The Importance of a “Just Right” Serum Potassium Level

Ankit Mehta Michael Emmett

Department of Internal Medicine, Baylor University Medical Center, Dallas, TX, USA

Referring to the composition of extracellular fluid (ECF), Claude Bernard stated: “The fixity of the milieu supposes a perfection of the organism such that the external variations are at each instant compensated for and equilibrated....” [1]. The “normal” or “reference” range for each of the ions and molecules dissolved in mammalian ECF has evolved over many millions of years. Persistently increased or decreased concentrations of virtually any of these ions/molecules are generally associated with a disease or disorder and often predict increased risk of morbidity and/or mortality. These risk increases are related to both the inherent risk of underlying diseases and disorders that have generated the chemical or biochemical abnormalities and also because, in many cases, the abnormal concentration of the ion or molecule can directly generate additional pathology. In the case of the routinely measured plasma electrolytes: sodium, potassium, chloride and bicarbonate, many studies, across a wide spectrum of diseases and settings, have demonstrated that either high or low values increase morbidity and mortality risk. Thus, the morbidity or mortality risk plotted against ion concentration results in a “U”, “J” or reverse “J” shaped risk profiles. In this regard, the serum potassium concentration is a particularly pernicious analyte.

Ion pumps energized by ATP, such as Na-K ATPase, together with a multitude of ion channels and transporters that exist in cell membranes generate ion concentration gradients, which then result in cellular transmembrane electrical gradients. The potassium gradients between cellular and ECF spaces are particularly important in this regard. These electrical gradients are critical for the appropriate functioning of central and peripheral nerve cells, cardiac conducting tissues and contraction of all muscle cells. As a result, both hypo and hyperkalemia are especially dangerous electrolyte disorders because of the many adverse effects they generate in muscle, nerves and cardiac electrical activity.

Whole body potassium homeostasis is achieved by the quantitative renal excretion of ingested potassium. Therefore, acute kidney injury and chronic kidney diseases (CKD) with the resultant fall in glomerular filtration and tubule function are important causes of hyperkalemia. These disorders may originate in the kidneys or the abnormalities may be the result of primary cardiovascular pathology. Another increasingly common cause of hyperkalemia is the therapeutic use of inhibitors or blockers of the renin-angiotensin-aldosterone system – angiotensin converting enzyme inhibitors, angiotensin receptor

blockers, direct renin inhibitors and mineralocorticoid receptor antagonists interfere with either the synthesis or action of aldosterone in the distal convoluted tubule and thereby reduce urinary secretion of potassium. Conversely, hypokalemia is usually due to the excessive secretion of potassium in the distal tubules and collecting ducts of the kidney in response to the use of loop or thiazide diuretics. Hypo or hyperkalemia can also be due to a large number of inherited genetic disorders.

In the current issue of the journal, Collins et al. [2] report on an “Association of Serum Potassium with All-Cause Mortality in Patients with and without Heart Failure, Chronic Kidney Disease, and/or Diabetes” [2]. They utilized a very large electronic medical record database to analyze the relationship between a single measurement of serum potassium and that patient’s mortality over the ensuing 18 months in almost 1 million individuals. These individuals were mostly (80%) outpatients but also included ER patients and inpatients. ICD-9 diagnostic codes were used to identify patients with heart failure, kidney disease, diabetes, cardiovascular disease and hypertension. The “control” group was free of these disorders but was obviously not a “control” group of healthy individuals.

Abnormal serum potassium concentrations were very common. Across the entire group, 27.6% had a potassium <4.0 mEq/L, and 5.7% had a value ≥5.0 mEq/L. This was similar to the rates of low and high potassium in the “control” group (26 and 4.3%, respectively).

With regard to 18-month (following the potassium measurement) mortality rates, it was not surprising that patients with diabetes, CKD, heart failure or combinations of all three diagnoses had a higher mortality than the “control” group (6.7, 16.6, 22.4, and 29.7% vs. the “control” 1.2%). When potassium concentrations were included in the mortality risk assessment, both low and high potassium levels increased the risk in all groups including the “controls.” Of importance, risk was lowest for all patient groups with potassium levels between 4 and <5 and begins to increase with levels above and below this range – levels that are initially still within the “normal” range of many laboratories. In the “control” group, either low or high potassium more than doubled mortality risk from 1.2 to 2.7%. But the risk increases were much more dramatic when high or low potassium levels occurred in patients with one or more of the ICD-9 morbidities listed above. The relationship between serum potassium and mortality rate is a “J” shaped curve, with the highest mortality rate associated with severe hyperkalemia. The 18-month mortality rate of those with several of the listed co-morbidities approached or exceeded 50%. In addition,

abnormal potassium levels had a greater mortality impact in older patients (over age 65 years).

