Evaluation of the Analytical Specificity and Clinical Application of a New Generation Hospital-Based Glucose Meter in a Dialysis Setting

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Background: The use of hospital glucose meters is widely established; however, the reliability of glucose meters can vary according to the type of patient group tested. Significant error rates can occur with point-of-care glucose level measurements owing to hematocrit effect and/or chemical interferences associated with drug therapy and patient treatment protocols. In addition, chemical interference with some current glucose meters because of dialysate composition has been observed in patients with renal disease undergoing peritoneal dialysis. The new generation StatStrip glucose meter (Nova Biomedical, Waltham, Mass) has been designed to compensate for interference effects commonly associated with other currently available glucose meters. A previous laboratory evaluation of StatStrip in our hands demonstrated good precision and correlation to the central laboratory hexokinase reference method. The aims of this study were to assess the response of StatStrip to analytical interferences likely to be encountered in hospitalized patients and to evaluate the reliability of StatStrip for application to patients attending a specialized dialysis care center.

The interference response of StatStrip was compared to 3 conventional glucose meter technologies: Accu-Chek Aviva (Roche Diagnostics, Mannheim, Germany), Freestyle (Abbott Diabetes, Alameda, Calif), and Elite XL (Bayer, Leverkusen, Germany). Chemical interference factors that were assessed included ß-hydroxybutyrate (ßHB), bilirubin, lactate, and maltose monohydrate. Interference studies were performed by adding each of the interferents to whole blood at 3 different glucose concentrations for a range of hematocrit values of 26% to 65%. Immediately after analysis on the glucose meters, all samples were centrifuged to obtain plasma for analysis on the reference method Dimension RxL analyzer (Dade Behring, Deerfield, Ill).

Methods: Within-run imprecision was studied using whole blood specimens spiked with glucose. A whole-blood specimen, spiked to yield samples with different glucose concentrations, was analyzed for glucose using the 4 strip-meter systems, and the results were compared to those from a reference hexokinase method. Common interferences, including hematocrit, ßHB, bilirubin, lactate, and maltose, which have previously been shown to affect measurements from current glucose meter technologies, were tested on each of the 4 strip-meter systems at low, medium, and high glucose blood levels. Whole blood samples from 37 patients in the Nephrology Clinic’s dialysis center were analyzed on each meter to determine the suitability of each in this patient care setting.

Results: Regression analyses, comparing glucose values from each strip-meter system to the reference hexokinase method on a whole blood specimen, suggested that the StatStrip system’s regression statistics, mean difference from the reference method, and percent bias were comparable to or better than similar statistics obtained from the other systems. Interferences studied included hematocrit, ßHB, bilirubin, lactate, and maltose. Of the 4 strip-meter systems tested for interference, only the StatStrip system remained within 0.555 mmol/L of their initial value (at a glucose concentration < 5.55 mmol/L) and less than 10% (at a glucose concentration > 5.55 mmol/L) after the addition of bilirubin, ßHB, lactate, or maltose. Maltose had a strong effect on the Freestyle and Accu-Chek Aviva systems. Hematocrit impacted all meter technologies except the StatStrip.

Conclusions: The StatStrip glucose meter gave (within-run) precision comparable to that determined on the other 3 glucometer systems tested. It correlated well with a clinical laboratory reference hexokinase method, was not susceptible to hematocrit, ßHB, bilirubin, lactate, or maltose interferences observed in 1 or more of the other blood glucose meters, and should minimize errors that are common to other glucometers. Our results indicate that StatStrip has good clinical reliability when used in a dialysis setting. An important consideration when selecting hospital glucose meters is to ensure that the specificity is optimal for the patient population with minimal interference effects. Maltose, a metabolite of Icdextrin or an additive in dialysis solutions, is a known interferant in certain glucose meter systems, making them unsuitable for use with patients on peritoneal dialysis. The new generation StatStrip glucose meter, which has been designed to compensate for hematocrit and chemical interferences, reduces the likelihood of erroneous results arising from these interference factors that influence current conventional glucose meters.

