Nova Multi-Well™
Glucose StatStrip® Technology
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Comparative Testing for Better Glycemic Control
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Comparative Evaluation of Three Point-of-Care Glucose Meters with Neonatal Patient Samples Exhibiting Varied Hematocrit and Triglyceride Concentrations

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1Clinical Laboratory, 2Dept. of Pediatrics, & 3Dept. Of Pathology, University of Arkansas for Medical Sciences, Little Rock, AR

Background
Waived point-of-care (POC) glucose meters are potentially attractive for use as a screening tool in neonatal populations. However, neonatal populations exhibit challenges for POC devices such as wide variation of hematocrit levels and increased lipid levels.

The goal of this study was to comparatively evaluate the performance of Nova Biomedical StatStrip®, the Abbott Precision PCx®, and the Johnson & Johnson LifeScan SureStepFlexx® POC glucometers in a neonatal population exhibiting a wide range of hematocrit and triglyceride concentrations. Measured glucose concentrations were compared to the Ortho Diagnostics Vitros® 350 glucose oxidase plasma reference assay, which is regarded as relatively insensitive to variations in hematocrit and lipemia.

Methods
A total of 140 neonates (<1 month old) that had a pre-existing order for a plasma glucose level were identified. Whole blood was collected at the bedside for concurrent glucose testing on the three POC instruments. A sample was also collected in a pediatric lithium heparin container. Hematocrit was obtained using a Clay-Adams MHCT II manual hematocrit centrifuge. The sample was centrifuged within 5 minutes of collection and then analyzed for glucose and triglycerides on the Vitros 350 analyzer.

Results
The Vitros 350 reference glucose measurements ranged from 10-251mg/dL (median of 76mg/dL). Relative to the Vitros 350 glucose determination (denoted as x), a least squares regression fit analysis of the measured glucose data yielded the following; Nova StatStrip®, = 1.13x - 2.6 (R2 of 0.97), Abbott PCx=1.22x + 8.8 (R2 of 0.95), LifeScan SureStep=1.11x + 4.0 (R2 of 0.96). The hematocrit within this patient set ranged from 25-66% (median of 45%) and the measured triglycerides ranged from 10-211 mg/dL (median of 51 mg/dL). The median percent bias of all measured glucose values relative to the Vitros 350 was +10% for the Nova StatStrip®, +32% Abbott PCx, and +16% for the LifeScan SureStep. Differing degrees of relative measured glucose percent bias was observed in samples with low hematocrit. The median relative bias for samples with <40% hematocrit (n= 41) was +12% for the Nova StatStrip®, +39% for the Abbott PCx, and +20% for the LifeScan SureStep. Elevated levels of triglycerides (greater than 150 mg/dL, n=10) did not appear to substantially affect the percent bias relative to the reference method for all POC glucometers. At our institution, there is a strong desire to not miss any hypoglycemic infants with a potentially hazardous reference glucose concentration of ≤45mg/dL. Samples that exhibit potentially low glucose values by POC screening can be further tested by the reference method. In this data set, 21 samples exhibited glucose concentration of ≤45mg/dL by reference method. For these samples, the highest observed Nova StatStrip®, concentration was 50mg/dL, the highest observed Abbott PCx concentration was 65mg/dL, and the highest observed LifeScan SureStep concentration was 55mg/dL.

Conclusions
Accuracy of POC glucose meters and the effects of common potential interferences, particularly hematocrit, should be investigated prior to adoption in the neonatal clinical setting. Institutions considering implementing POC meters should undertake studies to establish guidelines for repeating low glucose concentrations by their reference method.
Introduction

At least 3% of newborn babies develop hypoglycemia after birth (DePuy et al.). Hypoglycemia is a condition characterized by low blood glucose level with the symptoms of jitteriness, apnea, hypothermia, or lethargy though some infants may be asymptomatic. If hypoglycemia in the newborn is not treated in a timely manner, the low glucose levels in the blood may cause growth deficits, neurological damage or death. Timely and accurate blood glucose monitoring is essential in newborns that exhibit symptoms or have increased risk factors for hypoglycemia such as infants born to diabetic mothers, intrauterine growth restriction, premature, insulin therapy or sepsis.

Hyperglycemia is characterized by high glucose levels and is common among low birth weight infants that are parenterally fed. Prolonged hyperglycemia has been associated with longer hospital stays, intraventricular hemorrhage, and increases the risk for early death. Proper management of hyperglycemia requires an accurate glucose analytic method with minimum interferences.

Whole blood glucose monitoring in the neonate proposes a challenge because newborn blood differs from adult blood. Variables that directly impact blood glucose monitoring are lower concentrations of glucose in the blood, very low or high hematocrit and concentrated intravenous hyperalimentation fluid or lipids. Many glucose monitoring systems are proven to be less accurate when glucose concentrations are low or the hematocrit is higher, as with neonates; however, glucose testing is also more clinically important at these levels. Manufacturers of point of care glucometers have worked to minimize the effects of hematocrit, oxygen sensitivity, and electrochemical interferences in their devices. This study evaluated the performance claims of the hand-held point-of-care glucose monitors which include the Nova StatStrip®, the LifeScan Surestep Flexx®, and the Abbott Precision PCx®.

The goal of this study was to comparatively evaluate the performance of different glucometers in a neonatal clinical setting using specimens exhibiting a wide range of hematocrit and triglyceride concentrations. A secondary goal was to establish a range of acceptable accuracy for each instrument and a cutoff value at which a confirmatory diagnostic test would need to be performed. Measured glucose concentrations of the Nova StatStrip®, the Abbott Precision PCx®, and the LifeScan Surestep Flexx® were compared to the OrthoClinical Diagnostics Vitros® 350 glucose oxidase plasma reference assay.

Methods

A total of 140 neonates (<1 month old) were identified that had a pre-existing order for a plasma glucose and had a hematocrit performed within 12 hours of the collection time by either automated CBC or spun hematocrit. Whole blood was collected at the bedside for concurrent glucose testing on the three POC instruments at the time the plasma glucose was collected into a lithium heparin BD microtainer®. The plasma glucose sample was centrifuged within 5 minutes of collection and then analyzed for glucose and triglycerides on the Vitros 350 analyzer.

Automated hematocrits were performed on the Sysmex XE 5000. Spun hematocrits were performed using a Clay-Adams MHCT II® microhematocrit centrifuge. Comparisons between the two methods have demonstrated a bias of less than +/- 2%.

Specimen collection was performed by capillary heelstick, venous free flow method or umbilical arterial catheter. Specimen collection for the plasma glucose and the POC glucometers were performed by two technologists, trained in the use of the instruments, to minimize variations due to operator technique.

The Nova StatStrip® uses a modified glucose oxidase based amperometric methodology with hematocrit correction. The Abbott Precision PCx Plus® test strip uses a glucose dehydrogenase amperometric methodology. The LifeScan Surestep Flexx® glucometer uses a photometric glucose oxidase methodology. The reference method measurement was performed on plasma specimens using the Vitros 350® using the dry slide glucose oxidase method. The glucose dry slide was tested with intralipid at a concentration of 800mg/dL with no interference (bias <4.4 mg/dL).
Results

Comparison between the reference method Vitros 350 and each glucometer.

**Nova StatStrip® glucose regression analysis:**
- $R^2: 0.97380$
- Slope: 1.134
- Intercept: -2.586
- $N=140$

**Abbott PCx glucose regression analysis vs. reference method:**
- $R^2: 0.95483$
- Slope: 1.224
- Intercept: 8.745
- $N=140$

**LifeScan Surestep Flexx glucose regression analysis vs. reference method:**
- $R^2: 0.95936$
- Slope: 1.109
- Intercept: 4.008
- $N=140$
Results Cont’d
Bland-Altman difference plots versus the Vitros 350® for variation in sample hematocrit.

Nova Bias vs. Hematocrit

PCX Bias vs. Hematocrit

Lifescan Bias vs. Hematocrit
Results Cont’d

Bland-Altman difference plots versus the Vitros 350® for variation in sample hematocrit (%Bias).

Nova StatStrip % Bias vs. Hematocrit

Abbott PCx % Bias vs. Hematocrit

Lifescan % Bias vs. Hematocrit
Results Cont’d
Bland-Altman difference plots versus the Vitros 350® for variation in sample Lipemia.
Results Cont’d

All POC instruments demonstrated proportional bias relative to the plasma reference method. The Vitros 350 reference glucose measurements ranged from 10-251 mg/dL (median of 76 mg/dL). Relative to the Vitros 350 glucose determination (denoted as x), a least squares regression fit analysis of the measured glucose data yielded the following; Nova StatStrip®, \(=1.13x - 2.6\) (R2 of 0.97), Abbott PCx=1.22x +8.8 (R2 of 0.95), LifeScan SureStep= 1.11x + 4.0 (R2 of 0.96). The hematocrits within this patient set ranged from 25-66% (median of 45%) and the measured triglycerides ranged from 10-211 mg/dL (median value of 51 mg/dL). The median percent bias of all measured glucose values relative to the Vitros 350 was +10 % for the Nova StatStrip®, +32% Abbott PCx, and +16% for the LifeScan SureStep.

As can be seen in the Bland-Altman plots different degrees of relative measured glucose percent bias was observed in samples with low hematocrit. The median relative bias for samples with <40% hematocrit \((n=41)\) was +12% for the Nova StatStrip®, +39% for the Abbott PCx®, and +20% for the LifeScan SureStep Flexx®. Elevated levels of triglycerides (greater than 150 mg/dL, \(n=10\)) did not appear to substantially affect the percent bias relative to the reference method for all POC glucometers. Hematocrit effects on point of care meter glucose measurements in whole blood samples spiked with glucose has also been observed by Karon et al.

At our facility, there is a strong desire among attending physicians to not miss any hypoglycemic infants with a potentially hazardous reference glucose concentration of \(\leq 50\) mg/dL. Samples that exhibit potentially low glucose values by POC screening can be further tested by the reference method (“repeat protocol”). In this data set, 23 samples exhibited a glucose concentration of \(\leq 50\) mg/dL by reference method. For these samples, the highest observed Nova StatStrip®, concentration was 59 mg/dL, the highest observed Abbott PCx concentration was 69 mg/dL and the highest observed LifeScan SureStep concentration was 65 mg/dL. Similar analysis of the point of care instruments can be applied to other clinically indicated glucose concentration cutoffs and should be considered during the establishment of repeat protocols if POC glucose meters are used in the neonatal setting. The observed overestimation of glucose concentration by POC meters results in less concern when considering their use in screening for adverse levels of hyperglycemia.

Conclusions

Accuracy of POC glucose meters and the effects of common potential interferences, should be investigated prior to adoption in any clinical setting. In the neonatal setting, particular attention should be given to interferences such as hematocrit and lipemia given the high prevalence of abnormalities of these parameters in these populations. These results demonstrate substantial influences of measured glucose values by FDA approved point-of-care meters due to the range of hematocrit observed in a neonatal population. Institutions considering implementing POC meters should undertake similar studies to establish guidelines for repeating low glucose concentrations by their reference method to avoid missing potential critical values.

References


Acknowledgements

The authors would like to thank the Nova Biomedical, Lifescan, and Abbott as well as their representatives for providing meters and test strips to support these experiments.

The authors would also like to thank the staff of the neonatal intensive care unit for accommodating this study.
Comparative Testing for Better Glycemic Control

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Abstract

Objective: We compared 2 hospital-based glucose meter technologies for accuracy and compared them with a laboratory chemistry analyzer as a reference.

Methods: This study was done on 213 samples at 3 locations to compare our currently used LifeScan Flexx glucose meter with the newer StatStrip Nova glucose meter and we compared them with the laboratory-based Vitros Fusion analyzer.

Results: Regression analysis demonstrated lower intercept and a better bias plot along with meeting the total allowable error limit in 100% of the runs for the StatStrip Nova glucose meter. The analytical superiority was further complimented by improved satisfaction by the nonspecialist users.

Discussion: Better accuracy from the newer technology ensures improved patient care for critically ill patients on tight glycemic protocol.

Maintaining tight glycemic control (TGC) in critically ill patients is a big challenge. The challenge involves not just rapid turnaround time but also reliability of the methodology giving best accuracy. Point-of-care (POC) glucometers are the standard of care in bedside glucose management in most critical care units. The Food and Drug Administration standard for POC glucose analyzer accuracy recommends that average error be no more than 15% of reference values1; however, the American Diabetic Association 1996 consensus statement2 suggests the error in glycemic measurement should be no more than 5%. A major concern for accuracy in the analytical methods is the interference caused by various factors like abnormal hematocrit levels or the electrochemical abnormalities seen in the specimens of these hospitalized patients. Besides this, various medications used in the critical care setting and patient hematocrit have also been found to affect the performance of almost all glucose meter technologies available.3,4 Many studies have shown that low hematocrit gives a high bias to glucose and, conversely, high hematocrit causes a low bias in glucose levels, regardless of the meter technology used.5,6 In addition, the degree of correlation between hypoglycemic and hyperglycemic ranges is also quite variable with currently available meters.

Last but not least is the user friendliness of the technology, which determines the confidence in the technology adding to the analytical accuracy.

The objective of the current study was to compare 2 hospital-based glucose meter technologies for accuracy compared with a laboratory chemistry analyzer as a reference.

Materials and Methods

This study compared our currently used LifeScan Flexx meters and the newly introduced Nova StatStrip meters against the laboratory-based reference method to determine the methodology that has an edge over the other in terms of correlating to the laboratory reference method. Ortho Clinical Diagnostics Fusion 5.1 analyzer (Ortho Clinical, Raritan, NJ) was used as a reference assay to measure plasma glucose based on the glucose oxidase methodology. The 2 glucose meters used for comparison were LifeScan Flexx (LifeScan, Milpitas, CA), which uses a photometric glucose oxidase detection system and Nova StatStrip (Nova Biomedical, Waltham, MA), which uses a modified glucose oxidase based amperometric test system with hematocrit and interference correction.

A validation study was done before performing the comparative analysis by using 100 samples spiked with glucose spiking solution and obtaining different target glucose concentrations ranging from 10 mg/dL to 500 mg/dL. The samples were then tested parallel on both meters and then spun for obtaining plasma used for analysis on the reference analyzer.

After the completion of the validation study, the critical care nurses were trained and their competency was assessed by direct observation of quality control testing, patient testing, and maintenance checks.

A regression analysis study was then run by the Kaiser Permanente San Francisco laboratory for comparing data between Fusion and LifeScan, Fusion and Nova StatStrip, and LifeScan and Nova StatStrip. The data was obtained from patients in the cardiovascular intensive care unit (CVICU) transferred from the cardiovascular operating room (CVOR) after open heart surgery following their existing protocol of sending an arterial sample in lithium heparin tubes every 4 hours to the laboratory for immediate testing. A parallel bedside testing was also performed every hour using the glucose meters as per the TGC protocol. One to 4 samples per patient were obtained for analysis. There were 41 samples on which correlations were performed by registered nurses (RNs) on 2 Nova StatStrip and 2 LifeScan Flexx meters and by the clinical laboratory scientists on the reference Fusion instrument. Another 86 samples were tested by the RNs on both the Nova StatStrip and LifeScan Flexx meters.

A similar study was also conducted at the Kaiser Permanente Redwood City laboratory using 2 meters and also by Kaiser Permanente South Sacramento laboratory using 4 meters by the RNs on a total of 172 patients in the intensive care unit and comparing the Nova StatStrip and LifeScan Flexx with Vitros Fusion.

In addition, a precision study was performed to study the within-run precision of the Nova StatStrip meter and comparing it with the currently used LifeScan Flexx meter. Two lots of Nova StatStrip test strips and 1 lot of LifeScan test strips were used for testing.8 Ten replicates on 3 levels of whole blood dosed with glucose stock solution were tested on both meters.
Results

Results from both the meters across all 3 sites are shown in Table 1. Combined data from all 3 sites was used based on the results of analysis of variance (ANOVA): single factor analysis showed a lower F ratio (1.131 for Nova StatStrip and 0.062 for LifeScan Flexx) than the F critical value (3.038 for Nova StatStrip and 3.038 for Life Scan Flexx) for both meters. A lower F ratio than the F critical value suggests no difference in the regression equation variance between all 3 sites and statistically supports the consolidation of data in one large group. The mean reference glucose value was 113 mg/dL and the range of glucose covered was 68 to 153 mg/dL.

Linear regression analysis for all 213 samples by Deming’s method (Table 2) demonstrated a slope of 0.972 and an intercept of 5.3 mg/dL for the Nova StatStrip and Fusion meters (Figure 1). The values were noted to be consistently closer to the slope of 1.

The LifeScan and Fusion meters demonstrated almost the same slope (0.864) but with a much higher intercept of 22.5 (Figure 2). The values were noted to be lower for higher concentrations of glucose and higher for lower concentrations of glucose.

The Nova StatStrip and LifeScan Flexx meters had a slope of 0.890 and an intercept of 17.7 (Figure 3).

Both meters were also assessed for the total allowable error limits based on CLIA (Clinical Laboratory Improvement Amendment) guidelines as shown in Figure 4. Nova StatStrip was found to meet total allowable error limits in 100% of the runs.

Comparative analysis of the percent bias also shows good bias between the Vitros Fusion and Nova StatStrip (1.8) as compared with the percent bias between the Vitros Fusion and the LifeScan Flexx (5.3) and between the Nova StatStrip and the LifeScan Flexx (3.5) as shown in Figure 5.

The within-run precision study gave acceptable results for the coefficient of variation (CV) as less than 5% on both meters when tested with controls. Results with both analyzers at 3

### Table 1. Regression Analysis (Deming’s Method) Performed at 3 Different Facilities Using Laboratory-Based Fusion as Reference Method

<table>
<thead>
<tr>
<th>Name of Meter</th>
<th>Kaiser San Francisco</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope (F s.d.)</td>
<td>Intercept (F s.d.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LifeScan Flexx</td>
<td>0.935 (0.962–0.982)</td>
<td>27.3 (18.8–26.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nova StatStrip</td>
<td>0.957 (0.865–0.914)</td>
<td>4.0 (3.8–6.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Consolidated Analysis from all 3 Sites Based on Results of Analysis of Variance (ANOVA)

<table>
<thead>
<tr>
<th>Comparison Method</th>
<th>N</th>
<th>Slope (95% Confidence Interval)</th>
<th>Intercept (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nova StatStrip and Fusion</td>
<td>213</td>
<td>0.972 (0.962–0.982)</td>
<td>5.3 (3.8–6.9)</td>
</tr>
<tr>
<td>LifeScan and Fusion</td>
<td>213</td>
<td>0.864 (0.840–0.888)</td>
<td>22.5 (18.8–26.2)</td>
</tr>
<tr>
<td>Nova StatStrip and LifeScan</td>
<td>213</td>
<td>0.890 (0.865–0.914)</td>
<td>17.7 (13.9–21.5)</td>
</tr>
</tbody>
</table>

(95% confidence intervals are shown in parentheses)
levels of controls are shown in Table 3. Although not used as a major monitor for achieving TGC, a lower CV was observed with the Nova StatStrip meter.

Accuracy of the analyzers was also determined based on the fact that significantly more samples on the Nova StatStrip (29 of 41) fell within 10% of the reference method compared with the LifeScan Flexx (7 of 41). In addition, significantly fewer values on the Nova StatStrip differed by more than 15% from the reference method (1 of 41) compared with the LifeScan Flexx (26 of 41) meters.

Besides doing all analytical correlation and comparisons, a survey was also performed for CVICU nurses who were actually using the meter to analyze the user choice and reasons. One-hundred percent of the nurses concurred on the preference of Nova StatStrip over LifeScan Flexx meter. Faster results and higher reliability because of the values falling closer to the laboratory analyzer were the main drivers for building confidence.

Discussion

Regarding the differences in the CVs noticed with the precision study for both meters along with the extent to which the glucose meters correlated with the laboratory Fusion method, significant differences were noticed between the 2 meters. The Nova StatStrip technology demonstrated closest correlation with the laboratory Fusion method based on the assessment of the slope and intercept calculated by Deming’s regression analysis. Nova StatStrip was also able to meet the CLIA proficiency testing criteria for acceptable analytical performance by meeting the total allowable error limits 100% of the time.

Analytical performance has many ramifications on clinical decision making, both in diagnosis and monitoring. Assessment of such an effect is influenced by various recommendations and numerical quality specifications set by expert groups. These numerical quality specifications include imprecision, bias, or total allowable error as major analytical monitors to achieve TGC.10

Modeling of errors in insulin dosing showed that to provide the intended insulin dosage 95% of the time, the
bias and CV needed to be <1% to 2%. Using a Monte Carlo simulation, Boyd and Bruns 7 previously demonstrated that at 10% total error, 16% to 45% of sliding scale insulin doses would be an error, though small dosing errors would predominate. Larger dosing errors were common when total error exceeded 10% to 15%. 7

In conclusion, the improved performance on the Nova StatStrip as measured by regression analysis with the reference Fusion method, low bias, good precision, and a total allowable error of less than 10%, 100% of the time should result in fewer insulin dosing errors for patients. Along with the analytical edge, end-user satisfaction also ensures better compliance with enhanced acceptability. Together, this should allow for better management of critically ill patients on TGC protocols.

**Acknowledgments:** The authors would like to give special acknowledgement to the members of the Laboratory Technology Committee and particularly to Dr. Thomas Lorey and Carolyn Hoke for their support and consultation. Also thanks to Maggie Lin and Judy Chan at Kaiser Permanente Regional Laboratory for their statistical assistance in the study.

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9. CLIA Requirements for Analytical Quality. Available at: www.westgard.com/clia.htm
Evaluation of a New POCT Bedside Glucose Meter and Strip With Hematocrit and Interference Corrections

Cathy Holtzinger, MLT (ASCP),* Edwina Szela*, MHM, BSMT (ASCP),* Jeffrey A. DuBois, PhD,† Terry L. Shirey, PhD,† and Steven Presti, (ASCP), MT†

Introduction: Based on the expanding role of point of care testing glucose meters and the need to improve accuracy and precision, the new Nova Biomedical StatStrip was evaluated and compared with the LifeScan SureStepFlexx (current point of care testing meter).

Methods: Specimen volume variation, within-run imprecision, lot-to-lot bias, bias relative to a plasma hexokinase assay, and analytical interferences likely to be encountered in hospitalized patients were studied.

Results: Strip dosing did not affect the StatStrip meter but did affect the SureStepFlexx at 5- and 50-μL specimen volumes. Within-run precision for each glucose meter was less than 5% at 39 to 47 mg/dL of glucose, less than 1.7% at 215 to 265 mg/dL, and less than 2.6% at 370 to 470 mg/dL. Improper coding resulted in erroneous measurements on the SureStepFlexx. Each meter was compared with the Dade RxL hexokinase plasma reference method, giving the following correlation equations: StatStrip = 1.015 (hexokinase) + 1.412 (r² = 0.996); SureStepFlexx = 0.889 (hexokinase) + 8.865 (r² = 0.989). At [glucose] of 55 mg/dL, ascorbic acid interfered with the SureStepFlexx but did not affect StatStrip. Hematocrit also affected the correlation of whole blood glucose on the SureStepFlexx to the plasma hexokinase reference glucose but did not affect the StatStrip meter.

Conclusions: These studies suggest that the new StatStrip meter may be more accurate and precise (elimination of hematocrit effect and electrochemical interferences with no error because of strip dosing or calibration) than the SureStepFlexx meter. This reduction in total error may help achieve better glycemic control in hospitalized patients.

Key Words: glucose meter, point of care testing, accuracy

(Point of Care 2008;7:1–6)

Much attention is paid to the monitoring of glucose in hospitalized patients to achieve tight glycemic control and to minimize complications from hypoglycemia and hyperglycemia.1–4 Although hyperglycemia of hospitalized patients is common among patients with diabetes mellitus, it is not restricted solely to patients with this disease. In addition, glucose levels within hospitalized patients, particularly critically ill patients, can change rapidly depending on stress and medications. To maintain tight glycemic control for these patients, rapid turnaround time for glucose analysis is required. Point of care testing (POCT) reduces turnaround time dramatically from that obtained by traditional central laboratory testing. Glucose meters are generally the instruments of choice for POCT glucose testing.

A major current concern is the accuracy of POCT glucose meters.5 The target glucose range, used to guide insulin dosage in hospitalized patients, varies depending on the institution and is typically narrower than that in the ambulatory (home) setting. However, abnormal hematocrit levels and various electrochemical or chemical interferences, known to affect results from glucose meters, are frequently present in the specimens of hospitalized patients. Medications and hematocrit in these patients are found to affect the performance of almost all glucose meter technologies available.6–9 Ascorbic acid interfered with all glucose meter technologies available in the year 2000. Several studies demonstrated that low hematocrit gives a high bias to glucose, and conversely, high hematocrit causes a low bias in glucose levels for virtually all meters tested.3–9

In addition, the degree to which glucose meters correlate with plasma hexokinase glucose measurements (used frequently as a reference technology) varies greatly between glucose meter technologies.10 In particular, correlation in the hypoglycemic and hyperglycemic ranges is highly variable with most currently available meters.11

This study was designed to compare our current glucose meter with a new glucose meter that uses both interference and measured hematocrit corrections. The study compared the accuracy of both POCT hospital-based glucose meters with the reference plasma hexokinase method and also evaluated the effect of drug/chemical interferences and hematocrit on each meter at 3 glucose levels.

MATERIALS AND METHODS

Instrumentation

This study compared 3 glucose assays. The reference assay hexokinase method on the Dade-Behring Dimension RxL analyzer (Dade-Behring, Deerfield, Ill) was used to measure plasma glucose. Hexokinase methods are suitable for use as reference methods for glucose determination because they correlate closely to definitive mass spectrometry.1,12 The 2 glucose meter technologies studied were the SureStepFlexx (LifeScan, Malpitas, Calif), which uses a photometric glucose oxidase detection system and a new meter techr...
StatStrip (Nova Biomedical, Waltham, Mass), which uses a modified glucose oxidase–based amperometric test system with hematocrit and other interference correction.

**Strip Dosing Study**

Whole blood droplets of varying volumes (5–30 μL) from blood specimens containing 4 different glucose levels (as determined by the reference Dade RxL instrument) were placed on Parafilm on a flat surface. The StatStrip meter, loaded with a strip, was touched to a droplet, as if it were on a patient’s fingertip, and the specimen was drawn into the test strip by capillary action to measure the glucose. This process was repeated 6 times each droplet volume (5–30 μL) at the 4 different glucose levels. The SureStepFlexx was evaluated using whole blood droplets of varying volumes (5–50 μL) that were pipetted directly onto the test pads of the strips. This process was repeated in replicates of 6 at each of the 4 glucose levels.

**Within-Run Precision Study**

For within-run precision, venous heparinized whole blood was drawn 12 to 24 hours in advance of performing the study. Aerated blood was divided into three 2-mL aliquots, which received different volumes of a concentrated glucose solution, such that the aliquots had 20 to 60, 200 to 300, and 450 to 550 mg/dL of glucose. Each aliquot was then tested 20 times on each meter.

**Calibration Code Study**

A limited study of calibration bias from strip lot to strip lot included looking at glucose values across 4 strip lots of StatStrip (which all use the same company-designated calibration with no lot-to-lot variation) and 2 strip lots of SureStepFlexx (each having been assigned its own calibration code numbers). Six replicate analyses for each StatStrip at 3 glucose levels were performed using the same calibration code across strip lots. Six replicate analyses for each of 2 strip lots of SureStepFlexx using 2 calibration codes (ie, strip A with calibration code A, strip B with calibration code B, strip A with calibration code B, and strip B with calibration code A) were also run for each strip lot at 3 glucose levels.

**Method Correlations Using Patient Specimens**

Two hundred fresh, venous, whole blood newly discarded specimens in green top tubes were used in this study. A drop from each well-mixed green top tube (spiked or unspiked) was removed and wicked onto 1 StatStrip strip and 1 SureStepFlexx strip for immediate analyses. The tubes were then immediately centrifuged, after which, a plasma sample was removed and tested using the hexokinase reference method on the Dade RxL analyzer. In some cases, the green top tubes were allowed to sit at room temperature for approximately 24 hours on a rocker, allowing the red cells to metabolize glucose and lower the [glucose]. To study a wide dynamic glucose range, 50 of the 200 glucose specimens in lithium heparin green top tubes were spiked with small volumes of concentrated spiking solution (20,000 mg/dL glucose in water).

**Interference From Exogenous Materials**

For the interference studies, freshly drawn, heparinized, venous blood from healthy donors, 1 donor per interferant tested, was allowed to sit at room temperature for 12 to 24 hours before concentrated solutions of glucose and/or interfering substances were added. The concentrated solutions of glucose and the interfering substances were gravimetrically prepared. These concentrations were prepared as follows: 20,000 mg/dL glucose in water, 1000 mg/dL acetaminophen in water, 1000 mg/dL ascorbic acid in water, and 10,000 mg/dL D(+) maltose monohydrate in water. Immediately before each interference study, aliquots of donor blood were spiked with glucose concentrate, bringing them into 3 predetermined ranges. This was followed by the division of each of these aliquots into 3 volumes, 2 of which were then spiked with the interfering material. Concentrations of each interferant tested were chosen to reflect (at maximum concentration tested) 5 to 10 times the therapeutic drug level, similar to what has been described previously." All specimens were rocked for at least 10 minutes but not longer than 20 minutes. The next step was to analyze the [glucose] in each specimen with 6 strips from both devices. After completing the testing on the strips, the specimens were immediately centrifuged. The plasma from each specimen was analyzed using the hexokinase method on the Dade RxL.

**Hematocrit Effects on Glucose Measurements**

For the studies using variable hematocrit levels, a fresh 30-mL whole blood pooled specimen from a single donor was allowed to sit at room temperature for 12 to 24 hours before division into 3 aliquots of 5 mL. The three 5-mL aliquots were each brought to a different glucose level using the stock glucose solution. Each of the 3 primary 5-mL aliquots was then centrifuged, followed by precalculated plasma volumes being micropetted from some of the tubes and dispensed into others, such that the 5 tubes contained different hematocrit levels. All specimens were rocked for at least 10 minutes and then rapidly analyzed, in less than 10 minutes, on the 2 glucose meters in replicates of 6. Hematocrit (percentage) values were obtained for each of the prepared specimens in this study using a spun hematocrit analyzer, the HemataStat II (Separation Technology, Altamonte Spring, Fla). All specimens were centrifuged to remove a plasma sample for analysis on the Dade RxL analyzer.

**Statistical Analyses**

The patient specimen data for each meter and the reference hexokinase method were analyzed to determine the slope, intercept, and correlation coefficient ($r^2$) for the data sets. Mean bias (glucose meter minus hexokinase glucose) was also calculated for each meter.

To assess the impact of each interferant at 3 [glucose], the baseline (zero interferant) glucose measurement was used to calculate deviation from baseline at increasing concentration of interferant. Results are expressed as change from baseline glucose in percent ([meter glucose with interfering substance – meter glucose at baseline]/meter glucose at baseline)
TABLE 1. Effect of Strip Dosing

<table>
<thead>
<tr>
<th>Glucose, (mg/dL) (n = 1)</th>
<th>StatStrip Glucose, mg/dL (%CV, where n = 6)</th>
<th>SureStepFlexx Glucose, mg/dL (%CV, where n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Sample Volume)</td>
<td>(Sample Volume)</td>
</tr>
<tr>
<td></td>
<td>5 µL</td>
<td>10 µL</td>
</tr>
<tr>
<td>50</td>
<td>52 (9.1)</td>
<td>52.3 (6.8)</td>
</tr>
<tr>
<td>158</td>
<td>146.7 (1.71)</td>
<td>147.2 (3.02)</td>
</tr>
<tr>
<td>260</td>
<td>265.3 (1.5)</td>
<td>266.5 (1.94)</td>
</tr>
<tr>
<td>372</td>
<td>375.2 (1.82)</td>
<td>375.3 (2.09)</td>
</tr>
</tbody>
</table>

Specimen droplets of varying size, having 4 different glucose (as measured by the Dade RxL), were wicked onto StatStrip and SureStepFlexx strips. Each glucose concentration (mg/dL) represents the mean of 6 readings on the appropriate strip from the indicated droplet size. The %CV refers to the variation in values associated with each set of 6 readings.

RESULTS

Strip Dosing Study

Table 1 (Strip Dosing Study) suggests that the StatStrip and the SureStepFlexx handled 10- to 30-µL droplets comparably with minimal changes in the means of 6 readings at each of the 4 glucose levels. The StatStrip seemed to be unaffected by varying the whole blood specimen volume. The SureStepFlexx, however, at 5 µL of whole blood specimen volume, gave erratic results. The SureStepFlexx also gave higher glucose values when 50 µL of whole blood was used. This is consistent with their claim that they can only measure specimen volumes up to 30 µL.

Within-Run Precision Study

Within-run precision was assessed by running pooled donor specimens manipulated to obtain glucose at low (46 mg/dL), medium (263 mg/dL), and high (439 mg/dL) levels 20 times in 1 day. The coefficient variation was less than 2.6% for each of the meters at the higher glucose level tested (Table 2).

<table>
<thead>
<tr>
<th>Glucose (mg/dL)</th>
<th>Imprecision, %CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dade RxL</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>263</td>
</tr>
<tr>
<td></td>
<td>439</td>
</tr>
<tr>
<td>StatStrip (n = 20)</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>259</td>
</tr>
<tr>
<td></td>
<td>457</td>
</tr>
<tr>
<td>SureStepFlexx (n = 20)</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>222</td>
</tr>
<tr>
<td></td>
<td>383</td>
</tr>
</tbody>
</table>

Calibration Code Study

Table 3 presents data demonstrating variability of glucose results if a meter is not properly calibrated or coded. Lot-to-lot variation across 4 StatStrip lots was small (a range of 3.7 mg/dL being seen at a glucose level of 53 mg/dL, 0.8% at glucose level of 226 mg/dL, and 1.1% at a glucose level of 436 mg/dL). Lot-to-lot variation across 2 SureStepFlexx lots was also small at the lowest glucose level (1.0 mg/dL at 53 mg/dL glucose) but higher at the higher glucose levels (10.2% at 226 mg/dL glucose and 6.2% at 436 mg/dL glucose). The actual glucose values provided by the StatStrip were much closer to the reference assay values (StatStrip biased low by 4.1 mg/dL at 53 mg/dL glucose, 2.6% above the reference method at 266 mg/dL glucose, and 1.6% below the reference value at 436 mg/dL glucose versus SureStepFlexx that was biased 9.7 mg/dL low at 53 mg/dL glucose, −7.3% mg/dL at the 255 mg/dL glucose, and 9.1% at the 436 mg/dL glucose level). The limited data gathered suggested that bias from the reference method depended on the calibration code given to a lot of SureStepFlexx.

Effect of Interfering Substances on Glucose Meter Accuracy

Acetaminophen (final specimen concentrations of 0, 5, and 10 mg/dL) was added to donor sodium heparin blood with a glucose level that had been adjusted to 55, 248, and 418 mg/dL, respectively, as described in the “Materials and Methods” section. Addition of acetaminophen did not change the mean glucose baseline by more than 1.2 mg/dL (2%) for StatStrip or 3.5 mg/dL (6%) for SureStepFlexx for experiments performed at 55 mg/dL glucose. At either 248 or 418 mg/dL, the glucose value did not change by more than 0.5% for StatStrip or more than 5.1% for SureStepFlexx. Thus, acetaminophen did not produce a clinically significant interference on either of the meter technologies.

Ascorbic acid (final specimen concentrations of 0, 5, and 10 mg/dL) was added to donor sodium heparin blood with the glucose level adjusted to 55, 268, and 420 mg/dL, respectively. At low glucose (55 mg/dL), ascorbic acid (5 mg/dL) produced a clinically significant (>10 mg/dL) interference with the SureStepFlexx glucose meter. At higher (268 and 420 mg/dL) glucose levels, ascorbate gave less than 4% interference. Ascorbate had minimal effect on the StatStrip system (<3% at 55 mg/dL glucose and <2% at the higher glucose). Maltose (final specimen concentrations of 0, 100,
### TABLE 3. Strip Lot Calibration Variation

<table>
<thead>
<tr>
<th>Glucose, mg/dL (n = 1)</th>
<th>Dade RxL</th>
<th>StatStrip</th>
<th>SureStepFlexx</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lot 1</td>
<td>Lot 2</td>
<td>Lot 3</td>
</tr>
<tr>
<td>53</td>
<td>47 (4.26)</td>
<td>50.7 (2.04)</td>
<td>47.2 (2.82)</td>
</tr>
<tr>
<td>266</td>
<td>272 (1.18)</td>
<td>274 (0.95)</td>
<td>274 (1.47)</td>
</tr>
<tr>
<td>436</td>
<td>427 (1.51)</td>
<td>432 (0.8)</td>
<td>429 (1.07)</td>
</tr>
</tbody>
</table>

Three specimens, having different [glucose] as determined by the Dade RxL, were analyzed by 4 lots of StatStrip and 2 lots of SureStepFlexx strips. Each glucose value represents the mean of 6 readings accompanied by its %CV. The same calibration value is applied to each of the 4 StatStrip strips. Each of the 2 SureStepFlexx strips come with its own calibration code. The data for the SureStepFlexx meter includes each strip lot with its accompanying calibration code (eg, lot A with calibration code A). It also includes crossing strip lots with the calibration codes (eg, lot A with calibration code B). *A ccA is lot A with calibration code for lot A; A ccB is lot A with calibration code for lot B, and so on.

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**FIGURE 1.** Hematocrit effects. Glucose concentration as a function of percent hematocrit is plotted for each of the 2 strip methods. Whole blood specimens with the 3 given [glucose] (as measured by the reference Dade RxL method) were manipulated to have 5 different hematocrit values. These specimens were tested for [glucose] by the 2 strip methods in replicates of 6 and then centrifuged to obtain plasma reference method analysis. A mean value (n = 6 replicates) for both strip methods and the reference method at 3 glucose levels (A–C) were determined at various hematocrit percentages. These glucose values are plotted against the measured hematocrit values.

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*ISO 15197 guidelines @ < 75 mg/dL glucose, bias is reported as mg/dL bias.*
and 200 mg/dL) was added to donor sodium heparin blood with glucose adjusted to 58, 297, and 375 mg/dL, respectively. Maltose had virtually no effect on either meter (<3% at each glucose concentration).

Glucose values measured on the SureStepFlexx were affected by variances in hematocrit, but the StatStrip was not affected (Fig. 1: hematocrit effect). In these experiments, hematocrit was adjusted to between 23% and 65% at glucose levels of 56, 242, and 426 mg/dL, respectively. At low glucose values (56 mg/dL), mean glucose difference (meter glucose minus reference glucose) changed by greater than 14 mg/dL between the lowest and highest hematocrit values tested on SureStepFlexx meter but less than 4 mg/dL for the StatStrip meter. At higher glucose levels (242 and 426 mg/dL), the SureStepFlexx meter demonstrated greater than 15% change in the mean glucose percent difference ([100 × meter glucose − reference glucose]/reference glucose) between the lowest and highest hematocrit values, whereas the StatStrip had less than 7% change. No significant difference due to varying hematocrit were observed with the StatStrip. The change in glucose values with increasing hematocrit was highly significant (P < 0.001) at each of the 3 glucose levels for the SureStepFlexx.

### Correlation With Reference Method

Correlation between glucose meter results and the plasma hexokinase reference method was performed by analyzing 150 freshly discarded lithium heparin venous whole blood specimens. An additional 50 blood specimens, some of which were allowed to sit for a period of time to reduce their glucose level were spiked with exogenous glucose and mixed and analyzed by comparison with the reference method. The mean plasma reference glucose value was 139.1 mg/dL for the entire sample set (n = 200), and the range of glucose values covered was 19 to 566 mg/dL. Linear regression analysis demonstrated a slope of 1.015, an intercept of −1.412 mg/dL glucose, and a correlation coefficient of 0.996 for the StatStrip and a slope of 0.889, an intercept of 8.865 mg/dL glucose, and a correlation coefficient of 0.994 for the SureStepFlexx. Mean bias from the reference method (meter value minus reference value) was 0.6 mg/dL for the StatStrip and 6.5 mg/dL for the SureStepFlexx.

### Relating Error in Glucose Values to Errors in Insulin Dosage

The work of Boyd and Bruns, using simulation modeling to predict errors in insulin dosing as a consequence of total error (imprecision and bias) in glucose analyses, led to the development of data shown in Table 4. Bolus insulin (augmenting basal and possibly parandial insulin) is frequently administered, depending on the measured glucose concentration. For example, 2 additional units of insulin might be used for every 50 mg/dL increment in the glucose concentration increase. Should a glucose value be in error by more than 50 mg/dL, the chances for having a 2-step insulin dosing error (eg, going from 6 to 2 units instead of 4 units of insulin) increases. Percent bias (as a measure of total error) was determined between the StatStrip and SureStepFlexx values relative to the reference Dade Rxl method for the 200 specimens in the correlation study above. The StatStrip total error is considerably less than that of the SureStepFlexx and, as a consequence, should reduce insulin dosing errors.

### DISCUSSION

The strip dosing study was performed because of comments from the nurses who expressed concern about variable blood volumes affecting the glucose results on the SureStepFlexx. The 2 meters accept blood specimens quite differently. A blood specimen is deposited onto the SureStepFlexx strip surface but is wicked by capillary action into the StatStrip and metered by the capillary channel. Although SureStepFlexx claims to accept specimen volumes ranging from 5 to 30 µL, we were unable to get consistent readings at the 5-µL specimen volume. Although the 50-µL volume is beyond the claim of the SureStepFlexx, the possibility for specimens of this size being administered by finger sticks in a busy critical care area (intensive care unit, neonatal intensive care unit, operating room, and emergency department) made it important to check the larger volume. Table 1 demonstrates that the SureStepFlexx gave different glucose results at the 50-µL specimen volume. The StatStrip, which claims to use only a 1.2-µL specimen, was unaffected by larger specimen volumes. The capillary channel of the StatStrip does not allow a larger specimen volume to reach the sensing area, thereby eliminating variability in glucose results reported.

The 2 glucose meter technologies tested demonstrated within-run precision %CV of less than 5% at the low glucose concentration tested (39–47 mg/dL) and less than 3% at the higher glucose levels (215–265 and 370–470 mg/dL).

The accuracy of blood glucose meters was evaluated in a clinical study that compared certain properly and improperly coded (calibrated) meters. Although modern blood glucose monitors are beginning to approach the recommended clinical performance criteria, it is clear from this study that the potential still exists with some devices for discrepancies in results (+30% or more), particularly when meters are inadvertently miscoded. The StatStrip, which requires no calibration or coding, showed minimal variation in glucose results among 4 different strip lots at each level of glucose tested. At the lowest glucose level studied, the SureStepFlexx...
did not demonstrate variability based on calibration coding, but at higher glucose (266 and 436 mg/dL, respectively), improper calibration significantly increased the variability of glucose results obtained on the SureStepFlexx.

The extent to which the glucose meters correlated with a plasma hexokinase reference method differed between meters, as has been observed previously. The StatStrip meter technology demonstrated the closest correlation with the hexokinase plasma glucose based on assessment of the slope (1.015, StatStrip; 0.889, SureStepFlexx) and intercept (−1.412 mg/dL, StatStrip; 8.865 SureStepFlexx) calculated by linear regression from the 200 specimens. The average glucose values determined for the 200 specimens by the 2 methods also differed from the reference method, with the StatStrip being 0.6 mg/dL high and the SureStepFlexx being 6.5 mg/dL low. This is of interest, considering that the StatStrip does not require calibration.

Acetaminophen, at levels up to 5 to 10 times the therapeutic level, did not significantly impact the glucose meters. This differs from 1 previous report on acetaminophen effects. That study used higher concentrations of acetaminophen and was performed on a previous generation of glucose meters.

Ascorbic acid has been reported to interfere with all glucose meter technologies that have been tested. We found that ascorbic acid interfered with the SureStepFlexx at a low glucose level (55 mg/dL), reducing the glucose values by greater than 10 mg/dL at 5 mg/dL ascorbate and greater than 20 mg/dL at 10 mg/dL ascorbate. At higher glucose levels (268 and 420 mg/dL), ascorbate gave less than 4% interference. Ascorbate had minimal effect on the StatStrip system (<3% at each of the glucose levels tested). Maltose interference has been reported with glucose dehydrogenase technologies and was not found in either of the technologies tested.

Hematocrit effect on glucose meter accuracy (correlation with hexokinase plasma values) was examined by manipulating a sodium heparin blood pool to obtain hematocrit values between 23% and 65% and glucose levels between 56 and 426 mg/dL. The SureStepFlexx gave a glucose range of greater than 14 mg/dL at a glucose level of 53 mg/dL as hematocrit changed from 23% to 65%; the StatStrip, less than 4 mg/dL over this hematocrit range. SureStepFlexx also gave a range of glucose values greater than 15% at the higher glucose levels (242 and 426 mg/dL) with varying hematocrit, whereas the StatStrip was less than 7%.

CONCLUSIONS

We evaluated glucose meter correlation with a reference hexokinase method and analytical interferences likely to be observed in hospitalized patients on 2 currently available glucose meter technologies. As reported by Dungan et al, correlation of whole blood glucose to a plasma hexokinase reference method continues to vary between glucose meter manufacturers. The StatStrip glucose meter, however, correlated best with the plasma hexokinase reference method over a wide range of glucose values and was least affected by hematocrit and other interfering substances. The StatStrip did not require calibration nor was it affected by specimen strip dosing. This new meter technology may improve the accuracy and precision of POCT glucose monitoring and may aid in achieving glycemic control in hospitalized patients.

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Accuracy and Reliability of the Nova StatStrip® Glucose Meter for Real-Time Blood Glucose Determinations during Glucose Clamp Studies

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Abbreviations: (EGA) error grid analysis, (PG) plasma glucose, (SMT) standardized meal tolerance test, (YSI) Yellow Springs Instruments

Keywords: Beckman, glucose clamp, glucose meter, plasma glucose, YSI

Abstract

Aims/Hypothesis:
The Andres clamp technique, which requires accurate and timely determination of glucose, utilizes the Beckman or Yellow Springs Instruments (YSI) glucose analyzers. Both instruments require maintenance, a dedicated operator, preparation of a plasma sample, and a duplicate measurement that takes ≥2 minutes. The Nova StatStrip glucose meter was evaluated for accuracy, reliability, and near-real-time availability of glucose.

Methods:
Blood samples from 24 patients who underwent 6-hour clamp studies and 12 patients who had a standardized meal tolerance test (SMT) were measured. Specimens were analyzed simultaneously and immediately upon collection by Beckman, YSI, and Nova.

Results:
Of 1004 data pairs for the Nova device versus Beckman, the Nova data points ranged from 32 to 444, while Beckman ranged from 42 to 412. The coefficient for the slope of Beckman versus Nova was 1.009 (r = 0.978). Using error grid analysis, the number and percentage of values for Nova were 976 (97.2%) in the A zone and 28 (2.8%) in the B zone. Of 399 data pairs for the Nova device versus YSI, the Nova data points ranged from 46 to 255, whereas YSI ranged from 47 to 231. The coefficient for the slope of YSI versus Nova was 1.023 (r = 0.989). All Nova readings fell in the A zone. Time required for final reading, in duplicate, was 15 seconds for Nova and 120–180 seconds for Beckman and YSI.

Conclusions:
The simplicity of Nova and its reliability, accuracy, and speed make it an acceptable replacement device for Beckman and YSI in the conduct of clamps, especially when perturbations require rapid glucose determination.

Introduction

The glucose clamp technique, first described by Andres and colleagues\(^1\) in 1966, is currently considered the state of the art technique for measurement of glucose homeostasis.\(^2\) The hyperinsulinemic–euglycemic clamp method allows assessment of peripheral tissue sensitivity to insulin. To evaluate beta-cell sensitivity to glucose, a hyperglycemic variant of the clamp can be used. As individuals with various disorders of metabolism—for example, the obese with type 2 diabetes mellitus—present to the medical system in ever-growing numbers,\(^3,4\) the clamp has become the “gold standard” methodology to assess and discriminate beta-cell responsiveness from insulin sensitivity.

In both the hyperinsulinemic–euglycemic and hyperglycemic stages of the clamp, the rate of glucose infusion is varied, based on the current blood glucose level, in order to maintain the subject at a targeted blood glucose level. Accordingly, the clamp method depends on accurate and timely determination of plasma glucose (PG) levels. Most investigators have used the Beckman or Yellow Springs Instruments (YSI) glucose analyzers, both of which utilize a glucose oxidase technology. They are considered the gold standard in near-real-time glucose measurement but have several important drawbacks. These devices require a dedicated technician to prepare a plasma sample from each whole blood specimen; the process from blood draw to measurement using Beckman or YSI can take 2 minutes or more. Given that the glucose infusion rate is typically changed every 5 minutes, this delay is significant. Moreover, Beckman was invented in the 1960s, and Beckman Coulter has announced that it will no longer support the device as of January 2009.\(^5\) The YSI instrument (YSI Life Sciences, Yellow Springs, OH), although as accurate as the Beckman device, takes even longer, and its self-calibration interferes with PG measurement. This limitation requires that a second YSI instrument be available during the clamp due to the long delay in calibration. Any inability to determine PG level and adjust the glucose infusion rate will result in significant changes from the goal during the clamp, which is especially apparent in volunteers with very good sensitivity to insulin or glucose. These devices also require significant amounts of supplies and regular maintenance.

