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SYMPOSIUM

Clinical Need for Continuous Glucose Monitoring in the Hospital

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Abstract

Automation and standardization of the glucose measurement process have the potential to greatly improve glycemic control, clinical outcome, and safety while reducing cost. The resources required to monitor glycemia in hospitalized patients have thus far limited the implementation of intensive glucose management to patients in critical care units. Numerous available and up-and-coming technologies are targeted for the hospital patient population. Advantages and limitations of these devices are discussed herewith in.

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Introduction

Hyperglycemia and hypoglycemia commonly occur in the hospital despite significant nursing time and hospital resources devoted to glucose control.[1–8] The majority of patients at risk for dysglycemia are monitored four to five times per day using fingerstick capillary blood and a point-of-care (POC) blood glucose (BG) meter with test strips. Manpower issues limit intensive insulin therapy (IIT) and frequent BG monitoring to a small number of patients managed in the operating rooms and critical care units.[3,9,10] Caregivers must carefully interpret BG measurements and adjust insulin therapy in relation to meals, medications, illness, and insulin sensitivity to control the concentration of glucose safely and effectively.[11–17] Titration of insulin in relation to the metabolic needs of the patient can be difficult. Twenty-one percent of all POC glucose measurements at our university hospital are greater than 200 mg/dl and 4% are less than 70 mg/dl (July 2009 RALS database).

Continuous glucose monitoring (CGM) systems developed for the hospital measure the concentration of glucose in blood, plasma, or interstitial fluid (ISF) every 1 to 15 minutes. Each type of CGM system has unique advantages and limitations when used to monitor patients in critical care and general floor environments.[10,18–30] Advancements in chemistry, outer membrane biocompatibility, electronics, optics, miniaturization, signal processing, and manufacturing have improved CGM accuracy, stability, sensitivity, specificity, and robustness.[10,31–35] Automation and standardization of the

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Abbreviations: (BG) blood glucose, (CGM) continuous glucose monitoring, (ICU) intensive care unit, (IIT) intensive insulin therapy, (ISF) interstitial fluid, (IV) intravenous, (POC) point of care

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glucose measurement process have the potential to greatly improve BG control, clinical outcome, safety, and cost.

In the near future we envision that high-risk patients will be monitored continuously in real-time from hospital admission to discharge to facilitate the timely detection and prevention of hyper- and hypoglycemia. The CGM sensor and display will travel with the patient from the emergency department or operating room to the critical care unit, radiology, and general floor. Caregivers will observe the CGM display during each patient encounter to assess the (1) glucose concentration (mg/dl or mmol/liter), (2) direction of glucose change (increasing, decreasing, or stable) and (3) rate of glucose change (slow, fast, or stable).[10,20,36–39] One, 3, or 6 hours of glucose trend data will be displayed at the bedside, central monitoring station, and personal digital assistant. The dose of intravenous (IV) and subcutaneous insulin will be adjusted frequently according to glucose trend data using clinical protocols and computer algorithms.[8,12,29,35,40–50]

Vascular catheter blood glucose CGM systems may become the standard of care for the management of glucose levels in critical care environments of the hospital. The systems automatically transfer whole blood from a radial artery, peripheral vein, or central vein catheter to an external flow-through sensor. Standardization of blood sample acquisition, analysis, and calibration increase the accuracy and precision of glucose measurement,[51] a major advantage of CGM systems compared to routine clinical methods.

