Factors Interfering With the Accuracy of Five Blood Glucose Meters Used in Chinese Hospitals

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Background: The prevalence of diabetes is increasing in China. Glucose control is very important in diabetic patients. The aim of this study was to compare the accuracy of five glucose meters used in Chinese hospitals with a reference method, in the absence and presence of various factors that may interfere with the meters. **Methods:** Within-run precision of the meters was evaluated include Roche Accu-Chek Inform[®], Abbott Precision PCx FreeStyle[®], Bayer Contour[®], J&J LifeScan SureStep Flexx[®], and Nova Biomedical StatStrip[®]. The interference of hematocrit level, maltose, ascorbic acid, acetaminophen, galactose, dopamine, and uric acid were tested in three levels of blood glucose, namely low, medium, and high concentrations. Accuracy (bias) of the meters and analytical interference by various factors were evaluated by comparing results obtained in whole blood specimens with those in plasma samples of the whole blood specimens run on the ref-

erence method. Impact of oxygen tension on above five blood glucose meters was detected. **Results:** Precision was acceptable and slightly different between meters. There were no significant differences in the measurements between the meters and the reference method. The hematocrit level significantly interfered with all meters, except StatStrip. Measurements were affected to varying degrees by different substances at different glucose levels, e.g. acetaminophen and ascorbic acid (FreeStyle), maltose and galactose (FreeStyle, Accu-Chek), uric acid (FreeStyle, Bayer Contour), and dopamine (Bayer Contour). **Conclusions:** The measurements with the five meters showed a good correlation with the plasma hexokinase reference method, but most were affected by the hematocrit level. Some meters also showed marked interference by other substances. J. Clin. Lab. Anal. 27:354–366, 2013. © 2013 Wiley Periodicals, Inc.

Key words: blood glucose; hematocrit; correlation; hexokinase

INTRODUCTION

The prevalence of diabetes mellitus is increasing and reaching a high level in China. According to the latest study, the age-standardized prevalence of total diabetes (including both previously diagnosed diabetes and previously undiagnosed diabetes) and prediabetes is 9.7% and 15.5%, respectively, accounting for 92.4 million adults with diabetes and 148.2 million adults with prediabetes (1). As such, diabetes is a serious public health problem. Because of limited health resources, the management of diabetes is a challenge in China (2).

Glucose control is very important in diabetic patients. Tight glucose control (maintenance of blood glucose be-

tween 80 and 110 mg/dl), which decreases mortality in critically ill patients, is accomplished via intensive intravenous insulin therapy (3). Much attention has been paid to the monitoring of blood glucose in hospitalized patients to achieve tight glycemic control and to minimize complications from hypoglycemia and hyperglycemia (3–6).

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Inaccurate blood glucose measurement can cause insulin dosage errors. For meters with a total analytical error of 5%, dosage errors occur in 8–23% of insulin doses. Large errors of insulin dose (two-step or greater) will occur >5% of the time when the coefficient of variation and/or bias exceed 10–15%. Total dosage error rates are affected only slightly by choice of sliding scale of insulin dosage or by the range of blood glucose (7). Insulin dosing is frequently based on measurements performed by glucose meters. Therefore, meter precision can have a major impact on the accuracy of insulin dosing (8). Many factors have been reported to affect the accuracy of glucose meters, such as oxygen tension, hematocrit level, ascorbic acid, acetaminophen, and dopamine (9,10). Many studies have found that glucose meters showed a positive bias at low hematocrit values and negative bias at high hematocrit values, regardless of the meter used (11–13).

The aim of the current study was to compare the accuracy of five glucose meters used in Chinese hospitals with a reference method, in the absence and presence of various substances. The reference plasma hexokinase method encompassed three levels of glucose concentrations.