The use of glucose meters in performing the clamp studies have been studied by several groups. The results were reported as suboptimal in two of these studies.\(^6,7\) A paper by Cohen and associates,\(^8\) however, found a handheld glucose meter to be an accurate device in the measurement of blood glucose during the clamp study.

The need for an accurate and fast method for the determination of PG levels during a clamp study has led us to test the Nova StatStrip Glucose Monitor (Nova Biomedical, Waltham, MA). The device is a handheld, battery-operated meter that uses a modified glucose-oxidase-based amperometric technology with hematocrit correction. It also has the capability to upload PG data to a computer for further analysis. The aim of this current study was to assess whether or not the Nova device is accurate enough to serve as a replacement for Beckman or YSI during clamp studies.

Methods

Sample Testing

A total of 24 subjects who had undergone hyperinsulinemic–euglycemic and hyperglycemic clamps were included in the study. All were undergoing metabolic testing either before or after bariatric surgery. A new variant of the glucose clamp technique was used in which a hyperinsulinemic–euglycemic clamp was combined with a hyperglycemic clamp. The 6-hour test consists of three steps. The first is a hyperinsulinemic–euglycemic clamp. After establishing the basal PG level, a 10-minute prime infusion of insulin is followed by a continuous infusion at 480 pmol/m\(^2\)/min\(^{-1}\) for 2 hours. This part is followed by an hour of recovery, during which plasma insulin levels will return back to basal state. During the second step, the PG levels are raised by 98 mg/dl above basal levels and held there for 2 hours. Finally, during the last hour of hyperglycemia, glucagon-like peptide-1 (7–36) amide is infused in a primed-continuous manner (5 ng/kg\(^{-1}\)/min\(^{-1}\)). The fall in PG level is then followed for the next 30 minutes. During the 6-hour clamp used in this study, arterialized venous blood samples were taken every 5 minutes to measure PG and adjust the infusion rates using a negative feedback principal. Blood samples from 14 patients were then simultaneously measured by both the Beckman glucose meter analyzer and the Nova StatStrip glucose meter and from 10 patients for YSI and Nova.

To assess and compare the blood glucose values obtained during studies in which the prevailing blood glucose level is allowed to change continuously, i.e., not clamped...
and therefore represent a broader range of glucose values, simultaneous measurements were also performed during a standardized meal tolerance test (SMT) in the same subjects undergoing clamp studies. A total of 474 ml of Ensure plus (Abbott Laboratories, Columbus, OH) were consumed within 15 minutes. For the SMT, two samples were obtained before consumption of the liquid meal, then samples were obtained at 5, 10, 15, 20, 30, 40, 60, 90, 120, 150, and 180 minutes. These venous blood samples were then immediately and simultaneously tested with both the Beckman analyzer and the StatStrip glucose meter. Half a milliliter of whole blood was centrifuged to obtain plasma for the Beckman analyzer. For the Nova StatStrip device, a test strip was loaded and was touched by a droplet of blood from the tip of the sample syringe to the end of the strip.

Samples were always analyzed with the Beckman and YSI devices in duplicate. When duplicates were performed on either device, they were tested sequentially and immediately, one after the other. Both Beckman and YSI instruments were regularly calibrated and maintained.

**Statistical Analyses**

Data from the clamp and SMT studies were entered into a computer database after each clamp. The Beckman and YSI devices were chosen as reference methods. To assess the accuracy of the Nova readings, every Beckman or YSI value obtained during a clamp at a given time was paired with a corresponding Nova value for PG level. The values used for the Beckman or YSI were the mean of the duplicate values for each device. More than 97% of the Beckman and YSI values were within 3 mg/dl of each other (for the Nova instrument, the first value was always used). Using the Beckman (or YSI) values as the reference and therefore independent variable and the Nova values as dependent variables, two ordinary least squares linear regressions were run using SigmaPlot 11.0 (Systat Software Inc., San Jose, CA).

Clinical acceptability of Nova glucose values were also analyzed using point error grid analysis (EGA). The EGA divides a graph showing the linear regression of Nova values on Beckman/YSI (reference) values into five zones, A, B, C, D, and E.9,10 Zones A and B contain results considered to be accurate or acceptable. Zone C values are considered not accurate, and their use may result in unnecessary actions that lead to poorer outcomes. Values in zone D are considered dangerous failures that may result in life-threatening actions, and values in zone E are considered inaccurate and may result in treatment contradictory to that actually required.

To assess any bias in Nova measurements across the possible range of blood glucose values, the mean difference between Nova and Beckman/YSI values was plotted against the Beckman/YSI reference values using the Bland–Altman analysis.11,12 This method also permits assessment of limits of agreement between the two devices, as determined by plotting lines showing two standard deviations above and below the mean difference between the two devices. Furthermore, another Bland–Altman plot was created to compare the precision of Nova duplicate values to Beckman duplicates.

Finally, data were analyzed using locally smoothed median absolute difference curve in order to reveal glucose meter accuracy patterns.13

**Results**

From 14 patients, all of whom underwent a 6-hour glucose clamp study, 1004 matching data points were obtained comparing the Beckman analyzer to the Nova glucose meter. From another 10 patients who also had a 6 hour glucose clamp, 399 matching data points were obtained comparing the YSI analyzer to the Nova glucose meter. Figure 1 shows a representative comparison of PG during the clamp study as measured by Beckman and NOVA instruments. The Beckman–Nova regression yielded a slope coefficient of 1.009 and a constant coefficient of 2.602. Pearson’s $r$ was 0.978. The YSI–Nova regression yielded a slope coefficient of 1.023 and a constant coefficient of 5.854. Pearson’s $r$ was 0.989.

![Figure 1. Comparison of PG values between Beckman and Nova devices during a hyperinsulinemic–euglycemic clamp (0–180 min), during a hyperglycemic clamp (180–200 min), and during recovery from hyperglycemia (300–330 min).](image-url)
The same scatter plots were graphed using EGA in Figure 2. Using the EGA with Beckman values as reference, 976 (97.6%) of the data fell in the A zone and the remaining 28 (2.4%) fell in the B zone. No values fell in zones C, D, or E. Similarly, using YSI values as reference, 399 (100%) of values fell in the A zone.

Bland–Altman plots of the mean difference between Beckman and Nova, or YSI and Nova, values against reference Beckman/YSI values are shown in Figure 3. Using Beckman values as reference, the mean difference between data pairs was 1.3 mg/dl, with a standard deviation of 11.6 mg/dl. As expected, of the 1004 data pairs, 48 (4.7%) disagreed by more than two standard deviations. Meanwhile, using YSI values as reference, the mean difference between data pairs was 8.5 mg/dl, with a standard deviation of 7.2 mg/dl. Of the 399 data pairs, 12 (3.0%) disagreed by more than two standard deviations.

Bland–Altman plots were computed to compare differences between Beckman duplicates with differences between Nova duplicates (Figure 4). The left panel of Figure 4 shows the differences between the Beckman duplicates, with the solid line showing the mean difference of 0.915 mg/dl and the dashed lines indicating two standard deviations above and below (sigma = 2.79 mg/dl). The right panel of Figure 4 shows differences between the Nova duplicates, which had a mean difference between data pairs was 1.3 mg/dl, with a standard deviation of 11.6 mg/dl. As expected, of the 1004 data pairs, 48 (4.7%) disagreed by more than two standard deviations. Meanwhile, using YSI values as reference, the mean difference between data pairs was 8.5 mg/dl, with a standard deviation of 7.2 mg/dl. Of the 399 data pairs, 12 (3.0%) disagreed by more than two standard deviations.
of 0.767 mg/dl but a standard deviation of 5.563 mg/dl, nearly twice that of the Beckman duplicates. Of the 210 Nova duplicates, 168 (80%) were within two standard deviations of the Beckman analyzer values (i.e., within $2 \times 2.79 = 5.58$ mg/dl).

Locally smoothed median absolute difference curves were created using a bandwidth of 15 mg/dl and X range from 57 to 218 mg/dl (Figure 5). A nearly flat curve was observed in the euglycemic range of 60–100 mg/dl. The curve was also flat in the range of 120–220 mg/dl at the higher level of 10 mg/dl.

**Discussion**

The glucose clamp methodology is the state-of-the-art technique to assess peripheral tissue sensitivity to insulin and beta-cell sensitivity to glucose in a controlled setting. Thus, the changes in these variables following various interventions can be assessed longitudinally because the stimulus remains unchanged. Many investigators across the world have used different variations of this technique to answer various questions about fuel homeostasis. Regardless of the study design, the clamp technique is unique in that it can assess glucose homeostasis in a precise and reproducible manner.

The collective effort required on the part of staff (nurses, technicians, and investigators), however, makes this technique a labor-intensive and expensive method for assessment of fuel homeostasis. One of the principal limitations is the requirement for timely, accurate, and precise measurement of PG levels to determine the 20% glucose infusion rates in a negative-feedback-controlled system.

The glucose clamp methodology creates unique demands for PG measurement—specifically, that the measurement device used be fast, accurate, and able to withstand repeated testing over the course of several hours. Accordingly, since Beckman Coulter has announced it will no longer support its glucose analyzer, the Nova StatStrip device was tested to see if it could fulfill these requirements as an effective replacement.
The Bland–Altman plot of the difference between Nova and Beckman readings for a given blood sample as compared to the reference Beckman readings did not show any upward or downward trend across a wide range of blood glucose values. No trend was observed in the same plot of the difference between Nova and YSI values. The Nova glucose meter, therefore, does not appear to bias readings in any direction across the range of PG levels measured. The vast majority of values were within two standard deviations of the mean difference of 1.3 mg/dl. However, with a standard deviation of the differences of nearly 12 mg/dl, this meant that some readings were rather widely discrepant. Values this far apart can, at times, make it difficult to run a successful clamp when targeting a tight range of PG values. Note that the data tend to cluster in two parts, representing, respectively, the euglycemic and hyperglycemic stages of the clamp study.

The locally smoothed median absolute difference curve clearly showed that, in both the euglycemic and the hyperglycemic glucose ranges, a relatively flat pattern was observed. However, in the hyperglycemic range, the differences are higher, and the glucose values must be carefully evaluated with respect to both the previous glucose level as well as the change in the 20% glucose infusion rate. If there is uncertainty, a third or even forth reading should be performed. Still, the rapid analysis of glucose determination has led the authors to believe that the performance of the instrument is acceptable and that the 5 mg/dl difference in duplicates can be achieved even during a hyperglycemic clamp.

The authors acknowledge that the accuracy of the Nova instrument is not as robust as the Beckman or YSI. However, the management of the glucose clamp, even with sophisticated software, requires familiarity with the “art” of the clamp. Therefore, it is suggested that unreasonable glucose values as determined by the Nova glucose meter can be identified easily with repeated glucose measurements. The previous PG level and the change in the 20% glucose infusion rate should always be considered as a guide for the reliability of the current value. It should be noted that discrepant values also occur with both the Beckman and the YSI, in which case a third reading is necessary.

The precision of duplicate values taken on the Nova glucose meter were compared to the Beckman analyzer and assessed (Figure 4). Though the mean differences between duplicates were similar for both devices, the standard deviation of difference for Nova duplicates was nearly twice that of Beckman duplicates. If the Nova is held to the Beckman standard by asking how many of the Nova duplicate differences fall within two standard deviations of the Beckman duplicate differences, only 168 of 210 (80%) of Nova duplicates are within those two standard deviations. This result reflects an occasional tendency of the Nova glucose meter to give readings that are not sufficiently accurate for the clamp study. For the Beckman instrument, manufacturer’s recommendation was followed that duplicates be within 3 mg/dl of each other. If they were not, a triplicate or, at times, even a quadruplicate was run. For the Nova device, the authors recommend that the duplicates must be within 5 mg/dl of each other and that a third or fourth measurement should be taken if necessary. From experience, even if a sample is run four times, an accurate value can be obtained in 30 seconds; duplicates are available within 15 seconds.

The Nova glucose meter has several key advantages not necessarily reflected in the data of this study that make it particularly suitable for the glucose clamp study. First of all, its real time of 6 seconds makes it ideal when the investigator needs to constantly vary the glucose infusion rate to maintain a stable euglycemia or hyperglycemia. Even if it becomes necessary to run a sample in triplicate on the Nova glucose meter, 20 seconds (three readings of 6 seconds each) is a far shorter time period than the time it takes for one sample to be measured with the Beckman or YSI devices. Moreover, unlike the Beckman, which usually takes at least 120–180 seconds to confirm a value, or the YSI, which takes at least 60 seconds longer than the Beckman (mechanical sampling arm versus manual pipetting, respectively), the Nova can confirm a value within 15 seconds (two readings of 6 seconds each). The Nova glucose meter is simple to use and does not require a dedicated technician. Supplies and maintenance for the
Nova analyzer are also far less intensive, and the Nova instrument is significantly less costly to purchase and operate.

This study has some limitations in evaluating the Nova glucose meter’s precision and accuracy in the hospital setting. The study group consists of obese patients without any major medical illnesses, such as anemia or acidosis. Therefore, the meter’s lack of interference with hematocrit and other variables claimed by the manufacturer could not be investigated by the design of our study. Furthermore, it was not possible to assess drug interference because the study population was not on any medications aside from oral vitamin supplements. The occasional use of Tylenol during the clamp studies was not observed to cause any changes in measured blood glucose values. Finally, though in critically ill patients, blood glucose measurements are usually performed with finger sticks, this study analyzed blood samples taken from intravenous lines. However, it should be noted that the instrument has been evaluated for hematocrit effect as well as analytical interference in a hospital setting.\textsuperscript{14,15}

In summary, results indicate that the Nova device is able to replicate blood glucose values obtained with the Beckman or YSI analyzers to a high degree of fidelity. Moreover, the Nova glucose meter is significantly easier to operate and is well suited to the glucose clamp study. The authors conclude that the Nova StatStrip glucose meter is an acceptable replacement for the Beckman or YSI glucose analyzers for real-time glucose determinations in glucose clamp testing. Moreover, the speed in which results can be obtained could counterbalance less precise agreement of duplicate readings.

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References:
Evaluation of the Impact of Hematocrit and Other Interference on the Accuracy of Hospital-Based Glucose Meters

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ABSTRACT

Background: Most glucose meter comparisons to date have focused on performance specifications likely to impact subcutaneous dosing of insulin. We evaluated four hospital-based glucose meter technologies for accuracy, precision, and analytical interferences likely to be encountered in critically ill patients, with the goal of identifying and discriminating glucose meter performance specifications likely to impact intensive intravenous insulin dosing.

Methods: Precision, both within-run and day-to-day, was evaluated on all four glucose meters. Accuracy (bias) of the meters and analytical interference were evaluated by comparing results obtained on whole blood specimens to plasma samples obtained from these whole blood specimens run on a hexokinase reference method.

Results: Precision was acceptable and differed little between meters. There were significant differences in the degree to which the meters correlated with the reference hexokinase method. Ascorbic acid showed significant interference with three of the four meters. Hematocrit also affected the correlation between whole blood and plasma hexokinase glucose on three of the four glucose meters tested, with the magnitude of this interference also varying by glucose meter technology.

Conclusions: Correlation to plasma hexokinase values and hematocrit interference are the main variables that differentiate glucose meters. Meters that correlate with plasma glucose measured by a reference method over a wide range of glucose concentrations and minimize the effects of hematocrit will allow better glycemic control for critically ill patients.

INTRODUCTION

Several recent studies have suggested that tight glucose control (maintenance of blood glucose between 80 and 110 mg/dL), accomplished via intensive intravenous insulin therapy, decreases mortality in critically ill patients.1,2 Use of handheld glucose meters allows for rapid treatment decisions for patients on intravenous insulin; however, target glucose concentrations are narrower for this patient population than for patients with diabetes using handheld meters to dose subcutaneous insulin. In addition, patients in the intensive care unit (ICU) are on multiple medications, and often have abnormal hematocrit and/or oxygen tension, all of which may affect the performance of handheld glucose meters.

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Oxygen tension and pH may affect a limited number of glucose meter technologies. Various medications used in the critical care setting and patient hematocrit have been found to affect the performance of almost all glucose meter technologies available. Multiple studies have found that glucose meters demonstrate a positive bias at low hematocrit and a negative bias at high hematocrit, regardless of the meter technology used. One new glucose meter technology with hematocrit measurement and correction was recently introduced to address hematocrit interference.

Besides analytical interference, the other major concern in monitoring tight glycemic control in the ICU is the accuracy of glucose measurement when tighter ranges of glucose control are desired. Since hexokinase glucose methods have been found to be suitable for use as reference methods for glucose determination, multiple studies have examined the correlation between glucose meter whole blood and plasma hexokinase glucose. The degree to which glucose meters correlate with plasma hexokinase measurement of glucose varies tremendously between glucose meter technologies, and correlation with laboratory hexokinase measurement in the hypoglycemic and hyperglycemic ranges is poor with most meters currently available. Thus there is still significant concern about the use of glucose meters for management of tight glycemic control in the ICU.

The aim of the current study was to compare four hospital-based glucose meter technologies for accuracy compared to a reference plasma hexokinase method, determine drug interferences, and measure the effect of hematocrit on the correlation between glucose meter and hexokinase glucose over a wide range of glucose concentrations.

RESEARCH DESIGN AND METHODS

**Instrumentation**

The reference assay was plasma glucose using the hexokinase method on the Roche Integra 400 Analyzer (Roche Diagnostics, Indianapolis, IN). This was chosen as the reference method because hexokinase methods have been found to be suitable for use as reference methods for glucose determination with close correlation to definitive methods that use mass spectrometry. Four glucose meter technologies were chosen as representing the major hospital-based technologies currently available: Accu-Chek® Inform® (Roche Diagnostics), which uses a glucose dehydrogenase-based amperometric strip; Precision PCx® (Abbott Diabetes, Alameda, CA), which uses glucose dehydrogenase amperometric detection; SureStepFlexx® (LifeScan, Milpitas, CA), which uses a photometric glucose oxidase detection system; and StatStrip® (Nova Biomedical, Waltham, MA), which uses a modified glucose oxidase-based amperometric test system with hematocrit correction.

**Precision studies**

**Within-run precision.** Venous heparinized whole blood was drawn 12–24 h in advance of performing the study. Aerated blood was divided into three 2-mL aliquots, which received different volumes of a concentrated glucose solution such that the aliquots had 20–60, 200–300, and 450–550 mg/dL glucose. Each aliquot was then tested 20 times on each meter.

**Day-to-day precision.** Two levels of control material manufactured by each glucose meter vendor were tested in duplicate, three times per day for 5 days (total of 30 readings for each control) on each meter. The controls used included: Nova Biomedical StatStrip glucose controls (lot 0413911081, range 48–78 mg/dL; lot 0414611083, range 247–317 mg/dL), J & J LifeScan SureStepFlexx controls (lot 6C1F64, range 35–59 mg/dL; lot 6C4F67, range 270–404 mg/dL), Abbott PCx controls (lot 17692, range 34–64 mg/dL; lot 17697, range 224–374 mg/dL); and Roche Accu-Chek controls (lot 60250, range 46–76 mg/dL; lot 60251, range 287–389 mg/dL).

**Patient specimens for method correlations**

Patient specimens were discarded heparinized (23.5 units/mL) arterial whole blood specimens obtained for blood gas analyses. These specimens were obtained within 90 min of collection in the ICU. Hematocrit (%) values for these specimens were calculated from hemoglobin values obtained from the ABL 725 blood gas analyzer (Radiometer, Westlake, OH). One hundred thirty-three whole blood
specimens (unspiked) were analyzed by the four handheld glucose analyzers (assembly- line set up) and immediately (within 5 min) spun down in order to obtain the plasma samples for analysis on the Roche Integra 400 Analyzer. Specimens from 52 additional patients were spiked with various volumes of glucose concentrate (20,000 mg/dL) and analyzed similarly to the unspiked specimens in an effort to extend the glucose range for method comparison purposes. The study design was approved by the Mayo Clinic Institutional Review Board.

Interference and hematocrit studies from donor blood samples

For the interference studies, freshly drawn, heparinized venous blood drawn from healthy donors was allowed to sit at room temperature for 12-24 h before concentrated solutions of glucose and/or interfering substances were added. The concentrated solutions of glucose and the interfering substances were gravimetrically prepared. These concentrates were prepared as follows: 20,000 mg/dL glucose in water, 1,000 mg/dL acetaminophen in water, 1,000 mg/dL ascorbic acid in water, 10,000 mg/dL D(+)-maltose monohydrate in water, 2,000 mmol/L lactate in water, 3,000 mmol/L beta-hydroxybutyrate in water, 12,000 IU/dL heparin in water, and 100 mg/dL epinephrine in water. Immediately prior to each interference study, aliquots of donor blood were spiked with glucose concentrate bringing them into predetermined ranges. This was followed by division of each of these aliquots into three volumes, two of which were then spiked with the interfering material. Concentrations of each interferant tested were chosen to reflect (at maximum concentration tested) five to 10 times the therapeutic drug level, similar to what has been described previously. Lactate and beta-hydroxybutyrate were tested at concentrations that would reflect extreme acidosis in critically ill patients. All samples were rocked for 10-20 min. Glucose concentration was then analyzed in each specimen with six strips from each of the four measuring technologies. After the testing on the strips was completed, the specimens were immediately centrifuged and sent for duplicate analysis on the Roche Integra 400 Analyzer.

For the studies using variable hematocrit levels, 30 mL of fresh whole blood from a single donor was allowed to sit at room temperature for 12-24 h before division into three aliquots of 5 mL per specimen. The three 5-mL aliquots were each brought to a different concentration of glucose using the concentrated glucose solution. Each of these three 5-mL aliquots were further divided into five aliquots of 1 mL. Centrifugation, using a Fisher Scientific (Pittsburgh, PA) Mini-Centrifuge, and plasma adjustments (taking some plasma from one tube and putting it into another) resulted in five aliquots with different hematocrit (%) levels for each concentration of glucose. All specimens were rocked for at least 10 min and then rapidly analyzed, within 10 min, on each of the glucose meters (assembly-line fashion) in replicates of six for each glucose meter and strip device. Hematocrit (%) values were obtained for each of the prepared specimens in this study using the Hemastat-STAT-II® microhematocrit centrifuge (Separation Technology, Altamonte Springs, FL). Specimens were centrifuged in order to remove a plasma sample for duplicate analysis on the Roche Integra 400 Analyzer.

Statistical analyses

For interference experiments, results are expressed as mean change from baseline glucose (meter glucose with interfering substance – meter glucose at baseline) in mg/dL for experiments where glucose concentration was adjusted to less than 100 mg/dL. Mean change from baseline glucose in percent [(meter glucose with interfering substance – meter glucose at baseline)/meter glucose at baseline x 100] was used when glucose was adjusted to >100 mg/dL (n = 6 all experiments). A clinically significant interference effect was defined as any concentration of interferant that changed the mean baseline (no interfering substance added) glucose value by more than 10 mg/dL (glucose <100 mg/dL) or 10% (glucose >100 mg/dL).

For experiments in which hematocrit was manipulated, the mean glucose difference (meter glucose – reference glucose, for glucose <100 mg/dL) or glucose percent difference [(meter glucose – reference glucose)/reference glucose x 100], for glucose >100 mg/dL was calculated for each meter technology. Statis-
TABLE 1. WITHIN-RUN AND DAY-TO-DAY PRECISION FOR GLUCOSE METERS, IN PERCENT CV

<table>
<thead>
<tr>
<th>Meter technology</th>
<th>Within-run (n = 20)</th>
<th>Day-to-day (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low glucose (39–55 mg/dL)</td>
<td>Medium glucose (180–250 mg/dL)</td>
</tr>
<tr>
<td>StatStrip</td>
<td>3.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Accu-Chek</td>
<td>3.9</td>
<td>2.4</td>
</tr>
<tr>
<td>PCx</td>
<td>3.2</td>
<td>1.7</td>
</tr>
<tr>
<td>SureStep</td>
<td>2.9</td>
<td>1.6</td>
</tr>
</tbody>
</table>

n = number of replicates tested.

The statistical significance of the effect of hematocrit was assessed using the two-sided unpaired t test, comparing mean glucose difference or mean glucose percent difference between the lowest and highest hematocrit levels used.

RESULTS

Precision

Within-run and day-to-day precision assessed at multiple glucose levels as described above resulted in coefficient of variation (CV) values of less than 5% for all meters tested with the exception of day-to-day precision at low glucose on the PCx meter, which was 5.1% (Table 1).

Correlation with reference method

Correlation between glucose meter results and the plasma hexokinase reference method was performed by analyzing 133 fresh lithium heparin arterial blood specimens and an additional 52 lithium heparin arterial blood specimens that were spiked with exogenous glucose for a total of 185 specimens. Mean reference glucose value was 168 mg/dL for the entire sample set (n = 185), and the range of glucose values covered was 39–754 mg/dL. Linear regression analysis demonstrated a slope of 0.90 and an intercept of <10 mg/dL glucose for the StatStrip and the Accu-Chek meters, while the PCx and SureStepFlexx meters had lower slopes and higher intercepts (Table 2). Median bias from the reference method (meter value minus reference value) was of lower absolute magnitude for the StatStrip and SureStepFlexx meters than for either the Accu-Chek or PCx meters (Table 2). There were also significantly more values within 10% of the reference method on the StatStrip (170 of 185) compared to the SureStepFlexx (134 of 185), Accu-Chek (127 of 185), or PCx (79 of 185) methods.

Exclusion of the 52 samples spiked with exogenous glucose resulted in slightly higher slopes and lower intercepts for all four meters (Table 2). Exclusion of the spiked samples also resulted in median bias that was of similar absolute magnitude for the Accu-Chek, PCx, and SureStepFlexx. Median bias on the StatStrip was smaller than median bias on the three other meter technologies whether

TABLE 2. CORRELATION DATA FOR GLUCOSE METERS VERSUS REFERENCE PLASMA HEXOKINASE METHOD (n = 185 or 133)

<table>
<thead>
<tr>
<th>Meter technology</th>
<th>Slope (n = 185)</th>
<th>Intercept (mg/dL) (n = 185)</th>
<th>r² (n = 185)</th>
<th>Median bias (mg/dL) (n = 185)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 185</td>
<td>n = 133</td>
<td>n = 185</td>
<td>n = 133</td>
</tr>
<tr>
<td>StatStrip</td>
<td>0.90</td>
<td>0.96</td>
<td>9.0</td>
<td>3.6</td>
</tr>
<tr>
<td>Accu-Chek</td>
<td>0.91</td>
<td>0.98</td>
<td>2.0</td>
<td>5.4</td>
</tr>
<tr>
<td>PCx</td>
<td>0.78</td>
<td>0.85</td>
<td>15.0</td>
<td>7.4</td>
</tr>
<tr>
<td>SureStep</td>
<td>0.83</td>
<td>0.91</td>
<td>23.0</td>
<td>15.0</td>
</tr>
</tbody>
</table>

The n = 185 data set includes 133 unaltered clinical specimens and 52 specimens spiked with exogenous glucose; then n = 133 data set includes only unaltered clinical specimens.
or not the 52 spiked samples were excluded from analysis.

Effect of hematocrit on glucose meter accuracy

Hematocrit effect was examined by manually adjusting the hematocrit of donor sodium heparin blood at glucose concentrations adjusted to 54, 247, and 483 mg/dL. At low glucose (54 mg/dL), mean glucose difference changed by more than 10 mg/dL between the lowest and highest hematocrit values tested on the PCx and SureStepFlexx meters. At higher (247 and 483 mg/dL) glucose concentrations, the Accu-Chek, PCx, and SureStepFlexx meters demonstrated greater than 10% change in the mean glucose percentage difference between the lowest and highest hematocrit values (Fig. 1). At low glucose changes in mean glucose difference were statistically significant for the PCx and SureStepFlexx ($P < 0.001$) between lowest and highest hematocrit tested. Changes in mean glucose percent difference between lowest and highest hematocrit tested were also statistically significant ($P < 0.001$) for the Accu-Chek, PCx, and SureStepFlexx technologies at higher glucose levels and marginally significant ($P = 0.0203$) at a glucose concentration of 483 mg/dL for the StatStrip (Fig. 1).

Effect of hematocrit on percentage bias in patient samples

To further investigate the effect of hematocrit on glucose meter accuracy, glucose meter percent bias versus hematocrit was plotted for the 133 patient specimen correlation data set described previously (Fig. 2). There is a clear trend for negative bias associated with increasing hematocrit for the PCx and SureStepFlexx meters (Fig. 2). Regression analysis on this data set resulted in slopes and intercepts (percent bias

![Figure 1](image1.png)

**FIG. 1.** (a) Mean glucose difference (meter glucose – reference glucose) and (b) and (c) mean glucose percent difference [(meter glucose – reference glucose)/reference glucose × 100] as a function of hematocrit at glucose concentrations of (a) 54 mg/dL, (b) 247 mg/dL, and (c) 483 mg/dL. Each point represents the mean ± standard deviation of the mean glucose difference or mean glucose percent difference ($n = 6$).
vs. hematocrit) that were significantly different from zero ($P < 0.0001$) for the PCx and SureStepFlexx meters. For the StatStrip and Accu-Chek meters, the slope of percent bias versus hematocrit was not significantly different from zero ($P > 0.05$). The calculated slopes, intercepts, and correlation coefficient ($r^2$) values for the regression of percent bias versus hematocrit are shown in Figure 2. Inclusion of the 52 specimens spiked with exogenous glucose did not change the slopes or intercepts for percent bias versus hematocrit but significantly decreased the correlation coefficient ($r^2$) for each (data not shown).

Effect of interfering substances on glucose meter accuracy

Acetaminophen (final sample concentrations of 0, 5, and 10 mg/dL) was added to donor sodium heparin blood with glucose concentrations that had been adjusted to 44, 145, 244, and 341 mg/dL, respectively. No concentration of acetaminophen changed the mean baseline (no acetaminophen added) glucose level by more than 10 mg/dL (for experiments performed at 44 mg/dL glucose) or 10% (for experiments performed at 145, 244, and 341 mg/dL, respectively) on any of the meters. Thus acetaminophen did not produce a clinically significant interference on any of the four meter technologies studied.

Lactate (final sample concentrations of 0, 10, and 20 mmol/L) was added to donor sodium heparin blood with glucose concentration adjusted to 29, 143, 255, and 357 mg/dL, respectively. Similar to acetaminophen, lactate (0–20 mmol/L) did not change mean baseline glucose by more than 10 mg/dL (at 29 mg/dL glu-
COMPARISON OF HOSPITAL GLUCOSE METERS

**FIG. 2.** Glucose percent bias ([meter glucose minus reference glucose]/reference glucose × 100] for the four strip methods are plotted against sample hematocrit values for the 133 patient sample set (no sample manipulation): (a) StatStrip, (b) Accu-Chek, (c) PCx, and (d) SureStep. Slope and intercept of the best-fit line for percent bias versus hematocrit and correlation coefficient are also shown.

cose) or 10% (at higher glucose) on any of the four meter technologies tested. Beta-hydroxybutyrate (final sample concentrations 0, 7.5, and 30 mmol/L) also did not significantly affect any of the four glucose meter technologies when added to donor blood adjusted to 32, 135, 227, and 371 mg/dL glucose.

Ascorbic acid (final sample concentrations of 0, 5, and 10 mg/dL) was added to donor sodium heparin blood with glucose concentration adjusted to 70, 141, 237, and 352 mg/dL, respectively. At low glucose (70 mg/dL), ascorbic acid produced a clinically significant (>10 mg/dL) interference with the Accu-Chek, PCx, and SureStepFlexx glucose meters (Fig. 3). At higher (141 and 237 mg/dL) glucose concentrations, ascorbic acid produced a clinically significant (>10%) interference on the Accu-Chek and PCx glucose meters (Fig. 3). None of the meter technologies was significantly affected by ascorbic acid at 352 mg/dL.

Maltose (final sample concentrations of 0, 100, and 200 mg/dL) was added to donor sodium heparin blood with glucose concentrations adjusted to 40, 109, 208, and 300 mg/dL, respectively. Maltose produced a clinically significant interference only on the Accu-Chek meter, with 200 mg/dL maltose producing threefold, twofold, 1.5-fold, and 1.4-fold increases in mean baseline (no maltose added) glucose at 40, 109, 208, and 300 mg/dL glucose respectively.
While epinephrine levels up to 1 μg/dL had little effect on any of the four glucose meters, the reference hexokinase procedure was affected significantly (>10 mg/dL at 32 mg/dL glucose and >10% at the 105 mg/dL glucose level) by epinephrine. Heparin at 20 units/mL had <10% effect on any of the technologies tested at a glucose level of 101 mg/dL.

**DISCUSSION**

Precision of glucose meters was acceptable and differed little between meter technologies (Table 1). The extent to which the glucose meters correlated with a plasma hexokinase reference method differed between meters, as has been observed previously. The StatStrip and Accu-Chek meter technologies demonstrated the closest correlation with hexokinase plasma glucose based on assessment of the slope and intercept calculated by linear regression, while the StatStrip and SureStepFlexx meters demonstrated the lowest absolute median bias (Table 2). Since the StatStrip, Accu-Chek, and SureStepFlexx use different measurement technologies, it appears that calibration of the strips by the individual manufacturers, rather than measurement technology, impacts the degree to which whole blood measurement cor-
relates with laboratory hexokinase methods. Our findings are consistent with one previous study of the PCx device, which found that the slope and intercept of whole blood capillary versus venous plasma (hexokinase) glucose were 0.85 and 12 mg/dL, nearly identical to the results obtained in our study using the nonspiked samples.

Correlation with the reference method was adversely impacted by inclusion of samples spiked with exogenous glucose for all meter technologies (Table 2). This may be due to the wider range of glucose concentrations covered by these experiments, but analytical artifacts or interferences created by the spiking procedure cannot be excluded. For this reason laboratory-based evaluation of meter devices should specify whether samples have been manipulated or spiked, and data summaries for both spiked and nonspiked data sets may be useful. Although laboratory-based experiments are powerful because of the range of glucose, hematocrit, and interfering substance concentrations that can be included, both laboratory and clinical evaluation of devices is necessary to get a complete picture of device performance.

The clinical significance of differences between whole blood and laboratory plasma glucose can be demonstrated by the number of samples within 10% or 15% of the reference method. Using Monte Carlo simulation Boyd and Bruns previously demonstrated that at 10% total error, 16–45% of sliding-scale insulin doses would be in error, though small dosing errors would predominate. Larger dosing errors were common when total error exceeded 10–15%. Significantly more samples on the StatStrip (170 of 185) fell within 10% of the reference method compared to the Accu-Chek (127 of 185), PCx (79 of 185), or SureStepFlexx (134 of 185). In addition, significantly fewer values on the StatStrip differed by more than 15% from the reference method (two of 185) compared to the Accu-Chek (26 of 185), PCx (58 of 185), or SureSteppFlexx (11 of 185) meters.

One recent study of the Accu-Chek meter in patients on intravenous insulin found that 74% of capillary whole blood samples fell within 10% of a reference plasma hexokinase assay, resulting in common small dosing errors. Our study demonstrated 127 of 185 (69%) samples on the Accu-Chek within 10% of the reference hexokinase method, consistent with the results obtained from capillary blood samples in patients undergoing intravenous insulin therapy. The improved performance of the StatStrip, as measured by correlation with a reference plasma hexokinase assay, should result in fewer insulin dosing errors for patients on both subcutaneous and intravenous insulin.

Hematocrit effect on glucose meter accuracy (correlation with hexokinase plasma values) was examined in two different experiments. Using sodium heparin blood pools that were manipulated to obtain hematocrit values between 25% and >60%, and glucose concentrations between 54 and 483 mg/dL, it is clear that the four meter technologies have differing sensitivity to hematocrit (Fig. 1). The hematocrit effect can also be observed in the experiment performed with fresh arterial whole blood specimens, where a significant trend between hematocrit and percent bias was observed for the PCx and SureStepFlexx meters (Fig. 2). Since hematocrit can vary widely in critically ill patients, glucose meter technologies that are insensitive to the effects of hematocrit should also improve accuracy and decrease insulin dosing errors in this population.

Finally, the effects of various medications commonly used in the critical care arena were tested for analytical interference on all the glucose methods, similar to experiments that have been published previously. Lactate and betahydroxybutyrate had no impact on glucose meter performance, similar to previous studies that showed no effect of sample pH on most glucose meters. Acetaminophen, at levels up to five to 10 times the therapeutic level, also did not significantly impact the glucose meters. This differs from one previous report on acetaminophen effects, though that study used higher concentrations of acetaminophen and was performed on a previous generation of glucose meters.

Ascorbic acid has been reported to interfere with all glucose meter technologies that have been tested. We found that ascorbic acid interfered with each of the glucose meters tested with the exception of the StatStrip (Fig. 3). Maltose interference has been reported with glucose dehydrogenase technologies and was
found to be significant for the Accu-Chek meter that uses this technology.

In conclusion, we evaluated glucose meter correlation with a reference hexokinase method and analytical interferences likely to be observed in critical care patients on four currently available hospital glucose meter technologies. Correlation of whole blood glucose to plasma hexokinase reference methods continues to vary between glucose meter manufacturers. Hematocrit had a significant impact on the correlation between whole blood and plasma glucose on most of the meters. The StatStrip glucose meter correlated best with a plasma hexokinase reference method over a wide range of glucose concentrations and was least significantly impacted by sample hematocrit and other interfering substances. This should allow for better management of critically ill patients on tight glycemic control protocols.

ACKNOWLEDGMENTS

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REFERENCES


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Abstract

Background

Recent studies have found that drawing samples from indwelling venous catheters (IVC) for point-of-care (POC) glucose testing in critically ill patients may result in unacceptable levels of positive bias and imprecision. Studies that have examined IVC POC glucose measurement in non-critically ill patient populations have had mixed results. It is unclear whether positive bias and increased imprecision from IVC sampling is due to exogenous glucose contamination of IVC blood, inherent bias and imprecision of devices used, or properties of IVC blood that interfere with POC glucose meter analysis.

Method

To determine how whole blood POC and laboratory plasma glucose measurement from IVC samples differs from the same measurements drawn by venipuncture, we compared glucose results from IVC samples to those obtained nearly simultaneously by venipuncture in 18 non-critically ill hospitalized patients. Each patient had a venipuncture performed for analysis of whole blood POC glucose on the Roche Accu-Chek Inform and analysis of plasma glucose, as the reference value, on the Roche Cobas Integra 400 Plus (Roche Diagnostics, Indianapolis IN). These results were compared to whole blood POC and laboratory plasma glucose analyzed from the same IVC sample, after a 10 mL flush and 5 mL discard volume according to institutional procedure.

Results

The mean (± standard deviation) bias between IVC glucose meter and venous plasma (reference) glucose was 9 ± 17 mg/dL, while the mean bias between venous meter and venous plasma (reference) was –1 ± 9 mg/dL. The close agreement between venous meter and venous plasma (reference) glucose indicates that inherent bias and imprecision of the meter is not responsible for bias and imprecision observed during IVC meter analysis. The mean bias between IVC plasma and venous plasma (reference) was 1 ± 6 mg/dL. The close agreement between IVC plasma and venous plasma (reference) glucose indicates that the positive bias and imprecision of IVC samples is not due to contamination of IVC blood with exogenous glucose, as the same sample was used for IVC meter and IVC plasma glucose analysis. 1 of 18 IVC glucose meter values was more than 20% higher than the venous plasma reference value, while all 18 venous meter and IVC plasma results were within 15% of the venous plasma reference value.

Conclusions

The positive bias and greater imprecision of glucose meter results, when sampled from an IVC, is not limited to critically ill patients. The cause of this bias and imprecision does not appear to be related to contamination of IVC samples with exogenous glucose, but rather properties of IVC blood samples that are not optimal for glucose meter analysis. Care should be taken when interpreting glucose meter values obtained from IVC samples.
**Introduction**

Multiple studies have found positive bias and frequent outliers when indwelling venous catheter (IVC) whole blood is used to monitor glucose concentration in critically ill patients.

- Little data exists for stable hospitalized patients.
- The cause of inaccurate glucose meter results on blood obtained from an IVC is not known.
- We designed the study to determine:
  - Whether IVC glucose meter results are accurate in stable hospitalized patients
  - Whether bias and imprecision in IVC whole blood glucose analysis is due to:
    1) Exogenous glucose contamination of IVC blood
    2) Inherent bias/imprecision of the glucose meters
    3) Properties of IVC whole blood that interfere with glucose meter measurement

**Methods**

- 50 total patients were enrolled in the study. The first 18 patients were presented in the abstract. The remaining 32 patients were enrolled following the submission of the abstract.
  - Patients were consented to venipuncture or glucose meter and reference plasma glucose testing.
  - The IVC was accessed for glucose meter and IVC plasma glucose testing.
- A subset of 27 patients had glucose meter measurements performed by two technologies.
  - Accu-Chek Inform (Roche Diagnostics, Indianapolis IN)
  - StatStrip® (Nova Biomedical, Waltham MA)
- The data is presented as median bias (inter-quartile range) between IVC whole blood and reference plasma (venipuncture) glucose.
- Outliers defined as either >10% or >20 mg/dL difference between IVC whole blood and the reference plasma (venipuncture) glucose.

**Results**

**Table 1**

<table>
<thead>
<tr>
<th>Specimen type</th>
<th>Accu-Chek Inform</th>
<th>Stat Strip®</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 10%</td>
<td>&gt; 20 mg/dL</td>
</tr>
<tr>
<td>IVC meter</td>
<td>15/50</td>
<td>9/50</td>
</tr>
<tr>
<td>(30%)</td>
<td>(18%)</td>
<td></td>
</tr>
<tr>
<td>Venous meter</td>
<td>9/50</td>
<td>5/50</td>
</tr>
<tr>
<td>(18%)</td>
<td>(10%)</td>
<td></td>
</tr>
<tr>
<td>All 50 patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27 patients measured on both meters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVC meter</td>
<td>11/27</td>
<td>8/27</td>
</tr>
<tr>
<td>(41%)</td>
<td>(30%)</td>
<td></td>
</tr>
<tr>
<td>(19%)</td>
<td>(15%)</td>
<td></td>
</tr>
</tbody>
</table>
Results Cont’d

Accuracy in stable hospitalized patients

- There were 15 of 50 (30%) Inform IVC whole blood samples and 9 of 50 (18%) Inform venous whole blood samples that differed by more than 10% from the reference glucose value; this indicates a decrease in meter accuracy when using IVC blood for glucose meter testing.

- The rate of outliers (>10% or >20 mg/dL compared to reference plasma glucose) with IVC blood was approximately two-fold greater than observed for venous whole blood for both meter technologies.

Exogenous glucose contamination

- Of 15 Inform IVC whole blood samples with > 10% difference from reference plasma glucose:
  Only 3 corresponding IVC plasma glucose values also differed by > 10% from reference plasma glucose; demonstrating that contamination of the IVC with exogenous glucose accounted for a small number (3 of 15) of IVC Inform outliers.

- Of 9 Inform IVC whole blood samples with > 20 mg/dL difference from reference plasma glucose:
  Only 2 of 9 corresponding IVC plasma glucose values differed by > 20 mg/dL from reference plasma glucose; again demonstrating that contamination of IVC blood with exogenous glucose accounts for only a small number of outliers obtained by IVC whole blood glucose analysis on the Inform.

Figure 1

- Median (inter-quartile range) bias between Inform IVC and venous (reference) plasma glucose was 7.5 (-0.75 to 18) mg/dL.
- 15 of 50 (30%) Inform IVC values differed by > 10% from venous (reference) plasma glucose.
- 9 of 50 (18%) of Inform IVC values differed by > 20 mg/dL from venous (reference) plasma glucose.

- In samples drawn by venipuncture and tested on the Inform meter:
  - Median (inter-quartile range) bias was 5 (-1 to 8.75)mg/dL.
  - Only 9 of 50 (18%) differed by > 10% from reference glucose.
  - Only 5 of 50 (10%) differed by > 20 mg/dL from reference glucose.

- Properties of IVC whole blood result in unique interferences on the Inform meter.
In 27 patients with analysis by both Inform and StatStrip® meters:

- Median (inter-quartile range) bias between IVC whole blood and reference glucose was 10 (1 to 26) mg/dL on the Inform vs. 3 (-1.5 to 10) mg/dL on the StatStrip® (p=0.04).

- 11 of 27 (41%) of Inform IVC vs. 5 of 27 (19%) StatStrip® IVC values differed by > 10% from venous (reference) plasma glucose.

- 8 of 27 (30%) of Inform IVC vs. 4 of 27 (15%) StatStrip® IVC values differed by > 20 mg/dL from venous (reference) plasma glucose.

- The data demonstrates that bias and interference with IVC whole blood is technology-dependent.

**Conclusions**

- Positive bias and outliers with IVC whole blood glucose analysis is not limited to critically ill patients.

- Exogenous glucose contamination does occur, but is not the predominant cause of positive bias and outliers in IVC whole blood glucose analysis.

- Significant differences exist between glucose meter technologies in accuracy of IVC whole blood glucose analysis.

- Properties of IVC whole blood can cause interference with some glucose meters; device selection is critical if IVC whole blood will be used to monitor glucose in hospitalized patients.
Comparison of Four Hospital Based Glucose Meter Technologies
Accuracy, Precision, and Interference Encountered
in Critically Ill Patients

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ABSTRACT
We evaluated four hospital-based glucose meter technologies for accuracy, precision, and analytical interferences likely to be encountered in critically ill patients. Precision of all four glucose meters, both within run and day-to-day, instruments. Accuracy (bias) of the meters and analytical interference were evaluated by comparing results obtained on whole blood specimens to plasma samples obtained from these whole blood specimens run on a hexokinase reference method.

There were significant differences in the degree to which the meters correlated with a reference hexokinase method. Ascorbic acid showed significant interference with 3 of the 4 meters. Hematocrit also affected the correlation between whole blood and plasma hexokinase glucose on 3 of the 4 glucose meters tested, with the magnitude of this interference also varied by glucose meter technology. The use of glucose meters to maintain tight glycemic control in critically ill patients may be impacted by the accuracy and hematocrit dependence of some glucose meter technologies.

GLUCOSE METHODS USED

- **Accu-Chek Inform®** (Roche Diagnostics, Indianapolis, IN)
  - Glucose dehydrogenase based amperometric strip
- **Precision PCx®** (Abbott Diabetes, Alameda, CA)
  - Glucose oxidase amperometric detection
- **SureStepFlexx®** (LifeScan, Malpitas, CA)
  - Photometric glucose oxidase detection
- **StatStrip®** (Nova Biomedical, Waltham, MA)
  - Modified glucose oxidase based amperometric test system
- **Roche Integra 400 Analyzer** (Roche Diagnostics, Indianapolis, IN)
  - Hexokinase method

TABLE 1

<table>
<thead>
<tr>
<th>Meter Technology</th>
<th>Low Glucose (mg/dL)</th>
<th>Medium Glucose (mg/dL)</th>
<th>High Glucose (mg/dL)</th>
<th>Low CV (%)</th>
<th>Medium CV (%)</th>
<th>High CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>StatStrip®</td>
<td>3.3</td>
<td>1.9</td>
<td>1.4</td>
<td>2.1</td>
<td>2.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Accu-Chek®</td>
<td>2.4</td>
<td>2.2</td>
<td>4.6</td>
<td>2.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCx</td>
<td>3.2</td>
<td>1.7</td>
<td>1.5</td>
<td>5.1</td>
<td>4.0</td>
<td>2.2</td>
</tr>
<tr>
<td>SureStep</td>
<td>2.9</td>
<td>1.6</td>
<td>1.9</td>
<td>2.9</td>
<td>2.2</td>
<td></td>
</tr>
</tbody>
</table>

- The coefficient of variation (CV) obtained from both within-run and day-to-day precision experiments was less than 5% for all meters tested except day-to-day precision at low glucose on PCx which was 5.1%

TABLE 2

<table>
<thead>
<tr>
<th>Meter Technology</th>
<th>Slope</th>
<th>Intercept (mg/dL)</th>
<th>r²</th>
<th>Median bias (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>StatStrip®</td>
<td>0.90</td>
<td>0.96</td>
<td>0.99</td>
<td>-3</td>
</tr>
<tr>
<td>Accu-Chek®</td>
<td>0.90</td>
<td>0.98</td>
<td>0.99</td>
<td>-9</td>
</tr>
<tr>
<td>PCx</td>
<td>0.78</td>
<td>0.86</td>
<td>0.97</td>
<td>-12</td>
</tr>
<tr>
<td>SureStep</td>
<td>0.83</td>
<td>0.91</td>
<td>0.98</td>
<td>2</td>
</tr>
</tbody>
</table>

n=133 data set, whole blood samples
n=185 data set, 133 whole blood samples and 52 spiked whole blood samples

- StatStrip and Accu-Chek meters correlate better with the reference hexokinase method, as measured by slope and intercept
- Median bias was lower for the StatStrip and SureStep meters

STUDY DESIGN

Method correlation was performed by analyzing 133 whole blood specimens and 52 spiked whole blood patient specimens on the 4 glucose meters, compared to plasma obtained from those specimens and run on the Integra (reference method).