Current and Future Technologies

The Biostator™ (Miles Laboratory), STG-22 (Nikkiso Inc.), and Glucostator (GmbH Inc.) remove blood through a dual lumen vascular catheter at a slow and constant rate. The blood is heparinized and transported to a flow-through glucose–oxidase electrochemical sensor. Glucose is measured every 1 to 5 minutes. Closed-loop algorithms direct the IV infusion of insulin and glucose.[52–54] Safe and effective performance has been demonstrated during surgery and in intensive care unit (ICU) patients. Sample acquisition may be problematic, especially from a peripheral vein, and blood loss may exceed 100 ml/day. Those systems are still large, complex, difficult to maintain, and not currently approved for clinical use in the United States.[47,52,54–58]

The GlucoScout™ (International Biomedical Ltd.) has Food and Drug Administration (FDA)-approved labeling to sample blood from a radial artery, peripheral vein, or central venous catheter every 5 minutes for 72 hours. Real-time CGM measurements can be used to adjust the dose of insulin. Blood is transported to an external sterile flow-through glucose–oxidase electrochemical sensor and returned back into the bloodstream followed by a 6-ml infusion of a glucose–salt solution. The flush solution automatically recalibrates the sensor prior to each sample acquisition.[30,59,60] Sample acquisition may be problematic, especially from a peripheral vein,[20] whereas frequent sampling and flushing into the radial artery may cause hand edema. Blood sampled from the proximal port of a central venous catheter may also be contaminated from adjacent infusions.

The OptiScanner™ (OptiScan Inc.) transports blood from a vascular catheter to an external monitor, extracts a plasma sample, and measures the concentration of glucose using mid-infrared spectroscopy. A large and diverse library of plasma spectra is used to produce a universal calibration algorithm. The optical measurement of plasma has low scattering and a high signal-to-noise ratio. Clinical trial data demonstrated satisfactory accuracy, sensitivity, and specificity for continuous glucose monitoring in the critical care setting. Blood loss and flush volume were clinically acceptable.[61]

The intravenous blood glucose monitor (developed jointly by Edwards LifeSciences and DexCom Inc.) transports a small volume of blood into the lumen of an IV catheter, measures the concentration of glucose using a sterile enzyme-based electrochemical sensor, and returns the sample back into the bloodstream using a glucose–salt solution. The measurement process and calibration are automated and standardized to ensure accuracy and precision. The very small sample volume is optimal for sample acquisition from a peripheral vein and also minimizes flush volume.

The GlucCath™ (Glumetrics Inc.) is a small diameter optical fiber that is inserted into the lumen of a peripheral vein. After removal of the introducer, only the small fiber remains intravascular for several days. Glucose passes through a porous membrane to interact with boronic acid fluorescent chemistry. Accuracy, sensitivity, and specificity have been optimized for the euglycemic and hypoglycemic ranges. There is a large and rapid change in the fluorescent signal following a small change in the BG level. Long-term stability permits infrequent calibration using a reference BG measurement.

The DIRAMO™ System for Continuous Blood Glucose Monitoring (Flowsion Medical) is a small diameter dialysis

catheter that is inserted into the lumen of a peripheral vein for up to 72 hours. Glucose molecules diffuse from the blood into the glucose-free dialysate solution through a microdialysis membrane. The glucose enriched perfusate then reacts with glucose oxidase in a microfluidic reaction chip. The concentration of glucose is continuously measured every second and detected optically by a chemiluminescent sensor. The glucose concentration is proportional to the chemiluminescence intensity.

The GlucoDay (Minarini Inc.) utilizes a small diameter dialysis catheter inserted in the subcutaneous tissue of the abdomen. Glucose molecules diffuse through the small-pore membrane from the ISF into the dialysate solution. An external flow-through glucose–oxidase electrochemical sensor measures the concentration of glucose every 3 minutes for 48 hours. Calibration requires a daily reference BG measurement.[19,23] Other dialysis catheter CGM systems use near-infrared spectroscopy or a physical change to measure the concentration of glucose.[62–64] Slow transport ensures complete equilibration but increases the time lag. Current dialysis catheters are fragile and prone to fracture and premature failure.[10]

The systems described so far require invasive methods for glucose sampling. Noninvasive CGM systems utilize near-infrared spectroscopy, electrical impedance, and physical changes to estimate the concentration of glucose in the skin and subcutaneous tissue. Noninvasive CGM systems have been limited by low sensitivity, specificity, signal-to-noise ratio, and difficulty maintaining a stable sensor–tissue interface.[65]

