Journal of Diabetes Science and Technology
Volume 5, Issue 4, July 2011

Preanalytic and Analytic Accuracy: Toward More Realistic and Meaningful Self-Monitoring of Blood Glucose Submissions for Regulatory Approval

George S. Cembrowski, M.D., Ph.D.

Abstract

Dr. Cembrowski provides an analysis of an article by Harrison and colleagues in this issue of *Journal of Diabetes Science and Technology* in which the authors describe the evaluation of a new device for self-monitoring of blood glucose, the Bayer CONTOUR® blood glucose monitoring system.

J Diabetes Sci Technol 2011;5(4):1014-1016

In this issue of *Journal of Diabetes Science and Technology*, Harrison, Leazenby, and Halldorsdottir[1] describe the evaluation of a new device for the self-monitoring of blood glucose (SMBG), the Bayer Contour®. Perusal of the article reveals a methodological weakness: substitution of the measurements of a significant number of capillary collections with measurements of sets of contrived venous specimens. The authors obtained a total of 74 *capillary* blood samples from patients with diabetes and immediately measured them with the Contour and the reference glucose instrument. Another 26 heparinized *venous* specimens were drawn from patients with diabetes. To simulate hyperglycemic blood, some of the venous specimens were spiked with glucose and measured by the Contour and reference instrument. To generate venous specimens with near hypoglycemia, analysis was delayed until glycolysis produced low glucose specimens.

I ask the reader to study Figure 2 of the article by Harrison and colleagues[1], which is a Clarke error grid representation of the 100 capillary and venous analyses. While the glucoses between 70 and 200 mg/dl crowd the ± 20% A zone, there is very little variation for the glucoses under 70 mg/dl. The terrifically good agreement between the SMBG and reference glucoses is an artifact of analyzing blood without intervening capillary punctures and the sampling of variably sized droplets consisting of a mixture of capillary blood, interstitial fluid, and some venous blood. With the removal of the puncture and sampling steps, the differences between the SMBG meter and reference will be quite small, representing any average difference (bias) between the SMBG and the reference device plus the imprecision encountered in repetitively measuring a low glucose blood sample. Not only are the puncture and sampling steps eliminated, so are any *in vivo* adrenergic and sympathetic responses to the hypoglycemic state, responses that can impair the accuracy of the glucose determination, e.g., hypotension/shock.[2] Barring an issue with the reference glucose, analysis of these highly contrived venous samples by the reference and Contour should yield predictably small, unimportant differences. These differences may not reflect the differences in blood glucose when hypoglycemic capillary blood is being sampled and tested.

The authors state that some of the *hyperglycemic* samples were not of capillary origin but prepared from glucose-spiked venous anticoagulated blood. While the spiked

Author Affiliation: Department of Laboratory Medicine and Pathology, University of Alberta Hospital, Edmonton, Alberta, Canada

Abbreviations: (ICU) intensive care unit, (SMBG) self-monitoring of blood glucose

Keywords: accuracy, blood glucose, evaluations, hyperglycemia, hypoglycemia, regulatory approval

Corresponding Author: George S. Cembrowski, M.D., Ph.D., University of Alberta Hospital, 4B1.24 Walter C. MacKenzie, 8440 112th St., Edmonton, AB, Canada T6G 2B7; email address *cembr001@cha.ab.ca*

samples' glucose readings are not demarcated in their Figure 2 Clarke error grid, the glucoses in question probably comprised glucoses that exceeded 400 mg/dl. Patients with abnormally high glucose will tend to have abnormal electrolytes, including low sodiums and chlorides, secondary to the osmotic effects of the elevated glucose. It has been reported that sodium concentration should decrease by 1.6 to 1.7 mmol/liter for every 100 mg/dl increase in serum glucose concentration.[3] **Figure 1** shows the relationship of plasma sodium to plasma glucose in patients in an adult general systems intensive care unit (ICU) as well as in a pediatrics ICU at the University of Alberta Hospital. Only for glucoses exceeding 400 mg/dl can a glucose–hyponatremia trend be discerned.

To increase the robustness of the SMBG evaluation, part of the evaluation will need to be conducted in clinical metabolic units where hypoglycemia can be safely provoked and monitored. The clinical investigator will need to be available at more flexible hours and work closely with the emergency department or the diabetologist in order to obtain capillary blood specimens from patients in diabetic ketoacidosis with glucoses exceeding 400 mg/dl. The end result should be a much more robust evaluation of the SMBG device's "goodness." As long as contrived specimens are permitted, the regulator should require that the analytic results arising from these samples be clearly labeled on the Clarke/Parkes error grid. Their usage should be minimal, and extensive inquiry should arise if they constitute the majority of hypoglycemic or highly glycemic specimens.

Based on decades of experience with reflectance analytic technologies, it seems that electrolyte abnormalities do not appreciably affect the accuracy of reflectance SMBG. As electrochemical technologies[4,5] rapidly supplant reflectance, especially in the hospital environment, the risk may increase that abnormal electrolyte milieus will impair electrochemical measurement of glucose. The use of contrived hyperglycemic specimens has probably diminished the opportunity to test hyponatremic and hypochloremic specimens and eliminates the discovery of other interesting preanalytic interferences. If it is discovered that electrochemical SMBG devices are susceptible to electrolyte variations in whole blood, then the use of these contrived specimens should not be an acceptable option.