Percent bias (meter result minus plasma result/plasma result) plotted as a function of hematocrit for the 133 whole blood specimens.

Interference studies were performed using ascorbic acid added to whole blood at 4 different glucose levels. Six strips tested on each meter at each concentration of interferant, mean used for data analysis. Clinically significant interference defined as > 10 mg/dL for glucose concentration < 100 mg/dL or > 10% (for glucose concentration > 100 mg/dL) change from baseline.

Hematocrit interference was tested using 3 glucose concentrations over a 25-60% hematocrit range, using six strips for each meter at each hematocrit range tested. Clinically significant effect of hematocrit defined as > 10 mg/dL (for glucose concentrations < 100 mg/dL) or > 10% (for glucose concentrations > 100 mg/dL) change between lowest and highest hematocrit tested.
Comparison of Four Hospital Based Glucose Meter Technologies
Accuracy, Precision, and Interference Encountered in Critically Ill Patients
Renee Scott, Brad S. Karon, Laurie Griesmann, Sandra C. Bryant, Jeffrey A. DuBois, Terry L. Shirey, Steven Presti, and Paula J. Santrach
Mayo Clinic, Rochester MN 55905, Nova Biomedical, Waltham, MA 02454

FIGURE 1

At low glucose (70 m/gdL), ascorbic acid produced a clinically significant (>10 mg/dL) interference with the Accu-Chek, PCx, and the SureStep meters. At higher (141 and 237 mg/dL) glucose, the Accu-Chek and PCx meters were significantly affected (>10% effect). None of the meters were significantly affected by ascorbic acid at 352 mg/dL.
Comparison of Four Hospital Based Glucose Meter Technologies
Accuracy, Precision, and Interference Encountered in Critically Ill Patients
Renee Scott, Brad S. Karon, Laurie Griesmann, Sandra C. Bryant, Jeffrey A. DuBois, Terry L. Shirey, Steven Presti, and Paula J. Santrach
Mayo Clinic, Rochester MN 55905, Nova Biomedical, Waltham, MA 02454

**FIGURE 2**

At low glucose (54 mg/dl), mean glucose difference changed more than 10 mg/dl between the lowest and the highest hematocrit values tested on the PCx and SureStep meters. At higher glucose levels (247 and 483 mg/dl), the Accu-Chek, PCx, and the SureStep meters had greater than 10% change in mean percent glucose.
Comparison of Four Hospital Based Glucose Meter Technologies
Accuracy, Precision, and Interference Encountered
in Critically Ill Patients
Renee Scott, Brad S. Karon, Laurie Griesmann, Sandra C. Bryant, Jeffrey A. DuBois,
Terry L. Shirey, Steven Presti, and Paula J. Santrach
Mayo Clinic, Rochester MN 55905, Nova Biomedical, Waltham, MA 02454

Mayo Clinic, Rochester, MN (Cont’d)

Glucose meter percent bias was plotted against hematocrit values for the 133 patient sample set (no sample manipulation). There is a clear trend for negative bias associated with increasing hematocrit for the PCx and SureStep meters. The Accu-Chek and StatStrip® were largely unaffected by hematocrit.
CONCLUSION

- Glucose meters vary in the degree of correlation to the hexokinase reference glucose methods.

- Most glucose meters continue to be affected by analytical interferences, especially hematocrit.

- The new StatStrip® glucose meter technology correlated closely with a reference hexokinase glucose method and did not demonstrate clinically significant interference from any of the substances tested.
Evaluation of the Nova StatStrip® Blood Glucose Monitoring System in Neonates

Dennis J. Dietzen1,2 and Tim R. Wilhite3

Departments of 1Pediatrics, 2Pathology and Immunology: Washington University School of Medicine, St. Louis, MO. 3St. Louis Children’s Hospital, St. Louis, MO

ABSTRACT

Hypoglycemia is a common emergency in neonates. Measurement of whole blood glucose in neonates presents challenges associated with limited blood volumes, high hematocrits, and accuracy at low glucose concentrations. The Nova Biomedical StatStrip® Glucose Monitoring System quantifies glucose in 1.2 microliters of whole blood employing a modified glucose oxidase, amperometric detection, and correction for hematocrit and other interferents. We compared the analytic performance of the StatStrip® in split-samples from 100 neonates (50% male, <26 days of age, median = 3 days) to whole blood measurement using the LifeScan SureStep® Pro and plasma measurement on the Ortho Diagnostics Vitros® 250 Chemistry System. Heparinized whole blood samples were obtained from well baby and special care nurseries of Barnes-Jewish Hospital and the neonatal intensive care unit of St. Louis Children’s Hospital. Aliquots were removed for determination of hemoglobin (HemoCue®) and whole blood glucose followed by separation of plasma within 10 minutes to prevent subsequent artifacts from glycolysis. Over the six week span of the study, the imprecision of the StatStrip® system across two meters and two strip lots was 3.6%, 4.6%, and 4.0% (CV, n = 19) at concentrations of 68, 118, and 300 mg/dL, respectively. Over the same time span, the imprecision of the SureStep (single strip lot and monitor) was 2.5% and 2.6% (CV) at 45 and 319 mg/dL, respectively. The imprecision of the Vitros (single slide lot) was less than 1.2% (CV) at both 96 and 280 mg/dL. In the 100 specimens studied, plasma glucose concentrations ranged from 25 to 118, and 300 mg/dL, respectively. Linear regression analysis of the StatStrip® vs. Vitros yielded the following: StatStrip® glucose = 0.985 x Vitros glucose – 3.25, Syx = 4.85, r = 0.995. Absolute bias between the StatStrip® and Vitros ranged from -23 to 11 mg/dL (mean = -8%). Regression analysis of the SureStep data yielded the following: SureStep glucose = 1.04 x Vitros glucose – 6.18, Syx = 3.26, r = 0.998. Absolute bias between the SureStep and Vitros ranged from -11 to 21 mg/dL (mean = -6%). Both the StatStrip® and SureStep met the ISO 15197 criteria as 100% of the meter results below 75 mg/dL were within 15 mg/dL of the Vitros result and 100% of the meter results greater than or equal to 75 mg/dL agreed to within 20% of the Vitros result. Bias between the StatStrip® system and the Vitros did not vary with hemoglobin (r = 0.081, P = 0.423). Likewise, bias between the SureStep and Vitros did not vary significantly with hemoglobin (r = 0.146, P = 0.147). Leroux (neonatal) error grid analysis (Laboratory Medicine 1994;25:592-595) of the results showed that 98% of the StatStrip® results were in Zone A (clinically correct) and 2% in Zone B (benign or no treatment error). We conclude that the StatStrip® Glucose Monitoring System is an accurate and precise alternative for near-patient glucose testing in neonatal settings.

INTRODUCTION

Hypoglycemia occurs in both premature and full term neonates and can precipitate acute metabolic decompensation and long-term neurologic complications if not detected promptly and treated effectively. Point of care glucose meters are often used to screen neonates for hypoglycemia and so must correlate well with central laboratory glucose measurements in plasma. The measurement of glucose in whole blood from neonates presents unique challenges, however. In addition to limited availability of blood, glucose concentrations are typically lower and the range of hematocrits is broader than in adult blood. The current study was designed to assess the performance of the Nova StatStrip® Blood Glucose Monitoring System in neonates. The StatStrip® quantifies glucose in 1.2 µL of whole blood using a modified glucose oxidase and amperometric detection with internal correction for hematocrit and other interferents. Performance of the StatStrip® was compared to central laboratory analysis (Vitros 250) and another commercial point of care blood glucose monitoring system (LifeScan SureStep® Pro).

MATERIALS AND METHODS

The study was performed over a six week period using samples obtained from the well-baby and special care nurseries of Barnes-Jewish Hospital and the neonatal intensive care unit (NICU) of St. Louis Children’s Hospital. The protocol was approved by the Washington University Human Subjects Committee and the Joint Practice Committee of St. Louis Children’s Hospital. Samples were obtained by heelstick (nurseries) or from indwelling catheters (nurseries and NICU) for medically indicated testing. A small volume (~30 µL) of whole blood was removed from the sample for hematocrit determination (HemoCue) and point of care glucose measurement. The remainder of the specimen was processed within 10 minutes for subsequent plasma analyses to prevent artifacts from glycolysis. Glucose analysis was performed using two StatStrip® meters and two strip lots. All instruments were calibrated and maintained according to manufacturer specifications. A single SureStep meter and strip lot was employed and a single Vitros instrument and slide lot were used during the course of the study. A single laboratory technologist performed all analyses. 97 samples from newborns less than 26 days of age were obtained and analyzed. The median age of the patients was three days. 49 samples were obtained from females, 48 were from males, and three pools of neonatal whole blood were supplemented with glucose to achieve glucose concentrations > 200 mg/dL. Eight samples were obtained from the NICU, two from general wards of St. Louis Children’s Hospital, and the remainder were from nurseries. Mean glucose concentration was 76 mg/dL (range = 25-411 mg/dL). Hemoglobin concentrations ranged from 10-22 g/dL (mean = 17) corresponding to a hematocrit range of 30-67%.
Table 1. Imprecision of Glucose Analyses
1. StatStrip® imprecision performed on two meters and two lots of test strips.
2. SureStep imprecision performed on single meter and single lot of test strips.

<table>
<thead>
<tr>
<th></th>
<th>Mean (mg/dL)</th>
<th>SD (mg/dL)</th>
<th>CV (%)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>StatStrip® (1)</td>
<td>68</td>
<td>2.5</td>
<td>3.6</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>118</td>
<td>5.4</td>
<td>4.6</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>300</td>
<td>12.0</td>
<td>4.0</td>
<td>19</td>
</tr>
<tr>
<td>SureStep (2)</td>
<td>45</td>
<td>1.1</td>
<td>2.5</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>319</td>
<td>8.3</td>
<td>2.6</td>
<td>19</td>
</tr>
<tr>
<td>Vitros</td>
<td>96</td>
<td>0.85</td>
<td>0.9</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>280</td>
<td>3.3</td>
<td>1.2</td>
<td>42</td>
</tr>
</tbody>
</table>

Figure 1: Regression analysis of StatStrip® vs. Vitros (left) and SureStep (right) glucose results. Glucose data was analyzed by least-squares analysis. Relevant statistics are cited within each plot. No differences between StatStrip® meter and strip lots were noted. ○ = StatStrip® meter/strip lot 1. ● = StatStrip® meter/strip lot 2.

Figure 2: Bland-Altman analysis of StatStrip® vs. Vitros (left) and SureStep (right) glucose results. Glucose results from the StatStrip®, SureStep, and Vitros were subjected to Bland-Altman Analysis. Difference plots are displayed above. Absolute bias of the StatStrip® against the Vitros (left) ranged from -15 mg/dL to 5 mg/dL at concentrations less than 110 mg/dL and did not display significant concentration dependence. Over the same concentration range, bias of the StatStrip® against the SureStep (right) ranged from -10 to 10 mg/dL.

Figure 3: StatStrip® Bias vs. Sample Hematocrit. The difference in glucose concentration between the StatStrip and Vitros was plotted vs. sample hematocrit. No significant correlation of this bias with hematocrit was observed.

Figure 4: Leroux Error Grid Analysis of StatStrip® Results. StatStrip® glucose results were compared to plasma results by means of the Leroux neonatal error grid (Lab Med 1994;25:592-595). Meter values in Zone A are clinically concordant with the central laboratory. Values in Zone B would lead to no treatment error. Values in Zone C may result in treatment opposite that called for. Meter values in Zone D may result in a failure to detect hypoglycemia and those in Zone E would likely lead to inappropriate therapy. 98% of StatStrip® results were in Zone A and 2% in Zone B.
SUMMARY AND CONCLUSIONS

1. Imprecision of the Nova StatStrip® was less than 5% (CV) across glucose concentrations from 68-300 mg/dL.

2. The Nova StatStrip® correlated well with plasma glucose and a second whole blood glucose analyzer across a wide concentration range (20-400 mg/dL) in neonatal blood specimens.

3. Sample hematocrit did not impact the relationship between the StatStrip® and plasma glucose concentration obtained using the Vitros 250 across a range of hematocrits from 30% to 70%.

4. StatStrip® glucose results were clinically concordant with plasma glucose values as shown by Leroux Error Grid Analysis.

5. The Nova StatStrip® is an accurate and precise alternative for measuring blood glucose in a neonatal setting.
Development and Use of a Methodology for the Evaluation and Implementation of POCT Devices

Sheila Cruthis, MT(ASCP)

Background

As point of care glucose testing technology has progressed, the need for regimented, controlled evaluation of POCT devices has increased. In 2008, Moses Cone Health System undertook an initiative to upgrade its glucose testing devices through clinical lab testing, user feedback, and advice from an outside consulting firm (Ernst & Young).

Objectives

• Capture blood glucose testing events for improved billing
• Interface glucose meters for communication to the LIS
• Improve glucose testing Accuracy for NICU and Point of Care
• Add Manual Test Entry capability for entering manual tests into the LIS
• Attain Faster Turnaround Times for Results
• Capture tight glycemic control reports for the prevention of CMS "Never" events

Materials and Methods

This study compared four hospital glucose monitoring systems for accuracy, interferences, cost, other test entry, wireless connectivity, and the ability to enter critical value comments. Accuracy testing was carried out versus a Beckman LXi lab analyzer (Beckman Coulter Diagnostics, Fullerton, CA). The four glucose meters compared were Nova StatStrip® (Nova Biomedical, Waltham, MA), Roche AccuChek Inform (Roche Diagnostics), Abbott Precision PCx (Abbott Diabetes, Alameda, CA), and LifeScan SureStepFlexx (LifeScan, Milpitas, CA).

For the lab bench studies, heparinized whole blood was obtained from 33 patient samples and immediately tested concurrently on the four glucose meters. Samples were spun down within 5-8 minutes of testing on the POC instruments. Testing on the LXi occurred within 15-20 minutes of testing on POC instruments.

We formed a committee consisting of all the people that touched the process of bedside glucoses. Our committee had representation from the following areas:
Point of Care Testing, Laboratory Information Systems, Management Systems -- both software and hardware areas, Staff Education, Laboratory Site Director, Pharmacy, Diabetes Treatment, Floor Nurses from each of our 5 campuses, Vice President, Nursery Department Head, Finance
Materials and Methods (Cont’d)

The committee developed a decision matrix and submitted it to 4 major vendors. After the vendors submitted their answers for the decision matrix, the committee eliminated all criteria that were the same for all vendors.

1. Vendors were invited on-site with their prospective connectivity vendors for a presentation to the committee.
2. The committee determined the top 6 criteria for meter selection -- accuracy, interferences, cost, other test entry, wireless connectivity, and critical value notes.
3. Laboratory accuracy and precision studies were performed using all 4 meters. To eliminate as many variables as possible, Point of Care staff performed the evaluations. We also did not want to present a meter to the nursing staff for trial or pilot study that would be eliminated based on other criteria.
4. Following the lab studies, the committee ranked the meters within the final decision matrix. The top two meters were selected for site visits.
5. The Nova StatStrip® was selected as the meter of choice based on accuracy, other test entry and charge capture ability.

Results

Moses Cone POC Glucose Testing System Decision Matrix

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Vendors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LifeScan / Telcor</td>
</tr>
<tr>
<td>Accuracy</td>
<td>3</td>
</tr>
<tr>
<td>Interferences</td>
<td>2</td>
</tr>
<tr>
<td>Cost</td>
<td>1</td>
</tr>
<tr>
<td>OTE(Other Test Entry)</td>
<td>3</td>
</tr>
<tr>
<td>Wireless</td>
<td>3</td>
</tr>
<tr>
<td>Critical Values Notes</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total Score</strong></td>
<td><strong>15</strong></td>
</tr>
</tbody>
</table>

From the committee meeting, glucose testing systems were ranked 1-4 with 1 being the first choice, etc. Cost aspects of the systems were ranked in reverse order with 1 being the least costly.

Regression Plots from Lab Bench Studies
Comparison between the reference method Beckman LXi and each glucose meter

- **NOVA**
  
  \[ y = 1.0171x - 0.5695 \]
  
  \[ R^2 = 0.9904 \]

- **Roche AccuChek Inform**
  
  \[ y = 1.0046x + 3.3978 \]
  
  \[ R^2 = 0.9887 \]
Results (Cont’d)

Regression Plots from Lab Bench Studies
Comparison between the reference method Beckman LXI and each glucose meter

Life Scan One Touch (current meter)


text

Abbott PCX


text

Bland-Altman difference plots for each meter vs. the Beckman LXI for variation in glucose level

Nova


Roche


LifeScan


Abbott


Wireless capability: True wireless connectivity is not currently available on any FDA-cleared meter. LifeScan has a wireless method with the serial/wireless server carried in the tote and a wire connecting the meter to the serial server. Telcor also offers wireless connectivity using a cable.

Manual Test Entry is available with all vendors. However, LifeScan and Telcor offer manual test entry through a web-based program located on a PC. Nursing representation on the committee stated that nursing staff would prefer not to introduce yet another computer program into their processes. Nova and Roche both offer Manual Test Entry on the meter.

Critical Test Value Comments Entry: With connectivity, documentation of actions taken on critical values becomes a quality issue. Nova had the only meter that allows the operator time to document actions on critical values. The other meter configurations will time-out and not allow the operator to return to the results for documentation. This timeout has been an issue for the last 7 years with LifeScan.
Conclusions

Goals met through selection of the Nova StatStrip:
- More revenue through the ability to bill at a higher rate (CPT 82947)
- Better able to concurrently monitor repeats and accuracy issues. No longer have overdose and under-dose values.
- More confidence with NICU samples due to the lack of interference from hematocrit
- Improved productivity through faster results

Additional goals met post-implementation:
- All glucose meters now interfaced to the LIS. Results flow through the LIS to the HIS interfaces and onto patient charts.
- Other Test Entry or Manual Test entry: We have pregnancy tests on the glucose meter and results flow through the glucose interface to the LIS. This has resulted in increased productivity and satisfaction for our nursing units. Nursing staff are looking forward to implementation of other manual tests on the meters.
- More robust connectivity with all glucose meters. Using a variety of connectivity solutions -- direct connect to the intranet through a data port and connectivity through a TrendNet device which connects to a pc that is on the network.
- Ability to generate Glycemic Control Reports.
- More efficient way of generating monthly data reports for glucose data. We can now have more pertinent data -- patient ID Error monitoring.
- Moved to mandatory Scan Only for inpatient units. Decreased patient ID errors by 50 - 60%.

Goals still to be accomplished:
- Addition of more manual test entry modules: Fern Testing, AmnioSwabs, Bilicheks, Urine Specific Gravity, Occult Blood. We have not been able to capture volumes or charges for the Fern, AmnioSwab or Bilicheks.
- Pilot a nursing unit with wireless connectivity. Cost benefit analysis of wireless connectivity.
- Addition of customized Tight Glycemic Control reports.
RGH’s Method for Evaluation and Implementation of Data-managed Bedside Glucose (POCTG) Monitoring

G. Smith¹, E. McNeil-Szostak¹, G. Ocrah¹, S. Rowland¹, R. Vargas¹

¹Rochester General Hospital System, Department of Pathology and Laboratory Medicine, Rochester, NY

Objective

Evaluate four data-managed glucose meters for use within Rochester General Hospital. The increasing demand for blood glucose monitoring at the bedside with connectivity was defined as a major process improvement objective for our medical center. Additional objectives included:

• Elimination of glucose errors and potential errors due to Maltose and ascorbic acid interference
• The ability to track manual test results (Visual UA, Urine Preg, Hemoccult, and Rapid Strep) electronically both on the meter and in the data management system
• Connection of RapidPoint 405 instruments into the data management system to track results electronically.

Methods

Four data-managed glucose meters were evaluated by the Point of Care team. The meters included: StatStrip®, Nova Biomedical Corporation, Waltham, MA; Accu-Chek Inform, Roche Diagnostics, Indianapolis, IN; SureStep Flexx, LifeScan, Malpitas, CA; Precision Xceed Pro (PXP), Abbott Diagnostics, Abbott Park, IL. Each glucose monitoring device was compared to the Vista hexokinase method central lab analyzer (Siemens Diagnostics, Tarrytown, NY) in an inter-instrument correlation (whole blood versus plasma). Each device was also compared to a whole blood analyzer Siemens 865 Blood Gas Instrument (whole blood to whole blood). Additionally, data was collected for determination of precision both within and between run with two levels of control on each device. We also compared the differences between lots. The linearity of each glucose monitor was tested. Interference was assessed for hematocrit and ascorbic acid by testing samples of 3 different glucose concentrations in which the hematocrit and ascorbic acid concentration was adjusted to varying levels. All samples were less than 24 hours old and were prepared based on CLSI guidelines and bench study techniques accepted by the FDA.

Performance against predetermined evaluation criteria was evaluated after each test category. Evaluation criteria consisted of:

• glucose meter precision
• acceptable comparison with lab reference methods
• performance in interference studies
• feedback from pharmacy liaisons for units using TGC procedures

The Point of Care team also evaluated connectivity options based on ability to support existing POC tests and the ability to expand as new POC tests are implemented.

September 22-25, 2010 AACC CPOCT 23rd International Symposium Boston, MA, USA
Results

Inter-Instrument Correlation (Siemens 865 reference) was performed by comparing the results of whole blood patient specimens tested on each glucose meter to whole blood glucose results of the same specimen tested on the Siemens 865 Blood Gas Instrument.

<table>
<thead>
<tr>
<th>Meter</th>
<th>n</th>
<th>Mean</th>
<th>Min</th>
<th>Max</th>
<th>Mean</th>
<th>Min</th>
<th>Max</th>
<th>Slope</th>
<th>y-Int</th>
<th>Coeff (r²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nova</td>
<td>15</td>
<td>78.2</td>
<td>48</td>
<td>134</td>
<td>81.8</td>
<td>50</td>
<td>136</td>
<td>1.014</td>
<td>-4.724</td>
<td>0.95388</td>
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<tr>
<td>Roche</td>
<td>15</td>
<td>77.5</td>
<td>48</td>
<td>127</td>
<td>81.8</td>
<td>50</td>
<td>136</td>
<td>1.026</td>
<td>-6.378</td>
<td>0.95755</td>
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<tr>
<td>Lifescan</td>
<td>15</td>
<td>90.0</td>
<td>55</td>
<td>140</td>
<td>81.8</td>
<td>50</td>
<td>136</td>
<td>0.999</td>
<td>8.249</td>
<td>0.97478</td>
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<td>Abbott</td>
<td>15</td>
<td>79.6</td>
<td>48</td>
<td>133</td>
<td>81.8</td>
<td>50</td>
<td>136</td>
<td>0.933</td>
<td>3.293</td>
<td>0.97010</td>
</tr>
</tbody>
</table>

Evaluation Criteria: \(r^2 \approx 0.95\); slope 0.95 - 1.05; small y-intercept

Inter-Instrument Correlation (Vista reference) was performed by comparing the results of whole blood patient specimens tested on each glucose meter to plasma glucose results of the same specimen tested on the Siemens Vista.

<table>
<thead>
<tr>
<th>Meter</th>
<th>n</th>
<th>Mean</th>
<th>Min</th>
<th>Max</th>
<th>Mean</th>
<th>Min</th>
<th>Max</th>
<th>Slope</th>
<th>y-Int</th>
<th>Coeff (r²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nova</td>
<td>48</td>
<td>188.0</td>
<td>48</td>
<td>559</td>
<td>186.7</td>
<td>55</td>
<td>552</td>
<td>1.007</td>
<td>0.000</td>
<td>0.99339</td>
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<tr>
<td>Roche</td>
<td>49</td>
<td>192.1</td>
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<td>176.3</td>
<td>48</td>
<td>485</td>
<td>195.4</td>
<td>55</td>
<td>610</td>
<td>0.821</td>
<td>15.914</td>
<td>0.98358</td>
</tr>
</tbody>
</table>

Evaluation Criteria: \(r^2 \approx 0.95\); slope 0.95 - 1.05; small y-intercept

The correlation studies revealed that all devices demonstrated acceptable performance except the Abbott Precision Xceed Pro (slope and intercept). It is noted that the Abbott representative stated during the tests that their meter does not perform well with old blood. The Accu-Chek Inform strips and the Abbott Precision Xceed strips did not achieve the specified precision criteria in the low control. The between run precision data demonstrated acceptable performance for each device. Linearity of each device was confirmed. The LifeScan SureStep Flexx showed significant interferences with high hematocrit and ascorbic acid.
Conclusions

The StatStrip® meter gave precisions (within-run and between day) comparable to that of the other three meters tested. StatStrip® demonstrated minimal effect due to hematocrit and ascorbic acid in the hematocrit and ascorbic acid interference studies. Results from the other meters tested were significantly influenced by these interferences. For these reasons and the excellent correlation to the Vista, we chose to implement the data-managed StatStrip® system for bedside POCTG.

Pharmacy liaisons for units using TGC procedures also recommended going with StatStrip® based on its accuracy.

We chose the LDS AegisPOC middleware for system connectivity because of its ability to support our existing and future connectivity requirements. The LDS product also allowed us to better utilize the manual test entry feature of StatStrip® for input of Visual UA, Urine Preg, Hemoccult, and Rapid Strep results.
Evaluation and Implementation of the Nova StatStrip® Bedside Glucose Monitor for Patients Undergoing Cardiopulmonary By-pass Graft Surgery (CABG)

Debra Russell, Matt Bohnsack

St. Vincent Mercy Medical Center, Toledo, Ohio

Background

Since the landmark publication by Van Den Berghe (NEJM, 2001) much attention has been paid the benefits of glycemic control in the SICU and the CICU. An integral part of the protocol to achieve glycemic control is the accurate measurement of glucose at the patient's bedside. Several publications have indicated the limitations of existing Point of Care (POC) devices due to the impact of abnormal hematocrit and other interferences. There had been numerous instances of lack of agreement between current POC device and the central lab analyzer.

Objective

In 2004, an insulin committee was formed to draft a tight glycemic protocol. Members of the committee included physicians, pharmacy, nursing, nursing management, point of care testing, and diabetic educators. Cardiac ICU was used to pilot the protocol. Nursing concerns hinged on the increased volume of glucose tests, increased time, and increase in the number of glucose meters needed. The TGC protocol defines the frequency of repeat glucose testing after an insulin drip is adjusted. Point-of-Care Testing provided patient glucose reports during this time so that adjustments to the protocol would be based on true glucose findings instead of nursing perception. By studying patient glucose results and trends while using the TCG protocol, Point-of-Care-Testing had a heightened awareness of the need for both fast and accurate measurements of glucose.

Another point of concern for the cardiac ICU, according to nurse manager Matthew Bohnsack, is the Surgical Care Improvement Project (SCIP). In 2002, The Centers for Medicare and Medicaid Services (CMS) and the US Centers for Disease Control (CDC) developed performance measures to decrease surgical site infections. All hospitals receiving Medicare reimbursements are required to report the standardized measurements to the CMS. For patients who have undergone cardiac surgery, 6 AM blood glucose levels should be at or below 200 mg/dL on the first 2 postoperative days. To meet this measure, the TGC protocol may be initiated by anesthesia during cardiac surgery.

The concerns raised in the literature and the needs of our TGC testing program caused us to re-evaluate our bedside glucose testing program. It was important for us to determine which meter system was least affected by the patient variables observed in hospitalized patients. We undertook an evaluation of a new meter, our current meter and one additional glucose meter system and compared them to the hexokinase on the central lab analyzer. The goal was to reduce the number of repeated glucose tests in the central lab and use a system that was more accurate and precise for use with these critically ill patients.

Materials and Methods

We studied precision, linearity, interferences, and correlation following the CLSI protocols and published protocols for glucose monitors (Tang et al, Karon). The systems studied were PCx (Abbott, Abbott Park, IL), SureStep Flexx (LifeScan, Milpitas, CA), and StatStrip® (Nova Biomedical, Waltham, MA). We calibrated all systems and followed each manufacturer’s recommendations for use of the devices and performance of QC. Whole blood was obtained from volunteers and was analyzed in the laboratory before conducting correlation of each device on whole blood specimens obtained in the clinical setting and then analyzed on the central lab analyzer, Advia 1650 (Siemens Diagnostics, Tarrytown, NY). Data obtained in these studies were analyzed statistically by standard statistical methods.

September 22-25, 2010 AACC CPOCT 23rd International Symposium Boston, MA, USA
Results

Correlations showed good agreement with StatStrip® data versus the central lab Advia analyzer with an $R^2$ of 0.976, slope of 0.989 and y-intercept of 0.855. The comparative performance of the Abbott PCx versus the Advia yielded an $R^2$ of 0.949, slope of 0.884 and y-intercept of 8.006. % bias for the PCx vs. the reference was as high as 15% as compared to the StatStrip® with a maximum bias of 8%.

Correlation Study
Results Cont’d

Hematocrit Interference Study

Conclusions and Discussion

These findings demonstrate that the StatStrip® Glucose monitor produces reliable results for the bedside determination of whole blood glucose compared to the conventional laboratory. The result of this study led our POC program to choose and implement the StatStrip® because it was comparable to lab glucose results.

StatStrip® also showed little effect from varying levels of hematocrit that are encountered in our hospital patients—especially those cardiac surgery patients on perfusion pumps. Endocrinologist Dr. Milo Engoren, who is responsible for the start up of our insulin protocol, expressed his concern about the accuracy of all monitoring devices, with the effects of abnormal hematocrits being an additional concern. He said that insulin drips would be set to different amounts depending on the glucose level and anything that caused an error in the glucose reading would affect the insulin drip amount and compromise treatment.
Methodist Specialty and Transplant Hospital, San Antonio, TX

Evaluation of Point of Care Bedside Glucose Monitors for Use in a Specialty and Transplant Hospital

Mary A. Weidner, BS, MT (ASCP)¹ and Melissa Flenniken, MSN, RN²

¹Department of Laboratory Medicine and Pathology, Point of Care Program,
²ICU Department, Nursing Staff, Methodist Specialty and Transplant Hospital, San Antonio, TX

Background

- Methodist Specialty and Transplant Hospital is a 379 bed facility providing a small variety of organ transplant services
- A Roche Accu-Chek® POC device is used post-operatively at our facility to monitor whole blood glucose in the ICU
- A positive bias has been observed for the Roche Accu-Chek whole blood glucose meter (Fig 1 is an example of this observation)
- A review of the medical literature revealed a number of substances (e.g., maltose, hematocrit, IVIG) can interfere with whole blood glucose meters.
- This potential for interference and subsequent discordance with central lab methods led to concern by the clinical staff about accuracy of POCT results and exploration of alternative glucose monitors

Objectives

To evaluate the accuracy, specificity, connectivity, and clinical performance of alternative POC glucose monitoring devices against the central laboratory for use within Methodist Specialty and Transplant Hospital.

Materials and Methods

Prior to testing these devices in a clinical setting, in lab linearity and precision studies were performed (data not shown). Each monitor tested performed acceptably. To assess the potential for interference two glucose meters available at the time (Accu-Chek and Precision PXP) were evaluated in two patients typical of our hospital. For this comparison arterial whole blood from central lines was taken at the times indicated in Fig 1 & 2, ran immediately on each meter at the patient bedside and then sent to the central laboratory for measurement on Siemens Vista. Mean % bias was calculated relative to the Vista comparative method. Fig 1 and 2 show the results of this comparison. A Nova StatStrip was acquired at a later time. Studies to evaluate the potential for known interferences such as hematocrit and maltose were assessed by testing samples at 3 different glucose concentrations in which the hematocrit and maltose concentration was adjusted to varying levels (Fig 3). Finally whole blood specimens were spiked with increasing concentrations of glucose and then ran on each glucose monitor. These specimens were subsequently spun down and plasma ran on the Vista hexokinase central laboratory method. Regression analysis was performed to determine concordance between the two methods (Fig 4). The Point of Care team also evaluated connectivity options based on ability to support existing POC tests and the ability to expand as new POC tests are implemented.
Results

Figure 1. Increased Bias Observed with Roche Accu-Chek. Arterial whole blood measurements were performed post-operatively as a function of time. Panel A shows a mean positive bias of 35% for the Roche Accu-Chek in a patient administered IVIG. Panel B also demonstrates a positive mean bias (16%) in a patient which underwent liver transplant procedure.
Results

Figure 2. Bias Also Observed with Abbott Precision PXP Glucose Monitor. Panel A shows a mean positive bias of 11% when the same specimens from Patient 1 from above were ran on the Abbott Precision PXP glucose meter. Panel B shows a mean positive bias of 3% when the above specimens for Patient 2 are ran on the Abbott Precision PXP. Relative to the Roche Accu-Chek, the Abbott Precision PXP had a mean bias ~3x less for patient 1 and ~5x less for Patient 2.
Results (Cont’d)

Figure 3. Effects of Hct and Maltose on Whole Blood Measurement of Glucose. Three different glucose concentrations were measured under conditions in which the hematocrit and maltose concentration was adjusted to varying levels. In both instances the Nova StatStrip® was not affected. However the Accu-Chek device was negatively affected by increasing Hct and positively affected by increasing maltose concentrations at all glucose levels studied.
Results (Cont’d)

**Figure 4. Glucose Meters vs. Central Laboratory.** When compared to the central laboratory method, Nova StatStrip demonstrated the strongest agreement with an $R^2 = 0.99790$, followed by the Abbott Precision PXP at $R^2 = 0.98567$ and then by Roche Accu-Chek $R^2= 0.97661$. Linearity as assessed by slope and y-intercept was best for Nova StatStrip with a slope of 0.988 and a y-intercept of 9.508.

![Graph](image)

**Conclusions**

- Both the Accu-Chek and Precision PXP demonstrated a large positive bias in the patients studied.
- Under the conditions studied, the Nova StatStrip is not affected by changing Hct and maltose. The Roche Accu-Chek demonstrated clinically significant interferences for both hematocrit and maltose. We were unable to test the Abbott PXP for hematocrit interference nor maltose interference.
Hematocrit Effect Outweighs Other Sources of Glucometer Error in Critical Care

Elizabeth A. Mann, RN, MS; Heather F. Pidcoke, MD; Jose Salinas, PhD; John Jones, BS; John B. Holcomb, MD; Steven E. Wolf, MD; Charles E. Wade, PhD

United States Army Institute of Surgical Research, Fort Sam Houston, TX 78234

Introduction

- Traditional single channel glucometers (SureStep Flexx™, LifeScan) overestimate true glucose values in anemic patients
- Studies suggest multiple biologic parameters such as oxygen tension, acid base balance, and various pharmacological agents also affect the accuracy of handheld glucometers
- A newly released 4-channel POC analyzer (StatStrip®, Nova Biomedical) measures and reduces the effect of the majority of these interfering substances

Hematocrit Effect:

- Low HCT (< 34%) results in falsely elevated glucose measurements
- Therefore, a single channel glucometer value of 70 in presence of 24% HCT is actually a serum glucose of 53
- FDA/industry accepts margin of error up to 20% NOT acceptable for intensive insulin therapy this increases risk of unrecognized hypoglycemia

Correction of Serum Glucose Value:

- Glucometer Correction Formula for single channel SureStep Flexx™ incorporates glucometer value and HCT

\[ \text{Expected serum glucose} = (\text{POCG} \times 0.2104 \times \ln(3.3249 \times \text{HCT}) - 11.3934) \]

- POCG = point-of-care glucometer value \( \ln = \) natural log
- Correction formula correlates with serum values
Results

Hematocrit Effect:

- Low HCT (< 34%) results in falsely elevated glucose measurements
- Therefore, a single channel glucometer value of 70 in presence of 24% HCT is actually a serum glucose of 53
- FDA/industry accepts margin of error up to 20% NOT acceptable for intensive insulin therapy this increases risk of unrecognized hypoglycemia

Correction of Serum Glucose Value:

- Glucometer Correction Formula for single channel SureStep Flexx™ incorporates glucometer value and HCT
  \[ E = (POCG \times 0.2104 \times \ln(3.3249 \times HCT)) - 11.3934 \]
  - POCG = point-of-care glucometer value  \( \ln = \) natural log
  - Correction formula correlates with serum values

![Graph showing percent error vs hematocrit percentage](image)

![Graph showing correction formula](image)
Results

With a zone of indifference set for ±5% the difference between analyzers was -0.67% (CI: -1.79% to 0.45%) demonstrating non-inferiority between methods.


Conclusion

- Utilization of a 4-channel glucometer demonstrated clinically indistinguishable results compared with mathematical correction for hematocrit, eliminating the necessity for such correction.
- This suggests that low hematocrit was the greatest contributor to single channel glucometer error.
- Therefore, the 4-channel effectively reflects the serum glucose value; however, when access to this technology is limited, mathematical correction of a single channel glucometer is a viable alternative.

Grant Support

The National Institutes of Health (1 R01 GM083120-04); The Technologies for Metabolic Monitoring (TMM)Julia Weaver Fund, A Congressionally Directed Program Jointly Managed by the USA MRMC, NIH, NASA; and the Juvenile Diabetes Research Foundation and Combat Casualty Care Division United States Army Medical Research and Materiel Command

References

1 Mann EA, Salinas J, Pidcoke HF et al. Error rates resulting from anemia can be corrected in multiple commonly used point-of-care glucometers, J Trauma, 2008;64:15-21
Assessing the Performance of Handheld Glucose Testing for Critical Care

Gerald J. Kost, M.D., Ph.D.,1 Nam K. Tran, B.S.,1 Richard F. Louie, Ph.D.,1 Nicole L. Gentile, B.S.,1 and Victor J. Abad, M.A.2

Abstract

Background: We assessed the performance of a point-of-care (POC) glucose meter system (GMS) with multitasking test strip by using the locally-smoothed (LS) median absolute difference (MAD) curve method in conjunction with a modified Bland-Altman difference plot and superimposed International Organization for Standardization (ISO) 15197 tolerance bands. We analyzed performance for tight glycemic control (TGC).

Methods: A modified glucose oxidase enzyme with a multilayer-gold, multielectrode, four-well test strip (StatStrip® , NOVA Biomedical, Waltham, MA) was used. There was no test strip calibration code. Pragmatic comparison was done of GMS results versus paired plasma glucose measurements from chemistry analyzers in clinical laboratories. Venous samples (n = 1,703) were analyzed at 35 hospitals that used 20 types of chemistry analyzers. Erroneous results were identified using the Bland-Altman plot and ISO 15197 criteria. Discrepant values were analyzed for the TGC interval of 80–110 mg/dL.

Results: The GMS met ISO 15197 guidelines; 98.6% (410 of 416) of observations were within tolerance for glucose <75 mg/dL, and for ≥75 mg/dL, 100% were within tolerance. Paired differences (handheld minus reference) averaged −2.2 (SD 9.8) mg/dL; the median was −1 (range, −96 to 45) mg/dL. LS MAD curve analysis revealed satisfactory performance below 186 mg/dL; above 186 mg/dL, the recommended error tolerance limit (5 mg/dL) was not met. No discrepant values appeared. All points fell in Clarke Error Grid zone A. Linear regression showed y = 1.018x − 0.716 mg/dL, and r2 = 0.995.

Conclusions: LS MAD curves draw on human ability to discriminate performance visually. LS MAD curve and ISO 15197 performance were acceptable for TGC. POC and reference glucose calibration should be harmonized and standardized.

Introduction

THE LOCALLY-SMOOTHED (LS) median absolute difference (MAD) curve method1 employs a nonparametric statistical algorithm that provides quantitative assessment of performance of a point-of-care (POC) test. Errors do not offset each other because there is no algebraic summing of positive and negative errors. For POC glucose testing, continuity of the LS MAD curve enhances simultaneous visual assessment of performance in hypo-, normo-, and hyperglycemic ranges and allows quick interpretation for glucose ranges relevant to tight glycemic control (TGC) protocols in critical care settings.

Our objectives were: (1) to use the LS MAD curve method and a modified Bland-Altman2 difference plot with superimposed International Organization for Standardization (ISO) 151973 tolerance bands to evaluate POC glucose testing performance across multiple institutions; (2) to evaluate a handheld glucose meter system (GMS) that corrects for hematocrit effect and compensates for oxidizing substances; and (3) to assess suitability for a TGC interval of 80–110 mg/dL and for the critical adjacent ranges immediately outside the TGC interval where insulin infusion rates are changed to achieve the target glucose level.

Materials and Methods

Multicenter strategy

The Point-of-Care Testing Center for Teaching and Research (POCT·CTRSM) (University of California, Davis,
Davis, CA) acted as an independent arbitrator without re-
muneration. The University of California Davis Medical Cen-
ter did not perform instrument comparisons or contribute a
dataset. The Institutional Review Board at the University of
California, Davis approved the multicenter-arbitrator strat-
ey. Subjects included patients in critical care sites (e.g., in-
tensive care unit, neonatal intensive care unit, operating
room, emergency room, and labor and delivery) and also di-
abetes clinics, the nursery, and outpatient centers.

Thirty-five U.S. medical centers anonymously provided
datasets obtained from parallel analysis of fresh remnant
lithium or sodium heparinized venous or blood gas syringe
samples (n = 1,703) using a uniform protocol, the GMS to
measure whole-blood glucose, and chemistry analyzers to
measure plasma glucose immediately following centri-
fugation (Table 1). No fingerstick samples were used. Glucose
was measured in singleton. At the majority of sites, the man-
ufacturer provided assistance with testing. Samples were
processed without delay except when placed on a rocker at
room temperature to allow glycolysis to produce low range
glucose levels.

GMS

Hospitals evaluated the StatStrip™ handheld glucose me-
ter (NOVA Biomedical, Waltham, MA), which uses a modi-
fied glucose oxidase enzyme method and multilayer-gold,
multielectrode, four-well test strip. No calibration codes or
lot numbers need be entered before measurement. The sam-
ple volume was 1.2 μL, and the analysis time was 6 s. Stat-
Strip measures hematocrit by an impedance method and cor-
rects glucose values for abnormal hematocrits. The StatStrip
received clearance from the Food and Drug Administration
(FDA) for use in neonatal testing and is intended for in vitro
diagnostic use with capillary, venous, and arterial whole
blood. It is approved for all hospital areas, including but not
limited to critical care, the operating room, inpatient sites,
and outpatient sites, such as diabetes clinics.

Quality control and reference instruments

GMS measurements were compared to parallel measure-
ments of plasma glucose performed within a few minutes
using 20 types of clinical laboratory chemistry analyzers at
35 U.S. hospitals (Table 1). Test strips consisted of approxi-
ately 20 different lots. Reference instruments were quality
controlled daily according to manufacturers’ specifications
as part of laboratory requirements for reporting patients’ re-
sults.

Glucose meters were operated within control according to
the manufacturer’s specifications. Three control levels were
provided: 46–76, 88–128, and 253–323 mg/dL; the middle

### Table 1. Clinical Laboratory Reference Instruments at 35 U.S. Medical Centers

<table>
<thead>
<tr>
<th>Manufacturer (<a href="http://www">www</a>.)</th>
<th>Reference instrument</th>
<th>Sites</th>
<th>Number of observations</th>
<th>Group</th>
<th>Bias (mg/dL) [SD, P], median (range)</th>
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<td>Abbott (abbott.com)</td>
<td>Architect</td>
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<td>51</td>
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<td>5 (−28 to +9)</td>
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<td>Integra</td>
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<td>30</td>
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<tr>
<td>Total multicenter observations</td>
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<tr>
<td>Median bias (mg/dL), all observations [range]</td>
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<td></td>
<td>−1 [−96 to +45]</td>
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range and one other control level were checked each 24 h. Only paired observations meeting these dual POC-laboratory quality control requirements were fulfilled were analyzed. The GMS linear range is 10–600 mg/dL. Linearity validation levels include 12–24, 46–76, 88–126, 253–323, and 454–574 mg/dL.

**LS MAD curve**

In brief, local smoothing transforms discrete points in the x-y plane into a curve that helps reveal underlying patterns. The LS MAD curve contains points \((x, y)\) where \(y\) is the median of the values, \(y^*\), for all original points \((x^*, y^*)\) in the range \([x - h, x + h]\). The bandwidth, \(h\), controls the degree of smoothing.

The LS MAD curve is continuous from start to end; it started at 35 mg/dL and ended at 220 mg/dL to ensure adequate points were included in the first (20–50 mg/dL) and last (205–235 mg/dL) computational bands. We set the bandwidth, \(h\), to 15 mg/dL, and therefore, \(2h\), or a span of 30 mg/dL, corresponded to the TGC interval of 80–110 mg/dL.

**Clarke Error Grid**

When plotted on a Clarke Error Grid, performance is considered acceptable if \(\geq 95\%\) of observations fall within zones A and B and no or negligible points fall in zones D and E. Note that the FDA does not require Clarke Error Grid analysis for device licensing.

**Modified Bland-Altman plot**

Bland-Altman plots base interpretation of performance on differences \((y\text{-axis})\) in paired GMS and reference values versus means \((x\text{-axis})\) of pairs. We used a modified Bland-Altman plot where the \(x\) variable represents the singlet reference result. Horizontal lines show zero bias and mean difference. Visual inspection reveals overall unacceptable bias or ranges where bias appears unexpectedly large. We combined this plot with the ISO 15197 guideline.

**ISO 15197 guideline and erroneous results**

The ISO 15197 guideline states that meter measurements should be within 15 mg/dL (0.83 mmol/L) of the reference result for glucose <75 mg/dL (4.2 mmol/L) and within 20% for glucose \(\geq 75\) mg/dL (4.2 mmol/L). A GMS is within the guideline if \(95\%\) of pairs satisfy these criteria separately for each range. We define erroneous results as all points falling outside the ISO 15197 tolerance bands. The ISO 15197 guideline does not represent a standard, but currently is under consideration for such by the FDA.

**Bracket predictive value (BPV)**

Positive BPV is defined as \([TP/(TP + FP)]\) where TP (true positive) represents the number of GMS-reference pairs within the TGC bracket (80–110 mg/dL), and FP (false positive) represents the number of pairs where the GMS result is inside the bracket and the reference result is not. Negative BPV is \([TN/(TN + FN)]\), that is, the number of GMS-reference paired observations outside the bracket divided by the number of GMS results outside the bracket. TN is true negative, and FN is false negative. Two-dimensional positive BPV additionally constrains GMS TP results to within 15 mg/dL of paired reference results, chosen to be equivalent to the bandwidth, 15 mg/dL, for the LS MAD curve.

**FIG. 1.** Modified Bland-Altman plot with superimposed ISO 15197 tolerance bands.
Discrepant values

Class I and II discrepancies represent GMS measurement errors that could significantly impact the effectiveness of TGC protocols. Class I discrepancies are pairs with reference <80 mg/dL and GMS >110 mg/dL. Class II discrepancies are pairs with reference >110 mg/dL and GMS <80 mg/dL. Class I discrepancies could lead to dangerous clinical decisions worsening hypoglycemia, while Class II discrepancies could lead to aggravation of hyperglycemia.

Statistics and units

We used SPSS version 14.0 (SPSS Inc., Chicago, IL) for descriptive statistics, analysis of paired differences (meter minus reference), Kruskal-Wallis nonparametric analysis of the equality of medians among groups, and least squares linear regression. Minitab® (version 14.20, 2005; Minitab, Inc., State College, PA) was used for Ryan-Joiner analysis of the normality of paired difference distributions. Nonparametric symmetric confidence intervals were calculated for the medians of the absolute differences. We report glucose in the conventional units, mg/dL, used by participant medical centers. Conversion calculations used [glucose] (in mg/dL) × 0.05551 = [glucose] (in mmol/L).

Results

Figure 1 presents the modified Bland-Altman plot with integrated ISO 15197 tolerance bands (dashed lines) for 1,703 paired observations. ISO 15197 bin populations (%, n, mg/dL span, and ISO target %) were: 12.0, 203, <50, 5; 18.0, 306, 50–80, 15; 25.8, 440, >80–120, 20; 15.7, 267, >120–200, 30; 10.6, 180, >200–300, 15; 9.1, 155, >300–400, 10; and 8.9, 151, >400, 5. The mean of the paired differences (meter minus reference) was −2.2 (SD 9.8) mg/dL (P < 0.001), and the median was −1 mg/dL (range, −96 to 45 mg/dL) (Table 1).

The paired difference distribution for all 1,703 observations was not normally distributed (P < 0.01). Individual distributions for the seven brand groups listed in the left-hand column of Table 1 were not normally distributed (P = 0.05), and in one case the distribution was somewhat bimodal. Kruskal-Wallis analysis for the seven brand groups showed P < 0.01.

In Figure 1, all GMS values were within tolerance when the reference glucose was ≥75 mg/dL. For reference glucose <75 mg/dL, 98.6% (410 of 416) were inside, and six (1.4%) were outside. Represented as (x; y, bias), these six were: (50, 34; −16), (52, 34; −18), (52, 29; −23), (57, 41; −16), (57, 40; −17), and (61, 43; −18) mg/dL, which reflected results from four different types of reference instruments and two different brands. This cluster of erroneous results is located below the lower tolerance band on the left in Figure 1.