Interstitial fluid CGM systems may be optimal for patients managed on general floors where ambulation and ease of clinical use are most important. Three subcutaneous tissue CGM systems have FDA-approved labeling for measuring the concentration of glucose in the ISF of ambulatory patients with diabetes every 1 to 5 minutes for 3 to 7 days. These CGM systems remain an adjunctive device, as any adjustment in insulin therapy requires a confirmatory BG measurement using a reference meter.[31,66]

The Guardian RT (Medtronic Diabetes Inc.), DexCom Seven (DexCom Inc.), and Navigator (Abbott Diabetes) are inserted easily into the subcutaneous tissue of the abdomen, flank, thigh, buttocks, upper arm, and chest. Novel porous membranes and electrochemistry enhance accuracy, sensitivity, specificity, and stability while minimizing the influence of hypoxemia, oxidizing compounds, and biofouling.[32,67]

Current CGM systems require at least an hour of run-in time after insertion due to an unstable sensor–tissue interface. Sensitivity often decreases and fluctuates after insertion for several hours. Accuracy depends greatly on the calibration method. Reference BG measurements should be obtained for calibration only when the blood/tissue glucose level is stable (<0.5 mg/dl/min rate of change). Frequent recalibration may be required in some patients due to ongoing changes in the sensor–tissue interface, membrane, enzyme, or electrochemistry.[68] A change in ISF CGM measurement may lag a BG change by 10 to 30 minutes (average 12 minutes).[28,69] Reference BG measurements should be time shifted when used for calibration of an ISF sensor.[70–72]

All CGM systems alarm when the glucose level exceeds a high or low threshold. Several systems have alarm algorithms that predict the onset of hyperglycemia and hypoglycemia 10 to 30 minutes into the future.[35,73] Sensitivity and specificity for hypoglycemia detection are improved when the algorithm considers rate of change and threshold.[66] False alarms, missed hypoglycemia events, and data loss can be decreased by averaging multiple CGM sensors (**Figure 1**). Two or more sensor output signals that move in parallel can be processed in real time to improve accuracy and robustness, whereas signals that deviate significantly from the mean can be used to detect sensor malfunction.[74] There is a trade-off among the number of sensors, complexity, practicality, and cost.

Clinical trials in the hospital typically compare CGM glucose data (every 5 minutes or 288 measurements/day) to intermittent BG data measured with a reference analyzer (every 20 to 240 minutes or 6 to 72 measurements/day).[22,23,75,76] Blood CGM systems have shown excellent accuracy when evaluated in patients requiring surgery and intensive care. Methods to sample blood frequently from a vascular catheter have improved significantly.[51,77,78]

Interstitial fluid CGM systems are easy to utilize in the hospital environment and provide clinically useful real-time glucose information (**Figure 2**). The majority of ISF sensors correlate closely with reference BG measurements.[79] The reason why some ISF sensors drift significantly over a short period of time or fail prematurely is not well understood.[18,25,68,76] Larger and longer clinical trials are currently underway to evaluate CGM safety and performance in a variety of hospital patient populations.

