Case Study: Recurrent Diabetic Ketoacidosis Resulting From Spurious Hypoglycemia: A Deleterious Consequence of Inadequate Detection of Partial Strip Filling by a Glucose Monitoring System

David A. Price, MD, FACE

PRESENTATION

E.K., a 28-year-old woman with poorly controlled type 1 diabetes of 10 years' duration, presented with mild nausea, occasional vomiting, dizziness, and recurrent, asymptomatic severe hypoglycemia. In phone consultations with the physician's office in the preceding week, she had reduced her insulin in half because of recurrent, very low (usually asymptomatic) glucose readings but sporadic low glucose levels continued to be problematic. She also had episodic, marked hyperglycemia complicating her dosing decisions. Her patterns of high and low glucose appeared discordant with food intake and insulin dosing.

Her history was remarkable for diabetes and recurrent, intermittent nausea, vomiting, and diarrhea presumed to be manifestations of autonomic neuropathy. She had known hypoglycemia unawareness but had not had problems with unconscious hypoglycemia or seizures. She had no other known autoimmune disorders and no retinopathy or renal dysfunction.

She often missed office appointments and, until recently, had been erratic in her glucose monitoring. At the time of her presentation, she was on 10 units of NPH insulin in the morning and 5 units at night, with small doses of lispro only taken to compensate for very high glucose readings.

Her exam was remarkable for dry mucous membranes and orthostatic hypotension, with a sitting blood pressure of 98/74 mmHg and pulse of 102 bpm and a standing blood pressure of 72/40 mmHg and pulse of 120 bpm. Otherwise, she had normal skin pigmentation and no lipohypertrophy or lipoatrophy, and her neck, heart, lung, abdomen, and extremities were all unremarkable.

Because of the frequent low glucose levels, her insulin was further decreased, down to 7 units in the morning and 2 units at night, and she was provided new bottles of her insulins and test strips. She was instructed to aggressively hydrate and closely monitor her blood glucose and urine ketone levels. Fasting laboratory tests were obtained the next morning. Her A1C was 14%, thyroid-stimulating hormone was 1.84 with a free T4 of 1.5 ng/dl, fasting plasma glucose was 391 mg/dl, cortisol was 31.1 µg/dl (normal 8–24), adrenocorticotropic hormone was 53 pg/ml (normal 9–52), and kidney function, liver function, and anion gap were normal.

She developed increased ketonuria and had continued labile glucose levels and was admitted several days later with mild diabetic ketoacidosis (DKA). She was hydrated, and after parenteral insulin, her insulin dose was increased. Her meter glucose was compared to the lab on several occasions and correlated well.

She was considered stable enough to be discharged for close outpatient follow-up. However, her glucose levels remained chaotic, bouncing from > 400 mg/dl to a "Lo" reading on her meter. Few of the low glucose levels were symptomatic. In response to the profound hypoglycemia, insulin was repeatedly decreased.

Once again, she developed marked hyperglycemia and ketosis and had several emergency room visits for hydration. During each of these visits, her insulin was increased, but because of frequent low glucose readings, she would subsequently decrease her insulin dose. She continued to do poorly and lost weight from her baseline of 150 down to 135 lb.

With her inability to control her glucose levels and impending ketoacidosis, she was readmitted. During this hospitalization, she was instructed to self-monitor her blood glucose with her usual meter (Glucometer Elite, Bayer Diabetes Care, Tarrytown, N.Y.). Several times, her meter displayed "Lo" results that were inconsistent with the hospital meter system and the laboratory. In reviewing the labeling for E.K.'s meter, a diabetes nurse

specialist noted that a "Lo" display could occur with incomplete strip filling (also called short or partial filling or short sampling). When her glucose monitoring technique was closely observed, it was discovered that she was visually filling the test strip using a minimal amount of blood. She was not waiting for the beep to confirm adequate strip filling as described in the meter's package instructions.

She was instructed on the proper use of her meter and was discharged. During the next several weeks, E.K. dramatically improved, gaining weight and stabilizing her insulin doses without further occurrences of unexplained hypoglycemia or ketoacidosis. She was then lost to follow-up.