Figure 2 presents the LS MAD curve. The breakout was at 186 mg/dL (10.32 mmol/L). Positive and negative BPVs were 87.1% (TP, 365; FP, 54) and 96.9% (TN, 1,244; FN, 40), respectively; two-dimensional positive BPV was 87.1% [363/(363 + 54)]. Only two GMS and reference pairs, (91, 107) and (86, 104), in the TGC interval had bias (16 and 18, respectively) greater than 15 mg/dL. There were no Class I or Class II discrepancies. Linear regression showed y = 1.018x − 0.716 mg/dL and r² = 0.995 (Fig. 3). The ranges of reference and GMS glucose values were 16–623 and 17–600 mg/dL, respectively. All points fell within Clarke Error Grid zone A.

Discussion

For hospital glucose meters, we recommend that the LS MAD curve not exceed an error tolerance limit of 5 mg/dL. Ideally, the LS MAD curve should be as close as possible to the x-axis (minimal offset), indicating congruence with the hospital laboratory chemistry analyzer from hypoglycemic through hyperglycemic ranges. The GMS studied performed satisfactorily in the vicinity of the TGC interval, where the MAD was approximately 4 mg/dL. Suitable performance in the ranges immediately adjacent to the TGC interval assures accurate glucose results for critical adjustments in insulin infusion rates and will help moderate glycemic variability attributable to asymmetric stochastic measurement error.

When used to monitor patients hourly in critical care settings, glucose meters should be optimized for the relevant span of the TGC interval, since a critical care team adjusts insulin therapy to maintain patients within the TGC interval. The GMS studied here generally met that criterion for 80–110 mg/dL. Other whole-blood glucose meters perform poorly in low (hypoglycemic) zones. They may generate er-
ronous results and discrepant values, including dangerous ones falling in Class I that could affect bedside decision-making adversely.1

The modified Bland-Altman plot with superimposed ISO 15197 tolerance bands (see Fig. 1) reveals deviations from the paired reference glucose in the form of asymmetrical scatter. We recommend that an ISO 15197 difference plot be used to identify erroneous results. Errors increased at high glucose levels (heteroscedasticity) but still fell within the ISO tolerance bands, which are not very demanding. BPV reflects whether meter results inside or outside the TGC interval reliably reflect paired reference results. BPVs were acceptable. There were no Class I or Class II discrepancies that, if present, potentially can impact patient outcomes adversely. Table 2 summarizes other performance evaluation tools and their utility.

Confounding variables and specimen sources (e.g., arterial, venous, or capillary) may influence measurement error. Fluctuations in O₂ pressure, CO₂ pressure, and pH, as well as in hematocrit, and myriad interferences,19–22 operator errors,23 environmental factors,24 and pathophysiological perturbations (e.g., low perfusion index, arterial hypotension, peripheral hypoperfusion, and generalized mottling with capillary samples25) can affect glucose meter performance adversely. A recent editorial cautions users regarding the potential harm that may result from inaccurate bedside results.26 The FDA has warned physicians of “... the potential for life-threatening falsely elevated glucose readings in patients who have received parenteral products containing (or metabolized to) maltose or galactose, or oral xylose, and are subsequently tested using glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) ...”27,28 However, the GMS test strip does not use GDH-PQQ chemistry. Other investigators29–31 showed that this GMS minimized hematocrit effects.

Limitations of the present study include: (1) reference instrument types reflected hospital choice and were not equally weighted in frequency of use; (2) plasma glucose reference measurements appeared not to be harmonized because of presumed differences in manufacturer calibration; (3) aggregated results from different hospitals and geographic locations derived from heterogeneous patient populations (and sampling sites), which were subject to a variety of confounding variables; (4) ISO 15197 bin populations differed from guidelines specifications mainly by overpopulating the critical range below 120 mg/dL; (5) measure-

FIG. 3. Least squares linear regression plot. Linear regression showed \( y = 1.018x - 0.716 \) mg/dL and \( r^2 = 0.995 \) for the 1,703 observations. The ranges were 16–623 mg/dL for \( x \) and 17–600 mg/dL for \( y \).
Bedside glucose testing in critical care demands careful attention to patient status in order to avoid adverse effects of confounding factors, such as peripheral hypotension and its impact on capillary glucose. Asymmetric stochastic measurement error may exacerbate glycemic variability.

We recommend that future licensing criteria for bedside glucose meters include the LS MAD curve pattern recognition approach for assessment of GMS performance. LS MAD curves with analyte-specific error tolerance limits also could be applied to other POC tests to help facilitate informed bedside decision-making.

Acknowledgments

The tables and figures were provided courtesy and permission of Knowledge Optimization®, Davis, CA. This study was supported by the Point-of-Care Testing Center for Teaching and Research (POCT • CTRSM), School of Medicine, University of California, Davis, and by a National Institute of Biomedical Imaging and Bioengineering Point-of-Care Technologies Center grant (G.J.K., Principal Investigator, National Institutes of Health grant number 1U54 EB007959-01). This content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Biomedical Imaging and Bioengineering or the National Institutes of Health.

Author Disclosure Statement

No competing financial interests exist.

References

LS MAD PERFORMANCE AND TIGHT GLUCOSE CONTROL


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Evaluation of a Glucose Meter with Negligible Hematocrit or Chemical Interference

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3Nova Biomedical Corporation, Waltham, MA, USA

Objective:
To compare precision and accuracy data from a new strip meter technology to three other commercially available strip meter technologies and a reference plasma hexokinase procedure.

Introduction:
The current study was designed to evaluate the analytical performance of four commercially available glucose meters (Nova StatStrip®, Roche Aviva, Abbott Precision Freestyle, LifeScan SureStep Flexx). In an attempt to mimic the complexity seen with critical care patients, common interferences such as hematocrit, maltose and ascorbate, were tested alone and in combination with one another at low, medium and high blood glucose concentrations. Accuracy of glucose analyses was established by comparing all values to a reference plasma hexokinase method and determining whether differences exceeded the ISO 15197 guidelines.

Relevance:
Considerable concern has been expressed in the literature regarding point-of-care (POC) glucose testing devices (meter-strip) and the considerable error they have demonstrated when compared to reference (plasma-hexokinase) methods.

Methods:
We compared the analytical performance of the newly introduced Nova Biomedical StatStrip®, glucose monitoring system and three other strip-meters systems (Roche Aviva, Abbott Precision Freestyle, LifeScan SureStep Flexx) to a laboratory plasma hexokinase reference method (Roche Hitachi 912). We determined within-run precision for the four meter strip systems using a freshly prepared whole blood sample spiked with concentrated glucose to give three glucose concentrations and day-to-day precision using aqueous control materials supplied by each vendor. Common interferences, including hematocrit, maltose and ascorbate, were tested alone and in combination with one another on each of the four strip-meter systems at low, medium and high blood glucose concentrations.

Four Glucose Strip-Meter Systems Evaluated:
1. Nova Biomedical StatStrip®
2. Roche Aviva
3. Abbott Precision Freestyle
4. Lifescan Sure Step Flexx

Parameters Measured:
1. Within run precision using the four strip-meter systems using freshly prepared whole blood spiked with concentrated glucose to give three glucose concentrations. Day to day precision using aqueous control materials supplied by each vendor.
2. Interferences, including hematocrit, maltose and ascorbate, were tested alone and in combination with one another on each of the four strip-meter systems as low, medium and high blood glucose concentrations.
3. Patient blood gas results (hematocrit and glucose) (n=154) were compared with those obtained with the four glucose meters.
**Calgary Laboratory Services, University of Calgary, Nova Biomedical (Cont'd)**

**Results:**

Within-run imprecision of the StatStrip® in spiked whole blood samples, as determined by the coefficient of variation, was < 4.5% for glucose concentrations between 4.15-20.70 mmol/L. Day-to-day imprecision using control materials was < 6%. Increasing hematocrit values, while significantly lowering the glucose values obtained from the Aviva, Precision Freestyle and the SureStep Flexx systems, had virtually no effect on the StatStrip® system. Of the four strip-meter systems tested for interference, only the StatStrip® remained within 5% of its initial value following the cumulative addition of ascorbate, and/or maltose at low and high hematocrit levels for the three glucose concentrations tested.

![Figure 1: Hematocrit-induced bias at 4.32 mmol/L glucose](image)

**Figure 1: Hematocrit-induced bias at 4.32 mmol/L glucose. SSA & SSB = StatStrip®, Aviva = Roche, FS = Abbott, SuSt = LifeScan**

<table>
<thead>
<tr>
<th>Strip Meter System</th>
<th>Glucose Conc.</th>
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<th>Glucose Conc.</th>
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<tr>
<td></td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
<td></td>
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<tr>
<td>Nova StatStrip®</td>
<td>4.15±0.13 (3.08%)</td>
<td>11.18±0.36 (3.19%)</td>
<td>20.70±0.54 (2.59%)</td>
<td>Nova StatStrip®</td>
<td>3.15±0.12 (3.92%)</td>
<td>16.32±0.17 (1.04%)</td>
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<td>Abbott</td>
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<td>10.08±0.66 (6.55%)</td>
<td>19.53±0.72 (3.69)</td>
<td>Abbott</td>
<td>6.09±0.26 (4.34%)</td>
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<tr>
<td>Roche</td>
<td>4.33±0.12 (2.82%)</td>
<td>11.06±0.33 (2.96)</td>
<td>21.80±0.51 (2.36)</td>
<td>Roche</td>
<td>2.38±0.10 (4.20%)</td>
<td>17.19±0.29 (1.66%)</td>
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<tr>
<td>LifeScan</td>
<td>4.31±0.13 (3.09%)</td>
<td>9.80±0.17 (1.69%)</td>
<td>19.82±0.18 (0.89%)</td>
<td>LifeScan</td>
<td>2.67±0.14 (5.31%)</td>
<td>20.45±0.48 (2.33%)</td>
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</table>

**Table 1: Within Run Precision [mean glucose concentration (mmol/L) ± standard deviation (coefficient of variation)]**

**Table 2: Day to Day Precision [mean glucose concentration (mmol/L) ± standard deviation (coefficient of variation)]**
Results (Cont’d):

Figure 2: Hematocrit effect in patient samples with hematocrit adjustment. Glucose concentration measured using Nova StatStrip® Meter and the radiometer 725 blood gas analyzer.

Figure 3: Hematocrit effect in patient samples with hematocrit adjustment. Glucose concentration measured using LifeScan Sure Step Flex Meter and the radiometer 725 blood gas analyzer.

Figure 4: Hematocrit effect in patient samples with hematocrit adjustment. Glucose concentration measured using Abbott Precision Freestyle Meter and the radiometer 725 blood gas analyzer.

Figure 5: Hematocrit effect in patient samples with hematocrit adjustment. Glucose concentration measured using Roche Aviva Meter and the radiometer 725 blood gas analyzer.

Conclusion:

The StatStrip® glucose meter gave precisions (within-run and between-day) comparable to that determined on the other three meter systems tested. The StatStrip® system was not susceptible to hematocrit, ascorbate or maltose interferences, either alone or in combination with one another. The other strip meter systems tested were significantly influenced by these interferences.

Acknowledgements::

Research supported by Nova Biomedical Diagnostics

References:
Predicted Discrepancies Between Direct Reading Whole Blood Biosensors and Central Lab Plasma Methods: Predicting and Avoiding Medical Error

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Abstract

Objective: A mathematical factor is used to convert measured whole blood glucose molality to plasma-equivalent molarity. The objective of this study was to determine the distribution of conversion factors for groups of patients with different acuity and to assess the gap or bias in plasma equivalent glucose that would occur if a constant conversion factor of 1.11 was used.

Methods: Distributions of hematocrit, red blood cell water and plasma water were determined in local patient groups from the community, hospital and adult intensive care unit. Conversion factor distributions and percentage glucose bias were determined for each group and compared by ANOVA.

Results: With increasing patient acuity the median hematocrit decreased, median plasma water increased and variation of the hematologic parameters increased. Variation in the hematological parameters were observed to contribute up to 10% variation in plasma-equivalent glucose results with a 3% positive bias for most critical care patients.

Conclusions: Changes in hematocrit and plasma water concentration are predicted to affect a gap or bias between whole blood direct reading biosensors and central laboratory plasma methods. This bias increases and becomes more variable as patient acuity increases.

Relevance

In general, direct reading biosensors are popular because they detect the chemical activity of a target analyte without diluting the specimen. The chemical activity detected by a biosensor is a function of the molality of the analyte (1). Current consensus is to report values in concentration units of molarity (1-3). The gap between molality and molarity in plasma is usually small and due to the displacement of water in plasma by proteins and lipid. This gap is larger in whole blood where hemoglobin occupies a larger portion of volume within erythrocytes. If the concentrations of plasma protein, lipid, erythrocyte-water and hematocrit are near mean values for healthy patients, then molality to molarity conversion with a constant factor derived from patient-means provides an accurate molarity estimate.

In 2001, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) consensus report recommended point of care glucose devices report only the plasma equivalent concentration of glucose (3, 4). The authors stated that whole blood point of care devices that detect glucose molality can report plasma equivalents of glucose molarity by assuming a hematocrit of 0.43, an average mass concentration of water in plasma to be 0.93 kg water/L and an average mass concentration of water in red blood cells to be 0.71 kg water/L. Based on these point estimate values, the consensus solution was to multiply whole blood glucose molality detected by direct electrode devices by a volume displacement conversion factor of 1.11 to obtain plasma-equivalent glucose molarity (2). The precise conversion factor used in commercially available products is seldom disclosed and is subject to vary with reagent and calibrator lots.
Study Objective

In the current study, we have examined populations of critical care, hospital and community patients to assess the variation of plasma water, red blood cell water and hematocrit that exists in local practice. Our goal was to determine individual-patient volume displacement conversion factors and estimate the potential gaps or biases in generating plasma equivalent glucose molarity that would be reported if a constant conversion factor of 1.11 was applied using the IFCC consensus approach.

Methods

Study Population: This research was reviewed and approved by the Conjoint Health Research Ethics Board, University of Calgary. Six weeks of hospital data and two weeks of community data was extracted from the LIS (Cerner Systems, Kansas City Mo) and partitioned by laboratory site and patient location. Results for complete blood count, or albumin or total protein were retained and linked by patient healthcare number. Replicate testing of patients was avoided: if tests were repeated for an individual patient during the study interval, then only that individual-patient’s mean for the test was included in the analysis.

Laboratory Analysis: Plasma albumin was determined using a bromocresol purple method on Hitachi 917 or Hitachi Modular P analyzers (Roche Diagnostics Canada, Laval). Hematocrit and mean corpuscular hemoglobin concentration (MCHC) were determined from CBC results on LH 780 instrumentation, (Beckman-Coulter Corp, Brea, CA). Plasma total protein concentration was derived from the sum of measured albumin and the mean globulin level (31 g/L) (7). Plasma water (PW) was derived from the plasma total protein using a partial specific volume for plasma protein of 0.000949 (PW=0.0932 at total protein of 71.5 g/L) (8). Red blood cell water (RW) was derived from the MCHC in g/L using the equation RW= 1.050 – (MCHC x 10^-3) described by Lew et al with the specific gravity of blood was reduced from 1.090 to 1.050 to account for membrane components of red blood cells (RW=0.715 at MCHC=335 g/L)(9, 10).

Volume Displacement Conversion Factors: The IFCC consensus method for conversion of whole blood glucose to plasma equivalents was applied to derive individual patient conversion factors based on hematocrit, RW and PW, (2) Equation 1. The distribution of conversion factors for patient groups was plotted. Expected glucose-bias attributed to inaccurate conversion to plasma equivalents was expressed as a percentage of the IFCC consensus conversion factor of 1.11.

Equation 1.

Conversion Factor = PW/ [(Hct*RW)+(1-HCT)*PW]]

Statistical Analysis: Data handling, one-way ANOVA and graphics were generated using Stata 11 statistical software (StataCorp LP, College Station, TX, USA). Box plots depict the median, the box of the central quartile ranges, whiskers 1.5 fold of the central (8) 50% interval and outlier data points. Reference interval distributions were derived from the adult reference intervals in use at Calgary Laboratory Services generated assuming each reference interval was 4 standard deviations wide and the mid-point was the mean. The reference distribution was derived using a random number generator function based on this mean and standard deviation with Microsoft Excel software.
Results (Cont’d)

Figure 1: Distributions of hematocrit values observed in community, hospital and critical care patient populations. Reference interval n=1000, Community patients n=15,108, Hospital patients n= 45,260 and Adult ICU n=1041. One-way ANOVA using Bonferroni method for multiple comparisons revealed the populations were distinct, p< 0.001.

Figure 2: Distributions of RW values observed in community, hospital and critical care patient populations. Reference interval n=1000, Community patients n=14,376, Hospital patients n= 45,014 and Adult ICU n=1041. One-way ANOVA using Bonferroni method for multiple comparisons revealed the populations were distinct, p< 0.001, except the Hospital and ICU populations, p = 0.271.
Results (Cont’d)

Figure 3: Distributions of PW values observed in community, hospital and critical care patient populations. Reference interval n=1000, Community patients n=3694, Hospital patients n= 10,714 and Adult ICU n=301. One-way ANOVA using Bonferroni method for multiple comparisons revealed the populations were distinct, p< 0.001.

Figure 4: Distributions of conversion factor values observed in community, hospital and critical care patient populations. Reference interval n=1000, Community patients n=3133, Hospital patients n= 4116 and Adult ICU n=87. One-way ANOVA using Bonferroni method for multiple comparisons revealed each population was distinct, p<0.001.
Results (Cont’d)

Figure 5: Cumulative distributions of expected glucose bias in community, hospital and critical care patients. Community patients n=3133, Hospital patients n=4116 and Adult ICU n=87. One-way ANOVA using Bonferroni method for multiple comparisons revealed each population was distinct, p< 0.001

Conclusion

In conclusion, changes in hematocrit, plasma water concentration are predicted to affect a substantial bias between whole blood direct reading biosensors and central (15) laboratory plasma methods. This bias increases and becomes more variable as patient acuity increases. These observations are a component of the technical limitation to achieving concordance of results between plasma-central lab and whole blood-direct reading biosensors.
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Estimates of Total Analytical Error in Consumer and Hospital Glucose Meters Contributed by Hematocrit, Maltose and Ascorbate

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Background

Patients and physicians expect accurate whole blood glucose monitoring even when patients are anemic, undergoing peritoneal dialysis or when ascorbate is slightly elevated. The objective of this study was to estimate analytical error in two consumer and two hospital glucose meters contributed by variation in hematocrit, maltose, ascorbate and imprecision.

Objectives

To estimate analytical error in two consumer and two hospital glucose meters contributed by variation in hematocrit and the presence of maltose and ascorbate.

Materials and Methods

The influence of hematocrit (20-60%), maltose and ascorbate were tested alone and in combination with each glucose meter and with a reference plasma glucose method at three concentrations of glucose. Precision was determined by consecutive analysis (n=20) at three levels of glucose. Multivariate regression analysis was used to estimate the bias associated with the interferences, alone and in combination. Total analytical error was estimated as |% bias| + 1.96 (% imprecision).

**Meter 1**: Hospital meter, glucose oxidase based amperometric, with hematocrit correction.

**Meter 2**: Hospital meter, glucose oxidase photometric.

**Meter 3**: Consumer meter, glucose dehydrogenase- pyrroloquinolinquinone (PQQ) amperometric, with hematocrit correction.

**Meter 4**: Consumer meter, glucose dehydrogenase-PQQ electrochemical.

**Comparative Method**: Hexokinase method for plasma glucose (Roche, Hitachi 912).

**Interference Studies**: The influence of hematocrit (20-60%), maltose (2.8, 5.6 mmol/L) and ascorbate (0.29, 0.59 mmol/L) were tested alone and in combination with each glucose meter and with the comparative method at three blood glucose concentration ranges (3.9-4.7, 11.3-13, 20.6-24 mmol/L). Within run precision was determined by consecutive analysis of whole blood specimens (n=20) at three glucose levels.

**Data Analysis**: Multivariate regression analysis was conducted to estimate the bias (inaccuracy) associated with the interferences, alone and in combination, on the performance of each glucose meter. Analytical error was calculated as a sum of |% bias| + 1.96 (%imprecision)
Relevance

The inequality of glucose results determined by handheld meters and hospital central laboratories undermined confidence in medical decisions and fostered technological improvements and hundreds of studies on performance in various clinical settings in the past 15 years. The Clinical and Laboratory Standards Institute (CLSI) and International Standards Organization (ISO) have continued to develop and refine guidelines to assess glucose meter accuracy, most recently with the documents POCT12-A3 and ISO 15197. A recent audit found that only 16 of 27 Conformité Européenne systems met the ISO 15197 expectations. Previously, we screened two consumer and two hospital glucose meters for susceptibility to error due to hematocrit, maltose and ascorbate and developed a linear regression model to assess glucose meter performance. In this study, we extend the analysis of the data collected for the two consumer and two hospital glucose meters using linear regression to predict bias and then compare estimates of total analytical error with the ISO 15197 standards.

Results

**Equation 1:** Model for estimation of conditional means of coefficients that describe the influence of hematocrit on glucose meter results.

\[
E(\text{Glucose}_{\text{meter}}) = \beta_0 + \beta_1 \text{Glucose}_{\text{plasma, molar}} + \beta_2 \text{Hct} + \beta_3 \text{Hct} \times \text{Glucose}_{\text{plasma, molar}}
\]

**Equation 2:** Model for estimation of conditional means of coefficients that describe the influence of hematocrit and maltose (M) on glucose meter results.

\[
E(\text{Glucose}_{\text{meter}}) = \beta_0 + \beta_1 G + \beta_2 H + \beta_3 M + \beta_4 GH + \beta_5 GM + \beta_6 HM + \beta_7 GHM
\]

**Equation 3:** Model for estimation of conditional means of coefficients that describe the influence of hematocrit and ascorbate (A) on glucose meter results.

\[
E(\text{Glucose}_{\text{meter}}) = \beta_0 + \beta_1 G + \beta_2 H + \beta_3 A + \beta_4 GH + \beta_5 GA + \beta_6 HA + \beta_7 GHA
\]

**Equation 4:** Model for estimation of conditional means of coefficients that describe the influence of hematocrit, maltose (M) and ascorbate (A) on glucose meter results.

\[
E(\text{Glucose}_{\text{meter}}) = \beta_0 + \beta_1 G + \beta_2 H + \beta_3 M + \beta_4 A + \beta_5 GH + \beta_6 GM + \beta_7 GA + \beta_8 HM + \beta_9 HA + \beta_{10} MA + \beta_{11} GHM + \beta_{12} GHA + \beta_{13} HMA + \beta_{14} GMA + \beta_{15} GHMA
\]

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<th>Glucose:</th>
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<th>Medium, mmol/L</th>
<th>High, mmol/L</th>
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<tr>
<td>Meter 1</td>
<td>4.14 ± 0.13 (3.08%)</td>
<td>11.18 ± 0.36 (3.19%)</td>
<td>20.70 ± 0.54 (2.59%)</td>
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<tr>
<td>Meter 2</td>
<td>4.31 ± 0.13 (3.09%)</td>
<td>9.80 ± 0.17 (1.69%)</td>
<td>19.82 ± 0.18 (0.89%)</td>
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<tr>
<td>Meter 3</td>
<td>4.33 ± 0.12 (2.8%)</td>
<td>11.06 ± 0.33 (3.0%)</td>
<td>21.80 ± 0.51 (2.4%)</td>
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<tr>
<td>Meter 4</td>
<td>4.39 ± 0.33 (8.0%)</td>
<td>10.09 ± 0.66 (6.6%)</td>
<td>19.53 ± 0.72 (3.7%)</td>
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</tbody>
</table>

Table 1 Within-run precision assessment in whole blood. Glucose mean ± one Standard deviation in mmol/L and C.V % (n=20).
Results (Cont’d)

Figure 1: Effect of Hematocrit on Glucose Meter Results: Solid Lines: EQ line of method equivalence; Dashed lines represent estimated conditional mean values for glucose meters predicted from coefficients derived by linear regression at different hematocrit values. **Panel A** (a) Meter1 results (Nova Biomedical StatStrip®) — no variation with hematocrit; **Panel B** Meter2 (LifeScan SureStep Flexx). **Panel C** Meter3 (Roche Diagnostics Accu-chek Aviva). **Panel D** Meter4 (Abbott Diabetes Care Precision Freestyle Freedom). Dashed lines (a) Hct = 20%, (b) Hct=25%, (c) Hct=35%, (d) Hct=43%, (e) Hct=55%.

Figure 2: Effect of 2.8 and 5.6 mmol/L Maltose on Glucose Meter Results: Solid Lines: EQ line of method equivalence; Dashed lines represent estimated conditional mean values for glucose meters predicted from coefficients derived by linear regression at different maltose concentrations. **Panel A** Meter1 (Nova Biomedical StatStrip®) Dashed lines for 0, 2.8, 5.6 mmol/L maltose (overlapping, labelled ‘a’); **Panel B** Meter2 (LifeScan SureStep Flexx). **Panel C** Meter3 (Roche Diagnostics Accu-chek Aviva). **Panel D** Meter4 (Abbott Diabetes Care Precision Freestyle Freedom). Dashed lines (a, b, c: 0, 2.8, 5.6 mmol/L maltose).
Results (Cont’d)

Figure 3  Effect of modifying maltose (M), ascorbate (A) and hematocrit (Hct) on Glucose Meter

Results: Solid Lines: EQ line of method equivalence; Dashed lines represent estimated conditional mean values for glucose meters predicted from coefficients derived by linear regression. Panel A) Nova Biomedical StatStrip® a) untreated; b) 5.6mmol/L M; c) 0.59mmol/L A; d) 5.6mmol/L M and 0.59 mmol/L A. Panel B) LifeScan SureStep Flexx Dashed lines a), 0.59 mmol/L A; b) 5.6mmol/L M and 0.59 mmol/L A, Hct= 43%; c) 5.6mmol/L M and 0.59 mmol/L A, Hct= 20%; d) 5.6mmol/L M and 0.59 mmol/L A, Hct= 55%. Panel C) Roche Diagnostics Accu-chek Aviva Dashed lines a) untreated overlaps with the solid line of equivalence; b) 5.6mmol/L M c) 0.59 mmol/L A; d) 5.6mmol/L M and 0.59 mmol/L A, Hct= 43%; e) 5.6mmol/L M and 0.59 mmol/L A, Hct= 20%; Panel D) Abbott Diabetes Care Precision Freestyle Freedom Dashed lines a) untreated, b) 5.6mmol/L M c) 0.59 mmol/L A; d) 5.6mmol/L M and 0.59 mmol/L A, Hct= 43%; e) 5.6mmol/L M and 0.59 mmol/L A, Hct= 20%.

Figure 4: Estimates of Total Analytical Error at 10 mmol/L Glucose: Each glucose meter is denoted by number 1,2,3,4; U is untreated; A has 0.29 mmol/l ascorbate; M has 2.8 mmol/L maltose, AM has both ascorbate and maltose. For each glucose meter and interference condition, the first column (lightly shaded) represents the 40% hematocrit specimen, the second column (dark shade) illustrates the 60% hematocrit and the third column (no shading) represents the 20% hematocrit specimen. Meter 1 (Nova Biomedical StatStrip®); Meter 2 (LifeScan SureStep Flexx); Meter 3 (Roche Diagnostics Accu-chek Aviva); Meter 4 (Abbott Diabetes Care Precision Freestyle Freedom).

Conclusions

The susceptibility of glucose meters to clinically significant analytical biases is highly device-dependent and low hematocrit exacerbated the observed analytical error.
Interference Studies with Two Hospital-Grade and Two Home-Grade Glucose Meters

Martha E. Lyon, Ph.D., 1, 2, 3, 4 Leland B. Baskin, M.D., 4 Sandy Braakman, 5 Steven Presti, M.L.T., 6 Jeffrey Dubois, Ph.D., 6 and Terry Shirey, Ph.D. 6

Abstract

Background: Interference studies of four glucose meters (Nova Biomedical [Waltham, MA] StatStrip™ [hospital grade], Roche Diagnostics [Indianapolis, IN] Accu-Chek Aviva® [home grade], Abbott Diabetes Care [Alameda, CA] Precision FreeStyle Freedom® [home grade], and LifeScan [Milpitas, CA] SureStep Flexx® [hospital grade]) were evaluated and compared to the clinical laboratory plasma hexokinase reference method (Roche Hitachi 912® chemistry analyzer). These meters were chosen to reflect the continuum of care from hospital to home grade meters commonly seen in North America.

Methods: Within-run precision was determined using a freshly prepared whole blood sample spiked with concentrated glucose to give three glucose concentrations. Day-to-day precision was evaluated using aqueous control materials supplied by each vendor. Common interferences, including hematocrit, maltose, and ascorbate, were tested alone and in combination with one another on each of the four glucose testing devices at three blood glucose concentrations.

Results: Within-run precision for all glucose meters was <5% except for the FreeStyle (up to 7.6%). Between-day precision was <6% for all glucose meters. Ascorbate caused differences (percentage change from a sample without added interfering substances) of >5% with pyrroloquinolinequinone (PQQ)-glucose dehydrogenase-based technologies (Aviva and Freestyle) and the glucose oxidase-based Flexx meter. Maltose strongly affected the PQQ-glucose dehydrogenase-based meter systems. When combinations of interferences (ascorbate, maltose, and hematocrit mixtures) were tested, the extent of the interference was up to 193% (Aviva), 179% (FreeStyle), 25.1% (Flexx), and 5.9% (StatStrip). The interference was most pronounced at low glucose (3.9–4.4 mmol/L).

Conclusions: All evaluated glucose meter systems demonstrated varying degrees of interference by hematocrit, ascorbate, and maltose mixtures. PQQ-glucose dehydrogenase-based technologies showed greater susceptibility than glucose oxidase-based systems. However, the modified glucose oxidase-based amperometric method (Nova StatStrip) was less affected in comparison with the glucose oxidase-based photometric method (LifeScan SureStep Flexx).

Introduction

Accuracy of point-of-care glucose meters is a major current concern. 1–3 The target glucose concentration range, used to guide insulin dosage in hospitalized patients, varies depending on the institution and is typically narrower than that in the ambulatory (home) setting. In addition, various drugs, hormones, and additives detected in hospitalized patients have been found to affect the performance of all glucose meter technologies available. 4–7 Several studies have also demonstrated that low hematocrit causes a positive bias and conversely high hematocrit produces a negative bias to glucose concentrations for virtually all meters tested. 4–6, 8–10 Also, the degree to which glucose meters correlate with plasma hexokinase glucose measurements (used frequently as a reference technology) varies greatly between glucose meter technologies. 11 In particular, correlation in the hypoglycemic and hyperglycemic ranges is highly variable with most currently available meters. 12 Consequently, questions have been raised concerning the ability of point-of-care glucose technology to maintain tight glycemic control in a critical care setting such as those using intensive insulin therapy.

The current study was designed to conduct an interference study using four commercially available glucose meters:

Departments of 1 Pathology and Laboratory Medicine, 2 Pediatrics, and 3 Pharmacology and Therapeutics, University of Calgary; 4 Calgary Laboratory Services; and 5 Calgary Health Region, Calgary, Alberta, Canada. 6 Nova Biomedical Corporation, Waltham, Massachusetts.
The following blood glucose meters were tested in this study: two Nova Biomedical StatStrip hospital grade glucose meters, A and B (two slide lots with the meters; one slide lot was assigned to meter A, and the second slide lot was assigned to meter B); a Roche Diagnostics Accu-Chek Aviva home grade glucose meter; an Abbott Diabetes Care Precision FreeStyle Freedom hospital grade meter; and a LifeScan SureStep Flexx hospital grade glucose meter. Two slide lots of the Nova strips were evaluated to challenge the manufacturer’s claim of not requiring a calibration and to examine potential lot-to-lot differences in slide manufacturing. The StatStrip glucose strip technology is a modified glucose oxidase-based amperometric test system with hemocrit and other interference correction, the Aviva uses an electrochemical pyrroloquinolinequinone (PQQ)-glucose dehydrogenase-based amperometric strip and an electrode with hemocrit correction, the FreeStyle used an electrochemical PQQ-glucose dehydrogenase strip, and the Flexx uses a photometric glucose oxidase detection system. All meters are calibrated to report results in plasma equivalents, and results given presume a normal hematocrit. The manufacturer reported acceptable hematocrit ranges for each of the glucose meters is as follows: StatStrip, 30–60%; FreeStyle, 15–65%; Flexx, 25.9–54.5% capillary, 25.5–58.3% venous, and 25.7–54.5% arterial; and Aviva, 20–70%. At maltose concentrations >0.6 mmol/L, the manufacturer of the FreeStyle meter states that an overestimation of blood glucose results will occur. Similarly, the manufacturer of the Aviva meter reports that concentrations of maltose >0.38 mmol/L will result in an overestimation of glucose results. The manufacturer of the Flexx meter states that no significant effect on glucose results will be seen with ascorbate concentrations of up to 0.2 mmol/L. No ascorbate or maltose interference has been reported by the manufacturer of the StatStrip meter. A hexokinase method for measuring glucose in plasma (Roche Hitachi 912® chemistry analyzer) was used as the reference method. The coefficients of variation using Multiqual® (Bio-Rad, Hercules, CA) quality control material and the Hitachi 912 methodology were 1.9%, 1.6%, and 1.4% at glucose concentrations of 3.4, 6.8, and 19.5 mmol/L, respectively. The College of American Pathologists Comprehensive Chemistry External Proficiency Testing results indicated that the hexokinase method in our laboratory deviated by 0.09 mmol/L at both 3.3 and 13.6 mmol/L glucose (challenge specimens) from the mean of 18 other laboratories with similar methodology. Hemocrit was determined using a Clay Adams Brand (Becton Dickinson & Company, Sparks, MD) Autocrit Ultra 3® microhemocrit centrifuge.

Within-run precision study

Within-run precision was assessed by adding varying volumes of a glucose spiking solution (20 g of glucose/dL in deionized water) to three aliquots of heparinized whole blood. The specimen was collected from a healthy volunteer on the previous day and permitted to sit overnight for the glucose concentration to fall. The target glucose concentration ranges were 4–5 mmol/L, 9–12 mmol/L, and 19–22 mmol/L. Each of the three specimens was consecutively analyzed (n = 20) on the evaluated meters. To ensure homogeneity, specimens were mixed between analyses.

Between-day precision study

Day-to-day precision was evaluated using the control materials provided by each of the glucose meter manufacturers. Two levels of control (except one level of control was tested for the FreeStyle meter) manufactured by each vendor were tested in duplicate three times for 2 days and then in duplicate one time and triplicate two times on the third day, giving a total of 20 points for each level of control. The two StatStrip controls had low and high glucose ranges: 2.6–4.3 and 14.8–18.7 mmol/L. One FreeStyle control was used having a glucose range of 4.6–6.9 mmol/L. Two levels of control were used for the Aviva and Flexx meters: Aviva low range 1.4–3.1 mmol/L, high range 14.2–19.1 mmol/L; Flexx low range 1.8–3.2 mmol/L, high range 14.7–22.1 mmol/L.

Interference studies

Fresh heparinized blood specimens were obtained from healthy volunteers for each of 3 days: one day for ascorbate and hematocrit studies, a second day for maltose and hematocrit studies, and the third day for ascorbate, maltose, and hematocrit studies. Concentrations of ascorbate tested were chosen to reflect (at maximum concentration tested) five to 10 times the therapeutic drug level, similar to what has been described previously. Concentrations of maltose tested were chosen to reflect levels that might be encountered in the blood of patients receiving pharmacologic quantities of this additive. Prior to each day of analysis, the anticoagulated whole blood was allowed to sit at room temperature overnight to deplete the glucose concentration to the low glucose range (3.9–4.7 mmol/L). The blood was then divided into three equal volumes, two of them receiving small volumes of a concentrated glucose solution bringing them to the 11.3–13.0 mmol/L and 20.6–24.0 mmol/L ranges. Each of these three glucose samples was further divided into three equal volumes. Using centrifugation, the hematocrit levels of the three samples were adjusted to 21–24%, 43–45%, and 63–66%. This was accomplished by adjusting plasma volumes between the tubes over the packed red blood cells. The actual hematocrit values were determined using the microhematocrit centrifuge. Each of the glucose and hematocrit-adjusted samples was further divided into three volumes, which were then left with no added interferent or spiked with various interfering substances and combinations: 0.29 or 0.59 mmol/L ascorbate (day 1), 2.8 or 5.6 mmol/L maltose (day 2), 0.29 mmol/L ascorbate and 2.8 mmol/L maltose (day 3), or 0.59 mmol/L ascorbate and 5.6 mmol/L maltose (day 3). These adjusted whole blood samples were mixed for 10 min and analyzed using the four glucose meters. A portion of each of the prepared samples was centrifuged shortly after prep-
aration, and the glucose in the plasma was analyzed using the hexokinase method established on the Roche Hitachi 912 according to the manufacturer’s specifications. It has been previously reported that glycolysis can decrease glucose concentrations in a whole blood sample kept at room temperature by approximately 0.28–0.56 mmol/L in 1 h. In an effort to minimize the impact of glycolysis in the heparinized whole blood samples, all samples were assayed with each of the meters within 20 min and by the hexokinase reference method within 20 min of sample preparation.

Data analysis

Within-run precision was determined by calculating the coefficient of variation (CV) for the replicate values. Between-day precision calculations (means, SDs, and CVs) were determined over a 3-day period.

For interference and hematocrit studies, all samples were tested in quadruplicate with each of the glucose meters and centrifuged immediately after the meter readings, and the plasma subsequently was analyzed in duplicate using the hexokinase methods established on the Roche Hitachi 912 chemistry analyzer. All quadruplicate and duplicate values were averaged and treated as single values. To determine the hematocrit effect on the four glucose meters, the percentage bias of the averaged quadruplicate values from each of the meters was determined relative to the averaged duplicate value from the reference hexokinase method. The interference effects of ascorbate, maltose, or ascorbate-maltose mixtures were calculated as the percentage change from a sample to which no interfering substances were added. A clinically significant interference effect was defined as any concentration of interfering substance that changed the mean baseline glucose (no interfering substance added) value by more than 5%.

To determine the hematocrit effect on the four glucose meters, glucose concentrations from the hematocrit-adjusted samples at the three glucose concentrations were determined for each of the three consecutive days by each glucose meter. In order to generate Figures 1–3, the data from the 3 days were pooled. This meant taking an average of the glucose concentrations at each of the three glucose concentrations over the 3 days, as measured by the reference hexokinase method, and designating it as the reference glucose value (i.e., the low reference glucose concentration for the 3 days was the average of the three hexokinase results obtained (4.7 + 3.8 + 4.38)/3 = 4.32 mmol/L). It also meant averaging the difference between each glucose meter and the reference method over the 3 days and averaging the hematocrit values for the 3 days (i.e., hematocrit values of 63–66% over the 3 days were plotted as hematocrit = 64.5%).

Results

Within-run precision study

Within-run precision study values on whole blood [mean ± SD (CV)] at the three glucose concentrations are shown in Table 1.

Between-day precision study

Day-to-day precision values obtained using the vendor-provided control materials are illustrated in Table 2.

Table 1. Within-Run Precision

<table>
<thead>
<tr>
<th>Strip–meter system</th>
<th>Glucose level (mmol/L) [mean, SD (CV)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>StatStrip A</td>
<td>4.14, 0.13 (3.1)</td>
</tr>
<tr>
<td>StatStrip B</td>
<td>4.17, 0.18 (4.4)</td>
</tr>
<tr>
<td>FreeStyle</td>
<td>4.39, 0.33 (8.0)</td>
</tr>
<tr>
<td>Aviva</td>
<td>4.33, 0.12 (2.8)</td>
</tr>
<tr>
<td>Flexx</td>
<td>4.31, 0.13 (5.1)</td>
</tr>
</tbody>
</table>

Thirty replicates of control material at each glucose level were analyzed over a 3-day period using controls supplied from the manufacturers.

Table 2. Day-to-Day Precision

<table>
<thead>
<tr>
<th>Strip–meter system</th>
<th>Glucose level (mmol/L) [mean, SD (CV)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>StatStrip A</td>
<td>3.15, 0.12 (3.9)</td>
</tr>
<tr>
<td>StatStrip B</td>
<td>3.16, 0.18 (5.7)</td>
</tr>
<tr>
<td>FreeStyle</td>
<td>6.99, 0.26 (4.3)</td>
</tr>
<tr>
<td>Aviva</td>
<td>2.38, 0.10 (4.2)</td>
</tr>
<tr>
<td>Flexx</td>
<td>2.67, 0.14 (5.3)</td>
</tr>
</tbody>
</table>

Hematocrit interference study

The effects of hematocrit on the four glucose meters are shown in Figures 1–3. At each glucose concentration, increasing hematocrit levels caused a decrease in measured glucose with all glucose meters examined. However, the effect was less pronounced with the StatStrip meter.

Interfering substances study

Tables 3–5 show the interference error (percentage) seen with the four glucose meters when ascorbate and/or maltose were added to samples with varying glucose concentrations and hematocrit levels.

The ascorbate effect (Table 3) on the glucose meters was most pronounced at the lowest concentration of glucose tested (4.7 mmol/L). Ascorbate caused differences of >5% for the Aviva, FreeStyle, and Flexx meters at a glucose concentration of 4.7 mmol/L. In general, the PQQ-glucose dehydrogenase-based technologies demonstrated positive biases (0.3–26.3%) in the presence of ascorbate, whereas mainly a negative bias (0.9–25%) was observed with the Flexx glucose oxidase technology, and a bias of ~2.8% to 3.5% was detected with the StatStrip glucose oxidase technology. Reduced ascorbate effects were seen with higher glucose concentrations.

Maltose strongly affected the PQQ-glucose dehydrogenase-based technologies (Table 4). Significant positive biases (9.5–185%) in glucose measurement with increasing maltose concentrations at each tested glucose concentration were detected with the Aviva and FreeStyle meters. Higher hematocrit levels tended to reduce the observed bias with PQQ-glucose dehydrogenase-based technologies at the 3.9 and
11.9 mmol/L glucose concentrations tested. In general, glucose oxidase-based technologies (Flexx and StatStrip) were less influenced with combinations of maltose, glucose, and hematocrit. The exception was the Flexx measurement at 3.9 mmol/L glucose with either maltose concentration (2.8 or 5.6 mmol/L) at high hematocrit (63–65%).

The impacts of ascorbate, maltose, glucose, and hematocrit combinations on the measurement of glucose concentration using the evaluated glucose meters are shown in Table 5. Ascorbate and maltose combinations resulted in an additive interferent effect with the PQQ-glucose dehydrogenase-based technologies (Aviva and FreeStyle). This effect was most pronounced at the lowest tested glucose concentration (4.4 mmol/L), and it appeared to be independent of hematocrit. Interferent combinations influenced glucose oxidase-based technologies (Flexx and StatStrip) to a lesser extent. When ascorbate/maltose combinations of interferences were tested, a negative bias was detected with the Flexx meter, particularly with the lowest examined glucose concentration. Glucose measurement using the StatStrip was less affected by ascorbate and/or maltose. However, a negative bias of up to 5.9% was detected with combinations of the higher maltose and ascorbate concentrations at the low glucose concentration (4.4 mmol/L) tested.

**Discussion**

Glucose meters are widely used in hospital and point-of-care monitoring of blood glucose. These devices are easy to use, allow rapid turn-around times, and quantify measurements in very small volumes of specimen. Recent concerns have arisen regarding the accuracy of point-of-care glucose meters and the impact of common interferences such as patient hematocrit on the device performance. These concerns are particularly problematic when considering patient populations like the critically ill or neonates in which extremes in hematocrit are commonly encountered. The current study was designed to conduct an interference study using four commercially available glucose meters reflective of the continuum of care from hospital to home grade meters commonly seen in North America. In an attempt to mimic the complexity of critical care patients, common interferences such as hematocrit, maltose, and ascorbate were tested alone and in combination with one another at three blood glucose concentrations.

Within-run and between-day precisions were comparable between all of the tested glucose meters with the exception of the within-run precision of the FreeStyle, which was slightly worse, and the Flexx, which was slightly better. The impor-
The importance of glucose meter precision was highlighted by a simulation model developed by Boyd and Bruns. In this article, it was noted that CVs must be <1.5% to keep insulin dosing errors less than 5% for hyperglycemic patients.

Several suggestions have been offered to explain the hematocrit effect on glucose strips. An increase in the number of red blood cells in whole blood may mechanically impede diffusion of plasma into the reagent 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 layer. Additionally, the increased viscosity results in a slower rate of diffusion that leads to measurement errors. Even with the manufacturer’s claim, Louis and Ethier found inaccurate results on the glucose meters that related to hematocrit levels. Louie et al. concluded that the effects of low (25%) and high (54%) hematocrit levels can cause overestimated or underestimated glucose measurement with glucose meters, respectively. The current study provides additional data to support the latter’s conclusion. Hematocrit greatly affected the Aviva, FreeStyle, and Flexx meters, whereas the StatStrip meter was minimally influenced (Figs. 1–3). The manufacturers’ reported acceptable hematocrit ranges for the glucose meters are as follows: StatStrip, 30–60%; FreeStyle, 15–65%; Flexx, 25.9–54.5% capillary, 25.5–58.3% venous, and 25.7–54.5% arterial; and Aviva, 20–70%. The results of the current study indicate that the dynamic range for hematocrit might be wider than claimed for the StatStrip meter and less than claimed for the FreeStyle, Flexx, and Aviva meters.

### Table 3. Percentage Ascorbate Interference

<table>
<thead>
<tr>
<th>Glucose level, strip–meter system</th>
<th>22–23%</th>
<th>44%</th>
<th>63–64%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low glucose (4.7 mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>StatStrip A</td>
<td>1.1</td>
<td>1.0</td>
<td>1.1</td>
</tr>
<tr>
<td>StatStrip B</td>
<td>−0.4</td>
<td>1.1</td>
<td>1.7</td>
</tr>
<tr>
<td>Aviva</td>
<td>15.3</td>
<td>10.7</td>
<td>18.4</td>
</tr>
<tr>
<td>FreeStyle</td>
<td>−3.0</td>
<td>3.0</td>
<td>17.1</td>
</tr>
<tr>
<td>Flexx</td>
<td>−11.2</td>
<td>−9.3</td>
<td>−18.6</td>
</tr>
<tr>
<td>Mid glucose (11.4 mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>StatStrip A</td>
<td>0.4</td>
<td>−0.2</td>
<td>1.0</td>
</tr>
<tr>
<td>StatStrip B</td>
<td>−2.8</td>
<td>−2.0</td>
<td>−1.0</td>
</tr>
<tr>
<td>Aviva</td>
<td>7.4</td>
<td>2.0</td>
<td>7.4</td>
</tr>
<tr>
<td>FreeStyle</td>
<td>1.5</td>
<td>4.0</td>
<td>6.2</td>
</tr>
<tr>
<td>Flexx</td>
<td>−4.9</td>
<td>−2.9</td>
<td>−7.4</td>
</tr>
<tr>
<td>High glucose (24 mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>StatStrip A</td>
<td>0.3</td>
<td>−0.9</td>
<td>0.3</td>
</tr>
<tr>
<td>StatStrip B</td>
<td>2.0</td>
<td>2.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Aviva</td>
<td>2.6</td>
<td>4.0</td>
<td>3.7</td>
</tr>
<tr>
<td>FreeStyle</td>
<td>1.5</td>
<td>−0.8</td>
<td>1.1</td>
</tr>
<tr>
<td>Flexx</td>
<td>2.4</td>
<td>−0.9</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Ascorbate interference was checked at two concentrations for each meter–strip system at three glucose levels and at three hematocrit levels. Results are reported as percentage changes from specimen with no added interferent to that with interferent (0.29 mmol/L ascorbate or 0.59 mmol/L ascorbate).
The magnitude of the hematocrit-related error is very likely the most significant component of error generally seen for glucose meters. Overestimating glucose concentrations by 0.6–0.9 mmol/L in patients with a low hematocrit (23%) and a low endogenous glucose concentration could compromise the ability to identify hypoglycemia. Similarly, negative bias errors of 2.8–4.6 mmol/L in patients with a high hematocrit (>59%) and a high endogenous glucose concentration (22.3 mmol/L) could lead to underestimating insulin dosing for hyperglycemic patients.

The interference studies clearly confirmed that ascorbate and maltose as well as mixtures with extremes in magnitude of the hematocrit-related error are very likely the most significant component of error generally seen for glucose meters. Overestimating glucose concentrations by 0.6–0.9 mmol/L in patients with a low hematocrit (23%) and a low endogenous glucose concentration could compromise the ability to identify hypoglycemia. Similarly, negative bias errors of 2.8–4.6 mmol/L in patients with a high hematocrit (>59%) and a high endogenous glucose concentration (22.3 mmol/L) could lead to underestimating insulin dosing for hyperglycemic patients.

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Combined interference from ascorbate (0.29 and 0.59 mmol/L) and maltose (2.8 and 5.6 mmol/L) was determined at three glucose and three hematocrit levels. Results are reported as percentage changes from specimen with no added interferent to that with interferent (2.8 mmol/L or 5.6 mmol/L maltose).
MULTIPLE INTERFERENCES IN GLUCOSE METERS

hematocrit affect meter–strip technologies currently in use. In certain situations, the interfering mixtures appeared to have an additive bias effect (Table 5). Ascorbate caused a significant positive bias with the PQQ-glucose dehydrogenase-based technologies (Aviva and FreeStyle) when low glucose concentrations were evaluated. This could be an important consideration in the treatment of critically ill and burn patients that are receiving large doses of ascorbate. Ascorbate might be directly functioning as a substrate for glucose dehydrogenase.