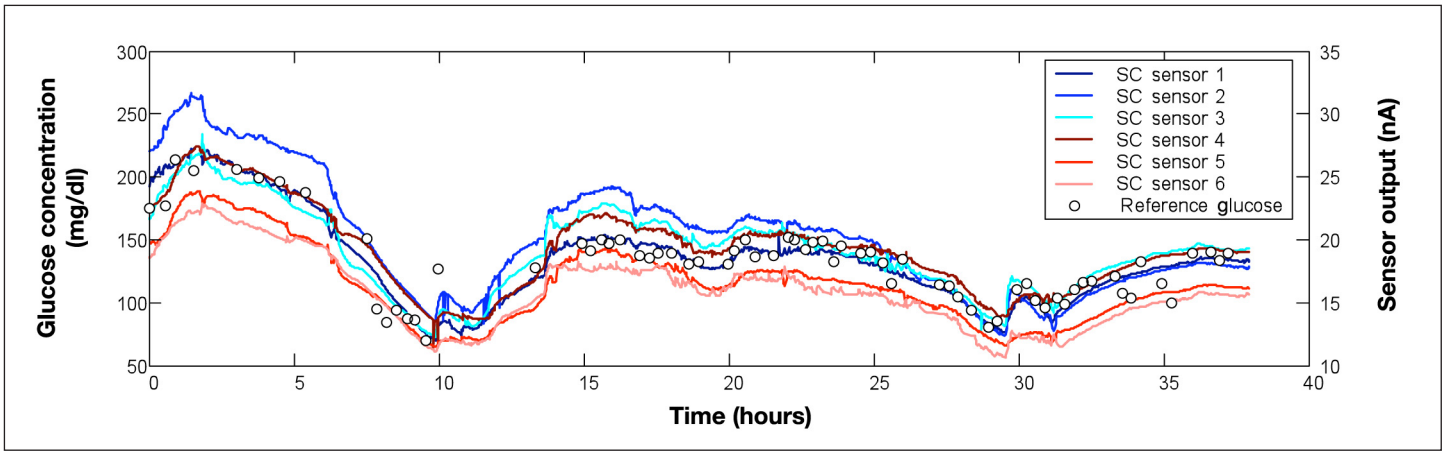

Figure 1. Glucose trend data measured simultaneously from six interstitial fluid continuous glucose monitors (modified research-only Guardian RT systems, Medtronic Diabetes, Northridge, CA) during and after major abdominal surgery. Patient had type 2 diabetes managed chronically with subcutaneous insulin and managed currently with an intravenous infusion of regular insulin. All CGM measurements moved in parallel (direction and rate of change) during the 38 hours of data collection. Several CGM sensors correlated closely with reference blood glucose measurements (blood sampled from a radial artery catheter and measured in duplicate using an Omni-9 analyzer; Roche Diagnostics). Several CGM sensors, however, demonstrated a consistent negative or positive bias relative to the reference BG measurements.

Pitfalls of BG Monitoring in Hospitalized Patients

Hospitals have not standardized or optimized the methods of blood sample collection, handling, or POC laboratory analysis to ensure an accurate and precise glucose measurement. Preanalytical and analytical errors are additive.[80–86] CGM accuracy depends on an accurate reference BG measurement.[72]

Capillary blood sampled from a fingertip may produce an erroneous glucose measurement due to tissue edema, low peripheral perfusion, or small sample size.[87] Blood sampled from a vascular catheter and stopcock may be contaminated with glucose-free or glucose-containing solution traveling through IV tubing or a collateral vein. A hemolyzed specimen may cause a low glucose measurement due to dilution with intracellular fluid. Ongoing glycolysis will decrease the glucose concentration of a blood sample sent to a central laboratory for analysis. The glucose concentration of a centrifuged specimen is higher than a noncentrifuged specimen due to the movement of proteins out of the plasma.[86,88]

Glucose measurements from a POC meter, ICU analyzer, and central laboratory analyzer may be significantly different, depending on the method of sample application, type of enzyme, chemistry of assay, type of transducer, and method of calibration. The accuracy, precision, and sensitivity of each analyzer may differ when measuring samples of whole blood or plasma in the hypoglycemic, euglycemic, and hyperglycemic ranges.[89] Some analyzers

