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.[3–5] 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.[6–9] 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.[7–9] One new glucose meter technology with hematocrit measurement and correction was recently introduced to address hematocrit interference.[10]

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,[11] 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,[12] and correlation with laboratory hexokinase measurement in the hypoglycemic and hyperglycemic ranges is poor with most meters currently available.[13] Thus there is still significant concern about the use of glucose meters for management of tight glycemic control in the ICU.[14]

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.[11] 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.[6] 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 HemataSTAT-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 × 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 × 100), for glucose >100 mg/dL] was calculated for each meter technology. Statisti-

TABLE 1. WITHIN-RUN AND DAY-TO-DAY PRECISION FOR GLUCOSE METERS, IN PERCENT CV

| | Precision, CV (%) | | | | |
| | Within-run (n = 20) | | | Day-to-day (n = 30) | |
Meter technology	Low glucose (39–55 mg/dL)	Medium glucose (180–250 mg/dL)	High glucose (365–430 mg/dL)	Low glucose (45–70 mg/dL)	High glucose (265–335 mg/dL)
StatStrip	3.3	1.9	1.4	2.1	2.6
Accu-Chek	3.9	2.4	2.2	4.6	2.8
PCx	3.2	1.7	1.5	5.1	4.0
SureStep	2.9	1.6	1.9	2.9	2.2

n = number of replicates tested.

cal 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 39–574 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)

Meter technology	Slope		Intercept (mg/dL)		r^2		Median bias (mg/dL)	
	n = 185	n = 133	n = 185	n = 133	n = 185	n = 133	n = 185	n = 133
StatStrip	0.90	0.96	9	3.6	0.99	0.99	−3	−1
Accu-Chek	0.91	0.98	2	−5.4	0.98	0.97	−9	−7
PCx	0.78	0.85	15	7.4	0.97	0.94	−12	−8
SureStep	0.83	0.91	23	15	0.98	0.97	+2	6

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
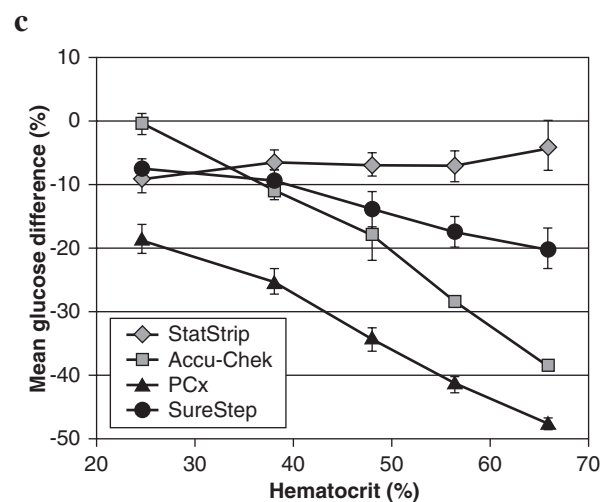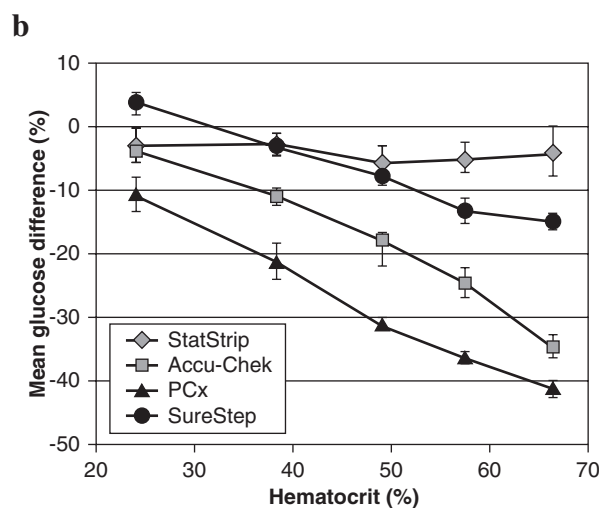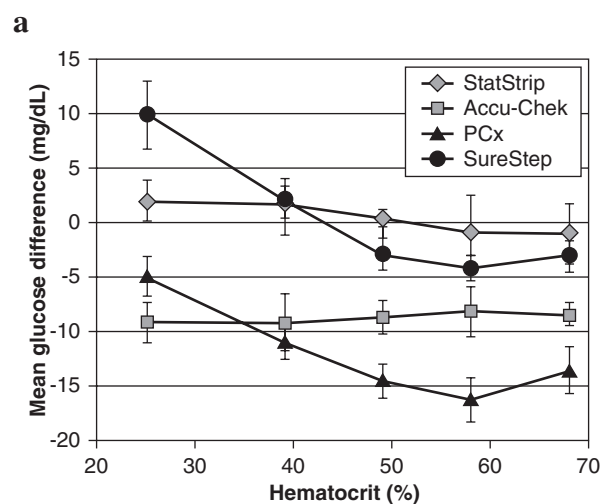