RESEARCH DESIGN AND METHODS

Instrumentation

Two hundred forty blood samples of diabetic patients were chosen to detect the levels of glucose. The reference assay for plasma glucose used the hexokinase method on the Johnson & Johnson Vitros 350 analyzer. Five glucose meters were chosen as representing the major hospital-based technologies currently available in China: Roche Accu-Chek Inform[®], Abbott Precision PCx FreeStyle[®], Bayer Contour[®], J&J LifeScan SureStep Flexx[®], and Nova Biomedical StatStrip[®].

Correlation Studies

Fresh, venous, whole blood samples were used for this study. Aliquots of well-mixed blood were applied to each of the above five meters for immediate analysis. The remainder of the blood samples was immediately centrifuged, then a plasma sample was tested in the reference Johnson & Johnson Vitros 350 analyzer.

Interference Studies in Donor Blood Samples

The interference of hematocrit level, maltose, ascorbic acid, acetaminophen, galactose, dopamine, and uric acid were tested in three levels of blood glucose, namely low, medium and high concentrations. To study the effect of Hematocrit, three different hematocrit levels (20–26%, 42–48%, and 60–65%), would be studied. Three con-

centration levels of glucose (target ranges as 20–60, 200–275, and 325–400 mg/dl) (1.1–3.3, 11.1–16.7, and 18.1–22.2 mmol/l) were used for the study. To study the interference effects of exogenous substances, freshly heparinized venous blood drawn from healthy donors was allowed to sit at room temperature for 12–24 hr before addition of concentrated solutions of glucose and/or a possible interfering factor. The original blood glucose solution with a concentration of 20,000 mg/dl (1,112 mmol/l), transferred to three appropriate target value for the level of glucose, thoroughly mix for at least 10 min. Spare the blood of 3 ml were placed in 2 ml microcentrifuge tube and labeled 1, 2, 3 bottles. Interference mixture of the two levels of concentration would be injected into the glass on the 2nd the 3rd. A concentration would be covering the upper limit of normal or therapeutic range, the second concentration would be in the toxic range (the details are shown in Table 1). We detected ten times in each blood glucose meter and then calculated the average. The concentrated solutions of glucose and other substances had been gravimetrically prepared.

Impact of Oxygen Tension on Blood Glucose Meters

Blood samples were taken from patients on oxygen therapy and not on oxygen therapy. Approximately 60% of the samples were from patients on oxygen therapy. The samples were obtained using standard arterial blood gas sampling techniques, and run on each of the five meters and the reference analyzer.

Statistical Analyses

For interference experiments, results were expressed as mean change from baseline glucose (meter glucose with interfering factor—meter glucose at baseline) in mmol/l for experiments where the glucose concentration was adjusted to less than 5.6 mmol/l. Mean change from baseline glucose in percent [(meter glucose with interfering factor—baseline glucose)/baseline glucose × 100] was used when glucose was adjusted to more than 5.6 mmol/l. A clinically significant interference effect was defined as any concentration of interfering factor that changed the mean baseline glucose value by more than 0.56 mmol/l (glucose < 5.6 mmol/l) or by more than 10% (glucose > 5.6 mmol/l).

Results

Correlation with Reference Method

Correlation between glucose concentration measured by each of the five meters and that measured by the

TABLE 1. Interfering Substances Concentration and Volume Added in 1 ml of Whole Blood