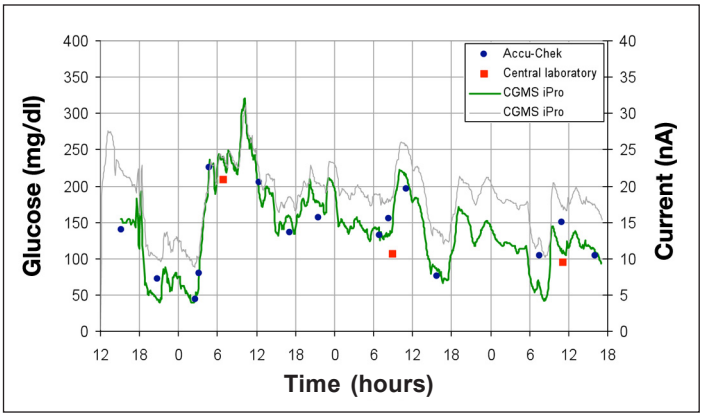

Figure 2. A continuous glucose monitor was inserted into the thigh of a hospitalized patient with type 2 diabetes managed with subcutaneous insulin. A CGMS iPro Recorder (Medtronic Diabetes, Northridge, CA) measured and recorded the concentration of interstitial fluid glucose every 5 minutes. Sensor output current (thin line) was calibrated to POC measurements from an Accu-Chek Inform meter (solid circles) and the hospital laboratory (solid squares) to produce an estimate of blood glucose (thick line). Recurrent hypoglycemia was recorded twice over the 72-hour study period.

are affected by changes in hematocrit, oxygen, pH, temperature, acetaminophen, uric acid, ascorbic acid, and carbohydrates that resemble glucose (e.g., maltose).[90–94]

Blood sampled simultaneously from the fingertip, radial artery, peripheral vein, superior vena cava, right atrium, and pulmonary artery will have a different BG concentration.[91,92,95,96] This difference is due to glucose uptake by the cells, mixing of blood from multiple tissue beds, hepatic glucose output, and changes in the plasma volume.

Sample type, method of sample collection, sample handling, and analyzer type should be standardized. Glucose measurements should be performed in duplicate or triplicate and averaged. In reality, nurses and technicians perform a single BG measurement every 1 to 6 hours with a POC meter and test strip. The outcome results of clinical trials performed in the ICU should be interpreted with caution due to variability in the type of blood sampled, blood sample handling, and type of analyzer used for glucose monitoring. A duplicate BG measurement is obtained only to confirm hypoglycemia or to double-check a measurement that does not fit the clinical situation.

Research studies have not reported whether the sample or analyzer type was similar for the treatment group and conventional group. For example, the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation trial did not determine the influence of sample type and analyzer type on the glucose measurement. This influence is especially important because the glucose difference between the IIT group and the conventional treatment group was 23 mg/dl and more than 50% of the BG measurements overlapped.[97,98]

Initial CGM Calibration and Recalibration

CGM accuracy depends greatly on the process of calibration. Regulatory agencies will require an initial calibration and recalibration of all CGM systems using patient blood samples or reference glucose standards one to three times per day and whenever sensor drift is suspected. Ideally, blood should be sampled from the same anatomic site as the CGM sensor is located. Blood sample collection, handling, and measurement should be standardized using the most accurate glucose analyzer available in the hospital. An optimal CGM system will calibrate the sensor frequently and automatically using an external glucose standard rather than a patient blood sample.

Interstitial fluid CGM systems should be calibrated during a period of glucose stability (e.g., around 6 a.m. after an overnight fast or 6 hours after the dinner meal). CGM trend data can be used to determine trend stability (<0.5 mg/dl/min change) and to detect an outlier BG measurement.[72] For example, a reference BG measurement that deviates significantly from the averaged, smoothed, and time-shifted CGM trend (International Organization for Standardization standard #15197; BG >20% above 75 mg/dl; >15 mg/dl below 75 mg/dl) should be considered an outlier and not used for patient management or CGM calibration.[68]

Frequency of BG Monitoring

Multiple hourly glucose measurements are required to accurately characterize the glucose waveform of a hospitalized patient. In reality, the concentration of BG is measured only four to five times per day in the majority of hospitalized patients with diabetes. A small number of hospitalized patients are treated aggressively with IIT and hourly glucose monitoring.[3–8] The risk of severe and prolonged hypoglycemia is increased greatly due to the low frequency of monitoring, especially on general floors.

