

Electrolyte disturbance with diuretics and ACEIs

Michael R. Kolber MD CCFP MSc Scott Garrison MD CCFP PhD Ricky D. Turgeon ACPFR PharmD

Clinical question

What is the risk of electrolyte disturbances with diuretics and angiotensin-converting enzyme inhibitors (ACEIs) and when should we check levels?

Bottom line

Moderate hyponatremia (sodium [Na] <130 mmol/L) and hypokalemia (potassium [K] <3.2 mmol/L) occur in about 4% of thiazide users; hyperkalemia (K >5.4 mmol/L) occurs in 4% of ACEI (and angiotensin receptor blocker) users. Limited evidence suggests checking electrolyte levels 2 to 4 weeks after starting or increasing doses of these agents, and at least annually thereafter.

Evidence


- The ALLHAT substudy¹ (n=19731 with normal baseline K levels) found the following results at 1 year.
 - Overall, 3.5% of those taking chlorthalidone (12.5 to 25 mg), 0.2% of those taking lisinopril (10 to 40 mg), and 0.3% of those taking amlodipine (2.5 to 10 mg) had K levels less than 3.2 mmol/L; 1.2% of those taking chlorthalidone, 3.6% of those taking lisinopril, and 1.9% of those taking amlodipine had K levels greater than 5.4 mmol/L. Further, 8% of those taking chlorthalidone were taking K supplements at 5 years.²
- The SHEP study³ of 4736 patients taking chlorthalidone (12.5 to 25 mg) or placebo found, within 4.5 years, 3.9% and 4.1% of those taking chlorthalidone had K levels below 3.2 mmol/L and Na levels below 130 mmol/L, respectively (vs 0.8% and 1.3% for placebo, respectively).
- The HYVET trial⁴ (indapamide vs placebo) excluded patients with abnormal K levels; compared with placebo, K levels were 0.05 mmol/L lower with indapamide at 2 years (Na levels were not reported).
- Chlorthalidone (12.5 to 25 mg) decreases K levels an average of 0.2 to 0.4 mmol/L^{5,6} (about 0.1 to 0.2 mmol/L more than the same dose of hydrochlorothiazide).⁶
- Angiotensin receptor blockers have rates of hyperkalemia similar to those for ACEIs.⁷

Context

- Diuretics are inexpensive first-line agents for patients with uncomplicated hypertension.⁸
- Limited evidence suggests that thiazide-induced hypokalemia or hyponatremia occur within the first days to weeks of therapy^{9,10} but can also develop years later.¹¹
- Hypokalemia and hyponatremia risk factors include being female^{1,12} and increasing age¹² or diuretic dose.¹²

- Mild hypokalemia is often asymptomatic, but symptoms can include weakness, myalgia, and cardiac arrhythmia.¹³
- Moderate to severe hyponatremia (Na <130 mmol/L) can cause lethargy, dizziness, nausea, and confusion.¹⁴

Implementation

Common nondrug causes of hypokalemia include vomiting, diarrhea, renal losses, congestive heart failure, or systemic alkalosis. If patients have hypokalemia from diuretics, adding ACEIs¹⁵ or using K-sparing diuretics (like amiloride)¹⁶ can help maintain normokalemia. Consider primary aldosteronism and Cushing syndrome in patients with hypertension who have hypokalemia before medical therapy. 

Dr Kolber and Garrison are Associate Professors in the Department of Family Medicine at the University of Alberta in Edmonton. Dr Turgeon is a clinical pharmacist at Vancouver General Hospital in British Columbia.

Competing interests

None declared

The opinions expressed in Tools for Practice articles are those of the authors and do not necessarily mirror the perspective and policy of the Alberta College of Family Physicians.

References

- Alderman MH, Piller LB, Ford CE, Probstfield JL, Oparil S, Cushman WC, et al. Clinical significance of incident hypokalemia and hyperkalemia in treated hypertensive patients in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. *Hypertension* 2012;59(5):926-33.
- ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. 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(23):2981-97.
- SHEP Cooperative Research Group. 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). *JAMA* 1991;265(24):3255-64.
- Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, et al. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008;358(7):1887-98.
- Savage PJ, Pressel SL, Curb D, Schron EB, Applegate WB, Black HR, et al. Influence of long-term, low-dose, diuretic-based, antihypertensive therapy on glucose, lipid, uric acid, and potassium levels in older men and women with isolated systolic hypertension: the Systolic Hypertension in the Elderly Program. *Arch Intern Med* 1998;158(7):741-51.
- 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):440-6.
- The ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;358(15):1547-59.
- Daskalopoulou SS, Rabi DM, Zamke KB, Dasgupta K, Nerenberg K, Cloutier L, et al. The 2015 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. *Can J Cardiol* 2015;31(5):549-68.
- Maronde RF, Milgrom M, Vlachaki ND, Chan L. Response of thiazide-induced hypokalemia to amiloride. *JAMA* 1983;249(2):237-41.
- Barber J, McKeever TM, McDowell SE, Clayton JA, Ferner RE, Gordon RD, et al. A systematic review and meta-analysis of thiazide-induced hyponatremia: time to reconsider electrolyte monitoring regimens after thiazide initiation? *Br J Clin Pharmacol* 2014;79(4):566-77.
- Leung AA, Wright A, Pazo V, Karson A, Bates DW. Risk of thiazide-induced hyponatremia in patients with hypertension. *Am J Med* 2011;124(11):1064-72.
- Sharabi Y, Illan R, Kamari Y, Cohen H, Nadler M, Messerli FH, et al. Diuretic induced hyponatremia in elderly hypertensive women. *J Hum Hypertens* 2002;16(9):631-5.
- Gennari FJ. Hypokalemia. *N Engl J Med* 1998;339(7):451-8.
- Hwang KS, Kim GH. Thiazide-induced hyponatremia. *Electrolyte Blood Press* 2010;8(1):51-7.
- Weber MA, Bakris GL, Jamerson K, Weir M, Kjeldsen SE, Devereux RB, et al. Cardiovascular events during differing hypertension therapies in patients with diabetes. *J Am Coll Cardiol* 2010;56(1):77-85.
- Brown MJ, Williams B, Morant SV, Webb DJ, Caulfield MJ, Cruickshank JK, et al. Effect of amiloride, or amiloride plus hydrochlorothiazide, versus hydrochlorothiazide on glucose tolerance and blood pressure (PATHWAY-3): a parallel-group, double-blind randomised phase 4 trial. *Lancet Diabetes Endocrinol* 2016;4(2):136-47.



Tools for Practice articles in *Canadian Family Physician (CFP)* are adapted from articles published on the Alberta College of Family Physicians (ACFP) website, summarizing medical evidence with a focus on topical issues and practice-modifying information. The ACFP summaries and the series in *CFP* are coordinated by Dr G. Michael Allan, and the summaries are co-authored by at least 1 practising family physician and are peer reviewed. Feedback is welcome and can be sent to toolsforpractice@cfpc.ca. Archived articles are available on the ACFP website: www.acfp.ca.