Key Words: glucose, hematocrit, hemodialysis, peritoneal dialysis, accuracy, precision, interferences, Stat Strip, maltose, glucose oxidase, hexokinase

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Monitoring blood glucose in hospitalized patients at the bedside is now widely established and is an important component in managing individuals with critical illness and with complications of diabetes mellitus. The implementation of safe and effective glycemic control for hospitalized patients can help to minimize complications arising from hypoglycemia and hyperglycemia.1–4 To monitor and maintain glycemic control, rapid and frequent testing of patient glucose levels is required.5,6 As a result, blood glucose testing in hospitalized patients has devolved from central laboratory testing to the use of near-patient blood gas analyzers or, more commonly, point-of-care (POC) glucose meters. However, many of the POC glucose meters now used in hospitals were developed for self-monitoring in the home environment. As reported, they may not have been fully validated in a hospital or clinic setting.7–9

Recently, there have been a number of reports highlighting the inaccuracy of POC glucose meters in hospital settings and the impact of this on clinical decision making.5–8 It is now
recognized that various drugs, hormones, and additives found in hospitalized patients can affect the performance of commonly used glucose strip-meter technologies.\textsuperscript{10-13} In particular, maltose can produce inaccurate blood results in glucose meters using strip technology based on the enzyme glucose dehydrogenase using pyrroloquinoline quinone method.\textsuperscript{14,15} This has consequences for monitoring diabetic patients on peritoneal dialysis, receiving dialysis fluid containing Icodextrin, a cornstarch-derived glucose polymer, which is converted into maltose after Icodextrin metabolism. In these individuals, accumulated maltose and other Icodextrin metabolites may interfere with some blood glucose technologies to produce a falsely elevated blood glucose reading, which may lead to an insulin-dosing error and risk of hypoglycemia.\textsuperscript{16}

In addition to this, several studies have reported that varying hematocrit levels present in hospitalized patients can lead to inaccurate glucose level measurements in most commonly used glucose meter systems.\textsuperscript{10-12,17-19} Recently, a new generation glucose meter, StatStrip, has been reported to demonstrate good accuracy in analytical studies.\textsuperscript{20,21} The StatStrip glucose meter was designed to compensate for, and overcome, interferences that affect the other commonly used glucose meters.

This study was designed to compare the performance of StatStrip with established commonly used glucose meters representing the different types of strip technology currently in use in hospitals. The analytical specificity of the meters was challenged with known interfering substances (varying hematocrit, maltose, bilirubin, lactate, and βHB levels). The clinical reliability of each meter system was assessed using whole blood specimens from 37 patients on peritoneal dialysis. The study compared the accuracy of the glucose meter readings with a reference laboratory hexokinase method. For the patients on dialysis, the accuracy of the meters was also assessed by comparing the deviation of the glucose meter readings from the reference method to the current International Organization for Standards (ISO15197) requirements for blood glucose monitoring systems.\textsuperscript{22}

**MATERIALS AND METHODS**

**Instrumentation**

Four blood glucose strip-meter systems representing different strip technology formats were evaluated in the study: StatStrip glucose meter (Nova Biomedical, Waltham, Mass), Accu-Chek Aviva (Roche Diagnostics, Mannheim, Germany), Freestyle (Abbott Diabetes, Alameda, Calif), and Elite XL (Bayer, Leverkusen, Germany). The StatStrip glucose strip technology is a modified glucose oxidase-based amperometric test system with hematocrit and chemical interference corrections, Accu-Chek Aviva uses a glucose dehydrogenase/coenzyme (pyrroloquinoline quinone)-based amperometric strip, Freestyle uses an electrochemical glucose dehydrogenase/coenzyme (nicotinamide adenine dinucleotide)-based coulometric strip, and the Bayer Elite XL uses a glucose oxidase-based amperometric detection system. The Dimension RxL analyzer (Dade Behring, Deerfield, Ill) plasma hexokinase method was used as the laboratory reference method for measuring glucose. Hematocrit levels were measured using an Omni S blood gas analyzer (Roche Diagnostics) that uses a conductivity method.

**Specimen Preparation for Analytical Studies**

Venous heparinized blood specimens were collected from volunteers 18 to 24 hours before each analytical study to allow for glycolysis and obtain a baseline glucose-depleted specimen. These glucose-depleted specimens were then modified with the addition of a stock glucose solution to prepare subsequent aliquots at 3 glucose concentrations for assessment of precision, method correlation, and interference.

**Within-Run Precision Study**

Within-run precision was assessed by adding varying amounts of a concentrated glucose solution to aliquots of the heparinized blood. Three target glucose concentration ranges were prepared: 1 to 3 (low), 11 to 16 (medium), and 18 to 22 mmol/L (high). Each aliquot was tested 20 times on each of the 4 meters and the results analyzed for imprecision.

**Method Comparison**

The samples used for the method comparison were prepared by adding varying volumes of a concentrated glucose solution to aliquots of the heparinized blood specimen. Aliquots were prepared to reflect the range of glucose levels that might be encountered in patients on dialysis or patients with diabetes. Each sample was assayed by each of the strip-meter systems.
The remainder of each specimen was centrifuged, and a plasma sample was analyzed by the Dimension RxL.