The average and maximum rates of BG change in hospitalized patients managed in the ICU and general floors have not been well studied. The concentration of BG changes slowly (<1 mg/dl/min) more than 90% of the time in an ambulatory patient with diabetes. The maximum rate of change is rarely greater than 3 mg/dl/min.[10] In the hospital, however, the concentration of blood/ISF glucose can fall faster than 3 mg/dl/min following a large IV dose of insulin, an abrupt decrease in nutrient delivery, or an acute increase in insulin sensitivity.[25,76,99] Thus, BG monitoring once per hour is insufficient to eliminate the risk of hypoglycemia.

Approximately 5 minutes of a caregiver's time is required to measure the concentration of glucose using a blood sample, glucose meter, and test strip. Hourly monitoring equates to more than 2 hours of a caregiver's time, dedicated solely to BG monitoring of an individual patient.[9] Manpower issues therefore limit frequent glucose monitoring to a small group of high-risk patients managed in operating rooms, critical care units, intermediate care units, and general floors.

Clinical Use of CGM and Hypoglycemia

Automation of glucose monitoring is anticipated to save significant nursing time while improving glucose control and safety. Clinical use of CGM should also minimize the risk of mild to moderate hypoglycemia and eliminate the risk of severe and prolonged hypoglycemia (**Figure 3**). A caregiver will typically assess the risk for hypoglycemia during each patient encounter by glancing at the bedside display. A steep downward slope of glucose trend data is recognized easily as a high-risk clinical situation requiring increased vigilance.[100] Intermittent visualization of the CGM trend will be the primary method for the detection of hypoglycemia in critical care and general floor environments. The CGM will alarm when hypoglycemia is detected or predicted.[73] Timely information will allow the caregiver to intervene with oral or intravenous carbohydrates to prevent an

adverse event. For CGM to become standard of care for all hospitalized patients at risk for hypoglycemia, clinical trials will need to demonstrate safe and effective performance in the ICU and general floor environments.

Hyperglycemia in the Hospital

Approximately 7.5% of the U.S. population currently has diabetes. Twenty-two million Americans have type 2 diabetes, 1 million have type 1 diabetes, and 135,000 have gestational diabetes. One-quarter to one-third of U.S. patients with diabetes and prediabetes are unaware and untreated. Patients who do not have diabetes commonly develop hyperglycemia during the stressful portion of a medical illness or surgical procedure, a condition known as hospital-related hyperglycemia.[101,102] Insulin resistance of hepatic, renal, skeletal muscle, and adipose tissue is the hallmark feature of the stress response. The degree and duration of hyperglycemia correlate with the degree of tissue injury, autonomic nervous system activity, immune system activity, and the patient's ability to mount a stress response due to overall conditioning and nutrition.[103–105] Hyperglycemia is amplified by the rapid administration of IV glucose solutions and the administration of catecholamine and steroid medications.[106]

The optimal range of BG control in a specific patient population remains controversial. The BG range of 100 to 180 mg/dl has traditionally been recommended to minimize the risk of hypoglycemia and the adverse effects of hyperglycemia. Blood glucose levels greater than 180 mg/dl often exceed the ability of the kidney to reabsorb glucose, leading to glycosuria, dehydration, and electrolyte abnormality.[10] Observational studies have documented a lower risk for nosocomial infection, renal failure, and in-hospital mortality when the average BG level is maintained less than 200, 150, or 110 mg/dl.[1–4,6,107,108]

Several prospective randomized trials demonstrated a marked decrease in morbidity and mortality when hyperglycemia was controlled in the normal range (70 to 110 mg/dl) with hourly adjustments in IV insulin.[8,41,42] Outcome data supporting IIT and tight BG control are most consistent in patients with and without diabetes undergoing cardiac surgery,[1,108,109] whereas too aggressive insulin therapy may lead to increased morbidity and mortality.[110,111]

Intensive insulin therapy requires frequent BG monitoring and adjustments of the intravenous infusion dose of regular insulin (every 1 to 2 hours). Clinical

