EDITORIAL (SEE FRIAS ET AL., P. 728)

Finger-Stick Glucose Monitoring

Issues of accuracy and specificity

Since its introduction three decades ago, self-monitoring of blood glucose (SMBG) using finger-stick blood samples, test strips, and portable meters has aided diabetes management, principally by enabling patients—particularly those treated with insulin—to become full partners along with health professionals in striving for excellent glycemic control. Over time the use of glucose meters has become easier and faster with smaller and smaller blood samples yielding results in a matter of seconds. For this reason, glucose meters are now increasingly used in hospital wards, intensive care units, and other facilities such as dialysis units and infusion centers to provide point-of-care results that would take much longer through routine laboratory channels. This technology has largely taken the guess work out of diabetes management. Without such technology, intensive glucose control such as that achieved in the Diabetes Control and Complications Trial may not have been demonstrated to prevent or decrease microvascular complications; insulin pump therapy would not really be practical; and hypoglycemia would remain an even greater source of anxiety for patients and their families than it already is.

We have come to rely so much on finger-stick glucose that it is easy to forget its limitations. In considering this we will discuss accuracy, specificity, and, in light of those, inappropriate usage.

Accuracy

Although there is no universally binding standard, guidelines issued by the International Organization for Standardization (ISO) are widely acknowledged. ISO guideline 15197 suggests that for glucose levels <75 mg/dl, a meter should read within 15 mg/dl of the reference sample, and for levels ≥75 mg/dl, the reading should be within 20%. A meter also should be able to meet these targets in at least 95% of the samples tested (1).

Several examples serve to illustrate the implications of this degree of imprecision. Assuming a meter does indeed meet the ISO guideline, then a true glucose level of 55 mg/dl could in fact yield an SMBG reading of as low as 40 or as high as 70 mg/dl, and occasionally (1 time in 20) a reading beyond those limits. While a reading of 40 mg/dl is likely to prompt corrective action that could be quite appropriate for a true value of 55 mg/dl, the same is not likely to be the case for a reading of 70 mg/dl, which in many instances will be regarded by the patient as reassuring, if not cause for congratulation. This could be particularly inappropriate—and hazardous—in a patient with hypoglycemia unawareness whose glucose of 55 mg/dl is "on the way down" rather than stable or increasing.

At the other end of the spectrum, a true value of 350 mg/dl might register as low as 280 or as high as 360 mg/dl. Because all of these values are obviously much higher than desirable in any circumstance, it could be argued that this is of no consequence because they all should lead to glucose-lowering action. But this is true only up to a point since in these days of insulin infusion algorithms aimed at achieving excellent glycemic control in intensive care situations and the use of premeal corrective insulin doses in patients using multiple dose insulin regimens, the differences mentioned could quite conceivably compromise the success of those respective treatment strategies. It has been suggested that in critical care situations the error tolerance limit for bedside glucose testing should be 5 mg/dl (2).

Common experience tells us that the majority of patients using meters for SMBG are unaware of the magnitude of the potential inaccuracy of results, and we suspect that many health care providers also tend to ascribe greater accuracy than is warranted to portable glucose meter results. Comparison of results on the same blood sample obtained by different meters is instructive. One study found that the degree of difference between meter readings widened as the true glucose concentration increased from 70 to 200 mg/dl, with differences ranging from 5.7 to 32% in more than half of the comparisons (3). Furthermore, the conversion of whole blood glucose (measured using finger-stick test strips) to the plasma level reported by the devices will vary depending on hematocrit, which is typically lower and more variable in hospitalized and intensive care patients than in otherwise healthy outpatients (4). Potential user errors such as applying insufficient blood to the strip, using strips that are out of date or exposed to excess moisture or humidity, or failing to enter the proper code (required for some but not all systems) can further compromise accuracy.