Interference mixture	The original concentration	Concentration added to the first bottle	Concentration added to the second bottle	Concentration added to the third bottle
Acetaminophen	1,000 mg/dL	0 mg/dL	5 mg/dL	10 mg/dL
	66.2 mmol/L	0 mmol/L	0.33 mmol/L	0.66 mmol/L
		0 μ l	5 μ l	10 μ l
Ascorbic acid	1,000 mg/dL	0 mg/dL	5 mg/dL	10 mg/dL
	58.8 mmol/L	0 mmol/L	0.29 mmol/L	0.59 mmol/L
		0 μ l	5 μ l	10 μ l
Maltose	10,000 mg/dL	0 mg/dL	100 mg/dL	200 mg/dL
	278 mmol/L	0 mmol/L	2.8 mmol/L	5.6 mmol/L
		0 μ l	10 μ l	20 μ l
Uric acid	1,000 mg/dL	0 mg/dL	8 mg/dL	20 mg/dL
	59.2 mmol/L	0 mmol/L	0.47 mmol/L	1.18 mmol/L
		0 μ l	8 μ l	20 μ l
Galactose	10,000 mg/dL	0 mg/dL	100 mg/dL	200 mg/dL
	556 mmol/L	0 mmol/L	5.6 mmol/L	11.1 mmol/L
		0 μ l	10 μ l	20 μ l
Dopamine	1,000 mg/dL	0 mg/dL	5 mg/dL	10 mg/dL
	66.2 mmol/L	0 mmol/L	0.33 mmol/L	0.66 mmol/L
		0 μ l	5 μ l	10 μ l

TABLE 2. Correlation Data for Glucose Meters vs. the Reference Plasma Hexokinase Method ($n = 40$)

Meter technology	Slope	Intercept (mmol/l)	R^2	Median bias (mmol/l)
StatStrip	1.04	-0.47	0.99	0.20
LifeScan	1.15	-0.65	0.99	-0.10
Accu-Check	0.98	-0.03	0.98	0.30
FreeStyle	1.02	-0.38	0.99	0.30
Bayer contour	1.06	0.14	0.99	-0.40

plasma hexokinase reference method was performed by analyzing 40 fresh lithium heparin venous blood specimens. Mean reference glucose value was 7.7 mmol/l for the entire sample, and the range of glucose values covered was 1.4–28.0 mmol/l. The results of linear regression analysis and meter bias are shown in Table 2.

Effect of Hematocrit Level on Glucose Meter Accuracy

The effect of hematocrit level was examined by manually adjusting the hematocrit of donor sodium heparin blood at different glucose concentrations. At low glucose, the mean glucose measured changed by more than 0.56 mmol/l on the LifeScan meter when the hematocrit was at 74.20% (Fig. 1A). In medium glucose, mean glucose readings changed by more than 10% in four of five meters, not in the StatStrip meter (Fig. 1B). In the meters affected by the hematocrit level, the glucose value was lower than that measured by the reference method. At high glucose, mean glucose changed by more than 10% on all meters except StatStrip (Fig. 1C).

Effect of Acetaminophen on Glucose Meter Accuracy

Acetaminophen (final sample concentrations of 0, 0.33, and 0.66 mmol/l) was added into donor sodium heparin blood with glucose concentrations that had been adjusted to 2.23, 16.43, and 20.83 mmol/l. Higher concentrations of acetaminophen changed the mean glucose level by more than 0.56 mmol/l (for experiments performed at 2.23 mmol/l glucose) on one meter, the FreeStyle meter (Fig. 2A). However, in experiments performed at 16.43 and 20.83 mmol/l glucose, no meter displayed a change in glucose reading of more than 10% (Fig. 2B, C).

Effect of Ascorbic Acid on Glucose Meter Accuracy

Ascorbic acid (final sample concentrations of 0, 0.29, and 0.59 mmol/l) was added into donor sodium heparin blood with glucose concentrations that had been adjusted to 2.36, 14.67, and 24.07 mmol/l. Higher concentrations of ascorbic acid changed the glucose level by more than 0.56 mmol/l (for experiments performed at 2.36 mmol/l glucose) on one meter, the FreeStyle (Fig. 3A). For experiments performed at 14.67 and 24.07 mmol/l, no meter displayed a glucose change of more than 10% (Fig. 3B and C).

Effect of Maltose on Glucose Meter Accuracy

Maltose (final sample concentrations of 0, 2.8, and 5.6 mmol/l) was added into donor sodium heparin blood with glucose concentrations that had been adjusted to 2.43, 14.67, and 24.33 mmol/L. Higher concentrations

Fig. 1. (A) Effect of hematocrit level on glucose meter accuracy in low glucose concentrations. (B) Effect of hematocrit level on glucose meter accuracy in medium glucose concentrations. (C) Effect of hematocrit level on glucose meter accuracy in high glucose concentrations.