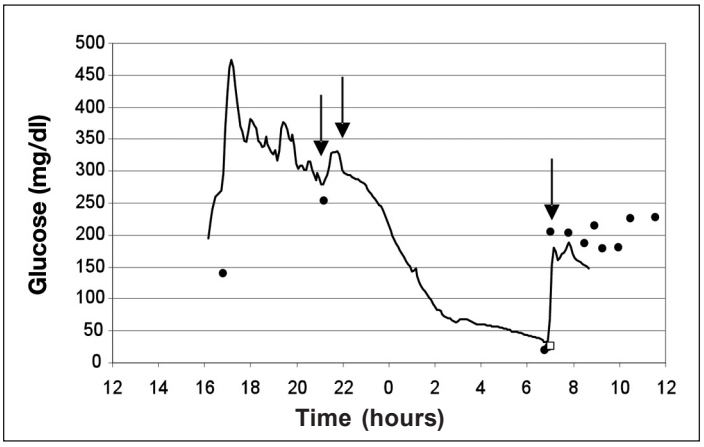

Figure 3. Severe hypoglycemia recorded in a hospitalized patient with type 1 diabetes 1 day after orthopedic surgery. The interstitial fluid glucose concentration (solid line) was measured and recorded every 5 minutes using a CGMS iPro Continuous Glucose Recorder (Medtronic Diabetes, Northridge, CA). CGM data were calibrated using a retrospective method using POC glucose measurements (solid circles) from an Accu-Chek Inform meter (Roche Diagnostics USA, Indianapolis, IN), thus the clinical nurse was blinded to real-time CGM data. Capillary BG measurements at 1700 and 2100 hours were elevated. Peakless and rapid-acting insulin were injected into the subcutaneous tissue around 2100 hours. The patient was found unresponsive at 0700 hours with a POC glucose of 18 mg/dl and a central laboratory plasma glucose of 26 mg/dl (open square). A bolus dose of 50% glucose (25 grams) was delivered into the IV catheter at 0710 hours. The patient recovered without permanent injury. This adverse event could have been prevented if the nurse had access to real-time CGM data.

algorithms consider the BG trend (direction and amount of change between measurements) to calculate each dose adjustment.[8,43,112] Computer algorithms have been commercialized (Endotool, Glucommander) that bring the hyperglycemic patient into good glucose control safely and effectively with a low incidence of hypoglycemia. Glucose measurements are entered manually into a bedside computer every 1 to 2 hours. The nurse adjusts the rate of insulin delivery for the next hour based on the computer recommendation. The computer algorithm recommends very frequent monitoring (every 15 to 30 minutes) when the BG concentration changes rapidly near the hypoglycemia range.[48–50]

Glucose Sensor-Augmented Insulin Delivery

The Biostator and GlucoScout have been used successfully to monitor surgical and medical patients in the operating room and ICU. The dose of insulin has been adjusted safely based on real-time CGM measurements. Real-time BG monitoring (a measurement every 5 to 15 minutes) has great potential to increase the safety and effectiveness of clinical protocols and computer algorithms that recommend insulin dose adjustments.[35,100]

First-generation CGM systems display the BG trend and alarm for impending hypoglycemia/hyperglycemia. Second-generation CGM systems will recommend an insulin dose adjustment based on the BG trend.[31,66] Future CGM systems will integrate infusion pumps that deliver IV insulin, IV glucose, and possibly IV parenteral nutrition and enteral tube feedings[10,113] to optimize both nutrition and BG control.[114–117] Algorithms will utilize pharmacodynamic models of regular insulin, glucose, total parenteral nutrition, partial parenteral nutrition, commercial nutrients, and meals to enhance insulin dose recommendations and alarms.[118]

Finally, computerized closed-loop systems will adjust the dose of IV insulin and IV glucose automatically every few minutes to clamp the BG level in the desired range. Closed-loop control will enhance safety and effectiveness when the clinical situation is changing rapidly.[10,29,44,45,47,52,53,57,113,119] Lessons learned in the hospital will help advance research toward an artificial pancreas for the ambulatory patient with insulin-dependent diabetes.[120,121]

Disclosure:

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