None of these errors is reason enough for advising against the use of this technology, but we need to do a better job educating patients and providers about the limitations. As an aside, we believe that finger stick self-monitoring of glucose by patients who do not have diabetes but who believe they experience (usually "reactive") hypoglycemia is inappropriate as a means to establishing a diagnosis. The likelihood that low glucose levels, documented by self-monitoring in such patients, truly represent a pathological degree of hypoglycemia is extremely small, yet the practice of encouraging such monitoring can help perpetuate a false belief that a disorder of glucose metabolism underlies the patient's symptoms.

Specificity

Enzymatic measurement of glucose concentration based on hexokinase is the gold standard widely used in clinical laboratories (5). Among the enzymes currently used in test-strip systems are glucose oxidase, glucose dehydrogenase nicotinamide adenine dinucleotide (GDH-NAD), GDH flavin adenine dinucleotide (GDH-FAD), and GDH pyrroloquinolinequinone (GDH-PQQ). Sensors based on glucose oxidase are more substrate-specific than those based on GDH, but oxygen, being the recipient of electrons from glucose oxidase, can negatively affect the results from glucose oxidase–based sensors (6). This is not a problem with GDH-based systems, but while GDH-FAD and GDH-NAD strips

are not subject to cross-reactivity from sugars other than glucose, the same is not the case with GDH-PQQ, which is nonspecific. Maltose, galactose, and xylose will be misinterpreted as glucose by GDH-PQQ–based sensors (7). This certainly has clinical relevance in certain situations.

The potential magnitude of error is illustrated by a report from Australia (8). A patient treated with intravenous immunoglobulin preparations containing maltose was found to have capillary glucose readings of 167 and 439 mg/dl using a GDH-PQQ meter but simultaneous lab-measured venous plasma glucose levels of 41 and 187 mg/dl, respectively. On its website, the U.S. Food and Drug Administration (FDA) draws attention to this hazard by listing the following items as being potential "interfering products" with GDH-PQQ strips: Extraneal (icodextrin) peritoneal dialysis solution; some immunoglobulins, including Octagam 5%, WinRho SDF Liquid, Vaccinia Immune Globulin Intravenous (Human), and HepaGamB; Orencia (abatacept); Adept adhesion reduction solution (4% icodextrin); and BEXXAR radioimmunotherapy agent (9). Additionally, the FDA warns that any product containing or metabolized into maltose, galactose, or xylose could be a potential hazard in this respect.

While it is likely that most *Diabetes Care* readers will not personally have encountered problems relating to GDH-PQQ strips, the article by Frias et al. (10) in this issue illustrates that the possibility of harm is not merely theoretical. In reviewing the FDA's Manufacturer and User Facility Device Experience (MAUDE) database (http://www.fda.gov/cdrh/MAUDE.html) and the medical literature, the authors identified 82 reported incidents with death occurring in 20%. The method of reporting to MAUDE precludes direct attribution of cause and effect in the cases where death ensued, but it seems almost inescapable that inappropriate insulin treatment leading to severe and unexpected hypoglycemia was a—or perhaps the—crucial factor. Almost 80% of the instances involved peritoneal dialysis using icodextrin. The authors declare an interest in that they are employees of LifeScan, a Johnson & Johnson Company that manufactures and sells monitoring systems based on glucose oxidase strips, but, in our opinion, this does not negate the import of their report.

A table listing the strips that use GDH-PQQ is displayed on the FDA website (9). Accu-Chek (Roche Diagnostics) and FreeStyle (Abbott Diabetes Care) are the most commonly used. To be fair, the manufacturers of these strips have issued warnings about the interfering sugars. The FDA advises to "avoid using GDH-PQQ glucose test strips in healthcare facilities" and cautions that if they are used "NEVER use them on patients . . . who are receiving interfering products" (9). Despite this, serious adverse events continue to be reported. A possible technical solution to the problem is the use of mutant forms of GDH-PQQ involving amino acid substitution, which have good enzymatic activity for glucose but reduced reactivity for other sugars (5).

We would favor the FDA withdrawing approval for use of GDH-PQQ strips (other than mutant GDH-PQQ)—rather than simply advising against their use—in situations specifically recognized as being problematical, such as icodextrin peritoneal dialysis or when maltose-containing immune globulin is used, and setting a date for the elimination of their use in health care facilities in general.

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