Fig. 2. (A) Effect of acetaminophen on glucose meter accuracy in low glucose concentrations. (B) Effect of acetaminophen on glucose meter accuracy in medium glucose concentrations. (C) Effect of acetaminophen on glucose meter accuracy in high glucose concentrations.

Fig. 3. (A) Effect of ascorbic acid on glucose meter accuracy in low glucose concentrations. (B) Effect of ascorbic acid on glucose meter accuracy in medium glucose concentrations. (C) Effect of ascorbic acid on glucose meter accuracy in high glucose concentrations.

Fig. 4. (A) Effect of maltose on glucose meter accuracy in low glucose concentrations. (B) Effect of maltose on glucose meter accuracy in medium glucose concentrations. (C) Effect of maltose on glucose meter accuracy in high glucose concentrations.

Fig. 5. (A) Effect of galactose on glucose meter accuracy in low glucose concentrations. (B) Effect of galactose on glucose meter accuracy in medium glucose concentrations. (C) Effect of galactose on glucose meter accuracy in high glucose concentrations.

Fig. 6. (A) Effect of dopamine on glucose meter accuracy in low glucose concentrations. (B) Effect of dopamine on glucose meter accuracy in medium glucose concentrations. (C) Effect of dopamine on glucose meter accuracy in high glucose concentrations.

Fig. 7. (A) Effect of uric acid on glucose meter accuracy in low glucose concentrations. (B) Effect of uric acid on glucose meter accuracy in medium glucose concentrations. (C) Effect of uric acid on glucose meter accuracy in high glucose concentrations.

Fig. 8. (A) Effect of oxygen tension on StatStrip glucose meter accuracy. (B) Effect of oxygen tension on Accu-Chek glucose meter accuracy. (C) Effect of oxygen tension on Contour glucose meter accuracy. (D) Effect of oxygen tension on FreeStyle glucose meter accuracy. (E) Effect of oxygen tension on LifeScan glucose meter accuracy.

of maltose changed the glucose reading by more than 0.56 mmol/L, or more than 10% on two meters, FreeStyle and Accu-Chek, in low, medium, and high glucose levels (Fig. 4A–C). There were no effects on the measurements of the other meters.

Effect of Galactose on Glucose Meter Accuracy

Galactose (final sample concentrations of 0, 5.6, and 11.0 mmol/L) was added into donor sodium heparin blood with glucose concentrations that had been adjusted to

4.90, 10.90, and 21.70 mmol/L. Higher concentrations of galactose changed the level by more than 0.56 mmol/L, or more than 10% on two meters, FreeStyle and Accu-Chek, in low, medium, and high glucose levels (Fig. 5A–C).

Effect of Dopamine on Glucose Meter Accuracy

Dopamine (final sample concentrations of 0, 0.3, and 0.6 mmol/L) was added into donor sodium heparin blood with glucose concentrations that had been adjusted to 2.60, 15.27, and 24.87 mmol/L. Higher concentrations

TABLE 3. Bias of Different Meters

	Bias (mmol/l)	SD (mmol/l)
StatStrip	0.18	0.49
LifeScan	-0.26	1.04
Accu-Chek	0.14	0.95
FreeStyle	-0.26	1.18
Bayer contour	0.95	0.95

of dopamine changed the glucose level by more than 0.56 mmol/L (for experiments performed at 2.43 mmol/l glucose) on two of the meters, Bayer Contour and Accu-Chek (Fig. 6A). For experiments performed at 15.27 or 24.87 mmol/l glucose, no meter changed the glucose reading by more than 10% (Fig. 6B and C).

