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EDITORIAL

Regulatory Controversies Surround Blood Glucose Monitoring Devices

David C. Klonoff, M.D., FACP

Blood glucose (BG) monitoring devices are coming under regulatory scrutiny because of a growing concern that (1) greater accuracy is needed, especially for use in hospitals and long-term facilities, and (2) various substances can interfere with accurate readings and lead to incorrect insulin dosing and hypoglycemia.

Upcoming Food and Drug Administration (FDA) Meeting about BG Meters

The FDA has announced that they will be presenting a meeting on "Clinical Accuracy Requirements for Point of Care Blood Glucose Meters" on March 16 and 17, 2010.[1] The meeting's goals are to: (1) raise public awareness about the accuracy and clinical use of BG meters; (2) obtain public input about the accuracy and clinical use of BG meters; and (3) work toward identifying solutions. The meeting's three sessions will cover: (1) clinical accuracy requirements for BG meters; (2) BG meter performance, interferences, and limitations; and (3) tight glycemic control, especially in the hospital setting.

Plans for this meeting were first disclosed on June 24, 2009 in an FDA response to a May 26, 2009 American Association of Clinical Endocrinologists (AACE) letter to the FDA. The AACE had written to express concern about the inaccurate performance of BG monitors. The reply from the FDA Center for Devices and Radiologic Health indicated that the FDA had received reports of several deaths and thousands of device-related failures every year associated with self-monitoring blood glucose (SMBG) device use.[2] The letter from the FDA pointed out that they recognize the current International Organization for Standardization 15197 document entitled "In Vitro Diagnostic Test Systems—Requirements for Blood Glucose Monitoring Systems for Self-Testing in Managing Diabetes Mellitus." This standard was ratified in 2003 and specifies glucose monitor performance. This standard specifies that at least 95% of BG monitor values be within 20% of the reference method when reference method glucose values are ≥75 mg/dl and that 95% of BG monitor values be within 15 mg/dl when reference method glucose values are <75 mg/dl.[3] The FDA letter stated that they are now recommending that the next version of this document should specify tighter performance standards in light of new technological advancements.[2] They also expressed concern that many hospitals are using SMBG devices that are not sufficiently accurate for that setting. On the final page of their letter, the FDA stated that they were considering a public workshop to discuss issues related to point-of-care glucose measurements.

Tight Glycemic Control in the Hospital

In the past few years, interest in creating novel products for monitoring glucose levels in patients with diabetes,

Author Affiliation: Mills-Peninsula Health Services, San Mateo, California

Abbreviations: (AACE) American Association of Clinical Endocrinologists, (BG) blood glucose, (FDA) Food and Drug Administration, (NICE-SUGAR) Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation, (GDH-PQQ) glucose dehydrogenase pyrroloquinoline quinine, (SMBG) self-monitoring blood glucose

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Corresponding Author: David C. Klonoff, M.D., FACP, Mills-Peninsula Health Services, 100 South San Mateo Dr., Room 5147, San Mateo, CA 94401; email address dklonoff@yahoo.com

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especially for hospitalized patients with hyperglycemia for any reason, has been at an all-time high. A variety of continuous, implanted, and optically based glucose monitoring devices are currently under development. Many of these devices are being touted as more accurate than the current blood glucose monitors used in many hospitals for dosing insulin and managing hyperglycemia to achieve tight glycemic control. The need for greater accuracy in point-of-care glucose testing in the hospital is becoming increasingly acute because of recent evidence supporting the benefits of intensive control of glycemia in this setting and the need for accurate glucose monitors to facilitate this type of control.

Throughout the first decade of this century, experts and agencies had increasingly been advocating tight glycemic control using intensive intravenous insulin therapy in critically ill patients.[4] This movement was supported by improved outcome data, but recent studies have questioned whether such an approach is worthwhile. Two recent meta-analysis studies of this topic have been reported. The first in 2008, of 29 trials containing 8432 patients of tight glucose control in critically ill patients, suggested limited benefits, if any, of tight glucose control in critically ill adults and a three- to fivefold increased risk of hypoglycemia. The authors concluded that tight glucose control is not associated with significantly reduced hospital mortality, but is associated with an increased risk of hypoglycemia.[5] The second in 2009, of 26 trials involving a total of 13,567 similar types of patients, concluded that intensive insulin therapy significantly increased the risk of hypoglycemia and conferred no overall mortality benefit among critically ill patients. However, the authors added a statement that this therapy may be beneficial to patients admitted to a surgical intensive care unit.[6] In many of these clinical trial studies, glucose was measured from a variety of samples with a variety of devices with differences in accuracy. Such possible user errors in sample selection and possible monitor inaccuracy may have contributed to the problematic outcomes in these meta-analyses.[7]

Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) Study

It was hoped that the NICE-SUGAR study would settle the debate as to whether tight glycemic control in the hospital is beneficial. This study was designed to be a pivotal multicenter, multinational trial of intensive insulin therapy in intensive care units involving 42 hospitals in Australia, New Zealand, Canada, and the United States. It studied 6104 patients and was the second largest randomized study sample in the history of critical care medicine.[8] The NICE-SUGAR study tested the hypothesis that intensive insulin therapy intended to achieve blood glucose levels below 108 mg/dl (compared to usual care, which was defined as target blood glucose levels of 144–180 mg/dl) would result in reduced mortality at 90 days. Many intensivists were expecting that the more intensively treated subjects would have better outcomes. In fact, in the NICE-SUGAR trial, intervention subjects whose target was below 108 mg/dl (compared with usual care subjects whose target level was 144–180 mg/dl) had greater mortality at 90 days (27.5% vs 24.9%, odds ratio for intensive control, 1.14; 95% confidence interval 1.02–1.28; $P = 0.02$). Severe hypoglycemia defined as a BG level ≤40 mg/dl was reported in 6.8% of the intensively treated subjects and in 0.5% of the conventionally treated control group ($P < 0.001$). This study concluded that intensive control results in worse outcomes than conventional control in an intensive care unit setting because of the significantly higher incidence of hypoglycemia in the intensively treated group.[9] NICE-SUGAR data were included in the previously described 2009 meta-analysis of intensive insulin therapy.[6]

Later, upon analysis of the NICE-SUGAR protocol, it turned out that the types of blood specimen and/or methods of analysis from the study sites were not actually specified. Many bedside glucose monitors have been shown to be unsuitable for this purpose.[10,11] Furthermore, depending on the sources of blood specimens, each glucose monitor may demonstrate greater or lesser accuracy,[12] but blood sources may not have always been matched to monitor specifications in this study. Data from 19,597 sites in College of American Pathologists proficiency tests show large variation. The coefficients of variation among the 17 types of meters tested were 12–14%, with bias between two types as high as 41%.[13] If a glucose meter has high bias (i.e., consistently reports higher values than the patient's actual glucose concentration), the patient will receive too much insulin and might develop hypoglycemia.[10] Inaccuracy of glucose measurements—due to both device error and user error—might have led to inappropriately high insulin doses with target glucose levels close to the hypoglycemic range and resulted in misguided insulin titration. Misguided dosing, in turn, could have resulted in a greater incidence of hypoglycemia, which was observed in the intensively treated cohort.

The FDA is now concerned whether BG monitors intended for home use are being used inappropriately in hospital settings and whether their performance in hospitals might not be adequate to safely drive intensive insulin therapy regimens because of the risk of insulin overdose.

Potential Advantages and Disadvantages of Greater Meter Accuracy

Greater performance by equipment usually comes with a price tag. Potential added costs to patients of improved blood glucose monitor performance must be taken into account by regulators, when tighter standards are mandated. These costs can include not only greater monetary expenditures for manufacturing, which will be passed on to the consumer as higher purchase prices, but also might have to include a requirement for more blood volume, more measurement time, more operating steps, or more training to obtain an accurate reading. If SMBG devices become less convenient, then patients might elect to test themselves less frequently, which could possibly result in an overall decrease in the amount of benefit patients would derive from this technology. The trade-off in mandating increased analytical accuracy from BG monitors consists of comparing the advantage of a lower risk of clinical error associated with using the device to make decisions with the potential disadvantage of greater inconvenience with using the monitor. In the hospital and long-term facility setting (compared to the outpatient setting), the clinical risks of poor analytical performance may be greater and the tolerance for increased costs or inconvenience of monitoring may also be greater. It is therefore possible that greater accuracy will be mandated for outpatient and long-term facilities than for outpatient settings in future standards.

