Antihypertensive Therapy-Associated Hypokalemia and Hyperkalemia
Clinical Implications

Theodore A. Kotchen

Editorial Commentary

Hydrochlorothiazide was introduced into clinical practice in 1957 and chlorthalidone shortly thereafter. Diuretics continue to be a mainstay of antihypertensive therapy. They effectively reduce blood pressure and decrease hypertension-related morbidity and mortality. In addition, they are relatively inexpensive. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends diuretics as first-line therapy for the treatment of hypertension.

The Antihypertensive and Lipid-Lowering Treatment to Preventing Heart Attack Trial (ALLHAT) was a prospective, randomized trial designed to compare the effects of diuretics with other antihypertensive agents on the incidence of coronary heart disease (CHD) and other cardiovascular disease (CVD) events. Beginning in 1994, 42000 participants aged ≥55 years with hypertension and ≥1 other CHD risk factor were randomized to receive initial therapy with chlorthalidone, lisinopril, amlodipine, or doxazosin. The doxazosin arm was terminated early because of a higher incidence of cardiovascular events, particularly congestive heart failure. During a mean follow-up of 4.9 years, there was no difference among the other 3 drug regimens in the primary outcome of combined fatal CHD or nonfatal myocardial infarction. Secondary outcomes were similar, except for higher rates of heart failure with amlodipine and higher rates of combined CVD, stroke, and heart failure with lisinopril compared with chlorthalidone. A decade ago, the ALLHAT investigators concluded that, “thiazide-type diuretics are superior in preventing 1 or more major forms of CVD and are less expensive. They should be preferred for first-step antihypertensive therapy.”

In response to concerns that low and high serum potassium concentrations may be associated with adverse cardiovascular effects, in this issue of Hypertension, ALLHAT investigators report the effect of the 3 drug regimens on serum potassium concentrations and their subsequent impact on cardiovascular morbidity and mortality over 3 to 7 years. Normokalemic participants at baseline were stratified by year-1 serum potassium levels. Year-1 incidences of hypokalemia (serum K⁺ <3.5 mmol/L) in the 3 randomized groups were chlorthalidone, 12.9%; lisinopril, 10.0%; and amlodipine, 21.1%. The incidence of hyperkalemia (serum K⁺ >5.4 mmol/L) was 1.2% in chlorthalidone-, 3.6% in lisinopril-, and 1.9% in amlodipine-treated groups. Overall, hypokalemic patients did not experience greater rates of CHD or a combined CVD end point. However, mortality was higher in hypokalemic than in normokalemic participants. Compared with normokalemic participants, mortality risk was 18% higher for CVD deaths and 23% higher for non-CVD deaths. Hazard ratios for hypokalemia-associated mortality differed across the 3 study groups. The risk of death in hypokalemic patients was lower in chlorthalidone-treated participants than in lisinopril- or amlodipine-treated participants. Consequently, the investigators suggest that cancer mortality and other transient conditions such as gastrointestinal losses (not documented), rather than a specific effect of chlorthalidone, contributed to the higher mortality in hypokalemic participants. Although relatively uncommon, hyperkalemia was associated with increased risk of combined CVD. The report concludes that, “. . . concerns about potassium levels should not influence the clinician’s decision about initiating hypertension treatment with low-moderate doses of thiazide diuretics.”

There is abundant evidence for increased risk of both hypokalemia and hyperkalemia in patients with CVD. In patients with acute myocardial infarction, both hypokalemia and hyperkalemia are associated with an increased prevalence of ventricular arrhythmias and increased mortality. Hypokalemia is also associated with increased mortality in patients with congestive heart failure. In several clinical trials for the treatment of hypertension, high-dose thiazide diuretics (50–100 mg daily) have been associated with an increased incidence of ventricular arrhythmias and sudden cardiac death. The risks of cardiac arrest and other coronary events are reduced by use of lower-dose diuretics (25 mg/d) and by the addition of a potassium-sparing agent to low-dose thiazide.