The enzyme glucose dehydrogenase, depending on its formulation (NAD, FAD, or PQQ), can react with maltose, a metabolite of icodextrin. Glucose measurement systems using this enzyme may give false-positive results. There have been reports of inappropriate insulin administrations resulting in life-threatening/fatal hypoglycemia as a consequence of erroneous test results obtained from patients receiving parenteral products containing maltose. The maltose effect on glucose measurement has been demonstrated by Janssen et al. These authors found that icodextrin metabolites can cause positive interferences that may lead to a missed diagnosis of hypoglycemia. The FreeStyle and Aviva glucose meters were very susceptible to maltose interference at all glucose concentrations tested with the greatest effect (percentage) occurring at the lowest glucose concentration (Table 4).

In conclusion, all evaluated glucose meter systems demonstrated varying degrees of interference by hematocrit, ascorbate, and maltose mixtures. PQQ-glucose dehydrogenase-based technologies showed greater susceptibility than glucose oxidase-based systems. However, the modified glucose oxidase-based amperometric method (Nova StatStrip) was less affected in comparison with the glucose oxidase-based photometric method (LifeScan SureStep Flexx).

Acknowledgments

The authors wish to thank Nova Biomedical Corporation for the generous donation of the StatStrip blood glucose monitoring system (meter and strips).

Author Disclosure Statement

No competing financial interests exist.

References


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Evaluation of a Point-Of-Care (POC) Glucose Meter Suitable for Use in Complex Tertiary Care Facilities

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1Department of Clinical Pathology, Sunnybrook Health Sciences Centre, Toronto, Ontario, M4N 3M5, 2Department of Pathobiology and Laboratory Medicine, University of Toronto and 3Gamma-Dynacare Medical Laboratories, Ontario, Canada.

Objective:

• To evaluate the performance and suitability of a single glucose meter for use in a complex tertiary care facility (TCF);

Introduction:

• POC glucose meters are commonly used in TCF, despite some known limitations and concerns.
• Clinical conditions associated with extreme body chemistries, use of potentially interfering medications & biologics, etc, are common in TCF and pose unique challenges to POC glucose testing.
• The ability to use a single, yet reliable and accurate POC glucose meter that can satisfy different clinical needs, will not only be cost effective, but also improve patient care and safety.

Methods:

• The StatStrip® glucose meter from Nova Biomedical, Waltham, MA, was evaluated for use in a 1300-bed (125 critical care), 3-site, teaching TCF in Toronto, involving 4 technologists and 20 front-line nurses (Table 1);
• Intra-assay and long term imprecision were determined using aqueous, commercial stabilized whole blood (SWB) and fresh whole blood materials. A CV<5% is deemed to be acceptable;
• Lab glucose measurements were made on the Modular analyzer from Roche, using a glucose oxidase method (CV<2%);
• Analytical interferences were tested for 9 substances at 3 glucose concentrations. A difference in meter glucose measurements greater than the larger of 10% or 0.33 mmol/L from the control sample is considered significant.
• Effects of endogenous parameters (Hct, Hb, pH, pCO₂, pO₂, HCO₃, lactate, Na, K, Cl and iCa measured on the ABL800 Flex, Radiometer) on meter glucose measurement were assessed by backward stepwise linear regression (SigmaStat 3.01 from SPSS), and discrepancies from lab measurement were compared at different levels of contributing parameters.
• Meter and lab glucose measurements were correlated using simple linear regression analysis and Pearson’s correlation coefficient was calculated (SigmaStat3.01, SPSS).
• Meter inaccuracy was assessed by:
  • Bias plot with ISO 15197/CSLI criteria [1,2]
  • Consensus grid analyses (EP evaluator release 8, David G. Rhoads Associates Inc).
  • Modified Locally Smoothed-Median Absolute Difference (LS-MAD) [3]
• Statistical significance were accepted at p<0.05
Table 1. Sampling procedures for Glucose Measurements by Meter and Central Laboratory

<table>
<thead>
<tr>
<th>Clinical Services</th>
<th>Sample Collection &amp; Meter Operators</th>
</tr>
</thead>
</table>
| Neonatal ICU               | **Meter:** capillary blood sample by heel prick; nurse operator  
|                            | **Lab:** plasma from capillary sample by heel prick collected into a microtainer tube                                                                                                                                                                                                                     |
| Diabetic Clinic            | **Meter:** capillary blood sample by finger prick; nurse operator  
|                            | **Lab:** separate venous blood into grey top tubes                                                                                                                                                                                                                                                     |
| CVICU                      | **Meter:** arterial blood drawn from Arterial line into a syringe; nurse operator  
|                            | **Lab:** plasma from arterial blood drawn from arterial line into a second syringe and then into a green top tube                                                                                                                                                                                      |
| Stat Lab (Operating Rooms and ICUs) | **Meter:** arterial blood in gas syringes; laboratory technologist operator  
|                            | **Lab:** same arterial blood for ABL 800 Flex (electrolytes & blood gas parameters), then spun down for plasma to be used for glucose measurement on the Roche Modular                                                                                                                                                              |
| Delivery Suite             | **Meter:** cord blood collected into gas syringes; nurse operator  
|                            | **Lab:** plasma from the same cord blood sample                                                                                                                                                                                                                                                      |
| Dialysis Unit              | **Meter:** arterial/venous blood drawn from fistula or central venous catheter into a syringe; nurse operator  
|                            | **Lab:** plasma from sample collected into a second syringe & then dispensed into a green top tube                                                                                                                                                                                                     |

“Operator” refers to personnel who operated the meter to measure the glucose levels using the blood sample described.

Table 2. Imprecision Study

<table>
<thead>
<tr>
<th>Material</th>
<th>N</th>
<th>Glucose Concentration, mmol/L</th>
<th>Imprecision, %CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aqueous</td>
<td>70</td>
<td>3.1</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>15.4</td>
<td>3.7</td>
</tr>
<tr>
<td>Stabilized whole blood</td>
<td>83</td>
<td>2.9</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td>83</td>
<td>10.4</td>
<td>4.1</td>
</tr>
<tr>
<td>Arterial Whole Blood</td>
<td>20</td>
<td>3.2</td>
<td>4.5</td>
</tr>
<tr>
<td>(within run)</td>
<td>20</td>
<td>8.2</td>
<td>4.2</td>
</tr>
<tr>
<td>Stabilized whole blood</td>
<td>22</td>
<td>2.9</td>
<td>4.7</td>
</tr>
<tr>
<td>(within run)</td>
<td>22</td>
<td>6.9</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>16.6</td>
<td>2.4</td>
</tr>
</tbody>
</table>
Results:

Imprecisions were all < 5% (Table 2);

Interferences: all were insignificant except total hemoglobin (Hb) at 10 g/L, showing a 9-18% reduction in measured glucose values (Table 3);

Backward stepwise linear regression identified pCO₂ & Na as contributing factors on the meter glucose measurement, but effects were negligible (mean difference over lab value< 0.3 mmol/L);

Correlation of meter and lab results: slope=1.01 (95% CI 0.99-1.03), intercept=0.01 (-0.13-0.15), r=0.985 (Figure 1);

Consensus grid analysis: 97% and 3% in regions A and B respectively (Table 4), and 97% met ISO 15197 & CSLI (formerly NCCLS) criteria (Figure 2 & 3).

LS-MAD showed median differences were stable up to about 10 mmol/L and started to increase afterwards (Figure 4).

Table 3. Potentially Interfering Substances and Concentrations Tested

<table>
<thead>
<tr>
<th>Substances Tested</th>
<th>Glucose Concentration, mmol/L</th>
<th>Glucose Concentration, mmol/L</th>
<th>Glucose Concentration, mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Units</td>
<td>Concentrations</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>%</td>
<td>27</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>49</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>68</td>
<td>2.9</td>
</tr>
<tr>
<td>Haematocrit, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb, g/L</td>
<td>0</td>
<td>2.3</td>
<td>8.3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2.3</td>
<td>7.9</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>2.1</td>
<td>6.7*</td>
</tr>
<tr>
<td>Acetaminophen, µmol/L</td>
<td>0</td>
<td>2.4</td>
<td>8.8</td>
</tr>
<tr>
<td></td>
<td>330</td>
<td>2.2</td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>660</td>
<td>2.1</td>
<td>8.7</td>
</tr>
<tr>
<td>Bilirubin, µmol/L</td>
<td>0</td>
<td>1.5</td>
<td>7.1</td>
</tr>
<tr>
<td></td>
<td>257</td>
<td>1.4</td>
<td>7.1</td>
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<tr>
<td></td>
<td>855</td>
<td>1.3</td>
<td>7.3</td>
</tr>
<tr>
<td>Ascorbic acid, µmol/L</td>
<td>0</td>
<td>3.2</td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td>290</td>
<td>3.2</td>
<td>9.2</td>
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<tr>
<td></td>
<td>590</td>
<td>3.2</td>
<td>9.0</td>
</tr>
<tr>
<td>Maltose, mmol/L</td>
<td>0</td>
<td>2.7</td>
<td>7.3</td>
</tr>
<tr>
<td></td>
<td>2.8</td>
<td>2.8</td>
<td>7.3</td>
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<tr>
<td></td>
<td>5.6</td>
<td>2.8</td>
<td>7.4</td>
</tr>
<tr>
<td>Galactose, mmol/L</td>
<td>0</td>
<td>1.6</td>
<td>7.2</td>
</tr>
<tr>
<td></td>
<td>5.6</td>
<td>1.8</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>11.1</td>
<td>1.8</td>
<td>7.4</td>
</tr>
<tr>
<td>Lactate, mmol/L</td>
<td>0</td>
<td>2.6</td>
<td>7.8</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>2.5</td>
<td>7.7</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>2.5</td>
<td>7.7</td>
</tr>
<tr>
<td>Uric acid, mmol/L</td>
<td>0</td>
<td>1.8</td>
<td>7.7</td>
</tr>
<tr>
<td></td>
<td>0.47</td>
<td>1.8</td>
<td>7.7</td>
</tr>
<tr>
<td></td>
<td>1.18</td>
<td>1.8</td>
<td>8.0</td>
</tr>
<tr>
<td>β-OH Butyrate, mmol/L</td>
<td>0</td>
<td>1.7</td>
<td>7.6</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>1.6</td>
<td>7.6</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>1.6</td>
<td>7.7</td>
</tr>
</tbody>
</table>

Each glucose concentration represents the mean of four glucose measurements using four different glucose meters. A difference of ≥ the larger of 10% or 0.33 mmol/L is considered significant and is denoted by *.
Table 4. Relative Accuracy of the Meter Glucose Measurement

<table>
<thead>
<tr>
<th>Clinical Service</th>
<th>N</th>
<th>% Error</th>
<th>95th centile</th>
<th>% in Region</th>
<th>ISO/CLSI Criteria Met, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Neonatal ICU</td>
<td>56</td>
<td>11.2</td>
<td>34.8</td>
<td>98</td>
<td>2</td>
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<tr>
<td>Diabetic Clinic</td>
<td>43</td>
<td>8.6</td>
<td>28.1</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td>CVICU</td>
<td>45</td>
<td>6.5</td>
<td>18.9</td>
<td>93</td>
<td>7</td>
</tr>
<tr>
<td>Stat Lab (Operating rooms and ICUs)</td>
<td>163</td>
<td>6.6</td>
<td>18.0</td>
<td>98</td>
<td>2</td>
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<tr>
<td>Delivery Suite</td>
<td>47</td>
<td>9.1</td>
<td>22.9</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Dialysis</td>
<td>32</td>
<td>7.1</td>
<td>27.5</td>
<td>94</td>
<td>6</td>
</tr>
<tr>
<td>Overall</td>
<td>386</td>
<td>7.8</td>
<td>21.8</td>
<td>97</td>
<td>3</td>
</tr>
</tbody>
</table>

1Consensus Grid acceptance criteria: 95% of data within Region A & no sample outside region B
2ISO/CLSI criteria: ≥95% of data with a difference ± 0.83 mmol/L for glucose concentration < 4.2 mmol/L or ±20% if glucose concentration is > 4.2 mmol/L

Figure 1. Linear Regression

Meter = 1.01 (0.99-1.03) *Lab + 0.01 (0.13 – 0.15)  r = 0.985
Glucose concentrations covered: Mean ± SD (range)
Lab: 7.03 ± 3.9 (0.5 – 27.1) mmol/L
Meter: 7.11 ± 4.0 (0.6 – 30.4) mmol/L
Discussion & Conclusions:

- The imprecision (CV<5%) is acceptable, and will rarely lead to major errors in insulin dose as suggested previously [4]. 1-1.5% CV will be ideal but is not achievable consistently by any known meters on the market.
- The StatStrip® meter is relatively free from common interferences seen in TCF such as Hct, maltose, etc. The effects of free Hb (as in hemolysis), pCO₂ and Na are marginal and will not compromise the meter performance significantly.
- The meter results compare very well with plasma values from the Laboratory, and meet the suggested acceptance criteria from CSLI and ISO, although fall short of those proposed by ADA (5% total error).
- No significant error (Type 1 & 2) was found with the current Tight Glycemic Control target of 5.1 – 8.0 mmol/L.
- Overall, StatStrip® meter is found to be a good candidate for general use in a complex TCF.

Figure 2. Bias Plot with ISO Limits

Figure 3. Consensus Grid Analysis
Figure 4. Modified LS-MAD  N=386

Note:
• 1.5 mmol/L (½ current Tight Glycemic Range of 5-8) was used instead of 0.83 mmol/L as suggested by Kost, et al [3].
• A 10.6% error limit (calculated based on meter and lab CV) shown instead of a fixed 0.28 mmol/L proposed.

References:
Performance of a StatStrip® Meter

A. Chittamma¹, J.A. DuBois², T. Shirey², M. Heinz², P. Santanirand³, U. Chaichanjarernkul¹, and S. Vanavanan¹

¹Division of Clinical Chemistry, Department of Pathology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
²Nova Biomedical Corporation, Waltham, MA, USA
³Division of Microbiology, Department of Pathology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Background
Glucose meters are widely used in self – and hospital monitoring of blood glucose. We examined the analytical performance of the newly introduced Nova Biomedical StatStrip® glucose monitoring system.

Methods
Linearity, % recovery and within-run imprecision were studied using whole blood specimens spiked with glucose. A total of 50 heparinized samples were used in method comparison using a plasma hexokinase on the Dade Dimension RxL analyzer as the comparison method. Common interferences, previously shown to effect current glucose meter measurement technologies, were tested on the StatStrip®, Roche Accu-Chek Advantage and the MediSense Optium blood glucose systems at low, middle and high glucose levels.

Results
The StatStrip® assay was determined to be linear within an allowable systematic error of 10% over the range of 27-600 mg/dL. The within-run imprecision of the StatStrip®, as determined by coefficient of variation, was < 2.5% for glucose concentrations between 64-286 mg/dL. Deeming regression analysis gave a slope of 1.000, an intercept of 1.361, and a $S_{y|x}$ of 1.132 (r=0.996) over the range 60-461 mg/dL. The mean bias relative to the Dimension RxL method was 1.36 mg/dL. The StatStrip® meter met the performance goals recommended by the CLSI/ISO 15197, the FDA and CLIA. Of the three meters tested, only the StatStrip® showed interference <10% for all levels of acetaminophen, ascorbic acid, maltose and hematocrit tested at all glucose blood concentrations.

Conclusions
The Nova StatStrip® glucose meter showed acceptable correlation, and precision when compared to a clinical laboratory reference method, was not susceptible to common interferences observed on other blood glucose meters, and is suitable for point-of-care hospital glucose testing.

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•73. June 2007 Copyright © by Walter de Gruyter Berlin New York
Glucose Regression Analysis
Nova StatStrip®/Dade Dimensional DxL

R²: 0.99137  SLOPE: 0.996  INTERCEPT: 2.083  N= 50

<table>
<thead>
<tr>
<th>StatStrip</th>
<th>Dade Dimension RxL</th>
<th>BIAS</th>
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</thead>
<tbody>
<tr>
<td>Min = 60</td>
<td>Min = 63</td>
<td>Min = 1.360</td>
</tr>
<tr>
<td>Max = 460</td>
<td>Max = 468</td>
<td>Max = 8.007</td>
</tr>
<tr>
<td>Mean = 169.760</td>
<td>Mean = 168.400</td>
<td>Mean = 1.030</td>
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Hematocrit Interference Study
Nova StatStrip®/Abbott MediSense Optimum

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<td>Nova</td>
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Mean:
62   63   61   51   60   37

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<td>211</td>
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<td>211</td>
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<td>229</td>
</tr>
<tr>
<td>216</td>
<td>246</td>
<td>222</td>
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Mean:
214  244  220  188  224  127

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<td>Abbott</td>
<td>Nova</td>
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<td>24</td>
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<td>353</td>
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<td>363</td>
<td>385</td>
<td>361</td>
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</table>

Mean:
358  390  355  326  363  251
Maltose Interference Study
Nova StatStrip® / Roche Accu-Chek
Rama Hospital, Bangkok, Thailand

Maltose Interference

- **Nova StatStrip®**
- **Roche Accu-Chek Advantage**

<table>
<thead>
<tr>
<th>Maltose (mg/dL)</th>
<th>Nova</th>
<th>Roche Accu-Chek Advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>73</td>
<td>56</td>
</tr>
<tr>
<td>100</td>
<td>65</td>
<td>68</td>
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<tr>
<td>200</td>
<td>105</td>
<td>159</td>
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<td>300</td>
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<td>500</td>
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<td>600</td>
<td>66</td>
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</tr>
<tr>
<td>700</td>
<td>162</td>
<td>161</td>
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</table>

Mean

- **Nova StatStrip®**
- **Roche Accu-Chek Advantage**

<table>
<thead>
<tr>
<th>Maltose (mg/dL)</th>
<th>Nova</th>
<th>Roche Accu-Chek Advantage</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>74</td>
<td>59</td>
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<td>100</td>
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<tr>
<td>200</td>
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<td>68</td>
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<tr>
<td>400</td>
<td>160</td>
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</table>

Mean

- **Nova StatStrip®**
- **Roche Accu-Chek Advantage**

<table>
<thead>
<tr>
<th>Maltose (mg/dL)</th>
<th>Nova</th>
<th>Roche Accu-Chek Advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>220</td>
<td>168</td>
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Mean

- **Nova StatStrip®**
- **Roche Accu-Chek Advantage**

<table>
<thead>
<tr>
<th>Maltose (mg/dL)</th>
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<th>Roche Accu-Chek Advantage</th>
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</thead>
<tbody>
<tr>
<td>0</td>
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<td>400</td>
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### StatStrip® Glucose Precision Study

#### Approx Target Glucose 48-78 mg/dl

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<th>Results</th>
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<tr>
<td>1</td>
<td>64</td>
<td>MEAN 64</td>
</tr>
<tr>
<td>2</td>
<td>63</td>
<td>SD 1.1</td>
</tr>
<tr>
<td>3</td>
<td>64</td>
<td>CV% 1.7</td>
</tr>
<tr>
<td>4</td>
<td>64</td>
<td>2SD RANGE 61.9 - 66.3</td>
</tr>
<tr>
<td>5</td>
<td>64</td>
<td>N 10</td>
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#### Approx Target Glucose 90-130 mg-dl

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<td>MEAN 110</td>
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<tr>
<td>2</td>
<td>110</td>
<td>SD 1.3</td>
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<tr>
<td>3</td>
<td>110</td>
<td>CV% 1.2</td>
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<tr>
<td>4</td>
<td>110</td>
<td>2SD RANGE 107.7 - 113.1</td>
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<td>5</td>
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#### Approx Target Glucose 257-327 mg-dl

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<tr>
<td>1</td>
<td>285</td>
<td>MEAN 286</td>
</tr>
<tr>
<td>2</td>
<td>288</td>
<td>SD 6.7</td>
</tr>
<tr>
<td>3</td>
<td>278</td>
<td>CV% 2.3</td>
</tr>
<tr>
<td>4</td>
<td>293</td>
<td>2SD RANGE 273.1 - 299.7</td>
</tr>
<tr>
<td>5</td>
<td>275</td>
<td>N 10</td>
</tr>
</tbody>
</table>

---

*Ramathibodi Hospital, Bangkok (Cont’d)*
Background

Glucose meters are used routinely in hospital wards and important clinical decisions are made from the results generated by these instruments.

In this study we evaluated the accuracy and precision of the following hospital glucose meters:
- Abbott Medisense Optium (glucose dehydrogenase)
- Roche Accu-Chek Inform (glucose dehydrogenase)
- HemoCue Glucose 201+ (glucose dehydrogenase)
- Nova StatStrip (modified glucose oxidase)

The Roche, HemoCue and Nova platforms all have the ability to transfer patient and quality control results electronically via hospital networks to electronic medical records and laboratory information systems.

Methods

Accuracy of the meters was evaluated by hospital nurses performing a finger stick capillary test on a patient. Immediately following this, a venous sample was taken and sent to the laboratory for testing on the Roche Modular (hexokinase based method). Lab samples taken more than 15 minutes after the capillary sample were not included in the study.

Accuracy was assessed using the ISO 15197 standard, which sets minimum acceptable accuracy for glucose meters. These guidelines state that a minimum of 95% of the individual results for the glucose meter must fall within ± 0.83 mmol/L at glucose concentrations ≤ 4.1 and ± 20% at glucose concentrations > 4.1 mmol/L of the reference laboratory method.

All nursing staff involved in the evaluation were trained on how to use each instrument by a medical scientist.

Precision was evaluated by nursing staff performing daily quality control testing while the instrument was in routine use. Quality control material supplied by the manufacturers was used for precision analysis.

Results

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Level</th>
<th>Median(mmol/L)</th>
<th>CV (%)</th>
<th>Level</th>
<th>Median(mmol/L)</th>
<th>CV (%)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott</td>
<td>1</td>
<td>2.8</td>
<td>6.2</td>
<td>2</td>
<td>15.9</td>
<td>4.8</td>
<td>87</td>
</tr>
<tr>
<td>Roche</td>
<td>1</td>
<td>3.1</td>
<td>6.6</td>
<td>2</td>
<td>17.4</td>
<td>5.1</td>
<td>121</td>
</tr>
<tr>
<td>Hemocue</td>
<td>1</td>
<td>2.3</td>
<td>9.5</td>
<td>2</td>
<td>9.3</td>
<td>4.3</td>
<td>30</td>
</tr>
<tr>
<td>Nova</td>
<td>1</td>
<td>3.1</td>
<td>4.0</td>
<td>2</td>
<td>15.9</td>
<td>2.6</td>
<td>32</td>
</tr>
</tbody>
</table>

Table 1. Precision analysis of the glucose instrument
Results (Cont’d)

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Results Within ISO 15197 Standard (%)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott</td>
<td>89.5</td>
<td>313</td>
</tr>
<tr>
<td>Roche</td>
<td>95.0</td>
<td>386</td>
</tr>
<tr>
<td>Hemocue</td>
<td>92.6</td>
<td>95</td>
</tr>
<tr>
<td>Nova</td>
<td>97.0</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2. Accuracy analysis of the glucose instruments compared to the hospital laboratory analyser according to the ISO 15197 standard.

![Graph A](image1.png) ![Graph B](image2.png) ![Graph C](image3.png) ![Graph D](image4.png)

Figure 1: Bland Altman correlations for the Abbott Medisense (A), Roche Accu-Chek Inform (B), HemoCue Glucose 201+ (C) and Nova StatStrip (D) compared with the Roche Modular Laboratory analyser.

Passing and Bablok analysis for each of the instruments compared with the laboratory analyser produced the following equations:
- Abbott Glucose = 1.07x – 0.17 (r = 0.95, P < 0.0001: n = 313: sample range = 3.0 – 20.3mmol/L)
- Roche Glucose = 1.00x – 0.20 (r = 0.94, P < 0.0001: n = 385: sample range = 3.2 – 16.4mmol/L)
- Hemocue Glucose = 1.00x – 0.60 (r = 0.97, P < 0.0001: n = 95: sample range = 4.6 – 17.5mmol/L)
- Nova Glucose = 1.00x – 0.30 (r = 0.98, P < 0.0001: n = 100: sample range = 0.9 – 16.0mmol/L)
Conclusion

The Nova StatStrip and Roche Accu-Chek inform platforms displayed the best accuracy and were the only two to meet the accuracy requirements set by the ISO 15197 standard.

The Nova StatStrip instrument displayed the best precision for both levels of control, whilst the other three instruments showed comparable precision results. The HemoCue showed the most imprecision for the low level control (CV = 9.5%).

Understanding of possible test interferences such as Haematocrit and Maltose is crucial in selecting hospital glucose meters for use.

The Roche instrument trialed in this study has known maltose interference. We are currently evaluating the new Roche Accu-Chek Inform II instrument and strips which has been reported as not having this interference. Preliminary results indicate that the new platform has improved accuracy compared to the Accu-Chek Inform I instrument (r=0.98, Y = 1.00x + 0.00 & 97.1% of results fell within the ISO 15197 guidelines, n=137).

Other important criteria to be considered when selecting appropriate glucose point of care instrumentation include ease of use, time to result, portability, storage requirements, appropriate QC material and connectivity.

Acknowledgements: We wish to thank staff of the Cardiac Care Unit at Flinders Medical Centre for their support during the trial and Roche Diagnostics Australia, Regional Health Care Group and HemoCue Australia for the supply of instruments and reagents used in this study.
Performance of the Nova StatStrip Point of Care Glucose Meter in a Neonatal Intensive Care Unit

Dorit Stahl, Kurt Herkner, Arnold Pollak, Andrea R. Prusa

Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Austria

Background

Many commonly used point of care (POC) glucose meters fail to achieve international quality standards when evaluated in NICU patients. A new glucose POC meter (Nova Biomedical StatStrip®) showed high accuracy in analytical studies and was unaffected by hematocrit and other interfering substances. The aim of this study was to assess the performance of Nova StatStrip® in a challenging preterm neonatal population.

Methods

Nova StatStrip® (Nova Biomedical, Waltham, MA) and the glucose meter Precision Xceed (Abbott Diabetes, Alameda, CA) were tested on 106 samples from 58 NICU patients. Specimens were heparinised whole blood samples obtained for blood gas analysis. Accuracy of the meter and analytical interferences were evaluated by comparing the results of the meter with the results of the blood gas analyser ABL 700 (Radiometer Medical ApS, Copenhagen, Denmark).

Results

The results of the StatStrip® glucose meter correlated much better with the reference method across a wide glucose concentration range compared to the Precision Xceed results (figure 1a and figure 1b).

![Figure 1a](image1.png)

**StatStrip® – BGA**
- slope: 1.00
- lower 95%-CL: 0.97
- upper 95%-CL: 1.06
- intercept: 3.00
- lower 95%-CL: -1.00
- upper 95%-CL: 5.59

**Figure 1a:** Passing-Bablok regression analysis. StatStrip® versus blood gas analyser (BGA) glucose results.

![Figure 1b](image2.png)

**Precision Xceed – BGA**
- slope: 0.89
- lower 95%-CL: 0.84
- upper 95%-CL: 0.95
- intercept: 8.11
- lower 95%-CL: 3.37
- upper 95%-CL: 14.25

**Figure 1b:** Passing-Bablok regression analysis. Precision Xceed versus blood gas analyser (BGA) glucose results.
Results (Cont’d)

The glucose results of the StatStrip® meter met ISO 15197 criteria, whereas the results of the Precision Xceed meter did not (figure 2a and 2b).

<table>
<thead>
<tr>
<th>glucose meter</th>
<th>glucose &lt; 75 mg/dl</th>
<th>glucose &gt; 75 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>sample number</td>
<td>%&lt;15mg/dl bias</td>
</tr>
<tr>
<td>StatStrip®</td>
<td>24</td>
<td>100%</td>
</tr>
<tr>
<td>Precision</td>
<td>25</td>
<td>96%</td>
</tr>
</tbody>
</table>

The glucose results of the StatStrip® meter correlated better with the reference method than the Precision Xceed results and were less affected by hematocrit (figure 3a and 3b) and pH changes (figure 4a and 4b).

The accuracy of results for both glucose meters was unaffected by other medications, e.g. Vitamin C and other factors, e.g. birth weight or patient’s age.

Conclusions

Nova StatStrip® showed good clinical accuracy and performance for measuring and monitoring glucose levels in NICU patients and is a suitable alternative to a blood gas analyser for measuring glucose in a challenging preterm neonatal population.
Reliability of Glucose Meters in Hospitals in Austria

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Central Lab, University Clinic for Pediatric, Vienna, ¹Department for Pediatric, Clinicum St. Poelten, St. Poelten, ³Geriatric Healthcenter Graz, Graz, ⁴Nova Biomedical Ges.m.b.H, Vienna.

Introduction
Rapid and accurate monitoring of blood glucose levels in hospitalised patients is important in managing glycemic control. Blood glucose meters developed for self-monitoring of diabetics are commonly used for glucose measurements in hospitalised patients. However recent studies have highlighted that the accuracy of many of these commonly used glucose meters is not sufficient for measuring glucose in critically ill patients. The accuracy of results can be influenced by abnormal hematocrit levels commonly present in hospitalised patients as well as common interference substances present in whole blood (drugs, metabolites).

StatStrip® (Nova Biomedical) is a new generation handheld glucose sensor specifically designed for hospital use. The design of the sensor corrects for common biochemical interference factors and also measures and corrects for hematocrit.

Aim
- To assess the analytical performance, accuracy and specificity of glucose meters commonly used in Austria.
- To challenge the performance of a new glucose meter StatStrip® in three hospital centres in Austria.
- To assess the reliability of glucose meters routinely used in Austria for use in hospitalised patients populations.

Method
Glucose Methods Used
- StatStrip® (Nova Biomedical)
- Accu-Chek® Go (Roche Diagnostics)
- Precision Xceed® (Abbott Diabetes).
- Ascensia Breeze® 2 (Bayer Healthcare).
- Glucocard™ X-Meter (A.Menarini diagnostics),
- OneTouch® Ultra® (LifeScan),

Comparison Methods Used
- Vitros 900 (Ortho Clinical Diagnostics)
- Hitachi 917 (Roche Diagnostics)
- Lisa 500 Plus (Leupamed Ges.m.b.H )

Method Correlation and Accuracy Assessment
Heparinised venous whole-blood specimens were collected from patients in the three sites and the glucose levels were measured and compared to the reference method. Accuracy was assessed by comparison to ISO15197 glucose performance criteria.
Method (Cont'd)

Hematocrit interference

Hematocrit interference was evaluated using 5 glucose concentrations over a hematocrit range of 20-70%.

Chemical interference

Interference studies were performed with acetaminophen, ascorbic acid, and maltose. Interference was evaluated using whole blood samples with different glucose levels spiked with different concentrations of each interfering substance.

Results

Method Correlation

StatStrip® showed the closest correlation to the reference methods and the lowest bias of all the meters tested.

<table>
<thead>
<tr>
<th>Correlation</th>
<th>StatStrip</th>
<th>AccuChek GO</th>
<th>Precision Xceed</th>
<th>Glucocard X</th>
</tr>
</thead>
<tbody>
<tr>
<td>R²</td>
<td>0.995</td>
<td>0.929</td>
<td>0.919</td>
<td>0.912</td>
</tr>
<tr>
<td>Slope</td>
<td>0.970</td>
<td>0.879</td>
<td>0.812</td>
<td>0.764</td>
</tr>
<tr>
<td>Intercept</td>
<td>3.042</td>
<td>9.668</td>
<td>20.232</td>
<td>11.428</td>
</tr>
<tr>
<td>Bias</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (mg/dL)</td>
<td>-3.84</td>
<td>-19.6</td>
<td>27.7</td>
<td>-46.1</td>
</tr>
<tr>
<td>sd (mg/dL)</td>
<td>13.39</td>
<td>51.75</td>
<td>56.83</td>
<td>63.4</td>
</tr>
<tr>
<td>%</td>
<td>-1.16</td>
<td>-6.09</td>
<td>-6.56</td>
<td>-16.63</td>
</tr>
<tr>
<td>number</td>
<td>149</td>
<td>97</td>
<td>89</td>
<td>97</td>
</tr>
</tbody>
</table>

Meter Accuracy – ISO 15197 criteria

StatStrip® demonstrated greater accuracy compared to the other meters used and was the only meter satisfying the requirements of ISO 15197 performance criteria.

Site A - Accuracy assessment
Results (Cont’d)

Site A - Accuracy assessment (Cont’d)

Hematocrit Interference

The accuracy of the meters routinely used in Austria were affected to varying degrees by abnormal hematocrit levels showing significant bias compared to the normal hematocrit glucose value and the reference method. The hematocrit interference occurred across all three glucose levels tested. The accuracy of StatStrip® was unaffected by abnormal hematocrit levels.
Results (Cont’d)

Site B - Hematocrit Interference (Cont’d)

Maltose Interference

The accuracy of the AccuChek and Glucocard meters were affected by varying levels of maltose showing significant bias compared to the control level and the reference method. The maltose interference occurred across all three glucose levels tested. The accuracy of StatStrip® and Precision Xceed was unaffected by maltose.

Site B
Results (Cont’d)

Site B - Maltose Interference (Cont’d)

Blood glucose 450-460 mg/dl

Drug Interference
The accuracy of the Breeze 2 and OneTouch Ultra meters at low glucose concentrations were affected by varying levels of ascorbic acid and acetaminophen. The other meters used, including StatStrip®, were unaffected

Site C

Conclusion
- The accuracy and specificity of some of the glucose meters used in Austrian hospitals can be compromised by interfering substances present in hospitalised patients.
- The use of inaccurate meters could lead to errors in managing patients on intensive insulin therapy.
- The accuracy of a new hospital glucose meter (StatStrip®) was not affected by any of the interfering substances and therefore offers improved clinical accuracy and reliability for measuring glucose in hospitalised patients.

A Roman¹, C Hanicq¹, P Flament ², T El Mahi², E Stevens¹,F Vertongen².

¹Intensive Care Department, ²Clinical Chemistry Department, CHU Saint-Pierre, Brussels, Belgium

Introduction

Maintaining blood glucose levels between 80 and 110 mg /dL in ICU patients lowers morbidity and mortality (1). This Tight Glucose Control ( TGC ) recommendation brought high interest on point-of-care glucometers that are required to titrate the insulin infusion. To achieve accuracy in this population, the use of glucometers included in blood gas analysers is advocated ( 2). We conducted a clinical evaluation of the Nova Biomedical StatStrip®, a glucometer that eliminates interference, particularly oxygen and hematocrit (3), with a blood gas analyser ( RapidLab 1265 ) and the reference method in the laboratory.

Materials and methods

In this prospective observational study, arterial blood glucose was simultaneously measured with RapidLab 1265 (blood gas analyzer), the StatStrip® Nova Biomedical and in the central laboratory as reference using the hexokinase method. Linear correlations, Bland-Altman and the Kanji (2) and a modified Kanji approaches were used to evaluate the accuracy.

Results

A total of 370 matched analysis were randomly performed in 315 patients admitted in an adult intensive care unit ( surgical, medical and acute cardiac care ). Mean SOFA score was 4,5 ( min : 0; max : 22 ). The range of the reference method for glucose was 34 - 526 mg/dL. One patient had 1025 mg/dl and was not included in statistical analysis as the glucometer indicated an high out-of range value. Linear correlations were very good for both glucometers as the Pearson R² was 0.9807 for the RapidLab1265 and 0.9822 for the StatStrip® Nova Biomedical. Biases were defined as point-of-care minus laboratory glucose values. These mean biases were -3.1 mg/dL for the RapidLab 1265 blood gas analyzer and -0.4 mg/dL for the StatStrip® Nova Biomedical. The analysis of the 20% discrepancy ( Kanji’s Approach) showed 1 case for each POC glucometer in the study of 369 that is out of the target. The 10% discrepancy reveals 24 (6.5%) and 25 (6.8%) cases out of this thinner target, as reported in table 1. Chi-Square test showed no statistical difference between this two proportions.

<table>
<thead>
<tr>
<th>Point-of-care method</th>
<th>number of comparisons</th>
<th>Bias ( mg/dL)</th>
<th>SD</th>
<th>number of &gt; 10 % discrepancies</th>
<th>number of &gt; 20 % discrepancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>RapidLab 1265</td>
<td>369</td>
<td>-3.1</td>
<td>10</td>
<td>25 ( 6,8% )</td>
<td>1 ( 0,3% )</td>
</tr>
<tr>
<td>Novabiomedical StatStrip®</td>
<td>369</td>
<td>-0.4</td>
<td>8</td>
<td>24 ( 6,5% )</td>
<td>1 ( 0,3% )</td>
</tr>
</tbody>
</table>
Conclusions

The very low biases (0.4 mg), the very low rate of significant (> 20%) discrepancy (0.3%) appear sufficient for safe tight glucose monitoring in adult ICU with StatStrip NovaBiomedical.

References:

Comparison of Accuracy of Three Point-of-Care Glucometers in an Adult ICU

A Roman1, C Hanicq1, P Flamet 2, T El Mahi2, F Vertongen2, E Stevens1

1Intensive Care Department, 2Clinical Chemistry Department, CHU Saint-Pierre, Brussels, Belgium

Introduction

Obtaining at bedside accurate blood glucose levels is mandatory to titrate insulin infusions in ICU patients under tight glycemic control. We evaluated concurrently the performance of 3 point-of-care devices: one blood gas analyzer, and two glucometers in an adult ICU.

Materials and methods

In this prospective observational study, arterial blood glucose was simultaneously measured with RapidLab 1265 (blood gas analyser), the Accu-chek Aviva Roche, the Nova Biomedical StatStrip® and in the central laboratory as reference using the hexokinase method. Bland-Altman and the Kanji (1) and a modified Kanji approaches were used to evaluate accuracy.

Results

A total of 330 matched analysis were randomly performed in 275 patients admitted in an adult intensive care unit (surgical, medical and acute cardiac care). Mean SOFA score was 4.5 (min : 0; max : 21). The range of laboratory glucose was 34 - 526 mg/dL. One patient had 1025 mg/dl and was not included in statistical analysis as glucometers all indicated an high out-of-range value. No patient was receiving peritoneal dialysis with icodextrin, none had paracetamol overdose. Biases are defined as point-of-care minus laboratory glucose values. These mean biases were -2.9 mg/dL for the RapidLab 1265 blood gas analyzer, -1.2 mg/dL for the Accu-Chek Aviva and -0.3 mg/dL for the StatStrip® Nova Biomedical. The analysis of the 20% discrepancy showed respectively 0, 5 and 1 case in the study while other 22, 40 and 20 cases revealed more than 10% discrepancy as reported in table 1.

Mc Nemar tests indicate statistical difference between the Accu-check Aviva distribution of discrepancy at 10% (p<0.001) when compared to RapidLab and the StatStrip® Nova, there was no difference between these two devices (p >0.5).

<table>
<thead>
<tr>
<th>Point-of-Care Method</th>
<th>number of comparisons</th>
<th>Bias (mg/dL)</th>
<th>2 SD</th>
<th>number of &gt; 10 % discrepancies</th>
<th>number of &gt; 20 % discrepancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>RapidLab 1265</td>
<td>329</td>
<td>-2.9</td>
<td>11</td>
<td>22 (6.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Accu-Check Aviva</td>
<td>329</td>
<td>-1.2</td>
<td>15</td>
<td>45 (13.6%)</td>
<td>5 (1.5%)</td>
</tr>
<tr>
<td>StatStrip® Novabiomedical</td>
<td>329</td>
<td>-0.4</td>
<td>11</td>
<td>20 (6%)</td>
<td>1 (0.3%)</td>
</tr>
</tbody>
</table>
Conclusions

The very low biases, the low rate of significant (> 20%) discrepancy appear sufficient for safe tight glucose control monitoring in adult ICU.

PERFORMANCE OF THE STATSTRIP GLUCOSE METER IN INPATIENT MANAGEMENT OF DIABETES MELLITUS

Vanja Radišić Biljak, Sandra Božičević, Marijana Vučić Lovrenčić, Nikica Car

Key words: diabetes mellitus, glucose meter, inpatient management, point-of-care

SUMMARY

The use of hospital point-of-care glucose meters in inpatient care is widely established despite unsolved issues regarding accuracy. The aim of this study was to validate the performance of the StatStrip Glucose Hospital Meter (Nova Biomedical, Waltham, USA) in performing glycemic profile in hospitalized diabetic patients undergoing intensified insulin therapy. We investigated total imprecision, inaccuracy, and analytical range limits by measuring glucose in 481 plasma samples of diabetic patients. Total imprecision was 2.4% and linearity ranged from 1.3 to 31.9 mmol/L. The results correlated well (r=0.9868) with the laboratory routine procedure with a determined bias of 2.1%. Total error of the method was 4.5%, which was within designated criteria for laboratory glucose measurement. Diagnostic testing revealed a 100% sensitivity and 100% specificity in detection of hypoglycemic episodes (n=16), respectively. StatStrip

Glucose Hospital Meter is a simple, accurate and reliable tool for assessing glycemia levels in inpatient management of diabetes mellitus.

INTRODUCTION

Diabetes is a chronic disorder requiring complex and continuous medical care (1). The World Health Organization has reported on a dramatic increase in its prevalence with a global estimate of 366 million people with diabetes by 2030 (2). Clinical evidence has clearly indicated that improved metabolic control leads to a significant reduction in microvascular complications associated with diabetes. Apart from achieving optimal glycemic control it is of great importance to avoid short-term fluctuations, i.e. periods of hyper- and especially hypoglycemia (1). Optimal everyday tuning of intensified insulin therapy requires establishment of glycemic profile by frequent blood glucose measurement (premeal, 90 min postmeal, prebed and at 3:00 A.M.), which is performed by patients, using self-monitoring blood glucose instruments (3). However, intensified insulin treatment at initiation and/or modification must be rigorously evaluated by accurate measurement of glycemic profile under controlled conditions during short-term inpatient management.

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E-mail: Vanja.Radisic.Biljak@ldb.hr
The use of hospital point-of-care glucose meters in these procedures is widely established, despite controversies regarding insufficient precision and inaccuracy of measurement due to various interferences (4). Point-of-care testing (POCT) is analytical testing performed outside central laboratory using a device or devices that can be easily transported to the vicinity of the patient. The main advantages of POCT are decreased amount of blood needed for testing and decreased total turnaround time (TAT). It is essential that its use can be managed appropriately and safely for both patients and staff (5). The variability of results between POCT glucose meters and central laboratory is partly due to the user-related errors, which can be overcome by intensified education and appropriate quality control (6). However, preanalytical patient-related variables (physiology, hemodynamics, drug treatment) and analytical performance of glucose meter are both factors of great importance when considering appropriate use of point-of-care technology for inpatient glucose measurement (7). Despite major advances in technology, most point-of-care glucose meters are still not up to rigorous criteria for accurate glucose measurement with a total allowable error set to 10% (8).

One of the new generation hospital point-of-care glucose meters is StatStrip Glucose Meter (Nova Biomedical, Waltham, USA), with a turnaround time of 6 seconds and the amount of blood of 1.2 μL per measurement. Its unique advantage is no interference from hematocrit, which can be substantially reduced in diabetic patients with kidney damage, and changed both ways in critically ill patients (9). Hemoconcentration and hemodilution are associated with falsely decreased and elevated glucose measurements, respectively, mostly due to changes in physical interactions of plasma with the strip reagent layer (7). StatStrip Glucose Meter technology provides actual measurement and correction for hematocrit together with glucose measurement on the same strip, resulting in significant reduction of hematocrit-related errors (10).

The aim of this study was to validate the performance of StatStrip Glucose Hospital Meter in performing 8-point glycemic profile in hospitalized diabetic patients treated with intensified insulin therapy.

MATERIALS AND METHODS

Instrumentation

The comparison method was routine laboratory glucose-oxidase chromogenic method on an AU400 routine laboratory analyzer (Beckman Coulter, Tokyo, Japan) (11). Tested glucose meter was StatStrip Glucose Hospital Meter (Nova Biomedical, Waltham, USA), which uses a modified glucose oxidase-based amperometric test system with unique hematocrit correction via actual measurement on the same strip. Test system is equipped with a chemical/drug-interference blanking system and a sampling control on the test strip. Results are expressed in plasma-glucose equivalents, according to current recommendations (1,12).

Blood sampling procedure

Blood samples were obtained from type 1 diabetic patients treated with intensified insulin therapy, during routine inpatient management.

Routine laboratory procedure: capillary blood (50 μL) was withdrawn with a calibrated pipette and immediately transferred to 1 mL of diluting reagent (100 mg NaF + 50 mg EDTA in 1000 mL saline). Diluted blood samples were centrifuged (10 min, 1200 g) and glucose was determined in diluted plasma supernatant. Total amount of capillary blood necessary for 8-point glycemic profile is 400 μL.

StatStrip Glucose Hospital Meter: blood sample was aspirated by the capillary system to the test strip from freely formed drop of blood, after a sample for the routine procedure was withdrawn from the same fingerprick. The amount of blood needed for one test is 1.2 μL and the total amount of capillary blood necessary for 8-point glycemic profile is 9.6 μL.
Precision studies

Within-run imprecision. Three venous EDTA whole blood samples with clinically relevant concentrations of glucose were tested 20 times on StatStrip Glucose Hospital Meter. The criterion for acceptable performance was $s_{w-run,TE_a} < 0.25$ TE$_a$ (TE$_a$ – total allowable error) (13).

Total imprecision. Three levels of commercially available control material were tested in duplicate, three times per day for 5 days (a total of 30 readings for each control). The control used included: Nova Biomedical StatStrip glucose controls: LEVEL 1 (range 2.4 – 4.1 mmol/L); LEVEL 2 (range 5.00 – 7.22 mmol/L); and LEVEL 3 (range: 14.0 – 17.9 mmol/L). The criterion for acceptable performance was $s_{tot,TE_a} < 0.33$ TE$_a$ (13).

Linearity

Nova StatStrip Glucose Linearity kit was used to examine analytical range limits. Linearity kit included 5 levels of glucose concentration: LEVEL 1 (range: 1.3-2.1 mmol/L); LEVEL 2 (range: 2.6-4.3 mmol/L); LEVEL 3 (range: 5.0-7.2 mmol/L); LEVEL 4 (range: 14.8-18.7 mmol/L); and LEVEL 5 (range: 25.2-31.9 mmol/L). We tested all glucose concentrations in triplicates and calculated mean values, which were plotted on the y-axis as observed values vs. values assigned by the manufacturer on the x-axis.

Inaccuracy

Comparison of methods was performed to estimate inaccuracy or systematic error (SE). A total of 481 capillary plasma samples were analyzed by the StatStrip Glucose Hospital Meter and AU400 analyzer.

Statistical analyses

All results were analyzed with MedCalc 9.4.2.0 statistical software (MedCalc Software bvba, Mariakerke, Belgium). For linearity experiment and comparison between analyzers, Passing-Bablok regression was used. For determination of bias both paired t-test and Wilcoxon test were used, as appropriate. For judging the performance of the method we used Westgard’s Method Decision Chart, with a total allowable error (TEa) criterion of 10% according to quality recommendations for laboratory glucose measurement (13,14). Performance of the StatStrip glucose meter in detecting hypoglycemia was assessed by a 2x2 table diagnostic test.

RESULTS

Precision

Within-run imprecision, calculated as a coefficient of variation (CV, %) from three blood samples, tested in 20 replicates, was 1.9% for low and high glucose concentration and 2.1% for normal glucose concentration. Total imprecision calculated as CV (%) for the control material with normal analyte concentration (QC LEVEL 2) was 2.4% (Table 1). This value was used as a measure of random error (RE) for the studied method.

<table>
<thead>
<tr>
<th>StatStrip Glucose Meter</th>
<th>Blood sample</th>
<th>Blood sample</th>
<th>Blood sample</th>
<th>QC-Level 1</th>
<th>QC-Level 2</th>
<th>QC-Level 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean glucose (mmol/L)</td>
<td>2.6</td>
<td>8.0</td>
<td>16.5</td>
<td>3.0</td>
<td>5.6</td>
<td>15.3</td>
</tr>
<tr>
<td>SD (mmol/L)</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
<td>0.1</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>CV (%)</td>
<td>1.9</td>
<td>2.1</td>
<td>1.9</td>
<td>3.3</td>
<td>2.4</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Acceptable performance criteria: 2.5/3.33
Linearity

Passing-Bablok regression showed no significant deviation from linearity, \( P>0.10 \) (Fig. 1). StatStrip glucose measurement was found to be linear from 1.3 to 31.9 mmol/L.

![Linearity Evaluation: Scatter Diagram and Regression Line](image)

**Figure 1. Linearity evaluation: scatter diagram and regression line for glucose measured on StatStrip Glucose Hospital Meter; standard value – assigned glucose values from Nova StatStrip Glucose Linearity Kit; observed values – measured glucose values from Nova StatStrip Glucose Linearity Kit.**

Inaccuracy

The results obtained using the StatStrip Glucose Hospital Meter correlated well \((r=0.9868)\) with the laboratory routine procedure in a wide range of clinically relevant glucose concentrations \((1.3-26.2 \text{ mmol/L})\) (Fig. 2).