It would be helpful to know exactly what the improved clinical outcomes associated with greater analytical accuracy of glucose monitoring are when determining a target level of analytical accuracy. Unfortunately, minimal data exist that address this topic. Two modeling studies have appeared in peer-reviewed journals that have estimated the frequency and magnitude of an insulin dosing error according to estimated levels of glucose monitor inaccuracy. One study modeled subcutaneous insulin dosing in the outpatient setting[14] and one modeled intravenous insulin dosing in the inpatient setting.[15] A meeting abstract has also reported modeled outcomes with intravenous insulin dosing.[16] These studies all demonstrated that insulin dosing errors occurred with greater frequency and magnitude with increasing monitor error. No empiric outcome data exist comparing glucose monitors with greater and lesser levels of accuracy.[17]

It is significant that in June 2009, in the FDA letter to the president of AACE, the FDA stated that a recent review of the last 31 devices that they had cleared showed that half of the meters could meet a tighter standard of within 10 mg/dl if the reference reading is less than 75 mg/dl and within 15% when reference readings are above 75 mg/dl. This statistic indicates that there may already be room for a tighter performance standard, which can be readily achieved already by many manufacturers.[2]

Interfering Substances

On August 13, 2009, the FDA posted a public health notification on its Web site about potentially fatal errors with glucose dehydrogenase pyrroloquinoline quinone (GDH-PQQ) glucose monitoring technology.[18] The concern was over certain nonglucose sugars, including maltose, xylose, and galactose, which may be found in some drug and biologic formulations or can result from the metabolism of a drug or therapeutic product. These sugars can falsely elevate glucose results using GDH-PQQ glucose monitoring technology, and these falsely elevated readings could mask a state of hypoglycemia or result in excessive insulin administration, leading to injury or even death. The FDA pointed out that other glucose test strip methodologies are not affected by the presence of nonglucose sugars. Unaffected methods include glucose oxidase, glucose dehydrogenase nicotine adenine dinucleotide, and glucose dehydrogenase flavin adenine dinucleotide, as well as laboratory-based blood glucose assays.

A list of products containing cross-reacting nonglucose sugars includes the following: (1) interfering products containing nonglucose sugars, e.g., extraneal (icodextrin) peritoneal dialysis solution; (2) some immunoglobulins, e.g., Octagam 5%, Gamimune N 5%, WinRho® SDF liquid, Vaccinia immune globulin intravenous (human), and HepaGam B; (3) Orencia® (abatacept); (4) Adept® adhesion reduction solution (4% icodextrin); (5) Bexxar radioimmunotherapy agent; and (6) any substance containing or metabolized into maltose, galactose, or xylose. The FDA recommended a four-point plan to reduce the risk of patients receiving cross-reacting nonglucose sugars from using GDH-PQQ glucose monitors and strips. The plan called for: (1) determination as to whether patients are receiving interfering products on admission and

periodically during their stay at a facility; (2) education of staff and patients about the potential for falsely elevated glucose results in the presence of certain nonglucose sugars when using GDH-PQQ glucose test strips; (3) consideration of using drug interaction alerts in computer order entry systems, patient profiles, and charts to alert staff to the potential for falsely elevated glucose results; and (4) periodic verification of glucose meter results with laboratory-based glucose assays if a patient is using GDH-PQQ test strips even if the patient is not receiving interfering products.

The FDA also reported that from 1997 to 2009 they received 13 reports of deaths associated with GDH-PQQ glucose test strips in hospitalized patients where there was documented interference from maltose or other nonglucose sugars. The FDA recommended that the use of GDH-PQQ glucose test strips in health care facilities should be avoided. To promote patient safety, if patients are receiving maltose, icodextrin, galactose, or xylose, then clinicians must review the package inserts of all test strips to determine the type of glucose monitoring system being used and to use only those systems whose tests strips contain glucose oxidase, glucose dehydrogenase nicotinamide adenine dinucleotide, or glucose dehydrogenase flavin adenine dinucleotide.[19] The problem with interference in glucose monitoring is that each enzyme that can be used in a glucose monitor has potential interference from its own list of analytes, and at this time no interference-free monitoring technology exists. At the FDA meeting later this month both FDA and industry representatives will discuss interferences and other limitations to glucose monitor performance as well as possible solutions to these problems.

Future Developments

It is now a task for the FDA to develop standards that will reduce error and unwanted clinical outcomes, but, at the same time, minimize increases in the cost or inconvenience with using more accurate monitors and strips. The public FDA meeting on March 16 and 17, 2010 will generate information, ideas, and opinions from the clinical, academic, patient, and industry communities, which will likely be considered carefully when further regulatory directives are put forth by FDA. The level of performance mandated by regulatory standards must be based on clinical needs but must also be linked to currently achievable performance.[20] Both data and expert opinion are necessary to determine standards. It appears that we could use more of the former, but there is no shortage of the latter. Regulatory controversies about blood glucose monitoring will be with us for the foreseeable future.

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