Inhibitors of the renin-angiotensin-aldosterone system have been shown to have major morbidity and mortality benefits in many disease states including HF, DM, CKD, and hypertension. However, they will often generate or exacerbate hyperkalemia. This can sometimes be managed by adding loop or thiazide diuretics. However, diuretics can adversely affect volume status and generate a number of negative metabolic consequences. The recent development of effective oral gastrointestinal potassium binding agents such as patiromer and ZS9 provides another way to manage hyperkalemia including drug-related hyperkalemia. Hypokalemia generated by diuretics can be prevented/treated with oral potassium replacement and/or K-sparing drugs such as aldosterone antagonists or distal tubule sodium channel blockers.

The fact that hypokalemia and hyperkalemia each predict increases in mortality has been reported in multiple community studies and in studies of a variety of disease populations including hypertension, CKD, atherosclerosis, and others [3–8]. All of this suggests that closer monitoring of serum potassium and more aggressive prevention or correction/repletion of even modest hypo or hyperkalemia may be appropriate. However, none of these large epidemiologic studies can demonstrate that prevention or correction of abnormal potassium concentrations has any beneficial impact on morbidity or mortality. For this, prospective intervention trials will be required to show that reversing an abnormal potassium level will reduce morbidity and mortality.

Disclosure Statement

M.E. has been a consultant for ZS Pharma.

References

- 1 Bernard C: Lectures on the phenomena common to animals and plants; in Hoff HE, Guillemin R, Guillemin L, trans. Springfield, Charles C Thomas, 1974 (1878).
- 2 Collins AJ, Pitt B, Reaven N, Funk S, McGaughey K, Wilson D, Bushinsky DA: Association of serum potassium with all-cause mortality in patients with and without heart failure, chronic kidney disease, and/or diabetes. *Am J Nephrol* 2017;46:213–221.
- 3 Chen Y, Chang AR, McAdams DeMarco MA, Inker LA, Matsushita K, Ballew SH, Coresh J, Grams ME: Serum potassium, mortality, and kidney outcomes in the atherosclerosis risk in communities study. *Mayo Clin Proc* 2016;91:1403–1412.

- 4 Nakhoul GN, Huang H, Arrigain S, Jolly SE, Schold JD, Nally JV Jr, Navaneethan SD: Serum potassium, end-stage renal disease and mortality in chronic kidney disease. *Am J Nephrol* 2015;41:456–463.
- 5 Korgaonkar S, Tilea A, Gillespie BW, Kiser M, Eisele G, Finkelstein F, Kotanko P, Pitt B, Saran R: Serum potassium and outcomes in CKD: insights from the RRI-CKD cohort study. *Clin J Am Soc Nephrol* 2010;5:762–769.
- 6 Hughes-Austin JM, Rifkin DE, Beben T, Katz R, Sarnak MJ, Deo R, Hoofnagle AN, Homma S, Siscovick DS, Sotoodehnia N, Psaty BM, de Boer IH, Kestenbaum B, Shlipak MG, Ix JH: The relation of serum potassium concentration with cardiovascular events and mortality in community-living individuals. *Clin J Am Soc Nephrol* 2017;12:245–252.
- 7 Alderman MH, Piller LB, Ford CE, Probstfield JL, Oparil S, Cushman WC, Einhorn PT, Franklin SS, Papademetriou V, Ong ST, Eckfeldt JH, Furberg CD, Calhoun DA, Davis BR: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group: 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;59:926–933.
- 8 Krogager ML, Torp-Pedersen C, Mortensen RN, Køber L, Gislason G, Søgaard P, Aasbjerg K: Short-term mortality risk of serum potassium levels in hypertension: a retrospective analysis of nationwide registry data. *Eur Heart J* 2017;38:104–112.