The regression equation was \( y=-0.07073+1.0366x \) and determined bias from paired t-test was 0.17 mmol/L or 2.1\% \((P<0.01)\). Bias was used as a measure of systematic error (SE) for the procedure under evaluation.

Additional analysis was undertaken to test the performance of the StatStrip glucose meter in detecting hypoglycemia. In a subset of samples with a measured plasma glucose of <3.2 mmol/L with routine method \((n=16)\), Wilcoxon paired test revealed statistically significant difference \((P<0.0012)\). However, median \((2.55 \text{ vs. } 2.30 \text{ mmol/L})\) and range values \((1.6-3.1 \text{ mmol/L} \text{ vs. } 1.3-3.2 \text{ mmol/L})\) for the routine and StatStrip glucose results, respectively, did not confirm clinical significance of this finding. Statistical diagnostic testing revealed 100\% specificity and 100\% sensitivity in detecting hypoglycemia with StatStrip glucose meter.

Total error (TE) of the method was calculated from random error (RE) and systematic error (SE):

\[
\text{TE}_{\text{calc}} = 2.1\% \text{ (SE)} + 2.4\% \text{ (RE)} = 4.5\%,
\]

which was within designated criteria for laboratory glucose measurement (10\%).

According to Westgard’s Method Decision Chart (13), whereby values for total allowable error, bias and random error are analyzed together, our method performance was rated as ‘good’ (not shown).

Since StatStrip Glucose Hospital Meter is intended to be used for monitoring therapy effects in inpatient settings, no verification of the reference interval(s), otherwise obligatory for method validation, was found to be relevant in this study.
DISCUSSION

StatStrip Glucose Hospital Meter is an easy-to-use point-of-care analyzer. Our evaluation of the analytical performance confirmed the compliance of the meter to the current quality requirements for laboratory glucose measurement (13,14). Both within-run imprecision and total imprecision met the criteria for acceptable performance. Calculated total error from random and systematic error(s) was 4.7%, which is much below the total allowable error (10%) for the laboratory methods of plasma glucose measurement.

The linearity range was wide, covering low glucose concentration level, which is of special interest for diabetic patients on insulin therapy for verifying hypoglycemic episodes. Our study revealed 16 hypoglycemic episodes in a total of 481 measurements, with a 100% compliance of the StatStrip glucose meter results to the laboratory routine measurement. Considering significant difference in the turnaround time between StatStrip glucose meter and laboratory routine procedure (6 seconds vs. 30 minutes) and clinical relevance of rapid detection and management of hypoglycemic episodes, StatStrip glucose meter was found to be a very reliable tool, particularly in patients suffering from hypoglycemia unawareness.

Apart from low turnaround time, StatStrip Glucose Hospital Meter has other advantages compared to determination of glucose in central laboratory. The amount of sample needed for 8-point glycemic profile is very small (<10 μL), which allows an improved comfort for diabetic patients. The connectivity to the laboratory information system (LIS) with bidirectional transfer of requisitions and results contributes significantly to the reduction of possible pre- and postanalytical errors in patient identification and result reporting.

Accuracy and specificity of the measurement is significantly improved due to new technology with hematocrit measurement and correction on the test strip (10). Our study samples included hematocrit levels ranging from 0.298-0.485 L/L, with no significant influence on the accuracy of the glucose measurement (not shown). However, further studies are needed to assess the possible influence of clinically extreme hematocrit levels on the StatStrip glucose measurement. The analytical performance of the StatStrip meter in tight glucose control in critically ill patients should also be verified in further studies. Results of this study indicated good method performance, with a total error within allowable limits for laboratory glucose measurement, which is a fundamental prerequisite in setting adequate treatment decisions and improve critically ill patient outcomes (8,15).

In conclusion, the StatStrip Glucose Hospital Meter is a simple, accurate, and reliable tool for assessing glycemic levels in inpatient management of diabetes mellitus.

REFERENCES


Testování glukometrů a jejich porovnání

E. Havelková, D. Dušková, A. Jabor, J. Franeková, M. Komínková

ÚVOD

V současné době se u hospitalizovaných pacientů po operaci nebo v kritických stavech uplatňují pravidla tzv. Portlandského protokolu pro kontinuální intravenózní aplikaci inzulínu u hyperglykémických pacientů po operacích s cílem udržení hodnoty glukózy na normální hladině (tzv. Tight Glycemic Control). To vyžaduje její pravidelné a přesné měření přímo u lůžka pacienta. Tato pravidla významně snižují pooperační komplikace (sepse, renální selhání, polineuropatie...), snižují nároky na medikaci, přispívají ke zkrácení doby pobytu pacientů na JIP, vedou ke snížení celkové mortality a též k celkové úspore finančních prostředků na pacienta (1,2,3).

Diskuse o všeobecném benefitu “tight glycemic control” sice pokračuje, ale nijak tím nejsou zneužívány nároky na analytickou kvalitu měření koncentrace glukózy.

Doporučení “Správné zavádění a používání POCT”(4) vydané ČSKB, přináší požadavek, aby všechny hodnoty glukózy pod 3 a nad 15 mmol/l byly ověřeny v laboratoři. Stejně tak musí být kontrolovaní pacienti na inzulinové pumpě nebo s rychlými změnami potřeby inzulínu. Dalším požadavkem z hlediska analytické správnosti je maximální povolená nesprávnost glukometru (bias) v rozmezí ±15% bez specifikace, pro jaké koncentrační pásmo se jedná (lze předpokládat, že se jedná o uvedené pásmo 3 – 15 mmol/l). Doporučení se nezabývá vlivem interferencí, ale výrobci udávají omezení způsobené více interferujícími faktory (hematokrit, vliv dalších sacharidů, léků a podobně).

Cílem naší studie bylo porovnat správnost měření glukózy z plné krve na pěti glukometrech s refe rentní laboratorní metodou a zjistit závislost měření koncentrace glukózy na hodnotě hematokritu.

METODIKA

1. Technické údaje glukometrů

Pro testování byly použity následující glukometry:

<table>
<thead>
<tr>
<th>Obchodní název</th>
<th>Výrobce</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. StatStrip</td>
<td>Nova Biomedical</td>
</tr>
<tr>
<td>2. Accu-Chek Go</td>
<td>Roche Diagnostics</td>
</tr>
<tr>
<td>3. One Touch Ultra</td>
<td>LifeScan, The Johnson&amp;Johnson Company</td>
</tr>
<tr>
<td>4. FreeStyle Freedom</td>
<td>Abbott Laboratories</td>
</tr>
<tr>
<td>5. Precision PCx</td>
<td>Abbott Laboratories, MediSense Products</td>
</tr>
</tbody>
</table>

Technická specifikace jednotlivých glukometrů je uvedena v tabulce č. 1.

Glukometry Accu-Chek Go, One Touch Ultra a FreeStyle Freedom jsou primárně určeny pro měření koncentrace glukózy v domácím prostředí (tzv. self-monitoring), lze je však za určitých výrobcem specifikovaných podmínek použít též pro vyšetřování v nemocnici přímo u lůžka pacienta (POCT). Zbývající dva glukometry jsou určeny pouze pro nemocniční vyšetřování prováděné proškoleným zdravotnickým personálem. Jejich použití v oblasti POCT umožňují i některé hardwarové a softwarové odlišnosti od glukometrů pro self-monitoring jako je např. integrovaná četka čárových kódů nebo dokovací stanice pro přenos naměřených výsledků včetně ID pacienta a operátora do LIS pro následné zpracování dat a jejich archivaci. Tyto dva typy jsou podle specifikace výrobků určeny též pro stanovení koncentrace glukózy u pacientů v kritických stavech a u neonatologických vzorků.

Glukometr StatStrip (Nova Biomedical) je v současné době jediný přístroj pro měření koncentrace glukózy v domácím prostředí (tzv. self-monitoring), lze je však za určitých výrobkem specifikovaných podmínek použít též pro vyšetřování v nemocnici přímo u lůžka pacienta (POCT). Zbývající dva glukometry jsou určeny pouze pro nemocniční vyšetřování prováděné proškoleným zdravotnickým personálem. Jejich použití v oblasti POCT umožňují i některé hardwarové a softwarové odlišnosti od glukometrů pro self-monitoring jako je např. integrovaná četka čárových kódů nebo dokovací stanice pro přenos naměřených výsledků včetně ID pacienta a operátora do LIS pro následné zpracování dat a jejich archivaci. Tyto dva typy jsou podle specifikace výrobků určeny též pro stanovení koncentrace glukózy u pacientů v kritických stavech a u neonatologických vzorků.
Zenopřípadným interferencím těchto sacharidů při měření glukózy (5,6). Technologie použitá při výrobě proužku vede k eliminaci analytických rozdílů mezi jednotlivými šaržemi, které ostatní výrobci řeší mandatorním zadáváním tzv. kalibračních kódů (spíše však korekčních faktorů) a snižuje tak chyby způsobené zadáním nesprávného kódu.

**Tabulka č. 1: Technická specifikace testovaných glucometrů**

<table>
<thead>
<tr>
<th>Výrobce</th>
<th>NOVA Biomedical</th>
<th>Roche Diagnostics</th>
<th>LifeScan Jonson&amp;Jonson Comp.</th>
<th>Abbott Laboratories</th>
<th>Abbott Laboratories Medisense Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obchodní název</td>
<td>StatStrip</td>
<td>Accu-Chek Go</td>
<td>OneTouch Ultra</td>
<td>FreeStyle Freedom</td>
<td>Precision PCx</td>
</tr>
<tr>
<td>Princip měření</td>
<td>směs enzymů a amperometrie</td>
<td>GHD–PQQ reflexní fotometrie</td>
<td>GOD amperometrie</td>
<td>GHD–PQQ coulometrie</td>
<td>GHD–NAD amperometrie</td>
</tr>
<tr>
<td>Rozsah měření mmol/l</td>
<td>0,6 – 33,3</td>
<td>0,6 – 33,3</td>
<td>1,1 – 33,3</td>
<td>1,1 – 27,8</td>
<td>1,1 – 27,8</td>
</tr>
<tr>
<td>Akceptovatelné vzorky krve</td>
<td>kapilární arteriální venózní</td>
<td>kapilární arteriální venózní</td>
<td>kapilární</td>
<td>kapilární venózní</td>
<td>kapilární arteriální venózní</td>
</tr>
<tr>
<td>Neonatologické vzorky</td>
<td>ano</td>
<td>ne</td>
<td>ne</td>
<td>ne</td>
<td>ano</td>
</tr>
<tr>
<td>Antikoagulant</td>
<td>heparin sodný, litný a ammoný</td>
<td>heparin amoný EDTA</td>
<td>heparin sodný, litný a ammoný</td>
<td>heparin sodný, litný a ammoný EDTA</td>
<td>heparinát sodný, litný EDTA</td>
</tr>
<tr>
<td>Udávaný povolený rozsah Hct</td>
<td>0,20 – 0,65</td>
<td>0,25 – 0,65</td>
<td>0,30 – 0,55</td>
<td>0,15 – 0,65</td>
<td>pro glu ≤16,7 pro glu &gt;16,7 0,20 – 0,60</td>
</tr>
<tr>
<td>Srovnávací metoda</td>
<td>YSI 2300</td>
<td>hexokininá- zová po deprotei- naci</td>
<td>YSI 2300</td>
<td>YSI 2300</td>
<td>YSI 2300</td>
</tr>
<tr>
<td>Kalibrace na</td>
<td>plasmu</td>
<td>plnou krev</td>
<td>plasmu</td>
<td>plasmu</td>
<td>plasmu</td>
</tr>
<tr>
<td>Primární určení</td>
<td>POCT</td>
<td>self-monitoring</td>
<td>self-monitoring</td>
<td>self-monitoring</td>
<td>POCT</td>
</tr>
<tr>
<td>Počet vzorků v paměti</td>
<td>1000</td>
<td>300</td>
<td>150</td>
<td>250</td>
<td>4000</td>
</tr>
<tr>
<td>Čas analyzy (s)</td>
<td>6</td>
<td>5 a délevx</td>
<td>5 a délevx</td>
<td>5 a délevx</td>
<td>20</td>
</tr>
<tr>
<td>Objem krve (µl)</td>
<td>1,2</td>
<td>1,5</td>
<td>min. 1</td>
<td>0,3</td>
<td>2,5</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Výrobce</th>
<th>NOVA Biomedical</th>
<th>Roche Diagnostics</th>
<th>LifeScan Jonson&amp;Jonson Comp.</th>
<th>Abbott Laboratories</th>
<th>Abbott Laboratories MediSense Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obchodní název</td>
<td>StatStrip</td>
<td>Accu-Chek Go</td>
<td>OneTouch Ultra</td>
<td>FreeStyle Freedom</td>
<td>Precision PCx</td>
</tr>
<tr>
<td>Kal. kódy pro jednotlivé šárce proužků</td>
<td>ne</td>
<td>ano</td>
<td>ano kód na balení</td>
<td>ano kód na balení</td>
<td>ano kód na proužku</td>
</tr>
<tr>
<td>Čtečka čárových kódů</td>
<td>ano</td>
<td>ne</td>
<td>ne</td>
<td>ne</td>
<td>ano</td>
</tr>
<tr>
<td>Dálková zpráva</td>
<td>ano</td>
<td>ne</td>
<td>ne</td>
<td>ne</td>
<td>ano</td>
</tr>
<tr>
<td>Přenos dat do LIS</td>
<td>ano</td>
<td>ne</td>
<td>ne</td>
<td>ne</td>
<td>ano</td>
</tr>
</tbody>
</table>

\* probíhá patentové řízení, konkrétní typ enzymů bude specifikován později  
\** doba analýzy je závislá na koncentraci glukózy

2. Příprava vzorků
Celkem bylo ke statistickému vyhodnocení naměřeno 88 vzorků. Vzorky heparinizované arteriální krev byly vybrány tak, aby pokryly co nejširší rozmezí hematokritu i glukózy. Vzhledem k tomu, že v nativních vzorcích se koncentrace glukózy pohybovala v rozmezí od 4 do 17 mmol/l, bylo nezbytné připravit vzorky o vyšší koncentraci glukózy přidavkem vodného standardního roztoku D(+) glukózy o koncentraci 20 000 mg/dl (1110 mmol/l). Vzorky s nízkou koncentrací glukózy byly získány 24 hodinovým stáním plné krve při laboratorní teplotě a následným promícháním. Stejně tak bylo nutné připravit vzorky s vyšší koncentrací glukózy o přidat o koncentraci 20 000 mg/dl (1110 mmol/l). Vzorky s nízkou koncentrací glukózy byly získány 24 hodinovým stáním plné krve při laboratorní teplotě a následným promícháním. Stejně tak bylo nutné připravit vzorky s vyšší koncentrací glukózy.

3. Postup měření

4. Měření kontrolních materiálů
Dodané kontrolní materiály k jednotlivým glukometrům byly měřeny každý den po celou dobu
testování. U glukometru OneTouch byla použita jedna hladina (střední koncentrace), u glukometrů Accu-Chek Go, FreeStyle Freedom a Precision PCx dvě hladiny (nízké a vysoké koncentrace), u glukometru StatStrip pak tři hladiny (nízké, střední a vysoké koncentrace). Kontrolní materiály pro glukometr firmy Nova Biomedical nejsou závislé na šarže proužku a používají se pro libovolné šarže jako standardní laboratorní materiály pro kontrolu jakosti. U ostatních kontrolních materiálů se používaly odpovídající šarže podle pokynů výrobce. Na analyzátoru Architect byly použity multiparametrové kontrolní materiály firmy BioRad o dvou koncentračních hladinách glukózy.

**VÝSLEDKY**

### 1. Výsledky měření kontrolních materiálů

Naměřené hodnoty jsou v tabulce č. 2. Ve všech případech naměřené hodnoty vyhovovaly povolenému rozmezí stanovené výrobci. Variační koeficient v žádném případě nepřesáhl hodnotu 5 %.

Tabulka č. 2: Výsledky měření kontrolních materiálů (MIN, MAX je minimální, resp. maximální hodnota, AVG je průměr, STD směrodatná odchylka, CV% je relativní směrodatná odchylka)

<table>
<thead>
<tr>
<th>QC</th>
<th>Architect</th>
<th>Stat Strip</th>
<th>Accu-Chek Go</th>
<th>OneTouch Ultra</th>
<th>FreeStyle Freedom</th>
<th>Precision PCx</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>level 1</td>
<td>level 2</td>
<td>level 1</td>
<td>level 2</td>
<td>level 1</td>
<td>level 2</td>
</tr>
<tr>
<td></td>
<td>MIN</td>
<td>3,45-3,75</td>
<td>6,65-7,15</td>
<td>2,6-4,3</td>
<td>5,0-7,2</td>
<td>14,8-18,7</td>
</tr>
<tr>
<td></td>
<td>MAX</td>
<td>3,6-7,0</td>
<td>6,8-7,6</td>
<td>2,9-5,7</td>
<td>5,3-15,5</td>
<td>14,9-19,1</td>
</tr>
<tr>
<td></td>
<td>AVG</td>
<td>3,5-3,6</td>
<td>6,8-7,0</td>
<td>2,9-5,7</td>
<td>5,3-15,5</td>
<td>14,9-19,1</td>
</tr>
</tbody>
</table>

2. Korelace s referenční metodou (regrese, bias)

Získaná data byla použita pro statistické vyhodnocení správnosti měření glukózy vzhledem ke referenční metodě, a to nejprve bez ohledu na hodnotu hematokritu pro všechna získaná měření. Pro výpočet parametrů korelace byla použita lineární regrese. Zároveň byly vypočítány odchylky (absolutní i procentuální) vzhledem ke zvolené referenční metodě. Výsledky byly zpracovány v grafické podobě ve formě rozdílového grafu. Meze správnosti byly stanoveny na základě doporučení Referenční laboratoře a ČSKB jako maximální bias ±15 %. Statisticky získané hodnoty jsou uvedeny

**Tabulka č. 3: Parametry lineární regrese, absolutní a relativní četnosti případů mimo povolenou toleranci (bias ±15 %) pro celou šíři hodnot hematokritu (0,21 – 0,65)**

<table>
<thead>
<tr>
<th>Hct</th>
<th>Architect</th>
<th>StatStrip</th>
<th>Accu-Chek Go</th>
<th>OneTouch Ultra</th>
<th>FreeStyle Ultra</th>
<th>Precision PCx</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>88</td>
<td>88</td>
<td>88</td>
<td>88</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>MIN</td>
<td>1,4</td>
<td>1,2</td>
<td>1,5</td>
<td>1,4</td>
<td>1,5</td>
<td>1,4</td>
</tr>
<tr>
<td>MAX</td>
<td>30,00</td>
<td>31,4</td>
<td>23,8</td>
<td>23,7</td>
<td>22,9</td>
<td>22,6</td>
</tr>
<tr>
<td>AVG</td>
<td>9,65</td>
<td>9,38</td>
<td>8,35</td>
<td>7,80</td>
<td>8,43</td>
<td>8,30</td>
</tr>
<tr>
<td>SLOPE</td>
<td>0,99</td>
<td>0,80</td>
<td>0,73</td>
<td>0,77</td>
<td>0,77</td>
<td>0,73</td>
</tr>
<tr>
<td>INTERCEPT</td>
<td>-0,19</td>
<td>0,64</td>
<td>0,80</td>
<td>1,02</td>
<td>1,27</td>
<td>1,27</td>
</tr>
<tr>
<td>R</td>
<td>1,00</td>
<td>0,99</td>
<td>0,94</td>
<td>0,97</td>
<td>0,96</td>
<td>0,96</td>
</tr>
<tr>
<td>R²</td>
<td>0,99</td>
<td>0,98</td>
<td>0,88</td>
<td>0,95</td>
<td>0,93</td>
<td>0,93</td>
</tr>
<tr>
<td>bias&gt;±15 %</td>
<td>6</td>
<td>26</td>
<td>49</td>
<td>23</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>relativní četnost %</td>
<td>6,8</td>
<td>29,5</td>
<td>55,7</td>
<td>26,1</td>
<td>43,2</td>
<td></td>
</tr>
</tbody>
</table>

**Graf 1 a 2: Graf lineární regrese a rozdílový graf pro glukometr StatStrip Nova Biomedical**

**Graf 3 a 4: Graf lineární regrese a rozdílový graf pro glukometr Accu-Chek Go Roche Diagnostics**
3. Vliv hematokritu na správnost měření

V tabulce č. 4 jsou uvedeny parametry lineární regrese pro zvolené hodnoty hematokritu. Porovnával se průměr měření koncentrace glukózy z tripletu hexokinázové metody s hodnotami zjištěnými na příslušném glukometru. Relativní četnost odchylek (proti porovnávací hexokinázové metodě) přesahujících ±15 % je vyjádřena ve vztahu k počtu měření v příslušném pásmu hematokritu.
Tabulka č. 4: Parametry lineární regrese, absolutní a relativní četnosti případů mimo povolenou toleranci (bias ±15 %) pro jednotlivé skupiny vzorků rozdělené podle hodnoty hematokritu

<table>
<thead>
<tr>
<th>Hct</th>
<th>0,21 - 0,35</th>
<th>0,36 - 0,55</th>
<th>0,55 - 0,65</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Architect</td>
<td>StatStrip</td>
<td>Accu-Chek Go</td>
</tr>
<tr>
<td>N</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>MIN</td>
<td>1,57</td>
<td>1,2</td>
<td>1,4</td>
</tr>
<tr>
<td>MAX</td>
<td>23,53</td>
<td>23,0</td>
<td>22,5</td>
</tr>
<tr>
<td>AVG</td>
<td>8,48</td>
<td>8,15</td>
<td>8,03</td>
</tr>
<tr>
<td>SLOPE</td>
<td>0,98</td>
<td>0,92</td>
<td>0,99</td>
</tr>
<tr>
<td>INTER-CEPT</td>
<td>-0,14</td>
<td>0,22</td>
<td>-0,33</td>
</tr>
<tr>
<td>R</td>
<td>1,00</td>
<td>1,00</td>
<td>0,96</td>
</tr>
<tr>
<td>R²</td>
<td>0,99</td>
<td>0,99</td>
<td>0,91</td>
</tr>
<tr>
<td>bias±15%</td>
<td>2</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>relat. četnost</td>
<td>6,7</td>
<td>3,3</td>
<td>36,7</td>
</tr>
</tbody>
</table>
Na základě průměrů jednotlivých měření glukózy v každé skupině s odlišným hematokritem byla porovnána správnost měření vzhledem k referenční metodě v závislosti na hladině hematokritu, a to jak absolutně v mmol/l, tak relativně v procentech úspěšnosti (referenční metoda = 100 %). Údaje jsou uvedeny v grafech č. 11 až 16.

**Graf 11 a 12: Porovnání správnosti měření glukózy na jednotlivých glukometrech pro hodnotu hematokritu 0,21 – 0,35**

**Graf 13 a 14: Porovnání správnosti měření glukózy na jednotlivých glukometrech pro hodnotu hematokritu 0,36 – 0,55**
DISKUZE

Regresní analýza ukázala rozdíly mezi jednotlivými technologiemi. Nejvyšší shoda s hexokinázovou metodou byla dosažena u výsledků získaných glukometrem StatStrip a to v širokém koncentračním rozmezí od hypo- až po hyperglykemické vzorky. Rozdíly mezi jednotlivými glukometry zdůrazňují potřebu jak jejich pečlivého výběru, tak monitorování jejich kvality ze strany laboratoře a požadavky ČSKB na testování glukometrů se jeví jako oprávněné.

Při testování vlivu hematokritu na správnost měření glukózy na vzorcích s různou hodnotou hematokritu se jeho vliv projevila v některých případech již v pásma 0,35 – 0,55 a především nad hodnotou 0,55. U glukometru StatStrip Nova Biomedical byl použit technologi Multi-WellTM vliv hematokritu na správnost stanovení glukózy v podstatě eliminován, a to v celém testovaném koncentračním rozmezí 1,4 – 30,0 mmol/l. U ostatních glukometrů byly výsledky při hladině hematokritu > 0,55 a koncentraci glukózy > 15,1 mmol/l až o 48 % nižší oproti cílové hodnotě, běžně pak o cca 30 %.

Požadavky na průběžné testování glukometrů za účelem příkazu jejich trvalé kvality dosud zahrnovaly především stanovení přesnosti a správnosti. Z uvedených výsledků je ale zřejmé, že by bylo žádoucí do protokolů pro testování spolehlivosti glukometrů v klinické praxi zahrnout i posouzení interferenc zvýšených hodnot hematokritu. Mezi další interferující faktory patří maltóza a galaktóza (i.v. nutrice, i.v. roztoky imunoglobulínů apod.), icodextrin (peritoneální dialýza) nebo xylóza (xylózový toleranční test).

ZÁVĚR

Mezi testovanými glukometry StatStrip (Nova Biomedical), Accu-Chek Go (Roche Diagnostics), One Touch Ultra (LifeScan, The Johnson&Johnson Company), FreeStyle Freedom (Abbott Laboratories) a Precision PCx (Abbott Laboratories, MediSense Products) byly zaznamenány rozdíly v reprodukovatelnosti měření koncentrace glukózy, které ale nepřesáhly akceptovatelnou hodnotu.

Výraznější rozdíly byly zaznamenány ve správnosti v porovnaní s laboratorním stanovením koncentrace glukózy hexokinázovou metodou. Rozdíly mezi jednotlivými glukometry byly výraznější a odchylka proti hexokinázové metodě se absolutně zvyšovala s rostoucí koncentrací glukózy.

Z porovnání hodnot glukózy naměřených jednotlivými glukometry s referenční metodou nebo referenční metodou se jasně vyplývá, že nejvyšší shoda se výsledky vykazuje glukometr StatStrip, a to v celém koncentračním rozmezí 1,4 do 30,0 mmol/l. Počet hodnot s nesprávnou hodnotou vyšší jak ±15 % bylo pouze 6 (tj. 6,8 %). Ostatní glukometry vykazovaly horší korelací a statisticky výrazně vyšší odchylky oproti referenční metodě. Accu-Chek Go naměřil celkem 26 hodnot mimo povolený limit (tj. 29,5 %), OneTouch celkem 49 (55,7 %), FreeStyle Freedom 23 (26,1 %) a Precision PCx 38 (43,2 %). Nejvíce hodnot mimo toleranci bylo u těchto čtyř glukometrů na koncentrace glukózy nad 15,1 mmol/l, kdy výsledky nevyhověly v 65 až 75 % případů. Tyto z analitického i klinického hlediska významné odchylky od cílové hodnoty mohou vést k nesprávnému dávkování inzulínu u hyperglykemických pacientů (7).
Při hodnocení správnosti měření koncentrace glukózy s ohledem na různou hodnotou hematokritu je evidentní vliv hodnoty hematokritu na správnost výsledku vzhledem k referenční metodě. U běžných glukometrů se vliv zvýšené hodnoty hematokritu projeví poklesem koncentrace glukózy. Pro hodnoty hematokritu v rozmezí 0,20 až 0,35 byla u všech testovaných glukometrů shoda průměrů jednotlivých měření koncentrace glukózy s referenční hodnotou v rozmezí 96,1 až 102,5 %. Všechny glukometry v tomto případě poskytovaly výsledky se zcela dostatečnou správností měření s odchylkou do 4 %. U hladiny mezi 0,36 až 0,55 byla u glukometru StatStrip shoda 97,3 % (odchylka -2,7 %), avšak u ostatních již pouze od 85,9 % (odchylka -14,1 %) do 82,2 % (odchylka – 17,8 %). V tomto případě se již významně projevil vliv hematokritu na stanovení glukózy. Nejvýraznější odchylky od cílové hodnoty pak byly u hladiny hematokritu 0,56 až 0,65. U glukometru StatStrip bylo dosaženo 98,2 % shody (-1,8 % od referenční hodnoty), u ostatních byla dosažena shoda s referenční hodnotou pouze mezi 79,6 (-20,4 %) až 65,2 (-34,8 %) procenty.

**LITERATURA**

4) Dokumenty ČSKB: Správné zavádění a používání POCT, 2006
6) Food and Drug Administration, www.fda.gov/cber/safety/maltose110405.htm, 2005
Evaluation d’un nouveau lecteur de glycémie intégrant une correction automatique de l’hématocrite

RÉSUMÉ
L’effet de l’hématocrite sur la réponse de sept systèmes de surveillance (lecteurs) de la glycémie en milieu hospitalier a été étudié à trois niveaux différents de glycémie : élevé, moyen et abaissé. Tous les lecteurs sauf un ont présenté un biais analytique significatif en relation inverse avec la valeur de l’hématocrite. Ce biais vient s’ajouter au biais systématique observé par rapport à une méthode de référence de détermination du glucose plasmatique. Le seul lecteur qui s’affranchisse de cette interférence ajuste le résultat par rapport à l’hématocrite qu’il détermine simultanément grâce à un dispositif embarqué.

MOTS-CLÉS
Lecteur de glycémie, hématocrite, exactitude

I - Introduction
En 2001, Van den Berghe et al. ont montré dans un article remarqué qu’un contrôle fréquent de la glycémie, tel que celle-ci puisse être maintenue par insulinothérapie i.v. intensive dans une fourchette étroite de 4,4 à 6,0 mmol/L, réduisait la mortalité des patients en phase critique dans les unités de soins intensifs de chirurgie (USI) (1). D’autres études ont confirmé par la suite le bénéfice que de tels patients pouvaient tirer de protocoles insuliniques intensifs. S’agissant d’éviter le passage du patient en hypoglycémie, ces protocoles imposent toutefois des déterminations répétées (2), effectuées à l’aide de systèmes délocalisés de surveillance (lecteurs) de la glycémie, ceux-là même qu’utilisent les patients diabétiques pour ajuster leur dose d’insuline sous-cutanée. L’AFSSAPS tolère pour ces lecteurs des écarts par rapport à la méthode du laboratoire central qui peuvent aller jusqu’à 20% (3) alors que Boyd et Bruns ont montré, en modélisation, qu’une erreur de 10% sur le glucose va se traduire par des écarts de posologie de l’insuline situés dans une fourchette de 16 à 45% (4). En conséquence, les biologistes et les cliniciens devraient de nouveau s’interroger sur la performance analytique des lecteurs de glycémie afin d’améliorer la rigueur du contrôle de la glycémie en USI. En USI, non seulement les cibles de concentration de glucose se resserrent mais la probabilité d’interférence analytique augmente considérablement. Les médications multiples et les variations de l’hématocrite affectent pratiquement tous les lecteurs, quelle que soit la technologie mise en œuvre (1). L’effet de l’hématocrite, en particulier, est prévisiblement reconnu par le fabricant et systématiquement vérifié (6, 7, 8), du fait du volume plasmatique déplacé par les globules rouges, une valeur abaissée de l’hématocrite se traduit par un biais positif de lecture de la glycémie et une valeur augmentée de l’hématocrite par un biais négatif. Les variations du pH (9) et de la pO2 (10, 11) constituent d’autres facteurs, bien que moins systématiques, d’imprécision. A ces sources d’erreurs reconnues vient s’ajouter l’inexactitude intrinsèque du lecteur qui laisse parfois à désirer. Plusieurs études ont montré que le degré de corrélation avec la détermination du glucose plasmatique au laboratoire central n’est pas satisfaisant et qu’il varie considérablement selon la technologie de lecteur mise en œuvre (12). Le laboratoire central utilise souvent une méthode de dosage à l’hexokinase, qui a un statut de méthode de référence, étroitement corrélée à la méthode « définitive » en spectrométrie de masse et la corrélation avec les lecteurs est particulièrement dégradée, dans les zones hypoet hyperglycémique (13).

Nous rendons compte ici de l’observation de l’effet de l’hématocrite. L’étude a porté sur un ensemble de six lecteurs, fréquemment rencontrés en milieu hospitalier, auxquels a été ajouté un septième appareil introduit sur le marché de façon relativement récente, le StatStrip® (Nova Biomedical) (14). Nous présentons ici un ensemble de résultats qui visent à démontrer l’intérêt de la technologie sur laquelle se fonde le fonctionnement de ce lecteur : la détermination du glucose couplée à une mesure de l’hématocrite avec correction automatique du biais correspondant.

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3Nova Biomedical – Waltham – MA 02451 – Etats-Unis
ÉVALUATION

II - Matériel et méthode

1. Instruments

La comparaison a porté sur sept systèmes de détermination du glucose dans deux sites différents, le Service de Biologie du Centre Hospitalier de Dourdan et le Laboratoire de Biochimie de l’Hôpital Edouard Herriot à Lyon. Le système de référence de détermination du glucose plasmatique était, pour le premier site, l’analyseur Dimension® Rxl™ de la société Siemens Medical Solutions Diagnostics, pour le second, l’analyseur Modular® de Roche Diagnostics. Tous deux mettent en œuvre une méthode à l’hexokinase, à ce titre bien corrélée avec les méthodes de référence basées sur la spectrométrie de masse. Six lecteurs de glycémie représentatifs des technologies actuellement utilisées en milieu hospitalier ont été retenus. Quatre de ces six lecteurs : Lecteur 1, Lecteur 2, Lecteur 3, Lecteur 4 ont été testé sur le site de Dourdan. Les Lecteurs 5 et 6 ont été testés sur le site de Lyon. Le septième lecteur, le StatStrip® de la société Nova Biomedical a été testé sur le site de Lyon. Le septième lecteur, le StatStrip® de la société Nova Biomedical a été testé sur le site de Dourdan. Les Lecteurs 5 et 6 ont été testés sur le site de Lyon. Le septième lecteur, le StatStrip® de la société Nova Biomedical a été testé sur les deux sites. L’ajustement du résultat, réalisé par cet appareil en fonction de l’hématocrite, repose sur la mise en œuvre d’une bandelette comportant trois électrodes capillaires. La première, revêtue d’enzyme, réalise une mesure ampérométrique « classique » de la concentration en glucose. La deuxième, dépourvue d’enzyme, effectue une correction de mesure en soustrayant au signal ampérométrique déterminé la part due aux interférences électrochimiques. Enfin, la troisième réalise la détermination de l’hématocrite au moyen d’une mesure d’impédance et introduit cette valeur dans un algorithme de calcul de la concentration du glucose plasmatique.

Chacun des instruments a été utilisé conformément aux instructions du fabricant, « calibré » c’est-à-dire affecté d’une courbe d’étalonnage pré-enregistrée correspondant au lot de bandelettes utilisé, à l’exception du StatStrip® qui ne requiert pas de tel réglage, et vérifié à l’aide des solutions de contrôle fournies par le fabricant.

2. Méthode

Pour l’étude de l’interférence de l’hématocrite, trois tubes (Vacutainer®) de 7 mL de sang hépariné ont été prélevés chez un donneur et laissés à température ambiante pendant 12-24 heures avant d’être additionnés d’une solution concentrée (20 g/L) de glucose pour amener la glycémie dans l’une des trois zones cibles hypo-, normo- et hyperglycémiques. Chacun de ces mélanges a été à son tour divisé en six parts aliquotes de 1 mL que l’on a centrifugées dans une minicentrifugeuse de la société Fisher Scientific avant de modifier leur hématocrite par déplacement de volumes de surnageant et de culot, à l’aide d’une micropipette, comme indiqué sur la Figure 1. On a réalisé ainsi une gamme de cinq valeurs égales à 22 %, 35 %, 45 %, 53 % et 62 %, pour un hématocrite de départ de 45 %. Le contenu des tubes 1 à 5 a été ré-homogénéisé avant d’être mesuré à six reprises dans chacun des systèmes étudiés. Les mélanges ont été immédiatement centrifugés à l’issue de ces mesures, leur surnageant séparé et leur concentration de glucose déterminée par une méthode à l’hexokinase dans les analyseurs, Dimension® Rxl™, site de Dourdan, et Modular®, site de Lyon.

III - Résultats

Les résultats obtenus sur les lecteurs ont été transformés et reportés sur deux types de graphiques de manière à comparer, d’une part, l’effet de l’hématocrite sur la réponse de chaque lecteur pris isolément, sans préjuger de la relation de cette réponse avec la méthode appliquée au laboratoire central, et, d’autre part, l’effet combiné de l’hématocrite et de l’inexactitude intrinsèque de chaque lecteur rapporté à une référence commune, la méthode appliquée au laboratoire central. Trois donneurs ayant été sollicités sur chaque site, soit un pour chaque niveau de glycémie, les valeurs de l’hématocrite ont été affectées d’une incertitude de ± 6 % pour tenir compte de la variation biologique interindividuelle (15). La Figure 2 illustre la première approche. On a reporté en ordonnées l’écart entre la glycémie observée sur le même lecteur pour la valeur de l’hématocrite la plus proche de 45 %. L’écart est exprimé en pourcent (%) de cette dernière valeur d’hématocrite, considérée comme réponse de référence. On observe que, à l’exception du StatStrip®, la réponse de chacun des lecteurs pris isolément s’écarte de sa réponse de référence dans une mesure qui lui est propre, significative bien qu’irrégulière, aux niveaux bas de concentration de glucose, et plus rigoureusement proportionnelle à l’hématocrite aux niveaux élevés. Tout se passe comme si le lecteur rapportait sa mesure du glucose plasmatique à un volume qui inclut celui des érythrocytes, admettant ainsi une dilution apparente du glucose.
Lorsque l'hématocrite s'écarte de la zone de référence, la réponse de sept lecteurs de glycémie, à trois niveaux de glycémie, se resserre mais la probabilité d'interférences est toujours présente. En USI, non seulement les cibles de concentration de systèmes délocalisés de surveillance (lecteurs) peuvent aller jusqu'à 20% alors que les patients pouvaient tirer de protocoles insuliniques intensifs. S'agissant d'éviter le passage du patient en soins intensifs de chirurgie (USI) (1), il est nécessaire de surveiller les patients en phase critique dans les unités de soins intensifs (USI) (1). D'autres études ont montré que le degré de corrélation avec un statut de méthode de référence, étroitement corrélée à la méthode « définitive » en spectrométrie, constitue d'autres facteurs, bien que moins systématiques, d'imprécision. À ces sources d'erreur s'ajoute l'inexactitude intrinsèque du lecteur qui laisse parfois à désirer. Plusieurs études ont montré que le degré de corrélation avec du lecteur qui laisse parfois à désirer. Plusieurs études ont montré que le degré de corrélation avec la détermination du glucose plasmatique au laboratoire central n'est pas satisfaisant et qu'il varie considérablement selon la technologie de lecteur mise en œuvre (12). Le laboratoire central utilise souvent une méthode de dosage à l'hexokinase, qui est une méthode reconnue et généralement reconnue par le fabricant et systématiquement utilisée dans les laboratoires de biologie. Les variations du pH (9) et de la pO2 (10, 11) peuvent également interagir avec l'hématocrite. L'étude a porté sur un ensemble de six lecteurs, fréquemment rencontrés en milieu hospitalier, auxquels a été ajouté un septième lecteur : la détermination du glucose couplée à une correction automatique de l'hématocrite

**Figure 2**
Déviation de la réponse de sept lecteurs de glycémie, à trois niveaux de glycémie, lorsque l'hématocrite s'écarte de la zone de référence.

**Figure 3**
Inexactitude de la glycémie en fonction de l'hématocrite, observée sur sept lecteurs à trois niveaux de glycémie.
Après le StatStripTM, le Lecteur 5 apparaît le moins sensible à l'effet de l'hématocrite et semble même présenter un comportement paradoxal aux faibles niveaux de concentration de glucose.

La Figure 3 (voir page précédente) illustre la seconde approche. On a reporté en ordonnées la différence entre les résultats fournis par les lecteurs et la concentration du glucose plasmatique mesurée sur l'analyseur du laboratoire central. L'écart est exprimé ici en % de la valeur cible. Ce diagramme fait ressortir l'inexactitude globale des lecteurs en fonction de l'hématocrite. Trois niveaux de glycémie sont étudiés dans les deux cas : abaissé, moyen et élevé.

**IV - Discussion**

Les lecteurs sont calibrés en usine pour donner le résultat le plus exact pour les échantillons dont l'hématocrite se situe dans l’intervalle de référence (37-54 %). Il est donc légitime, pour juger du seul effet de l'hématocrite, de faire varier l'hématocrite à glycémie constante et d’observer comment la lecture dévie lorsque l’échantillon s’éloigne de « l’hématocrite de référence ». La Figure 2 montre que l’effet de l’hématocrite varie considérablement selon la technologie mise en œuvre et qu’il apparaît minimal pour le StatStripTM. Ce résultat confirme l’efficacité d’une technologie qui permet de corriger automatiquement la concentration de glucose affichée sur la base d’une mesure simultanée de l’hématocrite par le lecteur lui-même.

En comparant, comme on l’a fait ci-dessus, chaque lecteur à lui-même on masque les écarts entre les différents lecteurs pour « l’hématocrite de référence ». La Figure 3 met ces écarts en évidence en rapportant tous les résultats sur une échelle commune de référence. On voit là encore que l’inexactitude intrinsèque de chaque lecteur varie considérablement selon la technologie mise en œuvre.

**V - Conclusion**

La mesure de la concentration de glucose au moyen d’un lecteur de glycémie dans le contexte d’une USI n’est pas un geste anodin. Les appareils actuels présentent des limites et notamment un biais analytique significatif variant de façon inversee proportionnelle avec la valeur de l’hématocrite. Les utilisateurs de ces appareils doivent donc être parfaitement informés sur ces limitations et leurs conséquences afin d’une part, de mettre en œuvre ces systèmes de façon efficace et, d’autre part, d’interpréter leurs résultats avec pertinence. À côté de ces informations essentielles, des solutions techniques permettent également d’aborder cette problématique. Une de ces solutions consiste à associer directement au lecteur de glycémie une correction du résultat grâce à la réalisation d’une mesure simultanée de l’hématocrite. Le lecteur de glycémie StatStripTM intègre cette solution et les résultats obtenus dans le cadre de notre étude démontrent l’intérêt de cette approche comparative à un ensemble de systèmes aujourd’hui couramment employés en milieu hospitalier.

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Inaccuracy of glucose meters. Automatic correction for hematocrit variations and the presence of exogenous interfering components

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\textsuperscript{3}Nova Biomedical, Waltham, MA 02453

Résumé. Sept systèmes de surveillance (lecteurs) de la glycémie en milieu hospitalier ont été évalués en portant une attention particulière aux interférences analytiques rencontrées chez les patients en soins intensifs. L’imprécision différait peu d’un lecteur à l’autre et se situait globalement dans les limites d’acceptabilité. L’inexactitude, mesurée par rapport à une méthode à l’hexokinase, présentait des différences significatives mais qui ne sortaient pas non plus des limites d’acceptabilité. Tous les lecteurs sauf un présentaient un biais important lorsque l’hématocrite s’écartait de l’intervalle de référence. Deux lecteurs ne distinguaient pas le maltose du glucose. Trois d’entre eux présentaient un biais positif important en présence de paracétamol et quatre un biais comparable en présence d’ascorbate. Seul un lecteur s’affranchissait à la fois de ces interférences exogènes et des variations de l’hématocrite, grâce à des dispositifs embarqués de mesure de l’hématocrite et de soustraction de blanc électrochimique. C’était aussi le plus étroitement corrélé avec les méthodes à l’hexokinase. A un moment où les patients en soins intensifs font l’objet d’un contrôle toujours plus rigoureux de la glycémie, il est souhaitable et nos résultats montrent qu’il est désormais possible de resserrer de même les critères d’acceptabilité des lecteurs de glycémie utilisés à cet effet.

Mots clés : glucose, lecteur délocalisé, inexactitude

Abstract. Seven hospital-based glucose monitoring systems (meters) were evaluated with particular attention to those analytical interferences encountered in intensive care patients. Imprecision differed little between meters and remained altogether within acceptable limits. Inaccuracy, as measured by comparison with a hexokinase method presented with significant differences, yet without exceeding acceptable limits either. All meters but one showed an important bias when hematocrit departed from the reference interval. Two meters would not distinguish maltose from glucose. Three showed an important positive bias in the presence of acetaminophen and four a comparable bias in the presence of ascorbate. Only one meter was unaffected by both such exogenous interferences and hematocrit variations, owing to built-in hematocrit and electrochemical blank measuring devices. This meter also showed narrowest correlation with hexokinase methods. At a time when intensive care patients are being submitted to ever tighter glycemic control, it is desirable and our results show that it is now possible to tighten accordingly the acceptability criteria of glucose meters used to this end.

Key words: glucose, point of care meter, reliability
Les dispositifs d’auto-surveillance (lecteurs) de la glycémie destinés aux patients diabétiques pour ajuster leur dose d’insuline sous-cutanée sont aussi utilisés dans les unités de soins intensifs (USI) dans le cadre de protocoles insuliniques IV pour maintenir dans des limites étroites la glycémie des patients en état critique [1]. Mais la cible de glycémie est alors plus étroite (4,4-6 mmol/L) ; les variations de l’hématocrite [2-5], du pH [6] et de la pO2 [7, 8], les glucides apportés par les perfusions, les médications multiples constituent autant de sources potentielles d’erreur. Et le risque de négliger le recalage du lecteur sur le lot de bandelettes utilisé augmente avec la fréquence des lectures. Si l’on considère enfin que leur inexactitude est très variable [9], surtout hors de l’intervalle de référence [10], on peut se demander si ces dispositifs sont à la hauteur de l’enjeu qui est de réduire la mortalité des patients en USI [11, 12]. Nous avons comparé la fiabilité et la sensibilité aux variations de l’hématocrite et à la présence de traitements courants, de six lecteurs rencontrés actuellement en milieu hospitalier avec les performances correspondantes d’un nouveau lecteur [13], annoncé comme capable de s’affranchir des sources d’interférences susmentionnées. L’évaluation de l’inexactitude et de l’imprécision a été effectuée selon le protocole de l’Afsaps [14].

Matériel et méthode

Instruments
La comparaison a porté sur sept systèmes de détermination du glucose sur deux sites différents, le laboratoire de biochimie de l’Hôpital Edouard Herriot de Lyon et le service de biologie du Centre hospitalier de Dourdan. Les systèmes de référence de détermination du glucose plasmatique étaient respectivement l’analyseur Modular® de Roche Diagnostics (2 avenue du Vercors, 38242 Meylan) et l’analyseur RxL® de Dade Behring (19/29, Rue du Capitaine Guynemer, 92903 Paris). Tous deux mettent en œuvre une méthode à la hexokinase, à ce titre bien corrélée avec les méthodes de référence basées sur la spectrométrie de masse. Six lecteurs de glycémie représentatifs des technologies actuellement utilisées en milieu hospitalier ont été retenus. Sur le premier site : Accu Chek GO® de Roche Diagnostics, Optimum Xceed® associé à la bandelette Medisense H® de Abbott (10 rue d’Arcueil, 94528 Rungis), One Touch Ultra 2® de Lifescan (division de Ortho Clinical Diagnostics France, 1 rue Camille Desmoulins, 92130 Issy les Moulineaux) et Ascensia Brio® de Bayer (13 rue Jean Jaurès, 92807 Puteaux). Sur le second site : Accu Chek Sensor® de Roche Diagnostics et Optimum Xceed® associé à la bandelette Medisense Plus® de Abbott. Le système StatStrip® de Nova Biome-
22 %, 35 %, 45 %, 53 % et 62 %, lorsque l’hématoctite de départ est de 45 %. Les cinq préparations ainsi obtenues pour chaque niveau de glycémie ont été ré-homogénéisées avant d’être mesurées, quasi simultanément sur chacun des lecteurs du groupe étudié, à six reprises. Pour minimiser les effets de la glycolyse, les préparations ont été traitées par ordre décroissant de glycémie. Ensuite immédiate de quoi, les mélanges ont été centrifugés et placés sur l’analyseur de référence, Modular sur le 1er site et RxL sur le 2e site.

**Étude des interférences chimiques exogènes**

Trois constituants représentatifs ont été retenus, le maltose, le paracétamol et l’ascorbate. L’effet de chaque constituant a été évalué à cinq niveaux de glycémie compris dans les intervalles cibles 1-3 mmol/L, 6-8 mmol/L, 11-17 mmol/L, 18-22 mmol/L et 24-28 mmol/L. Pour chaque constituant et chaque niveau de glycémie, 3 mL de sang hépariné ont été prélevés chez un donneur et laissés à température ambiante pendant 12-24 heures avant d’être additionnés, immédiatement avant le début de l’expérience, d’une solution concentrée de glucose pour amener la glycémie dans l’intervalle cible visé. L’échantillon a été alors divisé en trois volumes dont deux ont été addi-

**Traitement des données**

La moyenne, l’écart type et le coefficient de variation de chaque série de déterminations ont été calculés pour évaluer l’imprécision.

Pour chaque lecteur et chaque échantillon de patient analysé au cours de l’étude de corrélation, le résultat du lecteur en ordonnée (y) et celui de la méthode à l’hexokinase en abscisse (x) ont été reportés pour évaluer l’inexactitude. La pente et l’ordonnée à l’origine de la droite de régression linéaire de y sur x, la moyenne des valeurs absolues des écarts y-x et le coefficient de corrélation (r²) ont ensuite été calculés. Un diagramme des différences a été établi avec y-x en ordonnée et x en abscisse.