Effect of Uric Acid on Glucose Meter Accuracy

Uric acid (final sample concentrations of 0, 0.47, and 1.18 mmol/l) was added into donor sodium heparin blood with glucose concentrations that had been adjusted to 4.50, 10.57, and 22.83 mmol/l. Intermediate concentrations of uric acid changed the glucose level by more than 0.56 mmol/l (for experiments performed at 4.50 mmol/l glucose) in the FreeStyle meter, though the change was reversed at high concentrations, and by more than 10% (for experiments performed at 22.83 mmol/l glucose) in the Bayer Contour meter (Fig. 7A and C). For experiments performed at 10.57 mmol/l, uric acid did not change the glucose reading by more than 10% in any meter (Fig. 7B).

Effect of Oxygen Tension on Glucose Meter Accuracy

A total of 204 matched analyses were randomly performed in 204 patients. The range of the reference assay for glucose was 3.58–33.00 mmol/l. Linear correlation was high among glucometers in this study and the Pearson R^2 highest at 0.989 for the StatStrip (Fig. 8A). Linear correlations were almost the same for Accu-Chek and Contour (Pearson $R^2 = 0.963$ and 0.962). FreeStyle (Pearson $R^2 = 0.935$) and LifeScan (Pearson $R^2 = 0.949$) were the lowest (Fig. 8B–E). Biases were defined as point-of-care minus laboratory glucose values. The absolute lowest mean biases were 0.14 mmol/l for the Accu-Chek and 0.18 mmol/l for the StatStrip. The highest was 0.95 mmol/l for Bayer Contour. The details are shown in Table 3.

DISCUSSION

The correlation between the five meters and the reference method showed some differences. According to the

linear regression model parameters of the slope, the StatStrip, the Contour, and the Accu-Chek meters demonstrated the closest correlation with the reference meter (Table 2). The StatStrip and LifeScan meters demonstrated the lowest absolute median bias (Table 2). This suggested that calibration of the meters by the individual manufacturers, rather than the measurement technology, impacted the degree to which whole blood measurement correlated with the reference hexokinase method, as had been observed previously (9).

The hematocrit level was found to affect glucose meter accuracy at different glucose levels. Only the LifeScan meter was affected at low hematocrit levels in low glucose. At higher glucose concentrations, four meters showed marked reductions in glucose readings at a low hematocrit level. Only StatStrip showed little change (11–13).

We found that uric acid, dopamine, galactose, maltose, ascorbic acid, and acetaminophen all interfered with certain meters. Uric acid, ascorbic acid, and acetaminophen all interfered with the FreeStyle at low glucose levels, increasing the glucose reading by more than 0.56 mmol/l. Similar to our results, Holtzinger et al. reported that acetaminophen did not have a significant impact on the StatStrip and LifeScan glucose meters (14). However, ascorbic acid interfered with the Surestep meter at low glucose levels, reducing the glucose values by more than 0.56 mmol/l (14). Ascorbic acid is a common substance interfering with glucose meters and has been reported to interfere with all glucose meters except StatStrip (13, 14). However, in this study, it was found to interfere with the FreeStyle meter only. The influence of various factors showed variability according to glucose level. Dopamine interfered with Accu-Chek and Bayer Contour readings at low glucose levels, increasing the glucose values by more than 0.56 mmol/l, but had no significant effects on any meter at higher glucose levels. In contrast, galactose and maltose both interfered with Accu-Chek and FreeStyle at all three glucose levels and increased the glucose readings critically by more than 0.56 mmol/l or 10% at different glucose levels. Interference by maltose on glucose meters such as on FreeStyle and Accu-Chek meters, which we found in this study, had been reported previously in a US Food and Drug Administration alert (15).

CONCLUSIONS

There is a good correlation between glucose meters and a plasma hexokinase reference method in the measurement of whole blood glucose. Measurements can vary according to the meter, with most being affected by the hematocrit level, and some meters also show marked interference by other substances at different glucose levels.

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