QUESTIONS

1. What is the differential diagnosis of falling insulin requirements?
2. What are the causes of recurrent DKA?
3. What are the sources of error in self-monitoring of blood glucose (SMBG)?
4. What are the causes of short sampling?

COMMENTARY

In this case study, a patient had repeated, asymptomatic low glucose readings resulting in insulin dose reductions and culminating in repeated hospitalizations for DKA. After much detective work in which endocrine (adrenal, pituitary, and thyroid) and metabolic (renal, hepatic) derangements were ruled out, the low glucose readings were found to be the consequence of use error, failure to follow product labeling, and failure of the blood glucose meter to provide an error message with partial strip filling. Instead of an error message, "Lo" or low glucose readings were displayed on the glucose meter. Because both patients and health care professionals use glucose meter data to make treatment decisions,[1,2] it is imperative that either results are clinically accurate or an error message is provided if incomplete strip filling occurs.

Although the sample size requirement of many current blood glucose meters is small, short sampling can occur in numerous conditions, including states of vasoconstriction, use of small lancets and shallow lances, desire to minimize blood, and poor or rushed sampling technique. In a recent study by Grady et al.,[3] 200 subjects were asked to record their daily performance with SMBG using their current meter for 1 month. A simple questionnaire allowed each subject to record daily results from successful tests and to provide information about the reasons for any test failures. The main self-reported failure modes (573 failed tests out of 14,580 individual finger sticks) were "blood drop too small" (32.9%), "error on screen, (32.2%), "can't get blood in strip" (19.3%), and "did not trust the result" (15.5%). These results are evidence that significant problems may be encountered in blood sampling with current meters even by patients who have many years of SMBG experience.

Although current blood glucose meters are designed to detect and provide an error message if an inadequate blood sample is applied to the test strip, several published reports[4–7] suggest that inadequate sample application during blood glucose testing with some glucose meters could result in erroneously low glucose readings. The U.S. Food and Drug Administration[8] also recognizes that errors can be attributed to failure of glucose meters to detect an inadequate sample size. However, this is the first published report of deleterious health consequences attributed to this error.

There are several other potential sources of error with SMBG measurements that should be considered with unexplained high and low glucose readings.[2,3,9] These errors could be related to device factors, physiological factors, patient misuse of the meter, or medication interferences.[10–12] Each glucose meter has different enzymes, co-enzymes, mediators, electrode configurations, and manufacturing processes that lead to different characteristics, performance limitations, and interferences. The strip's enzyme activity can be affected by manufacturing variances, exposure to heat and humidity (such as improper storage of the strip outside a vial or failure to close a vial), and strip aging.

Physiological factors that may affect accuracy of some glucose meters include hematocrit extremes, oxygen extremes (for glucose oxidase–based systems) hyperuricemia, hypertriglyceridemia, and hyperbilirubinemia. In addition, marked dehydration, vasoconstriction, or rapidly changing glucose levels may influence the accuracy of glucose measurement at some body sites.

Patient use errors may result in falsely elevated or decreased glucose measurements. Skin contamination from failure to wash hands is problematic. Misapplication of blood, including underdosing (as in this case), sample smearing, slow application, repeat blood application, or strip movement during application or throughout the test process may affect results. Miscoding meters diminishes the accuracy of the measurements. Incorrect unit of measure settings, date and time settings, or recordkeeping errors can affect glucose reporting and data interpretation.

Finally, medications (acetaminophen, L-dopa, tolazamide, and

ascorbic acid) may interfere with some meters. When they occur, these interferences are often associated with levels of medication that significantly exceed physiological or desired levels. In some systems that use the enzyme GDH-PQQ, because it is not specific for glucose, falsely elevated glucose readings may occur in patients treated with agents that contain or are metabolized to maltose (i.e., icodextrin), galactose, or xylose.[13] The associated rise in "glucose" can be quite marked and has been associated with inappropriate insulin doses, severe hypoglycemia, and deaths.