### Chemical Interference Studies

The influence of bilirubin, \( \text{BHB} \), lactate, and maltose on the accuracy of glucose level measurements was separately assessed. A concentrated glucose solution was added to each of 3 aliquots of a heparinized glucose-depleted whole blood specimen to achieve glucose levels in the ranges of 1 to 3, 11 to 16, and 18 to 22 mmol/L. Varying volumes of a concentrated stock solution of each interfering substance were then added to the respective aliquots at each glucose level. The concentration of interfering substance was chosen to reflect levels that may be present in the blood of patients on dialysis or patients with diabetes. Each aliquot was tested 4 times by each of the strip-meter systems. The remainder of each aliquot was centrifuged, and the plasma glucose level was determined using the Dimension RxL plasma hexokinase reference method.

### Hematocrit Interference Studies

A heparinized glucose-depleted whole blood specimen was divided into three 1-mL aliquots, and these aliquots were spiked with concentrated glucose solution to achieve glucose levels in the ranges of 1 to 3, 11 to 16, and 18 to 22 mmol/L. Aliquots of each glucose level were further prepared, and the hematocrit level of each aliquot was adjusted after centrifugation and removal of red cells and/or the addition of plasma from the same donor specimen, ultimately yielding target hematocrit values of 26%, 37%, 46%, 53%, and 60%. The actual hematocrit level was confirmed using the Omni S blood gas analyzer (Roche Diagnostics). Each sample was tested 4 times by each of the strip-meter systems. The remainder of each specimen was

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**TABLE 3. Maltose Interferences—Shift in Glucose Reading Compared to 0 Maltose Sample**

<table>
<thead>
<tr>
<th>Maltose, mmol/L</th>
<th>StatStrip Δ mmol/L</th>
<th>Freestyle Δ mmol/L</th>
<th>Accu-Chek Δ mmol/L</th>
<th>Elite XL Δ mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.4</td>
<td>2.8</td>
<td>2.7</td>
<td>1.3</td>
</tr>
<tr>
<td>2.8</td>
<td>2.5</td>
<td>0.1</td>
<td>5.7</td>
<td>6.0</td>
</tr>
<tr>
<td>5.6</td>
<td>2.4</td>
<td>0.0</td>
<td>8.5</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Maltose was added to whole blood samples, which had been spiked to 3 glucose concentrations. Each interfering substance was introduced at 2 concentration levels and compared to a third sample in which no interfering substance was added. Interference was defined as any concentration of interfering substance that changed the mean baseline glucose value (no interfering substance added) by more than 0.555 mmol/L (at glucose levels < 5.55 mmol/L) or by more than 10% (at glucose levels > 5.55 mmol/L).

Glucose levels of less than 5.55 mmol/L acceptable Δ mmol/L less than 0.555 mmol/L from 0 maltose sample.

Glucose of more than 5.55 mmol/L acceptable Δ% less than 10% from 0 maltose sample.

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**FIGURE 1.** Hematocrit-induced bias at 2-mmol/L glucose. A whole blood sample containing 2-mmol/L glucose level was separated into 5 equal aliquot volumes. Samples with varying hematocrit levels were prepared by adjusting supernatant volumes for red cells that had been spun down in the 3 aliquots. After the reading of the samples (in quadruplicate) on each of the meters, the samples were spun down and the supernatants analyzed on a reference hexokinase procedure (RxL). Mean of 4 replicate measurement glucose level: each meter at each of the 5 hematocrit levels.
centrifuged, and the plasma glucose level was measured on the Dimension RxL.

**Clinical Accuracy Study**

Lithium heparin whole blood specimens were collected from 37 patients on peritoneal dialysis, attending a specialized dialysis care center. Each specimen was tested with StatStrip, Elite XL, and Accu-Chek Aviva. Plasma glucose from the remainder of each specimen was assayed on the Dimension RxL.

**Data Analysis**

Within-run precision was determined by calculating coefficients of variation (%CV) for the replicate values.