**Tableau 1. Données d’imprécision des lecteurs.**

<table>
<thead>
<tr>
<th>Glycémie (mmol/L)</th>
<th>Répétabilité CV % (N = 15)</th>
<th>Reproductibilité CV % (N = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accu-Chek GO</td>
<td>3,6</td>
<td>4,1</td>
</tr>
<tr>
<td>Accu-Chek Sensor</td>
<td>4,3</td>
<td>2,2</td>
</tr>
<tr>
<td>Optimum Xceed/H</td>
<td>n/a</td>
<td>4,1</td>
</tr>
<tr>
<td>Optimum Xceed/Plus</td>
<td>n/a</td>
<td>2,2</td>
</tr>
<tr>
<td>One Touch Ultra 2</td>
<td>n/a</td>
<td>3,3</td>
</tr>
<tr>
<td>Ascensia BRIO</td>
<td>5</td>
<td>3,5</td>
</tr>
<tr>
<td>StatStrip (Dourdan) I</td>
<td>2,4</td>
<td>1,8</td>
</tr>
<tr>
<td>StatStrip (Dourdan) II</td>
<td>1,9</td>
<td>2,6</td>
</tr>
<tr>
<td>StatStrip (Lyon) I</td>
<td>3,8</td>
<td>4,7</td>
</tr>
<tr>
<td>StatStrip (Lyon) II</td>
<td>2,8</td>
<td>4,7</td>
</tr>
<tr>
<td>Moyennes</td>
<td>3,6</td>
<td>2,3</td>
</tr>
</tbody>
</table>

**Tableau 2. Données de corrélation des lecteurs avec une méthode de référence à l’hexokinase.**

<table>
<thead>
<tr>
<th>Système évalué</th>
<th>Système de référence</th>
<th>N</th>
<th>Pente</th>
<th>Ordonnée à l’origine (mmol/L)</th>
<th>Coefficient de corrélation r²</th>
<th>Moyenne des écarts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accu-Chek GO</td>
<td>Dade RxL</td>
<td>60</td>
<td>0,93</td>
<td>0,17</td>
<td>0,99</td>
<td>6,5</td>
</tr>
<tr>
<td>Accu-Chek Sensor</td>
<td>Modular</td>
<td>49</td>
<td>1,00</td>
<td>0,07</td>
<td>0,98</td>
<td>6,4</td>
</tr>
<tr>
<td>Optimum Xceed/H</td>
<td>Modular</td>
<td>49</td>
<td>0,93</td>
<td>0,09</td>
<td>0,97</td>
<td>9,4</td>
</tr>
<tr>
<td>Optimum Xceed/Plus</td>
<td>Dade RxL</td>
<td>60</td>
<td>0,85</td>
<td>0,7</td>
<td>0,98</td>
<td>8,7</td>
</tr>
<tr>
<td>One Touch Ultra 2</td>
<td>Dade RxL</td>
<td>60</td>
<td>0,95</td>
<td>0,1</td>
<td>0,97</td>
<td>8,6</td>
</tr>
<tr>
<td>Ascensia BRIO</td>
<td>Dade RxL</td>
<td>60</td>
<td>0,942</td>
<td>1,1</td>
<td>0,96</td>
<td>11,9</td>
</tr>
<tr>
<td>StatStrip</td>
<td>Dade RxL</td>
<td>50</td>
<td>0,93</td>
<td>0,4</td>
<td>0,99</td>
<td>4,8</td>
</tr>
<tr>
<td>StatStrip</td>
<td>Modular</td>
<td>50</td>
<td>0,98</td>
<td>0,02</td>
<td>0,99</td>
<td>5,4</td>
</tr>
</tbody>
</table>
Conformément au protocole de l’Afssaps, les limites acceptables ont été tracées de part et d’autre, non pas de l’ordonnée zéro, mais de la différence des moyennes \( m_y - m_x \); ces limites sont de \( \pm 1,11 \text{ mmol/L} \) pour les valeurs < 5,55 mmol/L et de \( \pm 20 \% \) pour les valeurs \( \geq 5,55 \text{ mmol/L} \).

Pour évaluer les effets de l’hématocrite et des constituants exogènes, on a reporté en abscisse la source d’interférence que l’on faisait varier à glycémie constante et en ordonnée les écarts observés, en pourcentage (%) d’un « résultat de référence ». Chacun des points de mesure était la moyenne de six déterminations consécutives. Pour chaque source d’interférence et chaque niveau de concentration de glucose, la réponse des huit lecteurs, dont deux Stat-Strip, était reportée sur le même graphique. Deux types de graphique peuvent être établis selon que le « résultat de référence » est le glucose plasmatique déterminé par la méthode du laboratoire ou la propre réponse du lecteur en l’absence d’interférence. Le premier type, le plus compact, souligne la susceptibilité du lecteur à la source d’interférence étudiée, sans égard à son inexactitude en général. Le second type, plus dispersé, compare les lecteurs sur

**Tableau 1.**

<table>
<thead>
<tr>
<th>Glycémie (mmol/L)</th>
<th>2-4</th>
<th>4-8</th>
<th>15-20</th>
<th>2-4</th>
<th>4-8</th>
<th>15-20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moyennes</td>
<td>3.6</td>
<td>1.1</td>
<td>4.3</td>
<td>1.1</td>
<td>4.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Répétabilité CV % (N = 15)</td>
<td>2.3</td>
<td>1.0</td>
<td>3.2</td>
<td>1.0</td>
<td>3.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Réproductibilité CV % (N = 15)</td>
<td>4.4</td>
<td>1.0</td>
<td>4.3</td>
<td>1.0</td>
<td>4.3</td>
<td>3.4</td>
</tr>
</tbody>
</table>

**Figure 1.** Comparaison de huit lecteurs avec une méthode à l’hexokinase. La différence du résultat du lecteur avec celui de la méthode à l’hexokinase est en ordonnée ; ce dernier est en abscisse.
une échelle commune externe, celle même qu’utilise le clinicien. Dans les deux cas, la réponse est d’autant meilleure que la courbe se rapproche de l’axe horizontal d’ordonnée 0 %. Pour rendre les pentes des graphiques immédiatement comparables, on a ajusté toutes les échelles d’ordonnée pour qu’elles couvrent un intervalle de 100 % d’écart, soit -50 % à +50 %, -25 % à +75 %, etc. Seuls quatre diagrammes représentatifs sur les dix obtenus pour chacun des constituants sont représentés ici.

**Résultats**

**Imprécision**

Les résultats obtenus pour les dix lecteurs (dont quatre StatStrip) sont rassemblés dans le tableau 1. Les coefficients de variation ne diffèrent sensiblement ni pour la répétabilité ni pour la reproductibilité. Ils tendent à diminuer lorsque la concentration de glucose augmente. Si l’on excepte l’Ascensia Brio, ils ne dépassent pas 5 %. Le CV observé pour le StatStrip est en général inférieur à la moyenne.

**Inexactitude**

Les résultats obtenus pour les huit lecteurs (dont deux StatStrip) sont rassemblés dans le tableau 2. Les diagrammes de différences de la figure 1 font ressortir la bonne performance des technologies Accu Chek et StatStrip, comparées à celles des autres lecteurs.

**Effet des variations de l’hématocrite**

Les résultats obtenus sont illustrés par les diagrammes de la figure 2. Les lecteurs étant réglés en usine pour donner leur meilleur résultat dans l’intervalle de référence de l’hé-

---

**Figure 2.** Effet des variations de l’hématocrite à trois niveaux de glycémie sur la réponse de huit lecteurs. L’hématocrite est en abscisse et le pourcentage d’écart en ordonnée. Dans le 4e diagramme l’écart est pris par rapport au glucose plasmatique.
matocrite (37–54 %), on a considéré que cet intervalle définissait « l’absence d’effet ». Trois donneurs ayant été sollicités sur chaque site, soit un pour chaque niveau de glycémie, les valeurs de l’hématocrite ont été affectées d’une incertitude de ± 6 % pour tenir compte de la variabilité biologique interindividuelle [15].

On observe que, à l’exception du StatStrip, la réponse de chacun des lecteurs pris isolément s’écarte significativement de celle en l’absence d’effet, comme si le lecteur rapportait la mesure qu’il effectue de la concentration de glucose plasmatique à un volume qui inclut celui des érythrocytes, admettant ainsi une dilution apparente du glucose. L’importance de l’écart sur un résultat d’hypoglycémie est moins prévisible mais non moins marqué. Après le StatStrip, l’Accu Chek Sensor est le moins sensible à l’effet de l’hématocrite et semble même présenter un comportement paradoxal aux faibles niveaux de concentration de glucose.

**Interférence du maltose**

On observe d’emblée sur la figure 3 que les réponses de l’Accu Chek GO et de l’Accu Chek Sensor sont fortement perturbées : le maltose donne lieu à une réponse du même ordre de grandeur que le glucose. Du fait de l’utilisation de la glucose oxydo-réductase par ces deux lecteurs, ils ne distinguent pas les deux constituants. La réponse des autres lecteurs n’est pas ou peu perturbée par la présence de maltose. Le report des courbes sur l’échelle de référence (diagramme de droite) provoque leur dispersion, alors que celles du StatStrip se maintiennent au plus près de la méthode de référence à tous les niveaux de glycémie : +10 à -11 % pour le lecteur Dourdan et ± 5 % pour le lecteur Lyon.

![](image)

**Figure 3.** Effet de la présence de maltose à trois niveaux de glycémie sur la réponse de huit lecteurs. Le (maltose) est en abscisse, en mmol/L, et le pourcentage d’écart en ordonnée. Dans le 4ème diagramme l’écart est pris par rapport au glucose plasmatique.
Interférence du paracétamol
Les résultats obtenus sont illustrés par les diagrammes de la figure 4. On observe que la réponse de l’Ascensia Brio, de l’Accu Chek Sensor et du One Touch Ultra 2 pour une glycémie de l’ordre de 1-3 mmol/L est systématiquement biaisée dans le sens positif par la présence de paracétamol. Le report de ces courbes sur l’échelle de référence commune montre que la perturbation est encore détectable pour une glycémie de l’ordre de 6-8 mmol/L. L’interférence du paracétamol devient négligeable aux taux de concentration de glucose supérieurs. On a donc omis de représenter les diagrammes correspondants.

Interférence de l’ascorbate
Les résultats obtenus sont illustrés par les diagrammes de la figure 5. On observe d’abord (diagrammes de gauche) que la réponse du One Touch Ultra 2, de l’Ascensia Brio, de l’Optium Xceed utilisé avec la bandelette Medisense Plus et de l’Accu Chek GO est systématiquement biaisée dans le sens positif par la présence d’ascorbate pour des taux de glucose qui vont jusqu’à 6-8 mmol/L. L’interférence de l’ascorbate disparaît aux taux de concentration de glucose supérieurs, sauf pour l’Optium Xceed qui est affecté sur toute la gamme de glycémie. Le report de ces courbes sur l’échelle de référence commune n’appelle pas d’autre commentaire.

Discussion
Ce travail devrait d’abord attirer l’attention des utilisateurs sur les limitations des lecteurs de glycémie et les inciter à la prudence lors de l’interprétation de résultats, par exem-
Figure 5. Effet de la présence d'ascorbate à trois niveaux de glycémie sur la réponse de huit lecteurs. L’{ascorbate} est en abscisse, en mmol/L, et le pourcentage d’écart en ordonnée. Dans le 4e diagramme l’écart est pris par rapport au glucose plasmatique.

ple en les corrigeant en fonction de l’hématocrite. Il montre ensuite l’intérêt analytique d’un dispositif de correction embarqué. Le StatStrip se présente comme le seul des sept lecteurs évalués ici qui soit insensible aux variations de l’hématocrite et le seul à n’être affecté par aucun des trois constituants exogènes : maltose, paracétamol et ascorbate. L’efficacité de la technologie développée pour assurer un résultat exact en présence de ces sources potentielles d’interférences ne fait ainsi pas de doute. Cette technologie apparaît aussi comme plus solide que les autres dans la mesure où elle s’affranchit des calibrages tout en donnant les résultats les plus exacts. Quant à l’intérêt clinique de ce développement, on ne peut encore que le conjecturer faute d’expérience, précisément, avec des lecteurs de ce type. Le risque que des résultats de glycémie faussement élevée conduisent à des surdosages d’insuline, responsables d’hypoglycémies dangereuses, voire fatales pour le patient n’est pas nouveau. Ce risque est l’un de ceux que la recommandation qui est faite aux personnels soignants en USI de resserrer le contrôle de la glycémie, cherche à réduire. On peut conclure de ce travail que, faute d’un regard critique sur la technologie de lecture de la glycémie utilisée lors du traitement de patients diabétiques, anémiques, perfusés, médicalisés, etc. la recommandation pourrait aboutir à multiplier le risque plutôt qu’à le réduire. En attendant les études cliniques qui permettront de redéfinir les critères d’acceptabilité d’un lecteur de glycémie utilisé en USI, on dispose de travaux en modélisation d’erreurs. Ainsi, Boyd et Bruns [16] calculent qu’une erreur de 10 % sur le glucose, c’est-à-dire tolérée aux termes de l’Afssaps, entraîne des écarts de posologie de l’insuline de 16-45 %, montrant ainsi qu’il y a décidément place pour une nouvelle génération de lecteurs de glycémie.
Remerciements. Nous remercions Nova Biomedical pour la fourniture des instruments et des bandelettes utilisés au cours de ce travail.

Références
Galactose Interference on POCT Glucose Analysis

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Introduction

Monitoring of blood glucose levels in patients in a neonatal intensive care setting is important for managing and maintaining normalised blood glucose concentrations and reducing the risk of hypoglycaemia. Hypoglycaemia is a typical, potentially life-threatening symptom in classical galactosaemia with blood galactose levels considerably elevated (up to ~100 mg/dl). POC glucose meters and blood gas analysers are frequently routinely used for the measurement and management of glucose levels in NICU patients. However the accuracy of many glucose meters can be affected by the presence of nonglucose sugars and other interference substances occasionally present in the blood of hospitalised patients. It is well known that the accuracy of glucose measurements in patients receiving maltose supplementation or maltose based products can give rise to serious adverse incidents. Recently falsely elevated glucose readings have been reported for patients with galactosaemia.

Objective

The aim of this study was to access the influence of galactose on the accuracy of blood gas analysers and hand held point of care glucose measurement systems.

Method

Interference studies were performed using a concentrated galactose solution added to venous heparinised whole blood. Specimens were prepared combining four different galactose concentrations and two different glucose concentrations. The results obtained were compared to the control samples containing no galactose. Two glucose methods, StatStrip glucose (Nova Biomedical) and AccuChek Performa (Roche Diagnostics) were tested as well as two ABL835 blood gas analysers (Radiometer) routinely used in NICU.

Results

The accuracy of the glucose results obtained using the AccuChek Performa and two ABL835 blood gas analysers were affected by galactose (tables 1 and 2). The accuracy of StatStrip glucose results was unaffected by galactose.

Table 1. Galactose interference assessment with samples containing 55mg/dL glucose

<table>
<thead>
<tr>
<th></th>
<th>Galactose concentration (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>StatStrip</td>
<td>47 / 55 / 50 / 50</td>
</tr>
<tr>
<td>AccuChek Performa (GDH-PQQ)</td>
<td>61 / 63 / 63 / 65</td>
</tr>
<tr>
<td>ABL 835 (No 1)</td>
<td>48</td>
</tr>
</tbody>
</table>
Results (Cont’d)

Table 2. Galactose interference assessment with samples containing 0mg/dL glucose

<table>
<thead>
<tr>
<th></th>
<th>Galatose concentration (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>StatStrip</td>
<td>&lt;10/ &lt;10/ &lt;10/ &lt;10</td>
</tr>
<tr>
<td>AccuChek Performa (GDH-PQQ)</td>
<td>&lt;10/ &lt;10/ &lt;10/ &lt;10</td>
</tr>
<tr>
<td>ABL 835 (No 1)</td>
<td>2 / 2 / 2 / 1</td>
</tr>
<tr>
<td>ABL 835 (No 2)</td>
<td>1 / 1</td>
</tr>
</tbody>
</table>

Table 3. Galactose screening results in Lower Saxony (mature neonates, birth weight > 2.5 kg, day 2 – 7, 1st test)

<table>
<thead>
<tr>
<th>Total galactose (mg/dL)</th>
<th>Classic galactosemia, GALT deficiency</th>
<th>Galactokinase deficiency, GALK deficiency</th>
<th>Duarte Galactosemia D2/G</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>147.1</td>
<td>90.7</td>
<td>38.1</td>
</tr>
<tr>
<td></td>
<td>124.5</td>
<td>78.1</td>
<td>11.3</td>
</tr>
<tr>
<td></td>
<td>82.7</td>
<td>67.4</td>
<td>6.8</td>
</tr>
</tbody>
</table>

Standard values (Nov 1-Dec 8,09: n=9,460): percentiles P50, P80, P90, P99

|                         | 1.7 | 3.5 | 5.1 | 12.3 |

Some POCT glucose meters are not able to diagnose hypoglycaemia in the presence of galactose. GDH-PQQ and Glucose oxidase based systems can be influenced. Biosensors based on galactose oxidase-peroxidase can correct this interference.

Conclusion

Although galactosaemia is an uncommon occurrence following newborn screening the occurrence can be higher in neonatal patients admitted to NICU. Permanent or transient elevation of blood galactose can be found in neonates with galactosaemia, liver dysfunction or maturational delay of galactose transport or utilization. As such the influence of raised galactose levels on the accuracy of glucose meters and blood gas analysers needs to be taken into account in an NICU patient setting in order to manage hypoglycaemia effectively.
Measurement of blood glucose by means of bedside blood glucose (BG) monitoring systems (BGM) has become a worldwide diagnostic routine procedure. However, based on the underlying measurement technology, the sample hematocrit value and other chemical substances are known to interfere with the analysis results. The new BGM Nova StatStrip® from Nova Biomedical is designed to correct all values for interfering substances. In order to evaluate the accuracy of this device in comparison to competitive BGM systems (AccuCheck Aviva/Roche, AscenciaContour/Bayer, Freestyle/Abbott, OneTouch Ultra2/Lifescan), we performed a laboratory bench test with routine blood samples at low, normal, and high blood glucose concentrations and with different hematocrit (HCT: 24.7– 64.9 %) and spiked maltose concentrations (0, 10, and 20 mg/dl). A glucose oxidase method served as standard reference (SuperGL, Müller Gerätebau, Delecke-Möhnesee).

All BGMs with the exception of the StatStrip® showed an inverse relation between the hematocrit value and the BG levels. Next to StatStrip®, the observed drift was less pronounced with AccuCheck than with the other comparator devices (e.g. BG: 37 mg/dl, change in mean deviation with increasing HCT: StatStrip®: +6.7%, AccuCheck: -8.8%, Ascencia: -36.8%, Freestyle: -25.6%, Ultra2: -49.9%). In addition, a strong interference was seen by increasing maltose concentrations, with many devices (e.g.: blood glucose: 237 mg/dl, mean percent deviations at 0, 10 and 20 mg/dl maltose: StatStrip®: 5.5%/0.8%/6.6%, AccuCheck: 4.9%/60.6%/106.9%, Ascencia: -2.5%/-3.2%/-5.9%, Freestyle: -23.1%/-26.9%/-23.4%, Ultra2: -10.7%/37.2%/91.0%). The majority of glucose meter technologies tested are affected by analytical interferences by hematocrit and maltose. The StatStrip® glucose meter technology correlated closely with a reference and did not demonstrate clinically significant interference from any of the interfering agents tested, inclusive of hematocrit.
Das Blutzuckermesssystem StatStrip® ist nicht empfindlich für Interferenzen durch Hämatokrit oder andere bekannte Störsubstanzen

Thomas Schöndorf, Petra Musholt, Silvia Scherer, Mirjam Löbig, Ary Younessi, Jeffrey Dubois, Peter Aust, Thomas Forst, Andreas Pfützner


Mit Ausnahme des StatStrip® fand sich bei allen Geräte eine Abnahme des Messwertes mit steigendem Hkt (z.B. % Veränderung der mittleren absoluten % Abweichung (MAPD) vom eingestellten BZ-Wert bei 237 mg/dl mit steigendem Hkt: StatStrip®: + 6.7 %, AccuCheck: -8.8 %, Ascencia: -36.8 %, Freestyle: -25.6 %, Ultra2: -49.9 %).

Einen massiven Einfluß auf die Messwerte hatte in vielen Fällen auch Maltose oder AS (z.B. bei einem BZ von 237 mg/dl; MAPD bei 0, 10, und 20 mg/l Maltose: StatStrip®: 5.5%/0.8%/6.6 %, AccuCheck: 4.9%/60.6%/106.9 %, Ascencia: -2.5%/-3.2%/-5.9 %, Freestyle: -23.1%/-26.9%/-23.4 %, Ultra2: -10.7%/-37.2%/-91.0 %; prozentuale Veränderung MAPD bei 0 bis 10 mg/dl AS: StatStrip®: + 5.3 %, AccuCheck: +18.1 %, Ascencia: +23.8 %, Freestyle: +14.6 %, Ultra2: +22.9 %).

Genauigkeit des Blutzuckermesssystems StatStrip im Vergleich zu anderen Messsystemen und zu einer Standard-Labormethode

Petra Musholt1, Silvia Scherer1, Thomas Schöndorf1, Ary Younessi2, Jeffrey Dubois3, Peter Aust2, Thomas Forst1, Andreas Pfützner1
1Institut für klinische Forschung und Entwicklung GmbH, Mainz
2Nova Biomedical GmbH, Rödermark
3Nova Biomedical Inc., Waltham, MA, USA

Einleitung:


Methoden:


Ergebnisse:

Der Freestyle fiel nach den ersten Messungen wahrscheinlich aufgrund eines technischen Problems aus und konnte daher nicht abschließend beurteilt werden. Die Ergebnisse der linearen Regressionsanalysen für die einzelnen Geräte im Vergleich zur Laborreferenz finden sich in den Abbildungen 1-4. In Abbildung 5 sind die absoluten mittleren prozentualen Abweichungen vom Laborwert graphisch dargestellt. Die beste Korrelation mit der Labormethode fand sich beim StatStrip-Gerät (Korrelationskoefizient/Achsenngradient: 0,9970/0,966/1,3; AccuCheck Aviva: 0,9811/0,821/12,9; Ascencia Contour: 0,9820/0,787/1,9; OneTouch Ultra2: 0,9689/0,804/0,1), dass mit 3,2±2,2 % auch die geringste mittlere absolute prozentuale Abweichung aufwies (AccuCheck Aviva: 10,3±7,2 %; Ascencia Contour: 19,3±8,2 %; OneTouch Ultra2: 18,8±8,6 %, p<0,001 vs. StatStrip für alle Geräte).

Schlussfolgerungen:

Bereits in der Vergangenheit wurde von verschiedenen Fachgesellschaften für Blutzuckertestgeräte für die Patienten Selbsttestung mittels Teststreifen eine maximale Abweichung von ±5 % im Vergleich zu den Labormethoden gefordert, ohne dass dies von den aktuell verfügbaren Patienten Selbsttestgeräten erreicht wird. Mit dem StatStrip-System steht erstmals ein teststreifenbasiertes Point-of-Care Blutzuckermessgerät zur Verfügung, das diesem Anspruch gerecht wird.
Analytical Performance of an Interference-Resistant Glucose Meter

Britta Friederichs¹, Ghassem Younessi-Sinaki², Peter Aust², Jeffrey A. DuBois², Hans Guenther Wahl¹,³

¹Klinikum Luedenscheid, ³University of Marburg, Germany; ²Nova Biomedical, Waltham, MA, USA

Background

Much attention has been paid to the monitoring of glucose in hospitalized patients to achieve improved glycemic control (GC) and to minimize complications from hypo- and hyperglycemia. While hyperglycemia of hospitalized patients is common among patients with diabetes mellitus, it is not restricted to patients with this disease. In addition, glucose levels within hospitalized patients, particularly those that are critically ill, can change rapidly depending on stress and medication. In order to maintain GC for these patients, rapid turnaround times (TATs) for glucose analyses are required. Point-of-care (POC) testing reduces TATs dramatically from those obtained by traditional central laboratory testing. Glucose meters are generally the instruments of choice for POC glucose testing, but based on the recent literature current meters may not be acceptable for use in intensive insulin therapy to treat hyperglycemia in the hospitalized patient.

Study Objective

The aim of the current study was to compare current glucose meters with a new glucose meter that uses corrections made by both interferences and measured hematocrit. The study compared the accuracy of hospital-based glucose meters to a reference plasma hexokinase method, evaluated the extent of drug interferences on the meters, and determined the effect of hematocrit on the correlation between the glucose meters and the hexokinase glucose result at three (3) glucose concentrations.

Methods

Glucose meters:

• StatStrip® (Nova Biomedical)
• AccuChek® Aviva (Roche Diagnostics)
• Freestyle® (Abbott Diabetes),
• Ascensia Contour ® (Bayer).
• HemoCue 201+ (HemoCue)

Within run precision

Within run precision was assessed by using heparinized venous blood spiked to give three different levels of glucose (low, medium, high). Each specimen was tested 20 times.

Influence of hematocrit

Influence of hematocrit was evaluated using 3 glucose concentrations over a hematocrit range of 26-64%. Hematocrit results were determined using the HemataSTAT-II micro-hematocrit centrifuge (Separation Technology, Altamonte Springs, Florida). A portion of each of the prepared samples was centrifuged shortly after preparation and analyzed by the laboratory hexokinase reference method (Roche P-Module – Roche Diagnostics).

Interferences

Interference studies were performed with acetaminophen, ascorbic acid, and maltose. Heparinized blood specimens were spiked to give five glucose levels. Aliquots of each sample were spiked with stock solutions of each interference substance.

Method comparison

Heparinized venous whole-blood specimens were collected from 100 patients and glucose levels were measured using the four strip-meter systems and the results compared to the reference method.
Results

Within run precision
StatStrip® demonstrated good precision with both batches of strips.

Influence of hematocrit
The glucose results obtained with the Aviva, Freestyle and Contour meters were adversely affected by high and low hematocrit levels. StatStrip® was unaffected.

<table>
<thead>
<tr>
<th>Low glucose</th>
<th>Mid glucose</th>
<th>High glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean value (mg/L)</td>
<td>SD</td>
<td>CV%</td>
</tr>
<tr>
<td>StatStrip® batch 1</td>
<td>62</td>
<td>2.1</td>
</tr>
<tr>
<td>StatStrip® batch 2</td>
<td>60</td>
<td>1.4</td>
</tr>
</tbody>
</table>

![Graph of blood glucose 26-33 mg/L vs. hematocrit]

![Graph of blood glucose 270-290 mg/L vs. hematocrit]

![Graph of blood glucose 350-390 mg/L vs. hematocrit]
Results continued

Interferences
Acetaminophen had little effect on all four meters. The glucose results of the Aviva, Freestyle and Contour meters were adversely affected by ascorbate and the glucose results of the Aviva and Freestyle meters were significantly affected by maltose. StatStrip® readings were unaffected by any of the interfering substances.
Results continued

Method comparison
StatStrip® had the closest correlation to the reference method with a mean % bias much lower than the other meters. This is also substantiated by the bias plots. The results indicate that the StatStrip® meter met the performance goals recommended by the National Committee for Clinical Laboratory Standards/International Organization Standardization 15197, the Food and Drug Administration and CLIA.

<table>
<thead>
<tr>
<th>Meter</th>
<th>R²</th>
<th>Slope</th>
<th>Intercept</th>
<th>N</th>
<th>Mean Bias</th>
<th>SD</th>
<th>% Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>StatStrip®</td>
<td>0.993</td>
<td>1.002</td>
<td>3.86</td>
<td>100</td>
<td>4.41</td>
<td>12.60</td>
<td>1.55</td>
</tr>
<tr>
<td>Aviva</td>
<td>0.991</td>
<td>0.951</td>
<td>-13.30</td>
<td>100</td>
<td>-27.94</td>
<td>15.11</td>
<td>-9.59</td>
</tr>
<tr>
<td>Contour</td>
<td>0.986</td>
<td>0.822</td>
<td>10.07</td>
<td>100</td>
<td>-42.84</td>
<td>30.47</td>
<td>-12.55</td>
</tr>
<tr>
<td>Freestyle</td>
<td>0.991</td>
<td>0.902</td>
<td>4.48</td>
<td>91</td>
<td>-22.03</td>
<td>16.41</td>
<td>-7.38</td>
</tr>
</tbody>
</table>

Conclusion
Five (5) POC glucose technologies were compared to a reference hexokinase method and the results demonstrated that the correlation of glucose values from the strip-meter whole blood glucose methods vary among the different glucose meter manufacturers, as previously reported. The StatStrip® glucose meter correlated best with a plasma hexokinase reference method over a wide range of glucose concentrations and was least significantly impacted by sample hematocrit and other interfering substances. It also had the lowest total error, relative to the reference method, of all the meters studied. This improved performance will provide for better management of critically ill patients on intensive insulin therapy resulting in better glycemic control with improved outcomes and patient safety.
Suitability Assessment of a New Bedside Interference Free Glucose System for Use in Critical Care when Compared to Current Technology

Luca Germagnoli¹, Pierangelo Bonini¹, Jeffrey DuBois², Jack Bierens de Haan², Claudia Tartarotti³

¹ Laboraf Diagnostica e Ricerca San Raffaele, Milan, Italy ; ² Chair of Biochemistry Università Vita-Salute San Raffaele, Milan, Italy; ³ Nova Biomedical Corporation, Waltham, MA ; ⁴Gepa Srl, Milan, Italy

Introduction
Measurement of blood glucose in acute hospitalized patients by means of handheld blood glucose monitoring systems (BGM) has become a routine diagnostic procedure worldwide. Commonly used BGM's are based on design technology implemented for ambulatory glucose monitoring. The accuracy of these meters can be affected by several prevalent endogenous or exogenous compounds including abnormal hematocrit levels commonly found in critically ill hospital patients. The StatStrip® new generation BGM from Nova Biomedical is designed to correct for such interferences.

Aim
The aim of this study was to evaluate the specificity and accuracy of StatStrip® with interferants that commonly affect the accuracy of BGM's. In addition the clinical reliability and accuracy was evaluated in neonatal and neurosurgical ICU patients.

Method
Interference Study
In order to compare the accuracy of this device with that of commonly used BGMs we performed an analytical evaluation, to assess the affect of lactate, β-hydroxybutyrate, ascorbate, maltose and paracetamol, (at low and high concentration) on the measurement of glucose concentrations ranging from 2.5 to 25 mmol/l (45-455 mg/dl). In addition we also looked at the effect of wide ranging hematocrit levels (26-68%) on glucose concentrations ranging from 2.5 to 25 mmol/l. Results were compared to a Advia 2400 (Siemens) hexokinase reference method.

Glucose Systems Evaluated
• StatStrip® (Nova Biomedica)
• AccuChek Active (Roche)
• Precision Xtra (Abbott)
• Ascensia Breeze 2 (Bayer)

Precision
All BGMs were evaluated for within-run and between-day precision, and for correlation with the reference method.

ICU Study
We also evaluated StatStrip® in a neurosurgical ICU (NchHSR), concurrently with an Ascensia Breeze BGM; eighty seven (87) and ninety five (95) samples were tested respectively. Comparison results were obtained from a Cobas 6000 (Roche Diagnostics) hexokinase reference method
Results
Hematocrit

Levels of hematocrit outside of the normal reference range induces significant bias with the glucose measurement results of Ascensia, Precision and AccuChek, but not those of StatStrip® at all blood glucose levels tested.
Results continued

Other Interferences

Lactate or β-hydroxybutyrate had no effect on all four meters. Maltose affected AccuChek as if it were glucose with significantly raised results. Ascorbate produced a positive bias on Ascensia and AccuChek and a negative one on Precision, mainly at lower blood glucose levels. Paracetamol affected the Ascensia, at lower blood glucose levels. StatStrip® remained unaffected in all cases.
Results continued

Precision

Precision was satisfactory for all devices. Regressions of BGM/Advia bench result pairs were excellent, with slopes lying between 0.93 and 1.02 and intercepts between -16.2 and 5.4 mg/dL (–0.9 and 0.3 mmol/l).

ICU study

For the assessment of neurosurgical ICU patients the accuracy of StatStrip® correlated closely with the Cobas reference method with the difference plot complying with ISO15197 criteria. However the correlation of the Breeze 2 meter to the Cobas method was much poorer and results did not comply with ISO15187criteria.

Conclusion

The analytical performance of three current commonly used glucose meter technologies, though giving acceptable results in ambulatory patients, was affected by prevalent sources of interference to a magnitude that may seriously impair maintenance of patient glycermia in the ICU. The new generation StatStrip® glucose meter technology did not demonstrate clinically significant interference from any of the interfering agents tested, inclusive of hematocrit variations and therefore offers improved specificity and reliability compared to conventional glucose meters. When applied to a neurosurgical ICU patient population the StatStrip® readings were accurate and reliable whereas the Breeze 2 results demonstrated a significant deviation in accuracy compared to the reference method.

Robbert Slingerland, Wim Muller, Marion Fokkert, Rosie Dollahmoursid, Carolien Witteveen, Rita Munnikhuis, Jeffrey DuBois, Roger Clampitt, Euan Donald

1Isala Klinieken, Clinical Chemistry Laboratory, Zwolle, Netherlands
2 Nova biomedical Corporation, Waltham, MA, USA

Introduction

The use of point-of-care blood glucose monitoring systems (BGM) has become a worldwide diagnostic routine procedure. Many commonly used systems were developed for ambulatory use and have found their way into use in hospital settings. However it is recognised that the biochemical composition and matrix of blood can be more challenging to the specificity of BGM’s in hospitalised patients. Fluctuations in hematocrit levels can cause interference with conventional glucose meters giving rise to potentially erroneous results. In addition biochemical substances associated with patient regimes can also cause interference effects. A new generation BGM, StatStrip® from Nova Biomedical is specifically designed to correct for interfering substances.

Aim

To challenge the accuracy and specificity of StatStrip® using the TNO (Netherlands Organisation for Applied Scientific Research) approved protocol and to compare its performance with conventional BGM systems.

Methods

Blood samples were prepared at low, normal, and high blood glucose concentrations and with different hematocrit levels (HCT: 24.7 – 64.9 %) and spiked maltose concentrations (0, 10, and 20 mg/dl). Samples were tested by AccuCheck Inform (Roche), Hemocue (Quest Diagnostics), StatStrip® (Nova) and Precision PCx (Abbott). An isotopic dilution GC-MS aligned glucose hexokinase method using a perchlorate precipitation step served as the standard reference method (Isala Klinieken, Zwolle, Netherlands). Furthermore, we performed a method comparison between the Nova StatStrip® and the isotopic dilution GC-MS aligned ABL 735 from Radiometer using blood from neonates. Following the analytical performance we went on to assess StatStrip® in a neonatal intensive care unit on whole blood collected from 48 patients with hematocrit levels varying from 23-75%.

Results

Precision

All methods demonstrated good correlation with the reference method, hexokinase plasma equivalent method calculated from whole blood values (perchloric acid assay) or hexokinase in plasma (plasma assay)

<table>
<thead>
<tr>
<th>Method</th>
<th>P&amp;B regression</th>
<th>r</th>
<th>n</th>
<th>Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>StatStrip®</td>
<td>y=0.964 x–0.259</td>
<td>0.997</td>
<td>98</td>
<td>perchloric acid assay</td>
</tr>
<tr>
<td>StatStrip®</td>
<td>Y=0.992 x–0.171</td>
<td>0.997</td>
<td>98</td>
<td>plasma assay</td>
</tr>
<tr>
<td>AccuChek</td>
<td>y=1.002 x – 0.354</td>
<td>0.995</td>
<td>97</td>
<td>perchloric acid assay</td>
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<tr>
<td>AccuChek</td>
<td>Y=1.025 x – 0.202</td>
<td>0.995</td>
<td>97</td>
<td>plasma assay</td>
</tr>
<tr>
<td>PCx</td>
<td>y=0.917 x + 0.772</td>
<td>0.990</td>
<td>96</td>
<td>perchloric acid assay</td>
</tr>
<tr>
<td>PCx</td>
<td>Y=0.944 x + 0.882</td>
<td>0.989</td>
<td>96</td>
<td>plasma assay</td>
</tr>
<tr>
<td>HemoCue</td>
<td>y=1.085 x – 0.269</td>
<td>0.995</td>
<td>97</td>
<td>perchloric acid assay</td>
</tr>
<tr>
<td>HemoCue</td>
<td>Y=1.112 x – 0.117</td>
<td>0.995</td>
<td>97</td>
<td>plasma assay</td>
</tr>
</tbody>
</table>

Interference

StatStrip® and HemoCue were not affected by hematocrit interference. AccuChek was significantly affected by maltose interference.
Neonatal study

StatStrip® showed excellent correlation to ABL 735 achieving the accuracy requirements of the TNO protocol

CONCLUSION

The majority of the glucose meter technologies tested are affected by analytical interferences, eg hematocrit and/or maltose. The StatStrip® glucose meter technology correlated closely with the reference method and did not demonstrate clinically significant interference from any of the interfering agents tested, inclusive of hematocrit. The StatStrip® glucose meter has an acceptable performance and accuracy when applied to neonatal samples and is a candidate blood glucose meter for monitoring glucose levels in hospitalized neonatal patients.
Evaluation of the Nova Biomedical StatStrip® Glucose Meter

B. Mohn, P. Rowe, P. Cleave.

Chemical Pathology, Middlemore Hospital, Auckland, N.Z.

Introduction

We evaluated the Nova StatStrip® glucose meter for precision, accuracy, and interferences from hematocrit and maltose. The Nova StatStrip® was also compared with three other meters and two reference methods. Heparinized whole blood samples were analyzed on the meters. These results were compared with whole blood samples analyzed on the Radiometer ABL835 for the interference studies. Plasma samples, obtained from these whole blood samples, were measured on the Abbott CI8200 for accuracy studies.

Glucose Meters used:
- Nova Biomedical StatStrip®
- Arkray Glucocard
- Abbott Precision PCx
- Roche Accu-Chek Advantage

Reference Methods used:
- Abbott CI8200
- Radiometer ABL835

Methods and Procedures

Precision Study

The precision study on the Nova StatStrip® was performed by analyzing five heparinized whole blood samples at 20 replicates. The glucose range was between 1.0-34 mmol/l.

Meters used: Nova Biomedical StatStrip® compared with Abbott CI8200 (hexokinase method)
**Interferences Study**

For the interference study, we used freshly heparinized venous blood drawn from healthy donors and allowed it to sit at room temperature for 24 hours before concentrated solutions of glucose and interfering substances were added.

**Hematocrit interference:**

For the study we used two concentration levels of glucose (target ranges 1.1-3.3 and 18.1-22.2 mmol/l) at 3 different hematocrit levels (target ranges 20-26%, 42-48%, and 50-55%).

For each glucose meter there were 5 replicate measurements at 3 hematocrit levels and 2 different glucose levels, giving a total of 30 data points per meter.

The hematocrit interference graph was generated for each tested glucose level using the average recovered value of the 4 replicates obtained for each hematocrit level on each manufacturer’s meter.

Meters used: Nova Biomedical StatStrip®, Arkray Glucocard, Roche Accu-Chek Advantage, Abbott Precision PCx Plus and the reference method was Radiometer ABL 835

### Hct Interference Studies (Low BGL)

<table>
<thead>
<tr>
<th></th>
<th>0.21</th>
<th>0.41</th>
<th>0.52</th>
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</thead>
<tbody>
<tr>
<td>PCx Plus</td>
<td>2.5</td>
<td>2.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Advantage</td>
<td>2.4</td>
<td>2.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Glucocard</td>
<td>1.6</td>
<td>1.2</td>
<td>1.3</td>
</tr>
<tr>
<td>StatStrip</td>
<td>2.3</td>
<td>2.1</td>
<td>2.4</td>
</tr>
<tr>
<td>Reference</td>
<td>2.90</td>
<td>2.80</td>
<td>2.90</td>
</tr>
</tbody>
</table>

### Hct Interference Studies (High BGL)

<table>
<thead>
<tr>
<th></th>
<th>0.23</th>
<th>0.40</th>
<th>0.52</th>
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</thead>
<tbody>
<tr>
<td>PCx Plus</td>
<td>19.1</td>
<td>16.0</td>
<td>13.8</td>
</tr>
<tr>
<td>Advantage</td>
<td>19.3</td>
<td>18.2</td>
<td>15.6</td>
</tr>
<tr>
<td>Glucocard</td>
<td>20.6</td>
<td>16.7</td>
<td>13.9</td>
</tr>
<tr>
<td>StatStrip</td>
<td>19.3</td>
<td>17.6</td>
<td>17.7</td>
</tr>
<tr>
<td>Reference</td>
<td>20.9</td>
<td>20.8</td>
<td>21.0</td>
</tr>
</tbody>
</table>
Maltose Interference:

For the study we used two concentration levels of glucose (target ranges 1.1-3.3 and 18.1-22.2 mmol/l) at 3 different Maltose levels (concentration 0, 2.8 and 5.6 mmol/l).

For each glucose meter there were 5 replicate measurements at 3 maltose levels and 2 different glucose levels, giving a total of 30 data points per meter.

The maltose interference graph was generated for each tested glucose level using the average recovered value of the 5 replicates obtained for each investigated interference level on each manufacturer’s meter.

Meters used: Nova Biomedical StatStrip®, Roche Accu-Chek Advantage and reference method was ABL835

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**Maltose Interference Study (Low BGL)**

<table>
<thead>
<tr>
<th>Maltose Level</th>
<th>StatStrip</th>
<th>Advantage</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0 mmol/L</td>
<td>0.0</td>
<td>0.7</td>
<td>1.0</td>
</tr>
<tr>
<td>2.8 mmol/L</td>
<td>0.9</td>
<td>3.9</td>
<td>1.5</td>
</tr>
<tr>
<td>5.6 mmol/L</td>
<td>1.0</td>
<td>6.5</td>
<td>1.4</td>
</tr>
</tbody>
</table>

---

**Maltose Interference Study (High BGL)**

<table>
<thead>
<tr>
<th>Maltose Level</th>
<th>StatStrip</th>
<th>Advantage</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0 mmol/L</td>
<td>17.6</td>
<td>18.4</td>
<td>20.6</td>
</tr>
<tr>
<td>2.8 mmol/L</td>
<td>20.7</td>
<td>19.3</td>
<td>21.7</td>
</tr>
<tr>
<td>5.6 mmol/L</td>
<td>23.7</td>
<td>19.1</td>
<td>21.7</td>
</tr>
</tbody>
</table>
Correlation Study

The correlation method was performed by analyzing 120 heparinized whole blood specimens on the four glucose meters, compared to plasma obtained from those specimens and run on the CI8200 (reference method).

The glucose value was between 2.3-20.2 mmol/l.

Meters used: Nova Biomedical StatStrip®, Arkay Glucocard, Roche Accu-Chek Advantage, Abbott Precision PCx Plus and the reference method was Abbott CI8200 (hexokinase method)

**Nova Biomedical StatStrip® – CI8200 (reference method)**

**Arkay Glucocard – CI8200 (reference method)**

**Abbott Precision PCx – CI8200 (reference method)**

**Roche Accu-Chek Advantage – CI8200 (reference method)**
Results:
There were significant differences in the degree to which the meters correlated with the reference method. With the exception of the Nova StatStrip®, all meters were affected by variable hematocrit. Of the two glucose meters tested, the Nova StatStrip® did not show any maltose interference.

Conclusion:
The Nova Biomedical StatStrip® glucose meter did not show clinically significant interference from maltose or varying hematocrit levels.
In addition, the Nova Biomedical StatStrip® glucose meter demonstrated the best correlation with the reference glucose method.
In summary the Nova Biomedical StatStrip® glucose meter:
- Compares well with the reference method
- Hematocrit and maltose cause minimal interference
- Is user friendly and gives fast, reliable, clinically acceptable results
- Uses a small sample volume
- Calibrations are not required
Assessment of the Performance of Handheld POC Sensors for measuring 3-hydroxybutyrate

Helen Aitkenhead, Kirandeep Marwaha, Steffan Evans

Chemical Pathology, Great Ormond Street Hospital for Children, London WC1N 3JH

Introduction

Handheld POC sensors are now available for rapid blood ketone measurement. However, it is known that endogenous and exogenous interfering substances present in the blood of patients can affect the design and the accuracy of these types of sensors.

Ketone measurement is important in the differential diagnosis of children presenting with hypoglycaemia. In our hospital, children with hypoglycaemia undergo diagnostic fasts in order to elucidate the cause of hypoglycaemia. The degree of ketosis is an important diagnostic indicator. In another group of children, the ketogenic diet is used to manage and control epilepsy. To ensure that there is adequate ketosis, ketone levels are usually monitored by measuring plasma 3-hydroxybutyrate (3-OHB) concentrations in a central laboratory or by a urine ketone method.

Project Aims

1. To assess the analytical accuracy and reliability of two POC ketone sensors, StatStrip® Ketone (Nova Biomedical, Waltham, MA) and Optium Ketone (Abbott Diabetes, Alameda, CA)

2. To assess the clinical reliability of the StatStrip® Ketone measurements in children with hypoglycaemia (suspected hyperinsulinism) undergoing diagnostic fasts, and in children with epilepsy on the ketogenic diet, compared with the laboratory plasma 3-OHB method (Ranbut, Randox Laboratories on IL650 analyser, Instrumentation Laboratory Ltd).

Methods

Analytical Studies

Imprecision was assessed by measuring the 3-OHB concentrations of venous heparinised whole blood spiked with three concentrations of 3-OHB (n=10).

Interference studies were performed using ascorbate, acetoacetate and paracetamol (acetaminophen) added to whole blood at three concentrations of 3-OHB. Haematocrit interference was tested at three 3-OHB concentrations over a 26-64% haematocrit range.

Method correlation studies were performed by preparing venous heparinised whole blood spiked with varying concentrations of 3-OHB (n=20) and measuring them using the POC sensors and then in the plasma by the laboratory method (Ranbut, Randox Laboratories).

Clinical Studies

For children with hypoglycaemia, capillary blood specimens were measured using the StatStrip Ketone and a simultaneous venous heparinised blood specimens was measured by the laboratory method at the start, middle and end of the diagnostic fast.

For children with epilepsy on the ketogenic diet, venous heparinised blood specimens were collected at the Outpatient Clinic and the StatStrip® Ketone results were compared to the laboratory plasma 3-OHB method.

September 22-25, 2010 AACC CPOCT 23rd International Symposium Boston, MA, USA
Results

Analytical Studies

*Imprecision studies*

The StatStrip® Ketone demonstrated acceptable precision at all levels of 3-OHB tested with CV’s <10%. The Optium Ketone showed good precision for the low and high-level 3-OHB samples but more variability with the medium level 3-OHB sample.

<table>
<thead>
<tr>
<th>3-OHB mmol/L</th>
<th>Nova StatStrip®</th>
<th>Abbott Optium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>SD</td>
</tr>
<tr>
<td>Level 1</td>
<td>0.55</td>
<td>0.05</td>
</tr>
<tr>
<td>Level 2</td>
<td>2.28</td>
<td>0.11</td>
</tr>
<tr>
<td>Level 3</td>
<td>5.52</td>
<td>0.20</td>
</tr>
</tbody>
</table>

*Interference studies*

The effects of haemocrit, ascorbate, acetoacetate and paracetamol on the accuracy of 3-OHB measurement at a medium concentration are shown below. The accuracy of the Optium was affected at all concentrations of 3-OHB whereas the accuracy of the StatStrip® was not affected at any.
Results (Cont’d)

Analytical Studies

Method correlation studies
Both meters showed a reasonable comparison to the laboratory method. However, the StatStrip® showed a positive bias with results greater than 2.5 mmol/L whereas the Optium showed a negative bias with results less than 2.5 mmol/L.

Clinical Studies

Children with hypoglycaemia
The 3-OHB results obtained during diagnostic fasts using the StatStrip® compared well to the laboratory method and can be used to aid the investigation and management of children with hypoglycaemia.
Results (Cont’d)

Clinical Studies

*Children with epilepsy on the ketogenic diet*

The 3-OHB results obtained using the StatStrip® compared well to the laboratory method and can be used to inform the patient/carer that the diet is correctly formulated to provide adequate ketosis in the patients.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>3-OHB mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

**Conclusion**

- Both the StatStrip® and Optium showed acceptable imprecision and correlation with the laboratory method.

- The accuracy of the StatStrip® was unaffected by potential interferences and varying haemocrits whereas the accuracy of the Optium was affected.