FIG. 1. (**a**) Mean glucose difference (meter glucose − reference glucose) and (**b**) and (**c**) mean glucose percent difference [(meter glucose − reference glucose)/reference glucose × 100] as a function of hematocrit at glucose concentrations of (**a**) 54 mg/dL, (**b**) 247 mg/dL, and (**c**) 483 mg/dL. Each point represents the mean ± standard deviation of the mean glucose difference or mean glucose percent difference ($n = 6$).

a

$$y = 0.0079x - 0.67$$
$$r^2 = 0.0001$$

c

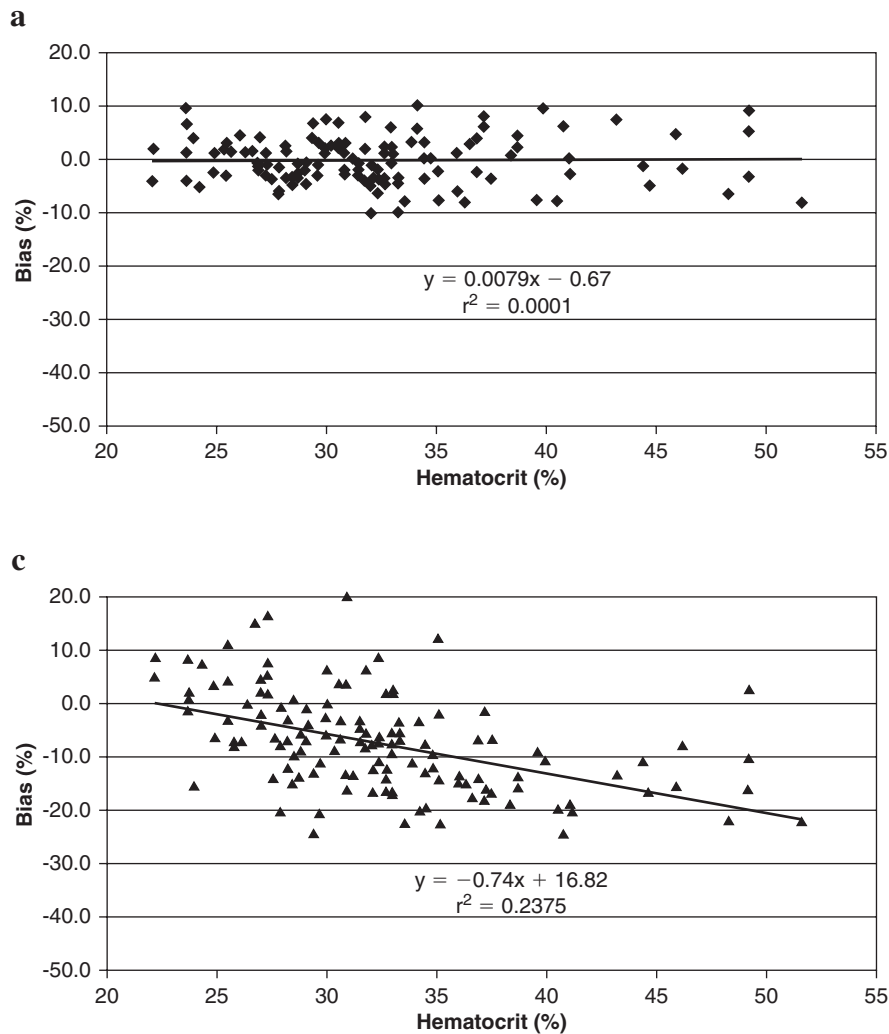$$y = -0.74x + 16.82$$
$$r^2 = 0.2375$$

FIG. 2a, c.