In a meta-analysis of 18 randomized, placebo-controlled trials, both high-dose (50 mg/d of hydrochlorothiazide or chlorthalidone) and low-dose (12.5–25.0 mg/d of hydrochlorothiazide or chlorthalidone) diuretics decreased the incidence of congestive heart failure and cardiovascular mortality, whereas only low-dose regimens decreased the incidence of coronary artery disease (28% reduction) and total mortality. Nevertheless, this does not necessarily indicate that hypokalemia associated with low doses of diuretics is innocuous. In the Systolic Hypertension in the Elderly Program, individuals aged ≥60

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years were randomized to low doses of chlorthalidone (12.5–25.0 mg/d) or placebo. After 1 year of treatment, 7.2% of participants randomized to active treatment had a serum potassium <3.5 mmol/L compared with 1% of participants randomized to placebo. Overall, active drug treatment reduced the incidence of stroke by 36% and the 5-year absolute benefit of major cardiovascular events. However, those individuals in the chlorthalidone arm of the trial who experienced hypokalemia had a similar risk of CVD, CHD, and stroke as those randomized to placebo.

Another potential adverse consequence of diuretic-associated hypokalemia is the development of diabetes mellitus. This contingency is not addressed in the current ALLHAT report. ALLHAT investigators have reported previously that mean fasting blood glucose concentrations and incidence of diabetes mellitus were slightly but significantly increased in chlorthalidone participants compared with the other study arms. In that earlier analysis, there was a suggestive but not a clear association of incident diabetes with hypokalemia. Further analysis of this question is warranted.

Although the diuretic in ALLHAT was chlorthalidone, hydrochlorothiazide is the most frequently prescribed diuretic in the United States. Chlorthalidone is generally considered a “thiazide-like” diuretic. It is structurally similar to hydrochlorothiazide, and both drugs act by blocking sodium-chloride cotransport in the early distal convoluted tubule. However, chlorthalidone has a longer half-life (40–60 versus 8–15 hours) because of its partitioning into red blood cells and slower elimination. The antihypertensive potency of chlorthalidone is 1.5 to 2.0 times that of hydrochlorothiazide on a milligram-per-milligram basis. Although it was not a randomized trial comparing the 2 agents, in retrospective cohort analyses of the Multiple Risk Factor Intervention Trial data, chlorthalidone was associated with greater reductions in blood pressure, less left ventricular hypertrophy, and lower mortality than hydrochlorothiazide. In a meta-analysis of 108 clinical trials with hydrochlorothiazide and 20 with chlorthalidone, in the lower dose ranges (12.5–25.0 mg), chlorthalidone produced greater reductions of blood pressure and slightly greater loss of potassium; differences in potassium loss between the 2 agents were greater at higher doses.

Not all hypertensives are equally responsive to the antihypertensive potency of diuretic therapy, and the current ALLHAT report suggests that there are identifiable subgroups with varying tendencies to chlorthalidone-associated hypokalemia. Participants who became hypokalemic were more likely to be black and to be women. In a search for genetic determinants of blood pressure responsiveness to thiazides, Turner et al have previously reported suggestive evidence that common genetic variants in WNK1, a lysine-deficient protein kinase that regulates thiazide-sensitive sodium-potassium cotransport, predict differences in blood pressure responsiveness to hydrochlorothiazide. It would be of interest and also of clinical relevance to determine whether the same polymorphisms that predict blood pressure responsiveness also predict potassium responsiveness to diuretics.

What are the clinical implications of antihypertensive drug-associated changes in serum potassium? The current ALLHAT report provides useful information for the management of hypertension in clinical practice. Incident hyperkalemia was associated with increased risk of CVD. Overall, the risk of death was increased in participants who became hypokalemic. Although chlorthalidone-treated participants had a relatively high incidence of hypokalemia, increased mortality associated with hypokalemia was not specifically related to chlorthalidone. Nevertheless, hypokalemia and hyperkalemia may attenuate the CVD protective effects of antihypertensive therapy. The obvious clinical corollary is that management of potassium homeostasis may enhance the beneficial impact of antihypertensive drug therapy on CVD prevention. It would seem prudent to recommend that prevention of hypokalemia and hyperkalemia be important goals of therapy.

Disclosures

None.

References

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Theodore A. Kotchen

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