- The StatStrip® Ketone appears to be suitable for monitoring children on the ketogenic diet, and for aiding in the differential diagnosis of children with hypoglycaemia although more data is needed.
Four Step Validation Procedure for Evaluating POCT Meters

A. Thomas ¹, S. Sall, N. Blount, M. Perkins, C. Roberts, and R Williams².

1. WEQAS Quality Laboratory, Cardiff & Vale University Health Board, Cardiff, Wales, UK.
2. IM&T Department, Cardiff & Vale University Health Board

Background

Glycaemic control of patients in a critical care hospital setting is an important part of the recovery process and has been shown to reduce patient morbidity and mortality. However, errors in glucose measurements can lead to insulin dosing errors resulting in serious adverse incidents. Implementation of glucose measurement systems into a large hospital setting is a major commitment extending over a 3-5 year period. As a result, the choice of meter needs thorough evaluation in order to ensure maximum patient benefit and minimal patient risk over this time period. It is now accepted that that the design and accuracy of most commonly used meters can be affected by varying levels of haematocrit as well as endogenous and exogenous interfering substances present in the blood of hospitalised patients. The selection of a glucose measurement system needs to take into account the impact of these design and performance deficiencies on the hospital patient population being tested. Our hospital is a prestigious University and tertiary referral Hospital, with >1000 beds, wide ranging medical specialties, multiple operating theatres, several Intensive Care Units and an operational Glycaemic Control Policy. Over 200 glucose meters are used throughout the organisation, generating 500,000 tests per annum. To ensure the right choice of glucose meter we implemented a procedure for evaluating glucose meters. Following the recent introduction of new UK guidelines recommending the use of whole blood ketone testing as a cornerstone of DKA management we have also applied this procedure to BHB meters.

Evaluation Process

The four-step evaluation process is aimed at identifying meters that meet the specification and the process includes:

1. Laboratory evaluation – precision, correlation, interference studies (haematocrit, non-glucose sugars, electrochemical interferences) based on CLSI guidelines.

2. Clinical study - Measured accuracy versus laboratory hexokinase method in NICU and Cardiac ITU setting, and compliance with ISO15197 combined with impact of haematocrit levels present in patient population.

3. User evaluation – based on Likkert scale questionnaire which covered ease of use and training.

4. IT connectivity evaluation - the functionality of the Data Management systems were assessed with regard to ease of use and integrity of data during a six-week period.
Results

Glucose meters evaluated included StatStrip Glucose (Nova Biomedical), AccuCheck Advantage (Roche Diagnostics) Optium Xceed (Abbott Diagnostics), Ascencia Contour (Bayer). Ketone meters evaluated included StatStrip Ketone (Nova Biomedical), Optium Xceed (Abbott Diagnostics).

Laboratory evaluation – only two of the four glucose meters and one of the ketone meters were unaffected by the range of interferences tested.

Clinical evaluation – Only one of the glucose meters achieved ISO 15197 accuracy target.

User evaluation – 170 completed questionnaires were received. Only one of the glucose meters consistently produced a high satisfaction score for all questions.

IT evaluation - Over 3000 glucose results were captured over the six week period. One of the manufacturers modified their device as a result of the study.

<table>
<thead>
<tr>
<th>Question</th>
<th>Bayer</th>
<th>Nova</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score (max = 100)</td>
<td>48.1</td>
<td>62.0</td>
</tr>
<tr>
<td>1 How easy was the application of blood to the glucose sensor strip?</td>
<td>82.9</td>
<td>75.6</td>
</tr>
<tr>
<td>2 How simple did you find the meter’s screen navigation?</td>
<td>34.8</td>
<td>64.9</td>
</tr>
<tr>
<td>3 How time efficient did you find the speed of analyzing and logging the patients results on the system?</td>
<td>34.3</td>
<td>59.1</td>
</tr>
<tr>
<td>4 How easy did you find the meter regarding use of attachment for reduction in cross infection risk?</td>
<td>33.3</td>
<td>52.3</td>
</tr>
<tr>
<td>5 How easy did you find the meter to use? Consider size, shape and weight?</td>
<td>44.8</td>
<td>51.1</td>
</tr>
<tr>
<td>6 Did the meter training meet all your requirements?</td>
<td>54.3</td>
<td>66.7</td>
</tr>
</tbody>
</table>

COMMENTS:
This evaluation approach helps to identify the performance and functional characteristics of different meter options which can then be applied to assess the risk of implementation of these meters in a hospital setting.

Summary of Outcome of Glucose meter Evaluation

<table>
<thead>
<tr>
<th>Specification</th>
<th>StatStrip</th>
<th>Contour</th>
<th>Xceed</th>
<th>Advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analytical Accuracy</td>
<td>√</td>
<td>√</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Clinical Accuracy</td>
<td>√</td>
<td>X</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Reliable (Cv&lt;5%)</td>
<td>√</td>
<td>X</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Specific</td>
<td>√</td>
<td>√</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Easy to Use</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Easy to interface</td>
<td>√</td>
<td>X</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Comparison of Four Hospital Based Glucose Meter Technologies for Accuracy, Precision and Interferences Encountered in Hospitalized Patients

B. Bewley¹, S. O’Rahilly¹, R. Tassell¹, J.DuBois², and R. Clampitt².

¹ Addenbrooke’s Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom
² Nova Biomedical Corporation, Waltham, MA, USA

INTRODUCTION

We compared four hospital based glucose meter technologies for accuracy, precision, and response to analytical interferences likely to be encountered in hospitalized patients. Meters included the StatStrip® (Nova Biomedical, Waltham, MA), Accu-Chek AVIVA® (Roche Diagnostics, Mannheim, Germany), Freestyle® (Abbott Diabetes, Alameda, CA), and Elite XL® (Bayer, Tarrytown, NY). Plasma glucose by the hexokinase method on the Dimension RxL Analyzer (Dade Behring, Deerfield, Il) was used as the reference method.

METHOD

Venous whole blood was spiked with varying concentrations of glucose for within-run precision testing (20 replicates for each level on each meter). Control materials were used for day-to-day precision studies by using two levels tested 3 times per day, in duplicate, for 3 days. Method correlation was performed by analyzing 97 whole blood patient specimens on the four glucose meters. Interference studies were performed using beta-hydroxybutyrate, bilirubin, lactate, and maltose monohydrate added to whole blood at 3 different glucose levels. Hematocrit interference was tested using 3 glucose concentrations over a 26-64% hematocrit range. Immediately following analysis on the glucose meters, all samples were spun down to obtain plasma for analysis on the reference method. For method correlation, linear regression was performed to determine slope, intercept, and correlation coefficient (r²) for the data sets. Median bias was also calculated for all four meters. For the interference experiments, the mean (X) of four replicates was used to determine the glucose concentration for the baseline and for each concentration of interferant used. A clinically significant interference effect was defined as any concentration of interferant that changed the mean baseline glucose value by more than 0.55 mmol/L (baseline glucose < 5.5 mmol/L) or 10% (baseline glucose > 5.5 mmol/L).

RESULT

Method correlation by least squares regression (using the Dimension RxL as reference standard) yielded a slope of 1.002 and intercept of 0.11 mmol/L for the StatStrip®, Freestyle yielded a slope of 0.946 and an intercept of 0.41 mmol/L, Accu-Chek AVIVA yielded a slope 0.91 and an intercept of 0.17 mmol/L, and the Elite XL yielded a slope of 0.858 and an intercept of 0.08 mmol/L. Data from the interference studies for bilirubin, lactate, and beta-hydroxybutyrate showed minimal differences on any of the four meters. Maltose interfered with the Freestyle and the Accu-Chek AVIVA. Hematocrit impacted all meter technologies except the StatStrip®. Precision differed little between the meters.

CONCLUSION

The Glucose meter technologies tested have variable correlation to a reference hexokinase glucose method. In addition, most glucose meters are affected by analytical interferences, namely hematocrit and maltose. The StatStrip® glucose meter technology correlated closely with a reference hexokinase glucose method and did not demonstrate clinically significant interference from any of the interfering agents tested, inclusive of hematocrit.
GLUCOSE REGRESSION ANALYSIS

$R^2$: 0.99137  SLOPE: 0.996  INTERCEPT: 2.083  N= 50

Whole Blood

StatStrip® 2  Dade Behring  BIAS
Min = 1.1  Min = 0.3  Min = -0.683
Max = 31.8  Max = 43.2  Max = 5.757
Mean = 14.034  Mean = 14.821  Mean = -1.182

Dade Behring mmol/L

StatStrip® mmol/L

StatStrip® 2 Dade Behring BIAS
Min = 0.3  Max = 43.2  Mean = -1.182

Mean = 14.821  Mean = 5.757

Whole Blood

Addenbrooke’s Hospital, Cambridge Univ. Hospitals, NHS Foundation Trust (Cont’d)
Maltose interference

Maltose (mmol/L)

Glucose (mmol/L)

Maltose interference

Maltose (mmol/L)

Glucose (mmol/L)

Maltose interference

Maltose (mmol/L)

Glucose (mmol/L)

Maltose interference

Maltose (mmol/L)

Glucose (mmol/L)

Maltose interference

Maltose (mmol/L)

Glucose (mmol/L)

Maltose interference

Maltose (mmol/L)

Glucose (mmol/L)

Maltose interference

Maltose (mmol/L)

Glucose (mmol/L)

Maltose interference

Maltose (mmol/L)

Glucose (mmol/L)

Maltose interference

Maltose (mmol/L)

Glucose (mmol/L)

Maltose interference

Maltose (mmol/L)

Glucose (mmol/L)
Evaluation of the Analytical Specificity and Clinical Application of a New Generation Hospital-Based Glucose Meter in a Dialysis Setting

Barbara Bewley, CSci, FIBMS,* S. O’Rahilly, MB, BCh, BAO, MD,* Rhys Tassell,* Jeff DuBois, PhD,† and Euan Donald, BSc†

**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 β-hydroxybutyrate (βHB), bilirubin, lactate, and maltose monohydrate. Interference studies were performed by adding each of the interferants 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, βHB, bilirubin, lactate, and maltose, which have previously been shown to effect measurements from current glucose meter technologies, were tested on each of the 4 strip-meter systems at low, medium, and high blood glucose 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, βHB, 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, βHB, 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, βHB, 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 icodextrin 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

(Part of Care 2009;8: 61–67)

**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.2–4 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. In particular, maltose can produce inaccurate blood results in glucose meters using strip technology based on the enzyme glucose dehydrogenase using pyrroloquinoline quinone method. 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.

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. Recently, a new generation glucose meter, StatStrip, has been reported to demonstrate good accuracy in analytical studies. 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 BHb 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.

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 hemocrit 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.

TABLE 1. Within-Run Precision

<table>
<thead>
<tr>
<th>Meter System</th>
<th>Low Glucose</th>
<th>Mid Glucose</th>
<th>High Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>%CV</td>
</tr>
<tr>
<td>StatStrip</td>
<td>2.2</td>
<td>0.31</td>
<td>14.1</td>
</tr>
<tr>
<td>FreeStyle</td>
<td>2.2</td>
<td>0.13</td>
<td>6.1</td>
</tr>
<tr>
<td>Elite XL</td>
<td>1.4</td>
<td>0.13</td>
<td>14.0</td>
</tr>
<tr>
<td>Accu-Chek</td>
<td>2.2</td>
<td>0.17</td>
<td>6.0</td>
</tr>
<tr>
<td>Dimension RxL</td>
<td>2.4</td>
<td>12.9</td>
<td></td>
</tr>
</tbody>
</table>

Twenty whole blood replicates were run at each glucose concentration for each of the strip-meter systems.

TABLE 2. Correlation Data for Each Glucose Meter Versus Plasma Hexokinase Method

<table>
<thead>
<tr>
<th>Meter System</th>
<th>n</th>
<th>Slope</th>
<th>Intercept</th>
<th>R²</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>StatStrip</td>
<td>97</td>
<td>1.002</td>
<td>0.12</td>
<td>0.996</td>
<td>-0.68</td>
</tr>
<tr>
<td>Freestyle</td>
<td>93</td>
<td>0.940</td>
<td>0.42</td>
<td>0.992</td>
<td>-2.11</td>
</tr>
<tr>
<td>Elite XL</td>
<td>95</td>
<td>0.868</td>
<td>0.08</td>
<td>0.979</td>
<td>-2.06</td>
</tr>
<tr>
<td>Accu-Chek</td>
<td>97</td>
<td>0.916</td>
<td>0.17</td>
<td>0.995</td>
<td>-1.52</td>
</tr>
</tbody>
</table>
The remainder of each specimen was centrifuged, and a plasma sample was analyzed by the Dimension RxL.

Chemical Interference Studies

The influence of bilirubin, 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

<table>
<thead>
<tr>
<th>Maltose, mmol/L</th>
<th>StatStrip</th>
<th>Δ mmol/L</th>
<th>Freestyle</th>
<th>Δ mmol/L</th>
<th>Accu-Chek</th>
<th>Δ mmol/L</th>
<th>Elite XL</th>
<th>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>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.8</td>
<td>2.5</td>
<td>0.1</td>
<td>5.7</td>
<td>6.0</td>
<td>3.3</td>
<td>1.3</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>5.6</td>
<td>2.4</td>
<td>0.0</td>
<td>8.5</td>
<td>5.7</td>
<td>9.4</td>
<td>6.7</td>
<td>1.2</td>
<td>-0.1</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.

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).
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 Aviva) 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. 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.

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. 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


Addenbrookes Hospital, Cambridge University Hospitals NHS Foundation Trust

Improved POC Meter Accuracy for Monitoring and Managing Glucose Levels in Dialysis Patients

B. Bewley, S. O’Rahilly, and R. Tassell,

Addenbrookes Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom.

Introduction:
Glucose meters are widely used for monitoring glucose levels in hospitalised patients. However the reliability of glucose meters can vary according to the type of patient group tested. Significant error rates can occur with glucose meters as a result of haematocrit interference or chemical interferences associated with drug therapy and patient treatment regimes. Patients with renal disease undergoing peritoneal or haemodialysis may have solutions utilised within their care regime that may give rise to chemical interference resulting in falsely elevated blood glucose readings. This may lead to an insulin-dosing error and risk of hypoglycemia. The new generation StatStrip® (Nova Biomedical, Waltham, MA), glucose meter has been designed to compensate for interference effects commonly associated with other routinely used hospital glucose meters. The aim of this study was to assess the performance and accuracy of StatStrip® for measuring glucose in peritoneal and haemodialysis patients.

Method:
The accuracy of StatStrip® was compared to two conventional glucose meter technologies; Accu-Chek AVIVA® (Roche Diagnostics, Mannheim, Germany), and Elite XL ® (Bayer, Tarrytown, NY). Venous whole blood samples were collected from 37 peritoneal dialysis patients and 27 haemodialysis patients. Glucose meter results were compared to the laboratory hexokinase method (Dimension RxL Analyzer, Dade Behring, Deerfield, IL). 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:
1. Peritoneal dialysis patients
AccuChek Aviva and Elite XL failed to meet the ISO15197 95% accuracy criteria with 43.24% and 13.5% of results respectively deviating by >20% compared to the laboratory analyser results. StatStrip® met the accuracy requirements of ISO15197 with all results falling within the criteria. AccuChek Aviva results were significantly falsely elevated in patients receiving Extraneal most likely due to maltose present in the peritoneal fluid. Approximately 21% of AccuChek Aviva results also deviated by >20% compared to the laboratory analyser for patients receiving other fluids.

All PD patients
Addenbrookes Hospital, Cambridge University Hospitals NHS Foundation Trust (Cont’d)

Patients receiving Extraneal

- StatStrip Bias comparison to ISO 15197 limits - Extraneal PD patients
- Elite XL Bias comparison to ISO 15197 limits - Extraneal PD patients
- AccuChek Aviva Bias comparison to ISO 15197 limits - Extraneal PD patients

Patients receiving other fluids

- StatStrip Bias comparison to ISO 15197 limits - PD patient other fluids
- Elite XL Bias comparison to ISO 15197 limits - PD patient population
- AccuChek Aviva Bias comparison to ISO 15197 limits - PD patients other fluids

2. Haemodialysis patients

AccuChek Aviva and Elite XL failed to meet the ISO15197 95% accuracy criteria with 11.1% and 59.25% of results respectively deviating by >20% compared to the laboratory analyser results. StatStrip® met the accuracy requirements of ISO15197 with 97.3% of all results falling within the criteria.

3. Haematocrit assessment

Haematocrit had no influence on the accuracy of StatStrip® glucose results. For Accu-Chek Aviva and Elite XL there was a deviation across the haematocrit range with glucose values increasing at lower haematocrit levels compared to normal haematocrit levels.

Conclusion:

Accuracy is a key requirement in selecting glucose meters for use in hospitalised patients. Meter accuracy can be affected by interfering substances commonly present in hospitalized patients causing erroneous results and leading to insulin dosing errors and possible life-threatening/fatal hypoglycemia.

In this study the accuracy of two commonly used glucose meters was inadequate for monitoring glucose levels in both haemodialysis and peritoneal dialysis patients. Only StatStrip® achieved the level of accuracy required for monitoring glucose in these patient populations. We conclude that the reliability of monitoring and managing glucose levels in dialysis patients can be improved by utilising a meter that corrects for common interferences.
Nova StatStrip®: Could this device be used to effectively implement Tight Glycaemic Control and triage blood glucose and insulin management in critical illness (device evaluation compared to Roche Cobas b221 reference methodology)?

Gary M Creed BSc MSC Laboratory Operations Manager
Department of Intensive Care and Critical Care Medicine,
Guy’s and St Thomas Foundation Hospital NHS Trust, London UK

Introduction:

Stress Induced Hyperglycaemia is common in critically ill patients with or without diabetes, in which insulin resistance due to increased catecholamine levels causes high blood glucose levels¹. The association between stress hyperglycaemia and adverse outcome has been observed in numerous patient groups ranging from patients admitted to the general ward² to myocardial infarction³, stroke patients⁴, after surgery⁵, burns and head trauma⁶.

Maintenance of strict Glycaemic control in diabetic and non-diabetic patients within surgical⁷,⁸ and medical⁹ intensive care units has shown a significant reduction in mortality and morbidity.

Rapid and precise methods of glucose determination are important aspects that require careful consideration before clinical implementation as part of a point of care strategy for managing critically ill patients. The aim of this evaluation was to determine whether the Nova StatStrip® glucose meter demonstrated the required level of accuracy and precision for implementation as an effective Point of Care Glycaemic protocol to triage critically ill patients.

Patients and Methods:

100 paired, random, arterial samples were analysed for glucose concentration using Nova StatStrip® (Nova Biomedical) and Roche Cobas b 221 (Roche Diagnostics) reference blood gas methodology. Statistical methods: Spearman Rank Correlation/Regression, Bland-Altman analysis.

Results:

1. Comparison between Nova StatStrip® and Reference methodology: Mean Glucose concentration was 6.21 ± 1.79 mmol/l using Roche Cobas b 221 and 6.34 ± 1.79 with Roche Performa glucose meter
2. Comparison between Nova StatStrip® and Reference methodology: correlation coefficient r²=0.99, slope=0.967 with intercept -0.09 (see figure 1)
3. Comparison between Nova StatStrip® and Reference Methodology: Bland Altman analysis mean bias=-0.16 mmol/l, SD=0.27 with limits of agreement -0.69 to 0.37 (see figure 2).
Conclusions:
Careful considered evaluation of POCT blood glucose device is required before routine adoption in triage of critically ill patients.

Nova StatStrip® demonstrated a statistically significant correlation with the Reference methodology. Bland Altman analysis demonstrated minimal variability across the working range, which would suggest that this device could be used effectively to triage critically ill patients. All values obtained using Nova StatStrip® fell within ISO 15197 tolerance bands suggesting StatStrip® is appropriate for Tight Glycaemic control and insulin infusion protocols in critical illness.

References:
An Evaluation of the Analytical Performance of a New-Generation Hospital-Based Glucose Meter and an Assessment of Its Clinical Reliability in a Neonatal Care Unit

Annette Thomas, MPhil,* Seetal Sall, MSc,* Claire Roberts, BSc,* Mark Drayton, MD,† Jeffrey DuBois, PhD,‡ and Roger Clampitt, PhD‡

Introduction: Glucose meters are widely used in hospitals for point-of-care monitoring of blood glucose. However, concerns about their accuracy and reliability in a neonatal setting have been expressed. We evaluated the analytical performance and clinical reliability of a new-generation glucose monitoring system (StatStrip; Nova Biomedical, Waltham, Mass) that corrects for interference factors by comparing results with a laboratory plasma hexokinase reference method, along with 3 other glucose meter systems.

Methods: Analytical studies for assessing precision and method correlation in the laboratory were performed comparing glucose to plasma glucose results from a reference hexokinase method. Challenge studies were performed with interfering substances including hematocrit, maltose, ascorbate, and β-hydroxybutyrate (βHBB) that have previously been shown to affect measurements from current glucose meter technologies.

Clinical reliability was assessed with 109 capillary blood specimens collected from neonatal intensive care unit (NICU) patients with varying hematocrit levels.

Results: Within-run imprecision was similar for all 4 meter systems, with the coefficient of variation generally less than 5%. Of the 4 meter systems, 2 (StatStrip and Contour [Bayer Healthcare Diabetes Care, Newbury, UK]) showed closer correlation to the reference hexokinase method after regression analyses on 75 spiked whole blood specimens. Linear regression analysis demonstrated a regression line slope of 0.960 for Contour and 0.920 for StatStrip, with lower slope values of 0.705 and 0.791 for Optium (Abbott Diabetes, Alameda, Calif) and Advantage (Roche Diagnostics, Indianapolis, Ind), respectively. The Contour and StatStrip glucose meter systems had the lowest mean biases compared with the hexokinase method. Of the 4 strip meter systems tested for interference, only the StatStrip and Opium systems remained within 0.55 mmol/L of their initial value at a glucose concentration <5.55 mmol/L and 10% (at a glucose concentration >5.55 mmol/L) after the addition of ascorbate, maltose, or βHBB. Maltose had a marked effect on the Advantage system, whereas ascorbate and βHBB had only minor effects on the Contour system. Increasing hematocrit values significantly lowered the glucose value readings for samples with medium to high glucose values tested by the Opium and Advantage systems. Varying hematocrit levels had minor and clinically insignificant effects on both the StatStrip and Contour systems. This was further substantiated after bias plot analysis of hematocrit levels in the NICU patient population. When applied to NICU patient samples, StatStrip showed close accordance with ISO 15197 performance criteria and good accuracy in comparison with the laboratory hexokinase method.

Conclusions: Managing glucose levels in a neonatal critical care setting is dependent on using reliable and accurate glucose meters with good specificity. The StatStrip and Contour meters performed well based on evaluation, with no interference observed for hematocrit, maltose, βHBB, and ascorbate. In the clinical study on the NICU patients, the StatStrip meter showed good correlation with the hexokinase method across the analytical range.

Key Words: glucose meter, clinical reliability, NICU

Monitoring glucose levels in patients in a neonatal intensive care setting is widely practiced and is important in managing and maintaining normalized blood glucose concentrations and reducing the risk of hypoglycemia.1–3 Point-of-care (POC) glucose meters are ideally suited for providing a quick turnaround in results at the bedside, enabling rapid intervention if abnormal glucose levels are found. In addition, POC glucose meters require small amounts of blood sample to generate a test result compared with laboratory analyzers. Although glucose meters were originally developed for self-monitoring of glucose levels in adult diabetic patients in a home environment, many of these meters have migrated into use in hospital units without full validation study, and thus, concern about their accuracy has been raised, particularly in a neonatal setting.4,5 As a result, central laboratory methods continue to be used for confirmation of low glucose results obtained with POC glucose meters.

It is likely that the designs of many commonly used meters have been optimized for application to nonhospitalized self-testing diabetic populations with normal to raised glucose levels, and in this setting, correlation to reference methods is usually acceptable. However, when applied to critically ill hospital patient populations or diabetic patients with complications, the correlation of some meters with a plasma hexokinase reference method can be poor, especially in the hypoglycemic and hyperglycemic ranges.6,7 Indeed, accuracy studies assessing the performance of commonly used glucose meters in the neonatal intensive care unit (NICU) have shown a failure to achieve certain national and international quality standards.5,8

The reaction kinetics of most commonly used meters are also optimized for normal hematocrit levels found in blood samples that were tested in an ambulatory setting. However, there is substantial evidence demonstrating that the accuracy of many of the most commonly used meters is adversely affected by the abnormal hematocrit levels often found in NICU or intensive care unit (ICU) patients.4,9–12 Low hematocrit levels can give rise to falsely elevated glucose readings, and conversely,
high hematocrit levels can give rise to falsely low glucose readings. Therefore, the use of meters affected by hematocrit may result in errors in patient care and contribute to an increased risk of iatrogenic or undetected hypoglycemia. In addition to hematocrit interference, other biochemical or biological substances, such as ascorbic acid and maltose, have been reported to affect the accuracy and performance of some current glucose meters when used in a hospital setting.9-11,13

The development of glucose meter technologies has focused primarily on improving turnaround time, providing ease of use, and minimizing sample test volume or data manipulation and not necessarily on improving accuracy in testing hospitalized patients. Recently, a new POC glucose sensor, StatStrip (Nova Biomedical, Waltham, Mass), specifically designed for use in a hospital setting, has been reported to give good accuracy in analytical studies.12,14-16 The design of the technology incorporates a glucose-specific reaction zone and 2 additional separate reaction zones for correcting interfering substances. Glucose readings are corrected against readings from the interference zones, eliminating the influence of hematocrit and chemical interferences. This study was designed to compare the analytical performance, accuracy, and specificity of StatStrip and 3 commonly used glucose meters along with a laboratory-based hexokinase method, the latter being a generally accepted reference method for evaluating POC glucose meters.17 The clinical accuracy and reliability of 2 meters (StatStrip and Contour [Bayer Healthcare Diabetes Care, Newbury, UK]), unaffected by the interfering substances, were assessed with blood specimens collected from a NICU patient population. In this patient setting, the accuracy of the meters was also assessed by comparing the deviation of the glucose meter readings from the reference method with the current International Organization for Standardization (ISO 15197) requirements for blood glucose monitoring systems.17

MATERIALS AND METHODS

Instrumentation

For the analytical studies, 4 blood glucose meter systems were evaluated: StatStrip (Nova Biomedical), Advantage (Roche Diagnostics, Indianapolis, Ind), Optium Xceed (Abbott Diabetes, Alameda, Calif), and Contour TS (Bayer Healthcare Diabetes Care). The StatStrip glucose strip technology is a modified glucose oxidase–based amperometric test system with hematocrit and other interference correction; Advantage uses a glucose dehydrogenase/coenzyme pyrroloquinolone quinone–based amperometric strip; Optium Xceed uses an electrochemical glucose dehydrogenase/coenzyme nicotinamide adenine dinucleotide–based amperometric strip; and Contour uses a photometric glucose oxidase detection system. The Advia 1200 (Bayer Corporation, Newbury, UK) plasma hexokinase method was used as the reference method for glucose measurements.

For the clinical studies using blood samples from the NICU patients, 2 meters were evaluated: the StatStrip (Nova Biomedical) and Contour TS (Bayer Healthcare Diabetes Care). The Aeroset (Abbott Laboratories Ltd Diagnostic Division, Maidenhead, UK) plasma hexokinase method was used as the reference method for glucose measurements.

Within-Run Precision

Lithium heparin whole blood from a volunteer was collected and mixed continuously 18 to 24 hours before commencing the study. In this specimen, red blood cell glycolytic activity reduced the glucose concentration to less than 2.0 mmol/L. This glucose-depleted specimen was then used to prepare aliquots for precision testing. Within-run precision was determined by adding varying amounts of a concentrated glucose stock solution to aliquots of the glucose-depleted specimen. The target glucose concentration ranges were 1 to 3 mmol/L (low), 10 to 15 mmol/L (medium), and 19 to 23 mmol/L (high). Twenty replicates of each of the 3 aliquots were tested by each of the 4 meters and statistically analyzed.

Method Correlation

Eighteen to 24 hours before commencing the study, a lithium heparin blood specimen from a volunteer was collected and mixed continuously. This glucose-depleted specimen was used to prepare aliquots of varying glucose concentrations for the method correlation. Appropriate volumes of a concentrated glucose solution were added to 75 aliquots (1.0 mL) of the baseline blood specimen to achieve a wide range of glucose concentrations. Each of the 75 aliquots was then assayed by each of the 4 meter systems, and the remainder of each aliquot was centrifuged to prepare a plasma sample for glucose analysis on the Advia 1200 laboratory analyzer.

Interference Studies

The influence of maltose, ascorbate, and β-hydroxybutyrate (βHβ) on meter glucose measurements was assessed. To obtain a glucose-depleted specimen for preparation of interference aliquots, we used the method previously described. Three glucose levels were prepared by adding the appropriate volume of a concentrated glucose solution (20% wt/vol) to aliquots of the volunteer blood (3 mL) to achieve target glucose values of 1 to 3, 10 to 15, and 19 to 23 mmol/L.

Each glucose preparation was further aliquoted (1 mL) and used to prepare 3 different concentration levels of each interfering substance by adding appropriate levels of a concentrated stock solution of each interfering substance to the corresponding glucose preparation, as follows: (1) the first aliquot contained no interfering substance, (2) the second concentration level reflected the low to mid therapeutic or biological interferent level that might be present in a patient, and (3) the third concentration level reflected a higher therapeutic or biological level. Each aliquot was mixed carefully for 10 minutes before testing 4 times by each of the strip meter systems. The remainder of each aliquot was centrifuged, and the plasma glucose level was assayed by the laboratory reference procedure.

### Table 1. Within-Run Precision

<table>
<thead>
<tr>
<th>Meter System</th>
<th>Mean</th>
<th>SD</th>
<th>%CV</th>
<th>Mean</th>
<th>SD</th>
<th>%CV</th>
<th>Mean</th>
<th>SD</th>
<th>%CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>StatStrip</td>
<td>2.9</td>
<td>0.1</td>
<td>5.0</td>
<td>13.0</td>
<td>0.4</td>
<td>3.1</td>
<td>21.2</td>
<td>0.7</td>
<td>3.2</td>
</tr>
<tr>
<td>Optium</td>
<td>2.7</td>
<td>0.1</td>
<td>3.9</td>
<td>10.2</td>
<td>0.2</td>
<td>2.4</td>
<td>21.2</td>
<td>0.4</td>
<td>2.8</td>
</tr>
<tr>
<td>Advantage</td>
<td>2.6</td>
<td>0.1</td>
<td>4.8</td>
<td>11.1</td>
<td>0.2</td>
<td>2.2</td>
<td>17.4</td>
<td>0.4</td>
<td>2.1</td>
</tr>
<tr>
<td>Contour</td>
<td>3.0</td>
<td>0.3</td>
<td>11.6</td>
<td>13.0</td>
<td>0.3</td>
<td>2.0</td>
<td>21.9</td>
<td>0.5</td>
<td>2.1</td>
</tr>
<tr>
<td>Advia 1200</td>
<td>3.1</td>
<td>13.4</td>
<td>21.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TABLE 2. Correlation Data for Each Glucose Meter Versus Plasma Hexokinase Method

<table>
<thead>
<tr>
<th>Meter System</th>
<th>n</th>
<th>Slope</th>
<th>Intercept</th>
<th>$R^2$</th>
<th>Mean Difference, mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>StatStrip</td>
<td>75</td>
<td>0.920</td>
<td>-0.05</td>
<td>0.993</td>
<td>-1.2</td>
</tr>
<tr>
<td>Optimum</td>
<td>75</td>
<td>0.705</td>
<td>0.55</td>
<td>0.993</td>
<td>-3.6</td>
</tr>
<tr>
<td>Advantage</td>
<td>75</td>
<td>0.791</td>
<td>0.41</td>
<td>0.993</td>
<td>-2.6</td>
</tr>
<tr>
<td>Contour</td>
<td>75</td>
<td>0.960</td>
<td>-0.07</td>
<td>0.994</td>
<td>-0.6</td>
</tr>
</tbody>
</table>

**Hematocrit Interference**

The influence of varying levels of hematocrit (range, 25%–68%) on glucose meter measurements was assessed. A lithium heparin whole blood specimen was collected and mixed continuously, as previously described, to prepare glucose aliquots for the determination of the hematocrit effect on each method. Three glucose levels were prepared by adding the appropriate volume of a concentrated glucose solution (20% wt/vol) to aliquots of donated blood to achieve target glucose values of 1 to 3, 10 to 15, and 19 to 23 mmol/L. Each glucose level was further aliquoted (5 × 1 mL), and the hematocrit levels were adjusted after centrifugation and dilution to provide hematocrit levels of 28%, 38%, 48%, 59%, and 68% across each of the 3 glucose concentrations.

The actual hematocrit value for each of the aliquot preparations was confirmed using a StatSpin MP microhematocrit centrifuge (Iris Sample Processing, Westwood, Mass). Each sample was tested 4 times by each strip meter system. The remainder of the sample was centrifuged immediately, and the plasma glucose level was tested by the plasma hexokinase method.

**NICU Clinical Accuracy Study**

One hundred nine capillary blood specimens from 39 NICU patients were collected and tested. Each specimen was tested by each of the strip meter systems. A lithium heparin venous whole blood specimen was collected and centrifuged, and the plasma sample glucose level was measured using the Aeroset plasma hexokinase method.

**Data Analysis**

Within-run precision was determined by calculating coefficients of variation (CVs) for the 20 replicate values. For the method comparison study, statistical analysis included linear regression analysis, the determination of correlation coefficient ($R^2$), mean difference between each of the 4 meter systems and the reference hexokinase procedure, and the SD of the mean differences. For interference and hematocrit studies, the mean of all 4 replicate results was used for data analysis. The interference effects from ascorbate, maltose, and βHB were expressed as the millimolar change in aliquots for glucose readings with concentrations less than 5.5 mmol/L or percent change in glucose readings for aliquots having glucose concentration greater than 5.5 mmol/L. Comparison was made with the corresponding glucose sample with no interfering substance. A clinically significant interference effect was defined as a concentration of interfering substance that changed the mean baseline glucose (no interfering substance added) value by greater than ±0.55 mmol/L at glucose levels less than 5.5 mmol/L or greater than ±10% at glucose levels greater than 5.5 mmol/L. To determine the hematocrit effect on the glucose recovery for all 4 meter technologies, the percent bias from the reference procedure was calculated and plotted at each hematocrit level.

For the clinical accuracy study, the percent bias of each glucose meter result compared with the reference hexokinase result was calculated and plotted on a Bland-Altman plot. The clinical accuracy was assessed by comparing the pattern of results with the ISO 15197 criteria specifying that glucose values should fall within 0.83 mmol/L for 95% of values at a glucose concentration of 4.2 mmol/L or +20% of values at a glucose concentration of 4.2 mmol/L or greater. To determine the influence of varying levels of hematocrit present in the NICU patient samples on the glucose results from all 4 meters, the percent bias from the reference procedure was calculated and plotted for each sample hematocrit level.

**RESULTS**

**Within-Run Precision Study**

The percent coefficient of variance (%CV) for all 4 meters across the 3 glucose ranges was similar (≤5%), with the exception of the Contour glucose meter that had a %CV greater

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**TABLE 3. Maltose Interference—Shift in Glucose Reading Compared With 0 Maltose Sample**

<table>
<thead>
<tr>
<th>Maltose, mmol/L</th>
<th>Nova StatStrip Δ, mmol/L</th>
<th>Abbott Optimum Δ, mmol/L</th>
<th>Roche Advantage Δ, mmol/L</th>
<th>Bayer Contour Δ, mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.73</td>
<td>2.50</td>
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<table>
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<tr>
<th>Maltose, mmol/L</th>
<th>Nova StatStrip Δ, %</th>
<th>Abbott Optimum Δ, %</th>
<th>Roche Advantage Δ, %</th>
<th>Bayer Contour Δ, %</th>
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<td>19.63</td>
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Glucose ≤ 5.55 mmol/L Δ mmol/L < 0.555 mmol/L.
Glucose > 5.55 mmol/L Δ mmol/L < 10%.
than 10% in the low glucose range (Table 1). The mean glucose values for StatStrip and Contour at each glucose level were in closer agreement to the laboratory reference method.

**Method Correlation**

The correlation between the glucose meters and the laboratory plasma hexokinase method was performed on the 75 aliquots prepared from the donated blood specimen, each spiked with a concentrated glucose solution to vary the glucose level. The mean plasma reference glucose value was 14.2 mmol/L, and the range of glucose levels was 3.2 to 27.9 mmol/L. Linear regression analysis demonstrated a slope of 0.960 for Contour and 0.920 for StatStrip, with lower slope values of 0.705 and 0.791 for Optium Xceed and Advantage, respectively. The Contour and StatStrip glucose meter systems had the lowest mean biases compared with the laboratory hexokinase method (Table 2).

**Effect of Interfering Substances**

β-Hydroxybutyrate (final specimen concentrations of 15 and 30 mmol/L) was added to the lithium heparin blood, with glucose levels that had been adjusted to 2.0, 12.7, and 19.7 mmol/L, respectively. In general, the addition of βHB did not result in a significant change in glucose readings compared with the baseline glucose readings in all 4 meter systems. There was, however, an apparent increase in the glucose reading (10%) obtained with the Contour glucose meter for the medium level glucose sample (12.7 mmol/L) with the highest βHB concentration (30 mmol/L). In general, however, the presence of βHB had minimal effect on the accuracy of all 4 glucose meter measurements.

Ascorbate (final specimen concentrations of 0.29 and 0.59 mmol/L) was added to lithium heparin blood with glucose levels that had been adjusted to 2.0, 12.9, and 19.8 mmol/L, respectively. In general, the addition of ascorbate did not result in a significant change in glucose readings compared with the baseline glucose readings in all 4 meter systems. There was a small increase in the glucose reading with the Contour glucose meter, with the low concentration (2.3 mmol/L) glucose aliquot giving an elevated value (0.60 mmol/L) at the highest ascorbate concentration level (0.59 mmol/L). The presence of ascorbate had minimal effect on the accuracy of the glucose meter measurements.

Maltose (final specimen concentrations of 2.8 and 5.6 mmol/L) was added to lithium heparin blood with glucose levels that had been adjusted to 2.5, 13.0, and 19.8 mmol/L, respectively. Maltose significantly affected the accuracy of the results of the Advantage meter at each of the glucose and maltose concentrations tested but had no effect on the other 3 systems (Table 3). The results demonstrate that maltose does not adversely affect the accuracy of the StatStrip, Contour, and Optium meters but does significantly affect the accuracy of the Advantage glucose meter measurements.

**Effects of Hematocrit Interference**

Hematocrit levels were adjusted to between 28% and 64% at glucose levels of 2, 14, and 20 mmol/L, respectively. At each glucose level, there was a minimal effect of varying hematocrit levels on the glucose measurements obtained by StatStrip and Contour, whereas the glucose measurements for Optium Xceed and Advantage were significantly affected by varying hematocrit levels across the glucose sample range (Figs. 1A–C). The Optium glucose meter readings deviated by more than 30% between the lowest and highest hematocrit levels at all 3 glucose concentrations, and a similar pattern of results was obtained for the Advantage glucose readings at the medium and high glucose levels.

The results demonstrate that varying levels of hematocrit do not adversely affect the accuracy of StatStrip and Contour glucose measurements, whereas the accuracy of Optium and Advantage glucose meter measurements are adversely affected to a clinically significant degree.
Clinical Accuracy for NICU Patients

Bland-Altman plot analysis of percent bias (test glucose meter - reference glucose reading) / reference glucose reading *100 was performed on 109 capillary blood specimens collected from the 39 NICU patients. StatStrip showed closer accordance with the ISO 15197 criteria and closer accuracy to the laboratory hexokinase method compared with Contour (Figs. 2A, B; Table 4). The hematocrit range in the 109 blood specimens varied from 22% to 78%, with a mean of 41%. Bland-Altman plot of percent bias versus specimen hematocrit levels showed no influence on the accuracy of both StatStrip and Contour meters (Figs. 3A, B).

DISCUSSION

Glucose meters have been widely available for use for several years. Initially, these were used primarily for self-testing, but in recent years, these have migrated into hospitals for clinical use. Developments in meter technology have been focused on improving ease of use, establishing information technology connectivity, and testing smaller blood volumes more rapidly. Despite the advent of performance guidelines and criteria to improve the specificity and accuracy of POC glucose meters in the hospital, there has been little development or advancement of the fundamental analytical technologies. The advent of monitoring and regulating glucose levels in hospitalized patients (particularly in the NICU, ICU, and surgical and trauma wards) has resulted in a more critical assessment of the accuracy of current glucose meters and their reliability for implementing safe and effective glycemic control procedures. Recently, concerns have been raised about the risk and incidence of


hypoglycemia arising from implementing tight glycemic control protocols, a consequence that could occur from using inaccurate glucose meters. Although several guidelines have been implemented as performance goals for glucose meters, evaluations of glucose meter systems are frequently performed on patient populations that do not adequately reflect or challenge the glucose meter for use in more critical clinical situations. Analytical studies on glucose meters in patient populations not reflective of the true clinical situation may show acceptable precision and method correlation in comparison to reference methods.

However, blood specimens derived from ICU, NICU, or trauma patients will contain varying levels of hematocrit and wide-ranging levels of biochemical (lipid and bilirubin) and chemical (drugs and nutrients) factors known to interfere in diagnostic tests. In this study, we substantiated that the technology and accuracy of current glucose meters can indeed be affected by hematocrit and maltose interferences.

The accuracy of the Advantage meter was significantly affected by both maltose and hematocrit interferences, whereas the accuracy of the Optium Xceed meter was adversely affected by variations in hematocrit levels. In this study, the accuracy of the Contour meter was only slightly affected by βHB and ascorbate at high concentrations. However, this only occurred at one glucose level, and further substantiation to confirm the impact on accuracy may be required. The accuracy of StatStrip glucose measurements was not affected by βHB, ascorbate, and maltose. The accuracy of StatStrip and Contour glucose measurements was also unaffected by varying percent hematocrit in both the analytical and patient studies. This observation was confirmed by the Bland-Altman bias plot analysis of the hematocrit levels present in the NICU patient specimens tested.

Assessment of StatStrip and Contour accuracy (in comparison with ISO 15197 criteria) for glucose measurements in the NICU patients showed that StatStrip gave better concordance to the ISO 15197 criteria and closer accuracy to the laboratory hexokinase method. A recent notification highlights concern about the accuracy of the Contour for glucose measurements in neonates younger than 24 hours. However, StatStrip and Contour meters performed well in the laboratory-based evaluation with no significant interference observed for hematocrit, maltose, βHB, and ascorbate. In the clinical study, the glucose results from the StatStrip meter showed good comparison with the laboratory hexokinase method across the analytical range and thus provided immediate and accurate results for evaluation by the clinical staff.

REFERENCES

Multi-site Evaluation of Point of Care Glucose Meters in a Neonatal Intensive Care Unit

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³ Alberta’s Children’s Hospital, Calgary, Canada,
⁴Isala Klinieken, Zwolle, Netherlands, ⁵St. James Hospital, Leeds, UK

Introduction

Rapid and accurate monitoring of blood glucose levels in a neonatal intensive care setting is important in managing glycemic control. Blood glucose meters developed for self-monitoring of diabetics are commonly used for glucose measurements in hospitalized patients. However recent studies have highlighted that abnormal hematocrit levels, which are commonly found in neonates, can adversely influence the accuracy of currently used glucose meters.

StatStrip® Glucose (Nova Biomedical) is a new generation handheld glucose sensor specifically designed for hospital use. The design of the sensor corrects for common biochemical interference factors and also measures and corrects for hematocrit.

Aim

• To assess the analytical performance, accuracy and specificity of the StatStrip® Glucose sensor in four different neonatal intensive care settings in Europe and North America.
• To compare the performance of StatStrip® Glucose to glucose meters routinely used in these settings.
• To compare results with established international quality standards for glucose measurements ISO 15197 and TNO (Netherlands Organisation for Applied Scientific Research) approved protocol for glucose meter measurements.

Method

Glucose Methods Used
• StatStrip® (Nova Biomedical)
• Advantage® (Roche Diagnostics)
• Optium Xceed® (Abbott Diabetes),
• Contour® (Bayer Healthcare).
• AccuChek Inform (Roche Diagnostics)
• Precision PCx® (Abbott Diabetes)
• Aviva® (Roche Diagnostics),
• Precision Freestyle® (Abbott Diabetes),
• SureStep Flexx® (LifeScan),

Comparison Methods Used
• Hitachi 912 analyzer (Roche Diagnostics)
• Aeroset analyser (Abbott Diagnostics)
• ABL 735 (Radiometer)
• RapidLab 1265 Blood gas analyzer (Siemens)

Hematocrit interference

Hematocrit interference was evaluated using 5 glucose concentrations over a hematocrit range of 20-70%.

NICU assessment

Whole blood samples were collected from neonatal intensive care patients and tested on the respective meters. The glucose meter results were compared with the central laboratory hexokinase method or blood gas analyzer. Hematocrit levels were determined for each patient.
Results

StatStrip® Method Correlation

StatStrip® correlated well with the routine laboratory or blood gas analyzer methods used in each study site.

<table>
<thead>
<tr>
<th>Site</th>
<th>R2</th>
<th>Slope</th>
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<tr>
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Hematocrit Interference

The accuracy of the meters routinely used was affected to varying degrees by abnormal hematocrit level readings showing significant bias compared to the reference method. The accuracy of StatStrip® was unaffected by varying hematocrit levels.

Site B - Hematocrit interference study
Results (Cont’d)

Bias plot analysis of the influence of patient hematocrit levels on meter accuracy also showed that StatStrip® readings were unaffected by varying hematocrit levels.

Site D - Hematocrit interference study

Site C - Hematocrit interference study
Results (Cont’d)

NICU Accuracy – ISO15197 criteria

In all four study sites StatStrip® demonstrated greater accuracy compared to the routine meters used with results meeting the requirements of ISO 15197 criteria.

Site A – Accuracy assessment

![Graph depicting StatStrip Bias comparison to ISO 15197 limits]

Site C – Accuracy assessment

![Graph depicting Contour Bias comparison to ISO 15197 limits]

![Graph depicting StatStrip Bias comparison to TNO Accuracy limits]

![Graph depicting Optium Xceed Bias comparison to ISO 15197 limits]

NICU Accuracy – TNO criteria

StatStrip® achieved the requirements of the TNO protocol

Site B - Accuracy assessment

![Graph depicting StatStrip Bias comparison to TNO Accuracy limits]
Results (Cont’d)

NICU Accuracy ≤ 4.2 mmol/L range

Analysis of consolidated study data demonstrates that StatStrip® glucose has good accuracy at a glucose range ≤ 4.2 mmol/L meeting the requirements of ISO 15197 (97.2% of values meeting criteria of ISO 15197)

Conclusion

• StatStrip® Glucose which is specifically designed to compensate for hematocrit and chemical interferences, was shown to provide the most accurate and reliable results for glucose measurements in NICU patients.
• The performance of StatStrip® Glucose was unaffected by the wide range of hematocrit levels found in NICU patients.
• StatStrip® Glucose met the criteria of established international quality standards for glucose measurements (ISO 15197 and TNO).
A Multi-Site Analytical Assessment of a New Hospital POC Glucose Meter for Accuracy, Precision, Correlation, and Interferences Encountered in Hospitalized Patients

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¹IKFE, Mainz, DE, ²Maerkische Kliniken, Luedenscheid, DE, ³University Klinik, Würzburg, DE, ⁴University Klinik, Muenster, DE

Introduction

Many glucose meters are inaccurate when applied to hospital patients and results can be adversely affected by interfering substances often present in the patient populations being monitored. Inaccurate results can lead to errors with insulin dosing in patients undergoing insulin therapy with serious consequences particularly in critically ill patients. StatStrip® Glucose is a newly available hospital glucose meter that has been designed to offer improved accuracy and to correct for and eliminate common interfering substances.

Patients and Methods

We assessed the accuracy and performance of StatStrip® Glucose (Nova Biomedical) in comparison to 6 other glucose meters commonly used in German hospitals. The study compared the accuracy of the hospital glucose meters in four centres by correlation to a reference plasma hexokinase method using heparinised venous whole blood samples. Meter reliability was also assessed by evaluating the extent of drug interferences (acetaminophen, maltose and ascorbic acid) and the effect of hematocrit (25–60%) on the correlation between the glucose meters and the hexokinase glucose result at three glucose concentrations.

Results

Linear regression and Bland Altman bias plot analysis highlighted accuracy differences between the meters and the reference method with most meters showing a negative bias and failing to achieve ISO15197 performance criteria. StatStrip® demonstrated a close correlation to the reference method with a low mean absolute bias value and % bias deviation that met ISO15197 performance criteria. The accuracy of StatStrip® was not affected by any of the interfering substances tested. Low and high hematocrit levels affected the accuracy of all six commonly used meters, with % bias results deviating by as much as -25% (high hematocrit levels) to 30% (low hematocrit levels) compared to normal hematocrit levels across the range of glucose levels tested. The accuracy of all six meters was also affected by the presence of ascorbate (5 and 10 mg/dL). Maltose and acetaminophen (10 and 20 mg/dL) also affected the accuracy of some meters.
Results

**StatStrip® Bias comparison to ISO 15197 limits**

**AccuChek Advantage Bias comparison to ISO 15197 limits**

**One Touch comparison to ISO 15197 limits**
Results (Continued)

Conclusions

The StatStrip® glucose meter was the only meter not affected by any of the interfering substances commonly present in hospitalised patients. The improved analytical performance of StatStrip® Glucose compared to the other commonly used meters was substantiated in all four clinical sites indicating that StatStrip® Glucose will provide a new improved level of clinical accuracy and reliability for managing glucose levels in hospitalized patients.

IKFE, Mainz, DE, Maerkische Kliniken, Luedenscheid, DE, University Klinik, Würzburg, DE, University Klinik, Muenster, DE (Cont’d)