MAYO CLINIC

Errors of Classification With Potassium Blood Testing: The Variability and Repeatability of Critical Clinical Tests

Paul A. Friedman, MD; Christopher G. Scott, MS; Kent Bailey, PhD; Nikola A. Baumann, PhD; David Albert, MD; Zachi I. Attia, MS; Dorothy J. Ladewig, BS; Omar Yasin, MD; John J. Dillon, MD; and Bhupinder Singh, MD

Abstract

Objective: To understand the performance of a currently used clinical blood test with regard to the frequency and size of variation of the results.

Patients and Methods: From November 29, 2012, through November 29, 2013, patients were recruited at 65 sites as part of a previously reported clinical trial (ClinicalTrials.gov Identifier: NCT01737697). Eligible outpatients who had been fasting for at least 8 hours underwent venous phlebotomy at baseline, 30 minutes, and 60 minutes to measure plasma potassium levels in whole blood using a point-of-care device (i-STAT, Abbott Laboratories). We analyzed the results to assess their variability and frequency of pseudohyperkalemia and pseudonormokalemia.

Results: A total of 1170 patients were included in this study. Absolute differences between pairs of measurements from different time points ranged from 0 to 2.5 mmol/L, with a mean difference of 0.26 mmol/L. The mean percentage differences were approximately 5% with an SD of 5%. Approximately 12% of differences between repeated fasting potassium blood test results were above 0.5 mmol/L (33% of the normal range), and 20% of patients (234) had at least one difference greater than 0.5 mmol/L. In 44.0% of the patients with a hyperkalemic average value (true hyperkalemia) (302 of 686), at least one blood test result was in the normal range (pseudonormokalemia), and in 30.2% of the patients with a normal average value (146 of 484), at least one blood test result was elevated (pseudohyperkalemia).

Conclusion: Expected variability and errors exist with potassium blood tests, even when conditions are optimized. Pseudohyperkalemia and pseudonormokalemia are common, indicating a need for thoughtful clinical interpretation of unexpected test results.

 ■ Mayo Clin Proc. 2018;93(5):566-572

For editorial comment, see page 551

From the Department of Cardiovascular Medicine (P.A.F., Z.I.A.), Division of Biomedical Statistics and Informatics (C.G.S., K.B.), Department of Laboratory Medicine and Pathology (N.A.B.), Department of Business Development (D.J.L.), Department of

Affiliations continued at the end of this article.

Hyperkalemia and hypokalemia are frequently asymptomatic yet may be life-threatening because of the associated risk of arrhythmias.[1,2] Potassium homeostasis can be impaired in patients with chronic kidney disease, heart failure, and adrenal disorders and in those taking medications like nonsteroidal anti-inflammatory drugs, renin-angiotensin-aldosterone system inhibitors, and diuretics. There is emerging evidence that even modest hyperkalemia in patients with cardiovascular or renal disease is associated with the risk of hospitalization and death.[3] After the Randomized Aldactone Evaluation Study results were published demonstrating the beneficial role of spironolactone (a potassium-sparing diuretic) in patients with heart failure, hospitalization for hyperkalemia increased 3- to 5-fold, and hyperkalemia-related mortality doubled.[4] In patients with acute myocardial infarction, potassium values below 3.5 or above 4.5 mmol/L were associated with significantly increased mortality.[5] In ambulatory patients with cardiovascular disease and chronic kidney disease (estimated glomerular filtration rate <60 mL/min per 1.73 m^2), the occurrence of a single hyperkalemic event (potassium level >5.0 mmol/L) was associated with increased all-cause mortality.[3,5] In

Mayo Clin Proc. ■ May 2018;93(5):566-572 ■ https://doi.org/10.1016/j.mayocp.2018.03.013
www.mayoclinicproceedings.org ■ © 2018 Mayo Foundation for Medical Education and Research

patients undergoing hemodialysis, the annual sudden death rate approaches 30%, often occurring immediately before scheduled dialysis following a 2-day hiatus (ie, in the 12 hours before Monday dialysis in patients undergoing Monday-Wednesday-Friday dialysis), supporting a potential causative role for hyperkalemia (although effects from changes in volume, blood pressure, or other electrolytes cannot be excluded).[6,7]

Given the essential role of potassium in health, understanding the frequency of laboratory test errors (potassium level misclassification) is essential. Moreover, the clinical importance of potassium homeostasis, the lack of symptoms associated with its derangement, and the development of effective pharmacological therapy to treat hyperkalemia safely[8,9] in conjunction with the development of potassium-binding therapies has created a clinical need for simple to use, self-administered, noninvasive potassium assessment, much as insulin therapy drove the need for patient glucose testing. Recently, noninvasive potassium measurement derived from the surface electrocardiography (ECG) that is amenable to home use has been reported.[10,11]

To assess new potassium tests and to understand the performance of currently used clinical blood tests to inform medical practice, we analyzed the results of prospectively collected repeated venous blood potassium tests in fasting, resting individuals.

PATIENTS AND METHODS

Study Population

From November 29, 2012, through November 29, 2013, patients were recruited at 65 sites in the United States, Australia, and South Africa (mean number of patients per site, 12) as part of a previously reported study assessing sodium zirconium cyclosilicate in hyperkalemia (ClinicalTrials.gov Identifier: NCT01737697).[8] Eligible patients were at least 18 years of age and were able to undergo repeated blood draws. Individuals receiving dialysis and those with diabetic ketoacidosis, a potassium concentration of more than 6.5 mmol/L, or cardiac arrhythmias requiring immediate treatment, and patients who had received organic polymer resins or phosphate binders within 1 week before enrollment were excluded. Patients who had been fasting for at least 8 hours underwent venous phlebotomy at baseline, at 30 minutes, and at 60 minutes utilizing a point-of-care device (i-STAT, Abbott Laboratories) to measure plasma potassium concentrations in samples of whole blood. The patients were instructed to remain inactive between blood draws. The i-STAT measures plasma potassium levels in samples of whole blood by direct ion-selective electrode potentiometry. The manufacturer package insert for the i-STAT states that the analytic measurable range is 2.0 to 9.0 mmol/L. In practice, the between-run imprecision (coefficient of variation) of potassium measurements using the i-STAT is typically less than 2% (1.8% at 2.8 mmol/L and 1.2% at 6.2 mmol/L when measured by a laboratory technologist).[12] Those individuals with an average serum potassium level of 5.0 to 6.5 mmol/L were enrolled in the previously reported trial.[8] For this analysis, all patients for whom all 3 blood test results were available were included.

Statistical Analyses

Potassium measurements at each time point were summarized by mean and SD. Differences in means between measurements were tested using repeated measures analysis of variance. Differences between measurements at each pair of time points was calculated and summarized. Absolute values of the differences were also summarized to show the magnitude. Percentage differences were calculated based on the first measurement in each pair. The paired t test was used to test whether observed differences between measurements 1 and 3 were larger (in absolute value) than the differences between measurements 1 and 2. Lin concordance correlation coefficients (CCCs) were used to summarize the association between pairs of measurements. This method is similar to the Pearson correlation coefficient but measures correlation along the line of identity. The method of Bland and Altman was used to look for patterns in differences by mean value and to demonstrate limits of agreement. Homogeneity of variance across subjects was also tested using the Anderson-Darling test and by comparing visually using a Q-Q plot vs the expected