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 so-

dium 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-
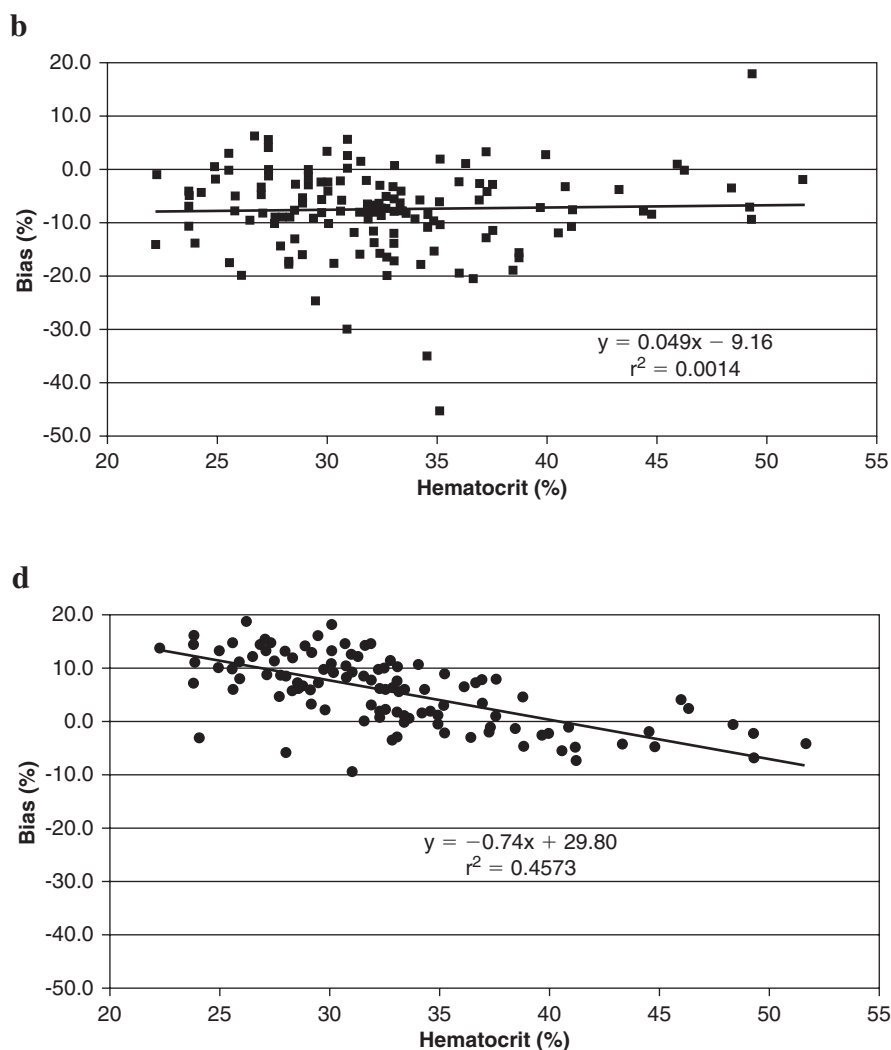
b

