AACC's Perspective on the Clinical Study Design and Performance of Indwelling Continuous Blood Glucose Monitors

Overview

The development of indwelling glucose sensors is a major technological advance in the treatment of diabetes and glycemic control. These devices may greatly improve the ability of people with diabetes to monitor and treat their condition, since more convenient, frequent testing can assist them in determining if and when to give an insulin injection. Some studies have indicated that the use of these sensors has resulted in patients significantly lowering their A1c values over time.

The emergence of this and related technology for continuous or near-continuous measurements of glucose may also help health care professionals manage and treat patients with diabetes or those suffering from stress-induced hyperglycemia during an acute illness. More specifically, in a hospital setting, the use of continuous or near-continuous measurements of glucose could reduce the number of blood collections—freeing up health care personnel for other duties while providing valuable real-time data for making short-term assessments and identifying important trends. The potential health gains associated with these technologies could be significant.

Since CLSI POC 05 (Performance Metrics for Continuous Interstitial Glucose Monitoring; POCT05AE) covers interstitial fluid sensors that measure glucose, AACC's response will not take into consideration this type of technology.

Intended Populations

FDA Questions: Who is the likely intended use population for these devices and how will they be used in patient management? For example, will they be used for general hospital, surgical, critically ill, pediatric patients, etc.? What are the study considerations for evaluating the devices in these different populations?

As medical device manufacturers continue to refine and improve the technologies, AACC expects hospitals to utilize continuous or intermittent blood glucose monitoring devices in a variety of settings, including: non-critically ill hospitalized inpatients and outpatients; critically ill hospitalized inpatients who may or may not be in an ICU; patients undergoing inpatient or outpatient surgery; inpatients or outpatients who are in the recovery room setting; and patients of any medical severity being seen in the emergency department. Adult and pediatric patients are included in all these categories. It is important to note that patients with diabetes (especially type 1) may be the most common patients in need of these types of monitors in hospital areas outside of the critical care arena.

AACC believes that the clinical accuracy studies for continuous or near-continuous glucose measuring devices need to include patients from the clinical settings in which they will be used,

since the risks associated with using these sensors will vary greatly depending on where and how they are used. For example, if the main objective for utilizing the sensor is to maintain tight glycemic control, especially at "near-normal" glucose concentrations, then the sensor needs to be highly accurate since health professionals will be making dosage adjustments and giving intravenous insulin based on those data.

Metrics and Device Accuracy

FDA Questions: How does the intended use of the device affect the design of the clinical studies and the evaluation and adequacy of device performance? For example, are the accuracy needs for a device used to monitor trends over time different from the accuracy needs of one where the individual glucose results are used to replace discrete glucose measurements? Is greater accuracy needed when the device is used in certain populations? What metrics can be used to evaluate whether or not results from these devices are sufficiently accurate and reliable for the proposed intended use(s)?

AACC believes a variety of metrics can be employed to evaluate whether or not results from these devices sufficiently attain glycemic control, such as:

- Central tendency – mean by patient and interquartile range of populations;
- Glucose Dispersion – standard deviation by patient and median or range of the SDs of a population; and
- Incidence of Hypoglycemia – severe and moderate (<2.2 and <3.9mmol/L; <40 and <70 mg/dL).

Intermittent values conceivably may be used for hourly or less-frequent changes in insulin infusion rates according to conventional current protocols for intensive insulin therapy/tight glucose control in ICUs. In this case, the point accuracy (accuracy of a measurement at a specific point in time) of the devices should be similar to that determined to be appropriate for glucose meters per CLSI, or other pertinent documents or guidelines. For the more likely situation, in which therapeutic decisions (such as the rates of insulin infusion) are based on a series of closely spaced measurements, infrequent outlier results are identified as such and are not used for decision making or, if used, will be followed in a short time (minutes) by repeated measurement and adjustment of the clinical decision. In this situation, the requirements for analytical performance will be different from those for glucose meters that are used infrequently and cannot identify outliers based on nearby results. This area needs more attention. Computer simulations may be useful in this area as they have been for estimating analytical requirements for glucose meters.

Interferences

FDA Questions: What conditions, medications, or therapies have the potential to cause interference and require evaluation? What kinds of studies/models are appropriate to evaluate interference?

AACC recognizes the challenges manufacturers face in trying to determine what conditions, medications, or therapies may interfere with the sensors and what kinds of studies/models are

appropriate for evaluating these interferences. Given that there are thousands of drugs used in hospital settings (particularly critical care units) it is impractical to test them all.

Fortunately, many of these devices are currently being evaluated in patients who are receiving the drugs most commonly used in critical care. If additional interference studies are required (beyond those encountered in these initial trials), AACC recommends that the drugs/substances tested be prioritized using the following criteria:

- Frequency of use in critical care settings;
- Drugs referenced in glucose meter package inserts as interfering; and
- Drugs with chemical structure that suggests the possibility of electrochemical interference.

One method for evaluating these interferences would be accuracy studies on patients receiving the drugs at the highest recommended dose which will likely come from clinical trials. An alternative option, if needed, would be to utilize bench (spiking) studies that follow CLSI EP-7 as closely as possible.

Differences in Glucose Concentrations

FDA Questions: Differences in glucose concentrations may be observed when testing arterial and venous blood samples from the same patient. How can the potential differences in blood glucose concentrations be addressed when conducting the clinical studies?

The devices currently under development vary in the samples they utilize (interstitial fluid devices are excluded from this discussion). These devices may use specimens from central venous lines, peripheral venous placements or central arterial lines, whereas others remove small amounts of blood at defined intervals and measure glucose on a nearby external device. We believe the optimal way to do an accuracy study is to compare like samples to like samples when possible. The comparative measurement procedure to estimate accuracy should be a FDA approved central laboratory procedure that uses venous plasma and has its calibration traceable to a JCTLM listed reference procedure.

Recommendations

In summary, AACC recommends that:

- Continuous or near-continuous glucose sensors need to be highly accurate;
- Clinical studies need to include the settings for which they may be used;
- Initial interference studies should focus on those drugs most frequently used in critical care settings;
- Devices are evaluated using specimens from similar collection devices, when possible; and
- The comparative measurement procedure used to evaluate accuracy should have its calibration traceable to a JCTLM listed reference procedure.

AACC believes that the refinement of continuous or near-continuous blood glucose measuring devices will substantially assist with glycemic control. With all stakeholders working together, these devices are likely to contribute to the improvement of patient care.

About AACC

AACC is the principal association of professional laboratory scientists--including MDs, PhDs and medical technologists. AACC's members develop and use chemical concepts, procedures, techniques and instrumentation in health-related investigations and work in hospitals, independent laboratories and the diagnostics industry worldwide. The AACC provides international leadership in advancing the practice and profession of clinical laboratory science and its application to health care.