Frequency histograms of electrolyte concentrations measured in large ICUs over extended periods (e.g., two years) might be used to determine the range for critically evaluating a meter's susceptibility to electrolyte variations. It is possible that two or more interferences may coexist. Should the manufacturer simulate and test specimens with multiple interferants? I would like to say no, based on approximately 1 year's results of pooled adult and pediatric ICU blood gas measured at the University of Alberta Hospital. **Figure 2**, a three-dimensional representation of simultaneously measured hematocrit and sodium, demonstrates the rarity of the co-occurrence of significant anemia and hypo- or hypernatremia.

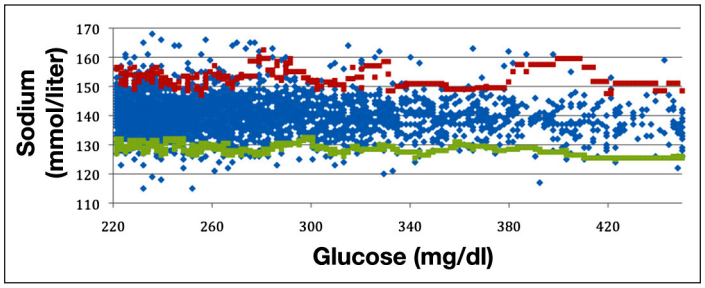

Figure 1. Glucose and sodium data obtained with Radiometer ABL 800 systems located within the General Systems ICU and Pediatrics ICU at the University of Alberta Hospital, Edmonton, Alberta. The blue symbols denote the individual patient sodium, and red and green symbols denote the running 97.5 and 2.5 percentile limits (n = 100) for sodium.

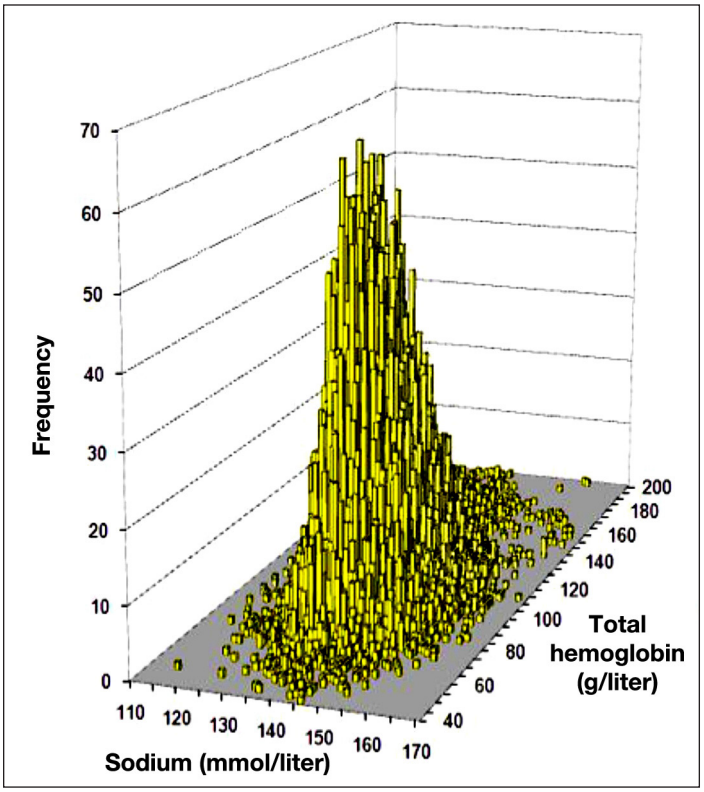

Figure 2. Frequency distributions of simultaneous measurements of hemoglobin and sodium of patients located in the General Systems ICU and Pediatrics ICU at the University of Alberta Hospital, Edmonton, Alberta. Hemoglobin and sodium were performed on Radiometer ABL 800s located in the ICUs. The x and y axes correspond to sodium and hemoglobin concentrations; the z axis represents the frequency of patient results.

Tighter SMBG precision and accuracy standards are imminent.[6,7] Inherent in these new specifications is the need for a complete protocol for specification evaluation.[8] The protocol consists of the steps required (numbers and types of specimens, how they are obtained, how they are assayed, and analysis and reporting methods including risk management) to provide evidence that the specifications have been met. The protocol that accompanies these specifications should minimize the use of contrived specimens. It should also establish realistic limits for testing interferences. In this way, future SMBG evaluations will be more meaningful and less prone to subjective interpretation.

References:

1. Harrison B, Leazenby C, Halldorsdottir S. Accuracy of the CONTOUR® blood glucose monitoring system. J Diabetes Sci Technol 2011;5(4):1009-13.
2. Best evidence topic reports. BET 1: should venous sample be used instead of capillary sample for estimation of blood glucose in patients with shock? Emerg Med J. 2010;27(10):788–9.
3. Oh G, Anderson S, Tancredi D, Kuppermann N, Glaser N. Hyponatremia in pediatric diabetic ketoacidosis: reevaluating the correction factor for hyperglycemia. Arch Pediatr Adolesc Med. 2009;163(8):771–2.
4. Heller A, Feldman B. Electrochemical glucose sensors and their applications in diabetes management. Chem Rev. 2008;108(7):2482–505.
5. Toghill KE, Compton RG. Electrochemical non-enzymatic glucose sensors: a perspective and an evaluation. Int J Electrochem Sci. 2010;5:1246–301.
6. Klonoff DC. The Food and Drug Administration is now preparing to establish tighter performance requirements for blood glucose monitors. J Diabetes Sci Technol. 2010;4(3):499–504.
7. FDA/CDRH Public Meeting: Blood Glucose Meters (March 16-17, 2010). *http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm187406.htm*. Accessed June 7, 2011.
8. Krouwer JS, Cembrowski GS. Towards more complete specifications for acceptable analytical performance - a plea for error grid analysis. Clin Chem Lab Med. 2011. Epub ahead of print.