d

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 concen-

trations, 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.
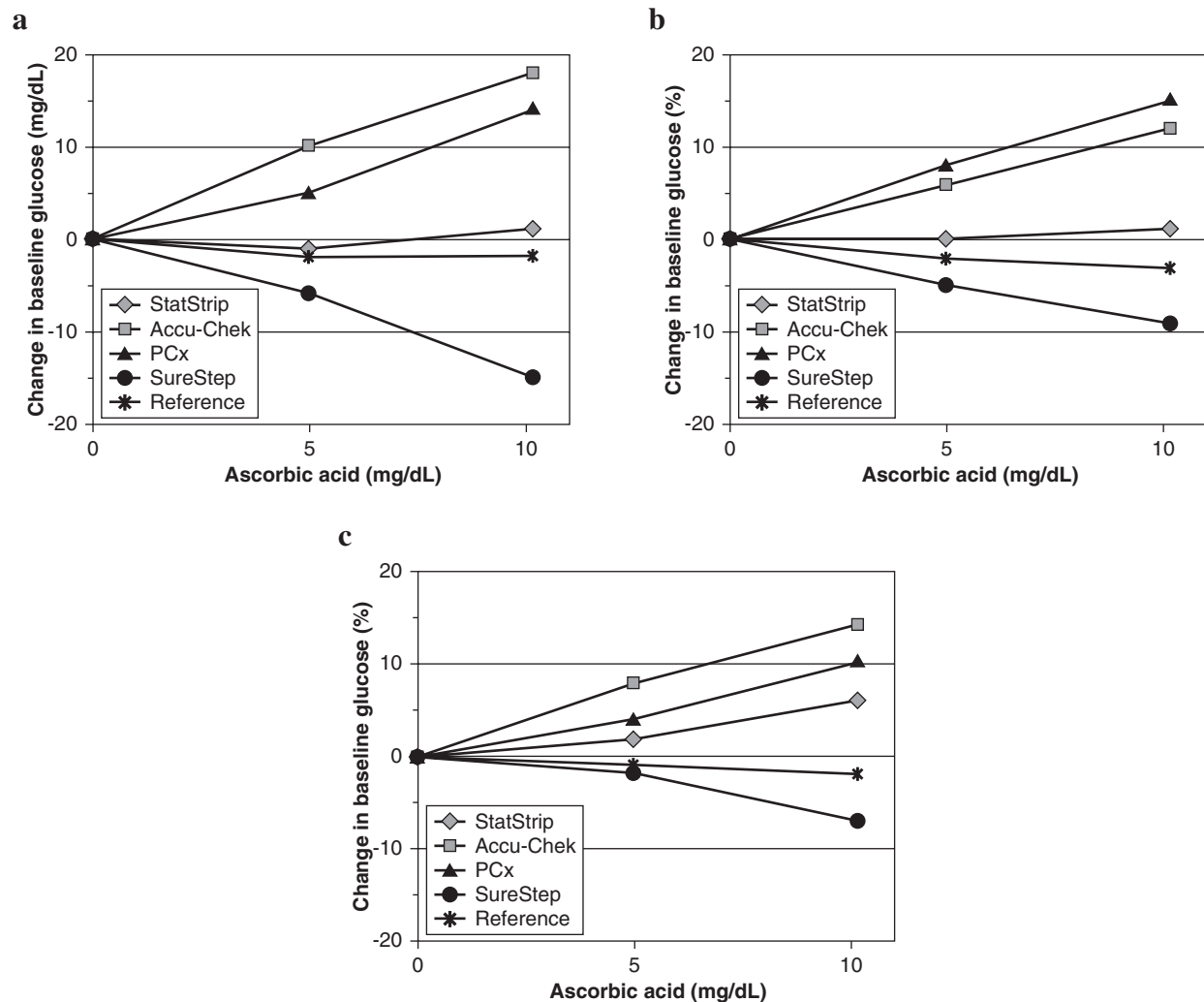
a

b

c

FIG. 3. (**a**) Change from baseline glucose (meter glucose in presence of ascorbic acid – meter glucose at baseline) versus concentration of ascorbic acid using a specimen adjusted to 70 mg/dL. (**b**) and (**c**) Change in baseline glucose expressed in percent change [(meter glucose with ascorbic acid minus meter glucose at baseline)/meter glucose at baseline × 100] using specimens adjusted to (**b**) 141 mg/dL and (**c**) 237 mg/dL glucose. Each point represents the mean of six measurements (strips). The effect of ascorbic acid on the reference method is also shown.

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 me-

ters correlated with a plasma hexokinase reference method differed between meters, as has been observed previously.[12] 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,[15] 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 non-spiked 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[16] 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%.[16] 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 SureSteppFlexx (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.[17] 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.[6] Lactate and beta-hydroxybutyrate had no impact on glucose meter performance, similar to previous studies that showed no effect of sample pH on most glucose meters.[5] 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,[6] 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.[6] 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[18] 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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