For the method comparison study, statistical analyses included linear regression, least-squares correlation coefficient ($R^2$), mean difference of each strip-meter system to the reference procedure, and percent bias of each meter. For the chemical interference and hematocrit studies, the mean of the 4 replicate readings was used for data analysis. In the chemical interference studies, deviation from glucose in the baseline aliquot was calculated for each aliquot containing an interfering substance to determine an interference effect. A clinically significant interference effect was defined as a concentration of interfering substance that altered the mean baseline glucose value by more than 0.555 mmol/L at glucose levels of less than 5.55 mmol/L (100 mg/dL) or greater than 10% at glucose levels of more than 5.55 mmol/L. For the hematocrit study, the mean glucose reading was plotted for each hematocrit level. For the clinical accuracy study, the percent bias of each glucose meter reading compared to the reference hexokinase result was calculated and plotted on a Bland-Altman plot for comparison to the actual reference hexokinase glucose reading. The clinical accuracy was assessed by comparing the pattern of results to the ISO15197 criteria that specify that glucose values should fall within 0.83 mmol/L for 95% of values at a glucose concentration of less than 4.2 mmol/L or 20% of values at glucose concentration of 4.2 mmol/L or more.

**RESULTS**

**With-In Run Precision Study**

The %CV of all 4 meters in the medium and high level glucose specimens was less than 5%, but was more variable at low glucose (Table 1).
whether the bias results achieved ISO15197 criteria.

TABLE 4. Results From Peritoneal Dialysis Study in Compliance With the ISO15197 Criteria

<table>
<thead>
<tr>
<th>Meter System</th>
<th>N</th>
<th>Compliant With ISO15197 Criteria?</th>
</tr>
</thead>
<tbody>
<tr>
<td>StatStrip</td>
<td>36</td>
<td>Yes</td>
</tr>
<tr>
<td>Elite XL</td>
<td>36</td>
<td>No</td>
</tr>
<tr>
<td>Accu-Chek</td>
<td>36</td>
<td>No</td>
</tr>
</tbody>
</table>

Accuracy assessment of results of dialysis patient study comparison to ISO15197 criteria. Thirty-seven samples collected from peritoneal dialysis were tested, and the percent bias of each reading compared to the reference hexokinase result was calculated. An assessment was made on whether the bias results achieved ISO15197 criteria.

ISO15197 criteria (Fig. 4), and the overall criteria of ISO15197 was not met (Table 4).

DISCUSSION

Accurate and reliable glucose level measurements are a prerequisite for ensuring safe and effective glycemic control in hospitalized patients. Many glucose meters commonly used have primarily been developed for self-monitoring in the home environment. In an ambulatory patient population, these meters have acceptable correlation and precision when compared with a reference method. In this study, all 4 glucose meter systems showed acceptable correlation to the reference method and good precision when assessed with specimens obtained from healthy donors. However, studies in a healthy ambulatory patient population may not truly reflect the accuracy and reliability of these meters for measuring glucose levels in hospitalized patients with critical illness or patients with diabetic comorbidities. There is increasing awareness that interfering substances present in hospitalized patients can affect the accuracy of these commonly used meters. As demonstrated in this study, the accuracy of 3 commonly used glucose meters (Freestyle, Elite XL, and Accu-Chek Aiviva) were adversely affected by maltose or hematocrit interferences. There have been reports of inappropriate insulin administration resulting to life-threatening/fatal hypoglycemia as a consequence of erroneous test results obtained from patients receiving products containing maltose and some evidence that there may not be widespread awareness of the problem. 4,16,23

A number of different reasons have been proposed to explain the hematocrit effect on commonly used glucose strips. An increase in the number of red blood cells in the whole blood may mechanically impede diffusion of plasma into the reagent reaction region of the strip by blocking the pores in the mesh membranes or decreasing the plasma volume available to diffuse to the reaction surface. Hematocrit changes may alter blood viscosity, therefore, decreasing the fluid permeability into the reagent reaction layer. In addition, the increased viscosity results in a slower rate of diffusion that leads to measurement errors. 10,11 Hematocrit levels outside the reference range are not uncommon in hospitalized patients, particularly patients in an intensive care unit or neonatal intensive care unit setting. 24–26 As a consequence, hematocrit interference is very likely to be the most significant cause of analytical errors occurring in commonly used glucose meters. The falsely low glucose readings obtained with the Freestyle, Elite XL, and Accu-Chek systems in patients with slightly raised hematocrit values (hematocrit of 48%) could affect therapy for glucose control in these patients. Patients with very high hematocrit values (eg, newborns, dehydrated patients, polycythemia vera, etc) are at an even higher risk of errors associated with falsely low glucose values given by these systems.

Designs of most current glucose strip-meter systems do not allow for correction of interfering substances. The design of StatStrip incorporates separate reaction zones that measure and correct for hematocrit levels and other interfering substances. As a result and as confirmed in this study, StatStrip achieves greater accuracy compared to other commonly used glucose meters when applied to samples with known interferences or to a challenging patient population such as a peritoneal dialysis patient population. Greater accuracy will ensure more reliable clinical decision making for managing the glycemic status of hospitalized patients.

REFERENCES