CLINICAL PEARLS

- Falling insulin requirements from recurrent hypoglycemia could occur with adrenal dysfunction, progressive renal insufficiency, hypothyroidism, placental insufficiency, changes in food intake or activity, surreptitious insulin administration, insulin errors, or glucose measurement errors. In the described case study, improper test strip filling and its lack of detection was determined to be the casual factor for spurious hypoglycemia, resulting in insulin dose reductions and culminating in repeated ketoacidosis.
- Glucose monitoring errors should be considered when glucose results are inconsistent or do not fit the clinical situation. These errors can be related to device or physiological factors, patient misuse, or external interferences and may result in falsely high or low glucose readings.
- It is important for patients and clinicians to understand the indications and limitations of the particular glucose meter they are using or recommending and should follow the labeled instructions for the device.
- Routine evaluation of patients' SMBG technique is recommended.[14]

REFERENCES

[1]Hirsch I, Bode B, Childs B, Close K, Fisher W, Gavin J, Ginsberg B, Raine C, Verderese C: Self-monitoring of blood glucose (SMBG) in insulin- and non–insulin-using adults with diabetes: consensus recommendations for improving SMBG accuracy, utilization, and research. *Diabetes Technol Ther* 10:419–439, 2008

[2]Heinemann L, Koschinsky T: Clinical application and challenges of blood glucose measurement technology for self monitoring. *Diabetes Technol Ther* 10 (Suppl. 1):S27–S34, 2008

[3]Grady M, Cameron H, Love J, MacLeod K, Bentata L: Problems in blood sampling may occur during home testing with conventional blood glucose monitoring systems [abstract]. *Diabetes* 56 (Suppl. 1):A527, 2007

[4]Heijboer A, Otten J, Jelles W, Blankenstein M, Vroonhof K: Importance of sample size in hospital point-of-care glucose measurements [letter]. *Clin Chem Lab Med* 46:874–875, 2008

[5]Velazquez F, Bartholomew D: Effect of small sample volume on five glucose monitoring systems [letter]. *Diabetes Care* 19:903–904, 1996

[6]Wiener K: Potential for error from underfilling Glucometer Elite test strips [letter]. *Diabet Med* 17:555–556, 2000

[7]Yared Z, Aljaberi K, Renouf N, Yale J: The effect of blood sample volume on eleven glucose monitoring systems [letter]. *Diabetes Care* 28:1836–1837, 2005

[8]Center for Devices and Radiological Health Home Health Care Committee: Home healthcare medical devices: blood glucose meters: getting the most out of your meter [article online]. Available from http://www.fda.gov/cdrh/cdrhhhc/bgm.html. Accessed 13 September 2009

[9]Bergenstal RM: Evaluating the accuracy of modern glucose meters. *Insulin* 3:5–14, 2008

[10]Ginsberg B: Factors affecting blood glucose monitoring: sources of error in measurement. *J Diabetes Sci Technol* 3:903–913, 2009

[11]Tonyushkina K, Nichols JH: Glucose meters: a review of technical challenges to obtaining accurate results. *J Diabetes Sci Technol* 3:971–980, 2009

[12]Hones J, Muller P, Surridge N: The technology behind glucose meters: test strips. *Diabetes Technol Ther* 10 (Suppl. 1):S10–S26, 2008

[13]Flore K, Delanghe J: Analytical interferences in point-of-care testing glucometers by icodextrin and its metabolites: a review. *Perit Dial Int* 29:377–383, 2009

[14]American Diabetes Association: Standards of medical care in diabetes—2009 [position statement]. *Diabetes Care* 32 (Suppl. 1):S13–S61, 2009

David A. Price, MD, FACE, is Executive Director of Clinical Affairs at LifeScan, Inc., in Milpitas, Calif.

Note of disclosure: *Dr. Price is an employee of LifeScan, Inc., and holds stock in its parent company, Johnson and Johnson. LifeScan, Inc., manufactures and sells blood glucose monitoring systems for people with diabetes.*