "order-drug-time" interaction in which patients receiving chlorthalidone had

significantly greater blood pressure reduction when the medication was given before the HCTZ arm. This trial was limited by its short duration.

The Eighth Joint National Committee recommends thiazide diuretics as one option for initial therapy for hypertension because of their effects on overall mortality and cardiovascular outcomes.[4] Further head-to-head comparisons between chlorthalidone and HCTZ would be useful to determine if either medication is superior in terms of cardiovascular benefits.

Address correspondence to Karyn Springer, MD, at karyn.springer@imail.org. Reprints are not available from the author.

Author disclosure: No relevant financial affiliations.

REFERENCES

1. Ernst ME, Carter BL, Zheng S, Grimm RH Jr. Meta-analysis of dose-response characteristics of hydrochlorothiazide and chlorthalidone: effects on systolic blood pressure and potassium. *Am J Hypertens*. 2010;23(4):440-446.
2. Roush GC, Holford TR, Guddati AK. Chlorthalidone compared with hydrochlorothiazide in reducing cardiovascular events: systematic review and network meta-analyses. *Hypertension*. 2012;59(6):1110-1117.
3. Ernst ME, Carter BL, Goerdt CJ, et al. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. *Hypertension*. 2006;47(3):352-358.
4. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8) [published correction appears in *JAMA*. 2014;311(17):1809]. *JAMA*. 2014;311(5):507-520. ■